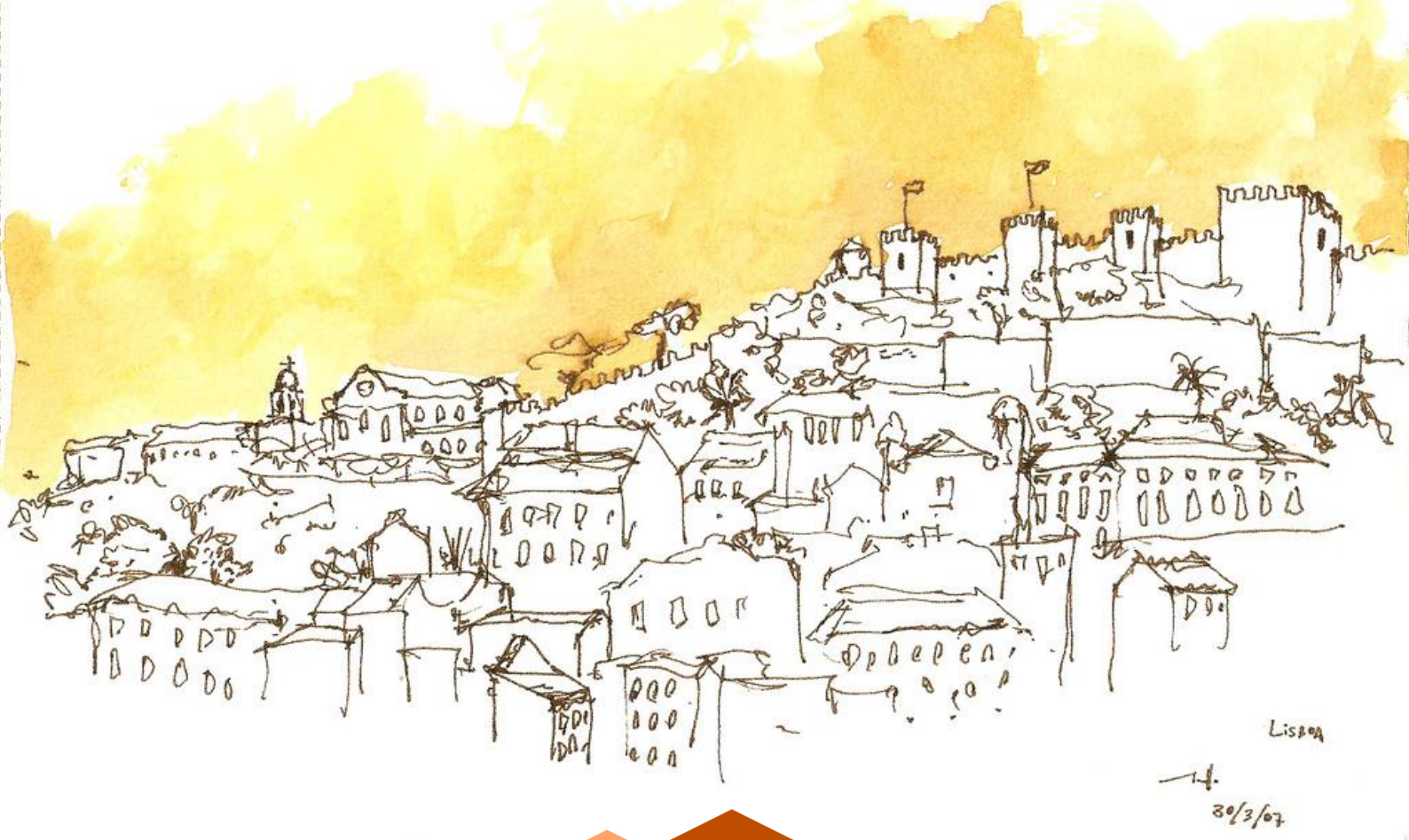

ESOC
2015

19th European Symposium on Organic Chemistry

12th - 16th July 2015 – Lisboa, Portugal

Ciências ULisboa Faculdade de Ciências da Universidade de Lisboa

U LISBOA | UNIVERSIDADE DE LISBOA

Sociedade Portuguesa de Química

EuCheMS European Chemical Sciences

19TH EUROPEAN SYMPOSIUM ON ORGANIC CHEMISTRY

BOOK OF ABSTRACTS

JULY 12TH – 16TH, 2015

LISBOA, PORTUGAL

Cover design: Ana M. Matos and Catarina Dias

Edited by: Amélia P. Rauter, Alice Martins, Ana M. Matos, Catarina Dias, Nuno M. Xavier, Rafael Nunes, Susana D. Lucas, Vasco Cachatra, Ana P. Paiva, Daniela Batista

ISBN 978-989-8124-11-1

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WELCOME

The Organizing Committee cordially welcomes all participants and accompanying persons to Lisbon for the 19th European Symposium on Organic Chemistry (ESOC 2015).This meeting aims at stimulating new emerging areas in organic chemistry. Particular emphasis is given to catalysis and synthesis, while contributions in topics covering recent advances in the chemistry of carbohydrates and proteins, natural products, materials and polymers are also presented and discussed.

The meeting, approved by EuCheMs and by IUPAC, has attracted sponsorship from industrial partners and science publishing companies, and the newest findings presented in this symposium clearly demonstrate the relevance of organic chemistry to innovation for health. Bringing together scientists, industrials and students with expertise in a diversity of areas covering organic chemistry, this symposium is a unique opportunity not only to share the most recent results but also to foster new collaborations between academic and industrial partners, offering also new perspectives for business opportunities and innovation in Europe.

We hope you will enjoy the sharing and exchanging of your expertise in this symposium, held in the beautiful and culturally rich city of Lisbon!

Amélia Pilar Rauter
Chair

ESOC HISTORY

The European Symposium on Organic Chemistry (ESOC) is a prestigious biannual event, first held in Cologne (Germany) in 1979. ESOC offers plenary and invited lectures, oral presentations and poster sessions, and brings together experts from Academia and Industry, and students whose research covers Organic Chemistry and related areas. Characterized by the excellence of their speakers, these prestigious events were held all over Europe. The last ESOC was held in Marseille, France (ESOC18) and below, ESOC meetings are listed in chronological order:

2013 - ESOC 18 Marseille, France, July 7-12

2011 - ESOC 17 Crete, Greece, July 10 -15

2009 - ESOC 16 Prague, Czech Republic, July 12 - 16

2007 - ESOC 15 Dublin, Ireland, July 8 - 13

2005 - ESOC 14 Helsinki, Finland, July 4 - 8

2003 - ESOC 13 Dubrovnik, Croatia, September 10 -15

2001 - ESOC 12 Groningen, The Netherlands, July 13 - 18

1999 - ESOC 11 Goteborg, Sweden, July 23 - 28

1997 - ESOC 10 Basel, Switzerland, June 22 - 27

1995 - ESOC 9 Warszawa, Poland, June 18 - 23

1993 - ESOC 8 Barcelona, Spain, August 29 – *September* 3

1991 - ESOC 7 Namur, Belgium, July 15 - 19

1989 - ESOC 6 Beograd, Yogoslavia, September 10 - 15

1987 - ESOC 5 Jerusalem, Israel, August 30 – *September* 3

1985 - ESOC 4, Aix-en-Provence, France, September 2 - 6

1983 - ESOC 3 Canterbury, England, September 5 - 9

1981 - ESOC 2 Stresa, Italy, June 1 - 5

1979 - ESOC 1 Cologne, Germany, August 20 - 23

The 19th European Symposium on Organic Chemistry will now take place in Lisbon, a historical city facing the ocean, near the most occidental point of the European continent.

COMMITTEE OF HONOUR

Chaired by His Excellency the President of the Portuguese Republic, **Aníbal Cavaco Silva**
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ACKNOWLEDGMENTS AND SPONSORS

The meeting is held under the high patronage of the President of the Portuguese Republic

Com o alto Patrocínio de Sua Excelência
Under the High Patronage of the President of the Portuguese Republic
O Presidente da República

The Organizing Committee is very grateful to the following sponsors:

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Springer International Publisher Science

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TCI Europe

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Thieme Chemistry

Turismo de Lisboa

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GENERAL INFORMATION

Meeting Venue

The Meeting will take place at the Rectory building of Universidade de Lisboa, located in Cidade Universitária, Alameda da Universidade.

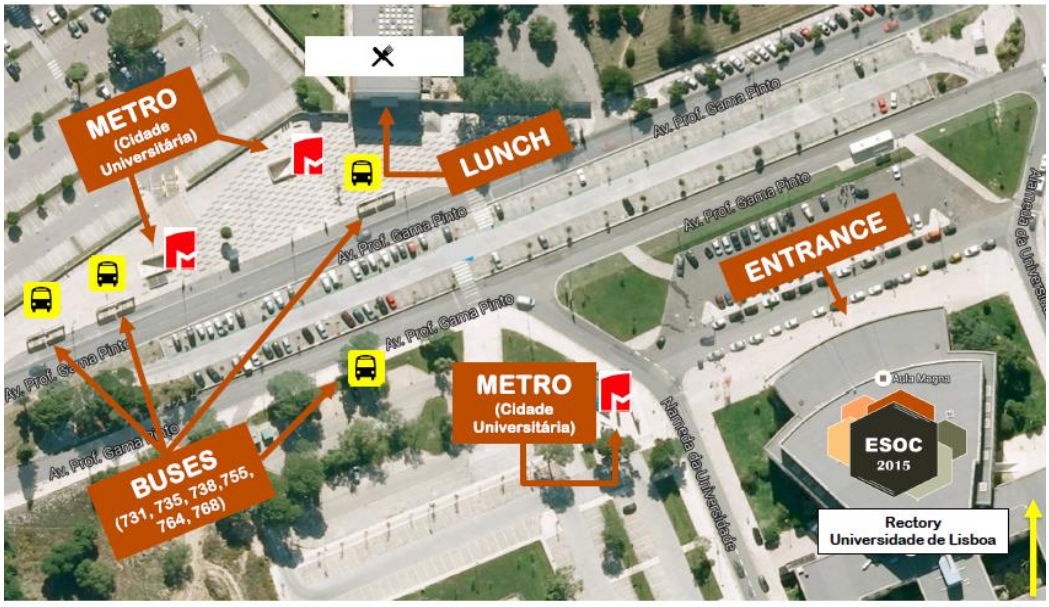
The Rectory building is easily accessed from Lisbon airport, either by taxi (5 -10 min, 10 – 15 €) or by Metro (Cidade Universitária subway station, yellow line). The following buses are also convenient to access the conference venue:

Bus 738, direction Quinta de Barros: Leave the bus at the stop "Cidade Universitaria or Cantina Universidade" located in front of the Lisbon University Rectory. The route of bus 738 provides an alternative transportation for participants staying at hotels in the city centre near the Avenida da Liberdade and the area of the Saldanha Square.

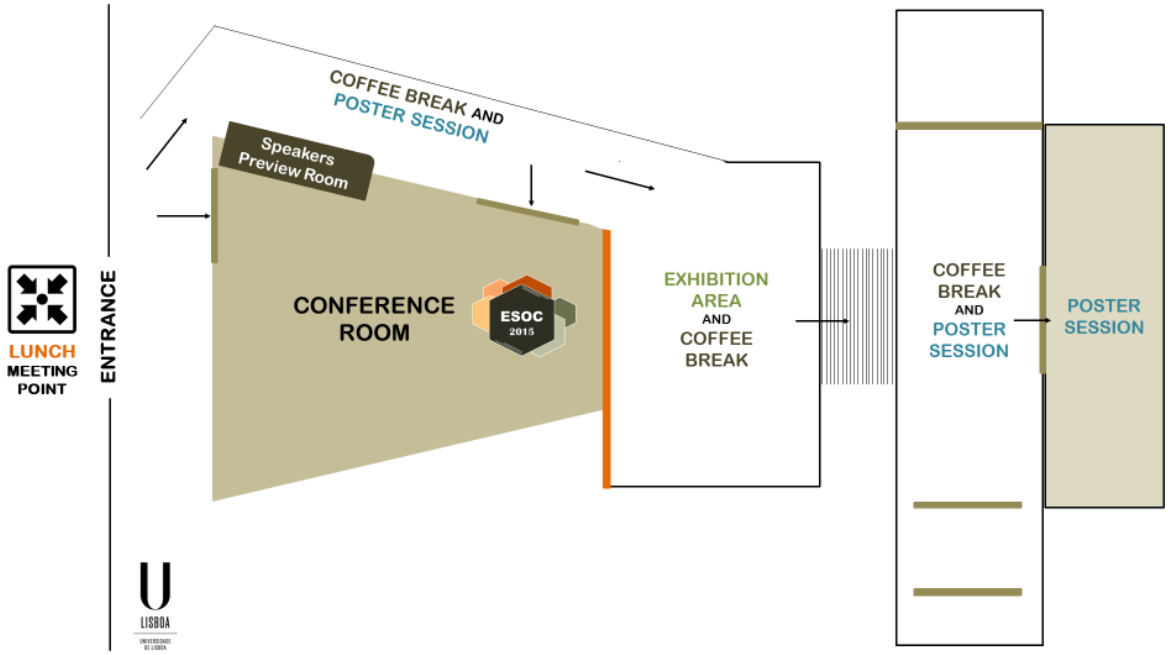
Bus 735, direction Hospital Santa Maria: Leave the bus at the stops Cidade Universitaria or Cantina Universidade located in front of the Lisbon University Rectory. The route of bus 735 provides an alternative transportation for participants staying at hotels at Avenida de Roma.

Bus 736, direction Odivelas: Leave the bus at the stop Campo Grande / Av. Brasil. Walk along the Avenida de Brasil towards the Alameda da Universidade. The route of bus 736 provides an alternative transportation for participants staying at hotels in the city centre, along the Avenida da Liberdade and the area of the Saldanha Square.

Some of the conference hotels are located within a walking distance from the Rectory building (15 minutes).



Inside the Rectory building, conference room, speakers preview room and exhibition, poster session and coffee break areas will be accordingly signposted, as illustrated in the map below.



Lunches

Lunches on monday, tuesday and wednesday (July 13, 14 and 15) will be served at the University restaurant, a few minutes walking distance from Rectory, and are included in the registration fee. We kindly ask all participants to present their lunch tickets to the staff.

WiFi

A temporary login for the wireless Academic Network (eduroam) has been created. Please use the following credentials:

Guest User Name**:** esoc

Password**:** esoc2015

Profile**:** guest-ULisboa

Language

English is the official language of ESOC 2015.

Voltage

In Portugal the line voltage is 220 V and the connection is made by a two-pin plug. Travellers from USA will require a voltage converter and those from UK will require a plug adapter.

Time Zone

The time zone in Lisbon is GMT.

Climate

In July, the temperature in Lisbon is on average 25ºC (Low of 18ºC and Max of 35ºC). Eventually, it could rain, although it is not usual.

Water

Tap water in Portugal is drinking water.

Insurance

All conference attendees are advised to arrange private travel insurance. The conference organizers and committee accept no liability for personal accidents or damage to property.

Banking and Post Offices

Several banks and ATMs are located within 5 min walking distance from the Rectory of UL. Most restaurants and shops will accept credit cards.

The national currency in Portugal is Euro. Banks are open from Monday to Friday between 8.30 am and 3 pm. Post offices are usually open between 8.30 am and 6 pm. Exchange houses operate everyday between 9 am and 1 pm and from 2 pm to 7 pm.

Shopping

Shops are opened from Monday to Friday, between 9 am and 7 pm, in some cases with lunch break from 1 pm to 3 pm. On Saturdays, shops open only in the morning, from 9 am to 1pm. The exception are the Shopping Centres that do a 10 am to 10 or 11 pm stretch 7 days a week. The large Supermarkets also stay open until 9 or 10 pm, 7 days a week.

SOCIAL PROGRAMME

Welcome Reception and Concert

The social programme starts with a welcome reception, included in the registration fee, on the 12th of July at 19h30, following a musical journey around Europe, a concert given at 18h30 by the EurJOC Young Researcher Awardee Nuno Maulide (piano) and the singer Armando Possante (baritone).

Gala Dinner

The Gala dinner is at CASINO ESTORIL on the 14th of July (20:00 h) and is also included in the registration fee. Buses will depart from the Rectory at 19h00 and will bring the participants to Casino Estoril. Dinner will be served at the Black and Silver Room, and will be followed by a musical, based on the history of Estoril, directed by Filipe la Féria, an acclaimed Portuguese producer with 47 years of experience in theatre and show production. Buses will bring participants back to the conference hotels after the show by 23h30.

Excursions on the 15th of July (not included in the registration fee)

The historical Lisbon tour, the excursions to Sintra, to Estoril and Cascais, and to Arrabida will start at 16h00 on the 15th of July. Departure will be from the Rectory of Universidade de Lisboa, and excursions will end also at the Rectory of Universidade de Lisboa. They will be organized provided they have at least 20 participants.

Historical Lisbon Tour

Lisbon is a remarkable City, with nearly 2.500 years of history. Highlights of this tour include the 12th century fortress of St George's, located on top of one of Lisbon's seven hills, overlooking downtown, the Tagus River and the former Moorish quarter of Alfama, where some of the buildings have survived the 1755 earthquake. Then, the historical Belem will be visited, from where, in the 15th century, the Portuguese Caravelas (sailing boats) departed in expeditions to find the maritime ways to Africa, Asia and Brazil, in glorious sea adventures. In Belem, the Jeronimos's Monastery, a master piece of the Manueline style, will be visited, followed by the famous landmarks Belem Tower and the Monument to the Discoveries.

Excursion to Sintra

The excursion to Sintra includes the visit to the Pena National Palace, one of the Seven Wonders of Portugal that stands on the top of a hill above Sintra, a UNESCO World Heritage Site. The palace constitutes one of ther major expressions of 19th century Romanticism in the world, which displays a unique and intentional mix of Gothic, the Portuguese manueline, islamic and Renaissance styles. It is really worth visiting!

Excursion to Estoril and Cascais

In this excursion Cape Roca, the most occidental point of continental Europe, will be visited. The tour will pass by Guincho beach, one of the most beautiful beaches near Lisbon. This wild paradise stands on an unspoiled dunes' area in the Sintra-Cascais natural park. This beach and surroundings are a wild paradise for surfing, biking, horse riding and walking!
Following the scenic road along the coast line, where the Tejo River meets the Atlantic Ocean, you will cross Estoril and Cascais, the Portuguese Riviera. This coast has attracted kings and queens since sea baths became fashionable at the end of the 19th century. Following the coastline, the tour will pass by Boca do Inferno (Hell's Mouth), an ocean carved spectacle in rock.

Excursion to Arrábida & the Southern Lisbon Wine Region

The excursion starts Heading South of Lisbon and crossing the Vasco da Gama bridge, one of the longest in Europe, 17 kilometers, on the way to Azeitão. This region is famous for a small creamy lamb's cheese and the excellence of its wines. The tour will stop for a visit to the historical wine-cellars of José Maria da Fonseca, the producers of "Moscatel" wine, as well as many other wine qualities. The tour proceeds for a scenic drive by the coastal road along the Arrábida Mountain, a preserved Natural Park due to its unique vegetation in Europe, offering superb views over the mouth of the Sado River and the Atlantic Ocean. The tour continues by passing through Setúbal, one of the most important fish-caning centers along the Sado River. A town of great traditions dated from the Celtic Cetobriga which housed the Roman settlers who held in Setúbal fish-salting tanks.

SCIENTIFIC INFORMATION

Presentation Preview Room

Speakers are kindly asked to contact the organizing committee (João Pedro Pais, Rafael Nunes, Catarina Dias or Ana Marta Matos) at the preview room 24 h before presentation. If the speakers use a Mac computer, previewing is also advised.

Posters

Posters will be displayed in the selected halls of the Rectory. Authors are requested to display their own posters on the boards on Sunday before the opening session. Material to attach posters will be available. Two poster sessions are scheduled on the 13th and the 14th of July from 16h15 to 17h30. Authors are requested to stay near their posters during both sessions in order to be able to answer any questions asked by the participants and by the evaluation pannel, in charge of selecting the posters to be awarded with Poster Prizes.

AWARDS AND PRIZES

In ESOC 2015, three Awards will be given, namely the PATAI-RAPPOPORT LECTURE AWARD, the EurJOC YOUNG RESEARCHER AWARD and the EuCheMS LECTURE AWARD.

Prof. Ilan Marek, Chief Editor of the PATAI series, is gratefully acknowledged for the creation of the **PATAI RAPPOPORT Lecture**, an award given for the first time in ESOC2015. The Awardee is Prof. Peter Chen (ETH).

For the first time, the **EurJOC YOUNG RESEARCHER AWARD** is given, on behalf of ChemPubSoc Europe, the organization of chemical societies that co-own the European Journal of Organic Chemistry. By recognizing excellence in research in Organic Chemistry by a young researcher, this award will motivate the young generation of organic chemists to continuing research in this scientific area and will stimulate them to strive for excellence when conducting research.
We are particularly grateful to Dr. Haymo Ross, the Editor of the European Journal of Organic Chemistry for the creation of the EurJOC Young Researcher Award. The Awardee is Prof. Nuno Maulide (University of Vienna).

The EuCheMS LECTURE AWARD honours outstanding achievements by a European chemist. It also serves to enhance the image of European chemistry and to promote scientific cooperation in Europe. The 2014 EuCheMS Lecture Award was co-attributed to Prof. Christina Moberg and it will be the Closing Lecture of ESOC2015.

Clarke, Modet & C Portugal Awards

The following awards will be given by Clarke, Modet & C Portugal to ESOC 2015 participants:

1 - Clarke, Modet & Cº Portugal - Provisional Portuguese Patent Application Award

This award comprises preparation, technical revision and patent application in Portugal at INPI

2 - Clarke, Modet & Cº Portugal - Industrial Property Diagnostics Award

This award comprises analysis of the technology, search for patent documents and eventually other modalities, and presentation of the report on Diagnostics of Industrial Property. Applications comprising potential provisional patent applications should be submitted to Clarke Modet & C Portugal, (info@clarkemodet.com.pt), for confidential purposes, until **September 30, 2015**. The two best applications will be chosen and the awards consist on a free provisional patent application and on an industrial property Diagnostics for free.

Clarke, Modet & C Portugal was founded in 1965. This company relies on 40 specialists in Intellectual Property (IP) in its offices in Lisbon and Oporto, which provide personalized management of customers throughout the process of innovation. It counts with professionals in several IP areas, namely Patents, Designs, Trademarks, Copyrights and Domain Names, Intelligence and Technological Surveillance, Evaluation of Patents and Trademarks and Technology Transfer.The offered services provide a complete support in identifying and selecting the most appropriate form of protection regarding the company's business strategy, as well

as on the process of management and exploitation of its IP assets. Clarke, Modet & Cº Portugal is part of the Clarke, Modet & Cº Group, specialized in Intellectual Property since 1879 with companies in Spain, Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay and Venezuela.

In addition to the described awards, **the best oral presentation prize** and **six poster communication prizes** will be given:

Best Oral Presentation Prize to award an oral communication or a flash presentation, sponsored by Organic and Biomolecular Chemistry – RSC

Organic and Biomolecular Chemistry Poster Prize

MedChemComm Poster Prize

ChemComm Poster Prize

SYNFACTS Poster Prize

The Portuguese Society of Chemistry Poster Prize

The ESOC 2015 Poster Prize

SPECIAL ISSUE DEDICATED TO ESOC 2015

Authors of plenary and invited lectures, and oral communications are invited to submit a paper to the IUPAC journal Pure and Applied Chemistry, that will dedicate an issue to ESOC 2015. Manuscript submission and review will proceed following the journal policy and submission deadline is October 31, 2015.

The authors are requested to send ESOC 2015 chair (Prof. Amélia Pilar Rauter) the title of their manuscript until the end of August.

SCIENTIFIC PROGRAMME

The scientific programme aims at stimulating new emerging areas in organic chemistry, namely those related to organic electronics for chemical sensing, photopharmacology, vaccines, among others. Contributions to organic/bioorganic chemistry e.g. in the areas of carbohydrates and proteins, natural products, small molecule and polymers, materials, and in synthesis and catalysis have demonstrated the importance of organic chemistry for new developments and innovation in a broad range of applications.

The programme comprises contributions on the following topics:

A - Synthesis

B – Catalysis

C – Domino Reactions

D – Medicinal Chemistry

E – Natural Product Chemistry

F – Biomolecular Chemistry

G – Green Chemistry

H – Polymer Chemistry

I – Materials

J – Physical Organic Chemistry

K – Other areas

The Meeting schedules 12 plenary lectures, 10 invited lectures, 24 oral and 8 flash communications, and two poster sessions.

PROGRAMME SCHEDULE

Time	July 12, Sunday	Time	July 13, Monday	July 14, Tuesday	July 15, Wednesday	July 16, Thursday
			SESSION 1 Chaired by: **A. Echavarren, C. Vaz** Sponsor: Hovione	**SESSION 5** Chaired by: **M. Chmielewski, A. Silva** Sponsor: BIAL	**SESSION 9** Chaired by: **W. Magnus, A.P. Rauter** Sponsor: Lilly	**SESSION 12** Chaired by: **J. Cavaleiro, I. Stary** Sponsor: AMSlab
		9.00 - 9.45	**PL1** I. Marek	**PL3** E. Giralt	**Lilly ESOC Plenary Lecture** **PL6** F.D. Toste	**PL8** T.M. Swager
		9.45 – 10.15	**IL1** B. Olofsson	**IL6** D. Gillingham	**IL9** G. Poli	**PL9** C.A.M. Afonso
		10.15 – 10.30	**OC1** R. Loureiro	**OC11** L. E. Kiss	**OC20** E.V. Eycken	
		10.30 – 10.40		**F1** U. Hanefeld		
		10.40 – 11.00	Coffee Break	Coffee Break	Coffee Break	Coffee Break
			SESSION 2 Chaired by: **J. A. Rodriguez, H. Wennemers** Sponsor: Bruker BioSpin	**SESSION 6** Chaired by: **A. Burke, P. Guiry** Sponsor: Tecnimede	**SESSION 10** Chaired by: **B. Chen, A. Minnaard** Sponsor: Fundação Jacqueline Dias de Sousa	**SESSION 13** Chaired by: **D. Cole-Hamilton** Sponsor: EuCheMS
10.30 – 16.00	**Registration**	11.00 – 11.45	**PL2** P. Seeberger	**PL4** H. Wennemers	**PL7** G. Lloyd Jones	**EuCheMS Lecture 2014** **C. Moberg**
		11.45 – 12.00	**IL2** A. Marx	**IL7** G. Kokotos	**YIL3** R. Martin	**Award Ceremony**
		12.00 – 12.15				**ESOC 2017**
		12.15 – 12.30	**OC2** A. Hermann	**OC12** F. Dénès	**OC21** M.E. Muratore	**OC/Poster Awards**
		12.30 – 12.45	**OC3** A.P. Antonchick	**OC13** Y. Queneau	**OC22** N. Krause	Final Remarks Closure
		12.45 – 14.00	Lunch	Lunch	Lunch	ESOC 2015

			SESSION 3 Chaired by: **F. Proença,** **Z. Witczak** Sponsor: nanalysis	SESSION 7 Chaired by: **M.L. Cristiano,** **M. Stratakis** Sponsor: GalChimia	SESSION 11 Chaired by: **S. Doron,** **R. Moreira** Sponsor: Thieme Chemistry
10.30 – 16.00	**Registration**	14.00 – 14.30	**IL3** M. Bandini	**PL5** D. Trauner	**IL10** D. Werz
		14.30 – 14.35			**F5** V. Hornillos
		14.35 – 14.40			
		14.40 – 14.45	**IL4** R. Orru		**F6** J. Dodonova
		14.45 – 14.50		**OC14** C. Bressy	
		14.50 – 14.55			**F7** J.F. Brière
		14.55 – 15.00			
16.00 – 16.30	**Opening Session**	15.00 – 15.15	**OC4** S. Riegel	**OC15** R. J. Estevez	**OC23** J. George
	PATAI RAPPOPORT Lecture 2015 **P. Chen** Chaired by: **I. Marek** Sponsor: Wiley	15.15 – 15.30	**OC5** S. Xie	**OC16** L. Branco	**OC24** W.F. Patureau
16.30 – 17.15		15.30 – 15.35			
		15.35 – 15.40		**F2** T. Gosh	
		15.40 – 15.45	**OC6** N.R. Candeias		**YIL4** G. Masson
		15.45 – 15.50		**F3** A. Gini	
		15.50 – 15.55			
17.15 – 17.30	**Award Ceremony**	15.55 – 16.00		**F4** S. Lemouzy	
	EurJOC Young Researcher Lecture 2015 **N. Maulide** Chaired by: **J. Jimenez-Barbero,** **H. Ross** Sponsor: PubSocChem	16.00 – 16.15	**YIL1** J. Codee	**OC17** G. Lemière	**Excursion**
		16.15 – 17.30	Coffee Break and **Poster Session 1**	Coffee Break and **Poster Session 2**	
17.30 – 18.15			**SESSION 4** Chaired by: **C. Maycock,** **T. Pinho e Melo** Sponsor: ScanSci	**SESSION 8** Chaired by: **L.L. Gundersen,** **A. Lobo** Sponsor: IUPAC	
18.15 – 18.30	**Award Ceremony**	17.30 – 17.45	**OC7** F.G. Zhang	**OC18** B. Hess	
		17.45 – 18.00	**OC8** E.M. Scanlan	**OC19** A. Millán	
	CONCERT *A musical journey around Europe* **Armando Possante,** Baritone **Nuno Maulide,** Piano Sponsor: TCI	18.00 – 18.15	**OC9** J.D. Wallis	**IL8** M. Garson	
18.30 – 19.30		18.15 – 18.30	**OC10** N. Eisink		
		18.30 – 19.00	**YIL2** J. Tomé		
19.30 – 21.30	**Welcome Reception**	19.00 – 19.30	**IL5** A. Gabibov		
		20.00 – 23.30		**Gala Dinner**	

DETAILED PROGRAMME

Sunday, the 12th of July 2015

10:30		Registration
16:00		Opening Ceremony
Chaired by Ilan Marek *Sponsor: Wiley*		
16:30	**Opening Lecture** A1	Catalytic Electrophilic Cyclopropanation without Diazo Compounds: De Novo Mechanistic Design and a Historical Twist **PATAI RAPPOPORT Lecture 2015** **Peter Chen** ETH, Switzerland
17:15	**Award Ceremony**	
Chaired by: Haymo Ross and Jesus Jiménez-Barbero *Sponsor: ChemPubSoc*		
17:30	A2	Catalytic Rearrangements as Tools for Bond Formation **EurJOC Young Researcher Lecture 2015** **Nuno Maulide** University of Vienna, Institute of Organic Chemistry, Austria
18:15	**Award Ceremony**	
Sponsor: TCI		
18:30	Concert	A musical journey around Europe **Nuno Maulide**, piano **Armando Possante**, Baritone
19:30	Welcome Reception	

Monday, the 13th of July 2015

SESSION 1 *Chaired by Antonio Echavarren and Cláudia Vaz* *Sponsor: Hovione*		
9:00	PL1	Preparation and Reactivity of Acyclic Trisubstituted Enolates **Ilan Marek** Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, Haifa, Israel
9:45	IL1	Green Arylations with Diaryliodonium Salts **Berit Olofsson** Department of Organic Chemistry, Stockholm University, Sweeden

10:15	OC1	Active Pharmaceutical Ingredients: Purification Scale-up Challenges **Rui Loureiro** Hovione FarmaCiência SA, Portugal
10:30	Coffee Break	
SESSION 2 *Chaired by Jean-A. Rodriguez, Helma Wennemers* *Sponsor: Bruker BioSpin*		
11:00	PL2	Fully Synthetic Carbohydrate Vaccines **Peter H. Seeberger** Max-Planck Institute for Colloids and Interfaces, Potsdam, Germany
11:45	IL2	Synthetic Tools to Study Protein and DNA Modifications **Andreas Marx** University of Konstanz, Germany
12:15	OC2	DNA as a Scaffold for Reactions, Catalysts and Protective Groups **Andreas Herrmann** Zernike Institute for Advanced Materials, University of Groningen, The Netherlands
12:30	OC3	Direct Oxidative Synthesis of Heterocycles **Andrey P. Antonchick** Max-Planck-Institut für Molekulare Physiologie and Technische Universität Dortmund, Germany
12:45	Lunch	
SESSION 3 *Chaired by Fernanda Proença and Zbigniew Witczak* *Sponsor: Nanalysis*		
14:00	IL3	New Opportunities for the Stereoselective Dearomatization of Indoles **Marco Bandini** University of Bologna, Italy
14:30	IL4	Multicomponent reactions: Advanced Tools for Sustainable Organic Synthesis **Romano V. A. Orru** VU University, Amsterdam, The Netherlands
15:00	OC4	Benchtop NMR Spectroscopy of Reation Monitoring **Susanne D. Riegel** Nanalysis Corp., Calgary, Canada
15:15	OC5	Perfluoraryl Azides: Pre-activated Dipole in Cycloadditions **Sheng Xie**, Olof Ramström, Mingdi Yan Department of Chemistry, KTH-Royal Institute of Technology, Stockholm, Sweden
15:30	OC6	Petasis Borono-Mannich Reactions in Glycerol **Nuno R. Candeias**, Tomi Rosholm, and Robert Franzen

		Department of Chemistry and Bioengineering, Tampere University of Technology, Finland
15:45	YIL1	A Sweet Twist: Conformational Behavior of Oxocarbenium Ions **Jeroen D. C. Codee** Leiden Institute of Chemistry, Universiteit Leiden, The Netherlands
16:15	Coffee Break and **Poster Session 1**	
SESSION 4 *Chaired by: Christopher Maycock and Teresa Pinho e Melo* *Sponsor: ScanSci*		
17:30	OC7	Brook Rearrangement as a Trigger for the Ring-Opening of Cyclopropanes **Fa-Guang Zhang**, Guillaume Eppe and Ilan Marek Schulich Faculty of Chemistry, Technion - Israel Institute of Technology, Haifa, Israel
17:45	OC8	Applications of Intramolecular Thiyl Radical Reactions in Synthesis **Eoin M. Scanlan** School of Chemistry, Trinity Biomedical Science Institute, Trinity College Dublin, Ireland
18:00	OC9	Bond Formation and Interactions in Peri-Disubstituted Naphthalenes Nerea Mercadal, Amélie Wannebroucq, Gizem Saritemur, Mateusz B. Pitak, Simon J. Coles, Gregory J. Rees, John V. Hanna and **John D. Wallis** School of Science and Technology, Nottingham Trent University, Nottingham, UK
18:15	OC10	Selective Modification of Unprotected Oligosaccharides **Niek N. H. M. Eisink**, Martin D. Witte, Adriaan J. Minnaard University of Groningen, The Netherlands
18:30	YIL2	Photoactive Molecules and Materials Based on Porphyrins and Phthalocyanines **João P. C. Tomé**, Department of Chemistry, University of Aveiro, Portugal and Department of Organic and Macromolecular Chemistry, Ghent University, Belgium
19:00	IL5	Modern Pharmacology: Magic Bullet & Combinatorial Approaches. Mechanisms of Antigen Degradation **Alexander Gabibov** Lomonosov Moscow State University, Russia

Tuesday, the 14th of July 2015

SESSION 5
Chaired by Marek Chmielewski and Artur Silva
Sponsor: BIAL

9:00	PL3	Peptides as Molecular Interactors **Ernest Giralt** Institute for Research in Biomedicine (IRB Barcelona) and Department of Organic Chemistry, University of Barcelona, Spain
9:45	IL6	Advances in Bioconjugation: New Twists on Old Reactions **Dennis Gillingham** University of Basel, Switzerland
10:15	OC11	COMT Inhibition as a Target for Drug Discovery **Laszlo E. Kiss** and Patricio Soares-da-Silva Laboratory of Chemistry, Department of Research & Development, BIAL, Portugal
10:30	F1	Enantioselective Addition of Water **Ulf Hanefeld**, Bi-Shuang Chen, Linda G. Otten, and Verena Resch Technische Universiteit Delft, Delft, The Netherlands
10:40	Coffee Break	

SESSION 6
Chaired by Anthony Burke and Patrick Guiry
Sponsor: Tecnimede

11:00	PL4	Controlling Supramolecular Assemblies with Proline-Rich Scaffolds **Helma Wennemers** Laboratory of Organic Chemistry, ETH Zürich, Switzerland
11:45	IL7	Design, Synthesis and Study of Phospholipase A_2 Inhibitors as Tools and Novel Medicinal Agents **George Kokotos** University of Athens, Greece
12:15	OC12	Chemoselective Access to Highly Substituted Butenolides via a Radical Cyclization Pathway: Mechanistic Study, Limits and Application Romain Bénéteau, Jean-Christophe Rouaud, Carole F. Despiau, Anne Boussonnière, Jacques Lebreton and **Fabrice Dénès** Université de Nantes, France
12:30	OC13	Synthesis of Sugar Phosphates Analogues of Agrocinopine A: Insights in the Binding Mode of the Protein accA of *Agrobacterium tumefaciens* Mohammed Ahmar, Si-zhe Li, Laurent Soulère, Abbas El Sahili, Denis Faure, Solange Morera and **Yves Queneau** Université de Lyon, INSA Lyon, France
12:45	Lunch	

SESSION 7
Chaired by Maria. L. Cristiano and Manolis Stratakis
Sponsor: GalChimia

14:00	PL5	Controlling Biological Function with Photopharmacology **Dirk Trauner** Ludwig-Maximilians-Universität, Munich, Germany
14:45	OC14	Amplification of Enantioselectivity During Organocatalyzed Desymmetrization of *meso* Diols **Cyril Bressy** Aix Marseille Université, Centrale Marseille, CNRS, Marseille, France
15:00	OC15	A New Contribution to Nitro Sugar Chemistry: Transformation of 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-*C*-(methoxycarbonyl)-6-nitro-α-D-glucofuranose into Highly Constrained β-Amino Acids and Seven Membered β-Imino Acids Amalia M. Estévez, Marcos A. González, Rosalino Balo, Juan C. Estévez, and **Ramón J. Estévez** Center for Research in Biological Chemistry and Molecular Materials (Glycochemistry Laboratory), Santiago de Compostela, Spain
15:15	OC16	Natural Chiral Organic Salts for Asymmetric Catalysis **Luís C. Branco**, K. Zalewska, Gonçalo Carrera and M. N. Ponte Department of Chemistry, Universidade Nova de Lisboa, Portugal
15:30	F2	Reduction of Aryl Halides by Consecutive Visible Light-Induced Electron Transfer Processes **Tamal Ghosh**, Indrajit Ghosh, Javier I. Bardagi and Burkhard König Institute of Organic Chemistry, University of Regensburg, Germany
15:40	F3	Tempo-Mediated *in situ* Formation and Trapping of Unstable Nitrones: Synthesis of *N*-Carbamoyl/Acyl Isoxazolines **Andrea Gini**, M. Segler, O. García Mancheño Institute for Organic Chemistry, University of Regensburg, Germany
15:50	F4	Stereospecific Synthesis of α and β Functionalised P-Chiral Tertiary Phosphine-Boranes **Sébastien Lemouzy,** Duc Hanh Nguyen, Laurent Giordano, Damien Hérault and Gérard Buono Aix Marseille Université, Centrale Marseille, CNRS, Marseille, France
16:00	OC17	Bismuth triflate-catalysed Cycloisomerizations Involving Allenes **Gilles Lemière,** Ilhem Diaf, Pierrick Ondet, and Elisabet Duñach Nice Institute of Chemistry, Université Nice Sophia Antipolis, France
16:15	Coffee Break and **Poster Session 2**	

SESSION 8
Chaired by Lise-L. Gundersen and Ana Lobo
Sponsor: IUPAC

17:30	OC18	Biosynthetic Mechanism of Lanosterol: Cyclization **B. Andes Hess, Jr.**, Nanhao Chen, Shenglong Wang, Lidia Smentek, and Ruibo Wu

		Department of Chemistry, Vanderbilt University, Nashville, Tennessee, USA
17:45	OC19	Total Synthesis of Clavosolide A **Alba Millán** and Varinder K. Aggarwal School of Chemistry, University of Bristol, UK
18:00	IL8	Natural Bioassay-Guided Isolation of Sesquiterpenes with Rare Carbon Skeletons from Marine Animals **Mary J. Garson** The University of Queensland, Brisbane, Australia
18:30		Photo
19:00		Departure to the Gala Dinner

Wednesday, the 15th of July, 2015

SESSION 9 *Chaired by Walter Magnus and Amélia P. Rauter* *Sponsor: Lilly*		
9:00	PL6	Concepts and Catalysts for Organic Synthesis **Lilly ESOC Plenary Lecture** **F. Dean Toste** University of California, Berkeley, USA
9:45	IL9	Palladium Catalysis in Sequential and Oxidative Transformations: Where Are We? **G. Poli** Sorbonne Université, UPMC Univ Paris 06, Paris, France
10:15	OC20	Gold-Catalysed Post-Ugi Heteroannulations and Domino Reactions **Erik V. Van der Eycken** Department of Chemistry, University of Leuven (KU Leuven), Belgium
10:30	Coffee Break	
SESSION 10 *Chaired by Beining Chen and Adriaan Minnaard* *Sponsor: Fundação Jaqueline Dias de Sousa*		
11:00	PL7	Reagents in Catalysis: Mechanism, Design and Control **Guy C. Lloyd-Jones** School of Chemistry, University of Edinburgh, UK
11.45	YIL3	Metal-Catalyzed Reductive Carboxylation with CO_2 **Ruben Martin** Institute of Chemical Research of Catalonia (ICIQ), Tarragona, and Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain
12:15	OC21	The Versatility of Gold(I)-Catalysis Applied to the Total Syntheses of (-)-Nardoaristolone B and Lundurine C

		Michael E. Muratore, Mariia S. Kirillova, Anna Homs, Ruth Dorel, and Antonio M. Echavarren Institute of Chemical Research of Catalonia, Tarragona, Spain
12:30	OC22	Sustainable Gold Catalysis: Synthesis of New Spiroacetals **Norbert Krause** Dortmund University of Technology, Germany
12:45	Lunch	
SESSION 11 *Chaired by Shabat Doron and Rui Moreira* *Sponsor: Thieme Chemistry*		
14:00	IL10	Carbopalladation Cascades – Not Only *Syn*, but Also *Anti* **Daniel B. Werz** Technische Universität Braunschweig, Germany
14:30	F5	Direct Catalytic Cross-Coupling of Organolithium Compounds **Valentín Hornillos**, Massimo Giannerini, Carlos Vila, Martín Fañanas-Mastral and Ben L. Feringa University of Groningen, The Netherlands
14:40	F6	2,4,6-Triarylpirrolo[2,3-*d*]pyrimidines by Suzuki Coupling and C-H Arylation Reactions **Jelena Dodonova** and Sigitas Tumkevicius Vilnius University, Lithuania
14:50	F7	Organocatalyzed Synthesis of Heterocycles: The Meldrum's Approach **Jean-Francois.Brière**, C. Berini, R. Noël, E. Pair, S. Postikova, T.Tite. M. Sabbah, and V. Levacher University of Rouen; INSA Rouen, Mont Saint Aignan, France
15:00	OC23	Biomimetic Synthesis of Chlorinated Meroterpenoids from *Streptomyces* bacteria **Jonathan H. George** Department of Chemistry, University of Adelaide, Australia
15:15	OC24	O_2-Mediated Radical Dehydrogenative Amination Reactions **Frederic W. Patureau** FB Chemie, TU Kaiserslautern, Germany
15:30	YIL4	Asymmetric Difunctionalization of Enamides via Hydrogen Bond Catalysis **Géraldine Masson** Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France
16:00	Excursion	

Thursday, the 16th of July, 2015

SESSION 12
Chaired by José Cavaleiro and Ivo Stary
Sponsor: AMSlab

9:00	PL8	Organic Electronics for Chemical Sensing **Timothy M. Swager** Massachusetts Institute of Technology, USA
9:45	PL9	From Biorenewable Resources to Heterocycles **Carlos A. M. Afonso** Faculty of Pharmacy, University of Lisbon, Portugal
10:30	Coffee Break	

SESSION 13
Chaired by David Cole-Hamilton
Sponsor: EuCheMS

11:00	A3	Recycling in Asymmetric Catalysis **EuCheMS Lecture 2014** **Christina Moberg** Department of Chemistry, KTH Royal Institute of Technology, Stockholm, Sweden
11:45	**Award Ceremony**	
12:00	ESOC 2017	
12:15	**OC/Poster Awards**	
	Closure	

LIST OF LECTURES

AWARD LECTURES

PATAI RAPPOPORT Lecture 2015

CATALYTIC ELECTROPHILIC CYCLOPROPANATION WITHOUT DIAZO COMPOUNDS: DE NOVO MECHANISTIC DESIGN AND A HISTORICAL TWIST
Peter Chen
Laboratorium für Organische Chemie, ETH Zürich, Switzerland **A1**

EurJOC Young Researcher Lecture 2015

CATALYTIC REARRANGEMENTS AS TOOLS FOR BOND FORMATION
Nuno Maulide
Institute of Organic Chemistry, University of Vienna, Austria **A2**

EuCheMS Lecture 2014

RECYCLING IN ASYMMETRIC CATALYSIS
Christina Moberg
Department of Chemistry, KTH Royal Institute of Technology, Stockholm, Sweeden **A3**

PLENARY LECTURES

PREPARATION AND REACTIVITY OF ACYCLIC TRISUBSTITUTED ENOLATES
Ilan Marek
Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, Haifa, Israel **PL1**

FULLY SYNTHETIC CARBOHYDRATE VACCINES
Peter H. Seeberger
Max-Planck Institute for Colloids and Interfaces, Potsdam, Germany **PL2**

PEPTIDES AS MOLECULAR INTERACTORS
Ernest Giralt
Institute for Research in Biomedicine (IRB Barcelona) and
Department of Organic Chemistry, University of Barcelona, Spain **PL3**

CONTROLLING SUPRAMOLECULAR ASSEMBLIES WITH PROLINE-RICH SCAFFOLDS
Helma Wennemers
Laboratory of Organic Chemistry, ETH Zürich, Switzerland **PL4**

CONTROLLING BIOLOGICAL FUNCTION WITH PHOTOPHARMACOLOGY
Dirk Trauner
Ludwig-Maximilians-Universität, Munich, Germany **PL5**

CONCEPTS AND CATALYSTS FOR ORGANIC SYNTHESIS
F. Dean Toste
University of California, Berkeley, USA **PL6**

REAGENTES IN CATALYSIS: MECHANISM, DESIGN AND CONTROL
Guy C. Lloyd-Jones
School of Chemistry, University of Edinburgh, UK **PL7**

ORGANIC ELECTRONICS FOR CHEMICAL SENSING
Timothy M. Swager
Massachusetts Institute of Technology, USA **PL8**

FROM BIORENEWABLE RESOURCES TO HETEROCYCLES
Carlos A. M. Afonso
Faculty of Pharmacy, University of Lisbon, Portugal **PL9**

INVITED LECTURES

GREEN ARYLATIONS WITH DIARYLIODONIUM SALTS
Berit Olofsson
Department of Organic Chemistry, Stockholm University, Sweeden **IL1**

SYNTHETIC TOOLS TO STUDY PROTEIN AND DNA MODIFICATIONS
Andreas Marx
University of Konstanz, Germany **IL2**

NEW OPPORTUNITIES FOR THE STEREOSELECTIVE DEAROMATIZATION OF INDOLES
Marco Bandini
University of Bologna, Italy **IL3**

MULTICOMPONENT REACTIONS: ADVANCED TOOLS FOR SUSTAINABLE ORGANIC SYNTHESIS
Romano V. A. Orru
VU University, Amsterdam, The Netherlands **IL4**

MODERN PHARMACOLOGY: MAGIC BULLET & COMBINATORIAL APPROACHES. MECHANISMS OF ANTIGEN DEGRADATION
Alexander Gabibov
Lomonosov Moscow State University, Russia **IL5**

ADVANCES IN BIOCONJUGATION: NEW TWISTS ON OLD REACTIONS
Dennis Gillingham
University of Basel, Switzerland **IL6**

DESIGN, SYNTHESIS AND STUDY OF PHOSPHOLIPASE A_2 INHIBITORS AS TOOLS AND NOVEL MEDICINAL AGENTS
George Kokotos
University of Athens, Greece **IL7**

NATURAL BIOASSAY-GUIDED ISOLATION OF SESQUITERPENES WITH RARE CARBON SKELETONS FROM MARINE ANIMALS
Mary J. Garson
The University of Queensland, Brisbane, Australia **IL8**

PALLADIUM CATALYSIS IN SEQUENTIAL AND OXIDATIVE TRANSFORMATIONS: WHERE ARE WE?
G. Poli
Sorbonne Universités, UPMC Univ Paris 06, Paris, France **IL9**

CARBOPALLADATION CASCADES - NOT ONLY *SYN*, BUT ALSO *ANTI*
Daniel B. Werz
Technische Universität Braunschweig, Germany **IL10**

YOUNG RESEARCHERS' INVITED LECTURES

A SWEET TWIST: CONFORMATIONAL BEHAVIOR OF OXOCARBENIUM IONS
Jeroen D. C. Codée
Leiden Institute of Chemistry, Universiteit Leiden, The Netherlands **YIL1**

PHOTOACTIVE MOLECULES AND MATERIALS BASED ON PORPHYRINS AND PHTHALOCYANINES
João P. C. Tomé
Department of Chemistry, University of Aveiro, Portugal and Department of Organic and Macromolecular Chemistry, Ghent University, Belgium **YIL2**

METAL-CATALYZED REDUCTIVE CARBOXYLATION WITH CO_2
Ruben Martin
Institute of Chemical Research of Catalonia (ICIQ), Tarragona, and Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain **YIL3**

ASYMMETRIC DIFUNCTIONALIZATION OF ENAMIDES VIA HYDROGEN BOND CATALYSIS
Géraldine Masson
Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France **YIL4**

ORAL AND FLASH COMMUNICATIONS

ORAL COMMUNICATIONS

ACTIVE PHARMACEUTICAL INGREDIENTS: PURIFICATION SCALE-UP CHALLENGES
Rui Loureiro
Hovione FarmaCiência SA, Portugal **OC1**

DNA AS A SCAFFOLD FOR REACTIONS, CATALYSTS AND PROTECTIVE GROUPS
Andreas Herrmann
Zernike Institute for Advanced Materials, University of Groningen, The Netherlands **OC2**

DIRECT OXIDATIVE SYNTHESIS OF HETEROCYCLES
Andrey P. Antonchick
Max-Planck-Institut für Molekulare Physiologie and Technische Universität Dortmund, Germany **OC3**

BENCHTOP NMR SPECTROSCOPY OF REACTION MONITORING
Susanne D. Riegel
Nanalysis Corp., Calgary, Canada **OC4**

PERFLUORARYL AZIDES: PRE-ACTIVATED DIPOLE IN CYCLOADDITIONS
Sheng Xie, Olof Ramström, Mingdi Yan
Department of Chemistry, KTH-Royal Institute of Technology, Stockholm, Sweden **OC5**

PETASIS BORONO-MANNICH REACTIONS IN GLYCEROL
Nuno R. Candeias, Tomi Rosholm, and Robert Franzen
Department of Chemistry and Bioengineering,
Tampere University of Technology, Finland **OC6**

BROOK REARRANGEMENT AS A TRIGGER FOR THE RING-OPENING OF CYCLOPROPANES
Fa-Guang Zhang, Guillaume Eppe and Ilan Marek
Schulich Faculty of Chemistry, Technion - Israel Institute of Technology, Haifa, Israel **OC7**

APPLICATIONS OF INTRAMOLECULAR THIYL RADICAL REACTIONS IN SYNTHESIS
Eoin M. Scanlan
School of Chemistry, Trinity Biomedical Science Institute, Trinity College Dublin, Ireland **OC8**

BOND FORMATION AND INTERACTIONS IN PERI-DISUBSTITUTED NAPHTHALENES
Nerea Mercadal, Amélie Wannebroucq, Gizem Saritemur, Mateusz B. Pitak, Simon J. Coles, Gregory J. Rees, John V. Hanna and John D. Wallis
School of Science and Technology, Nottingham Trent University, Nottingham, UK **OC9**

SELECTIVE MODIFICATION OF UNPROTECTED OLIGOSACCHARIDES
Niek N. H. M. Eisink, Martin D. Witte, Adriaan J. Minnaard
University of Groningen, The Netherlands **OC10**

COMT INHIBITION AS A TARGET FOR DRUG DISCOVERY
Laszlo E. Kiss and Patricio Soares-da-Silva
Laboratory of Chemistry, Department of Research & Development, BIAL, Portugal **OC11**

CHEMOSELECTIVE ACCESS TO HIGHLY SUBSTITUTED BUTENOLIDES VIA A RADICAL CYCLIZATION PATHWAY: MECHANISTIC STUDY, LIMITS AND APPLICATION
Romain Bénéteau, Jean-Christophe Rouaud, Carole F. Despiau, Anne Boussonnière, Jacques Lebreton,and Fabrice Dénès
Université de Nantes, France **OC12**

SYNTHESIS OF SUGAR PHOSPHATES ANALOGUES OF AGROCINOPINE A : INSIGHTS IN THE BINDING MODE OF THE PROTEIN ACCA OF *AGROBACTERIUM TUMEFACIENS*
Mohammed Ahmar, Si-zhe Li, Laurent Soulère, Abbas El Sahili, Denis Faure, Solange Morera and Yves Queneau
Université de Lyon, INSA Lyon, France **OC13**

AMPLIFICATION OF ENANTIOSELECTIVITY DURING ORGANOCATALYZED DESYMMETRIZATION OF *MESO* DIOLS
Cyril Bressy
Aix Marseille Université, Centrale Marseille, CNRS, Marseille, France **OC14**

A NEW CONTRIBUTION TO NITRO SUGAR CHEMISTRY: TRANSFORMATION OF 3-*O*-BENZYL-5,6-DIDEOXY-1,2-*O*-ISOPROPYLIDENE-5-*C*-(METHOXYCARBONYL)- 6-NITRO-α-D-GLUCOFURANOSE INTO HIGHLY CONSTRAINED β-AMINO ACIDS AND SEVEN MEMBERED β-IMINO ACIDS
Amalia M. Estévez, Marcos A. González, Rosalino Balo, Juan C. Estévez, and Ramón J. Estévez
Center for Research in Biological Chemistry and Molecular Materials (Glycochemistry Laboratory), Santiago de Compostela, Spain **OC15**

NATURAL CHIRAL ORGANIC SALTS FOR ASYMMETRIC CATALYSIS
Luís C. Branco, K. Zalewska, Gonçalo Carrera and M. N. Ponte
Department of Chemistry, Universidade Nova de Lisboa, Portugal **OC16**

BISMUTH TRIFLATE-CATALYSED CYCLOISOMERISATIONS INVOLVING ALLENES
Gilles Lemière**,** Ilhem Diaf, Pierrick Ondet, and Elisabet Duñach
Nice Institute of Chemistry, Université Nice Sophia Antipolis, France **OC17**

BIOSYNTHETIC MECHANISM OF LANOSTEROL: CYCLIZATION
B. Andes Hess Jr**.**, Nanhao Chen, Shenglong Wang, Lidia Smentek, and Ruibo Wu
Department of Chemistry, Vanderbilt University, Nashville, Tennessee, USA **OC18**

TOTAL SYNTHESIS OF CLAVOSOLIDE A
Alba Millán and Varinder K. Aggarwal
School of Chemistry, University of Bristol, UK **OC19**

GOLD-CATALYZED POST-UGI HETEROANNULATIONS AND DOMINO REACTIONS
Erik V. Van der Eycken
Department of Chemistry, University of Leuven (KU Leuven), Belgium **OC20**

THE VERSATILITY OF GOLD(I)-CATALYSIS APPLIED TO THE TOTAL SYNTHESES OF (–)-NARDOARISTOLONE B AND LUNDURINE C
Michael E. Muratore, Mariia S. Kirillova, Anna Homs, Ruth Dorel, and Antonio M. Echavarren
Institute of Chemical Research of Catalonia, Tarragona, Spain **OC21**

SUSTAINABLE GOLD CATALYSIS: SYNTHESIS OF NEW SPIROACETALS
Norbert Krause
Dortmund University of Technology, Germany **OC22**

BIOMIMETIC SYNTHESIS OF CHLORINATED MEROTERPENOIDS FROM *STREPTOMYCES* BACTERIA
Jonathan H. George
Department of Chemistry, University of Adelaide, Australia **OC23**

O_2-MEDIATED RADICAL DEHYDROGENATIVE AMINATION REACTIONS
Frederic W. Patureau
FB Chemie, TU Kaiserslautern, Germany **OC24**

FLASH COMMUNICATIONS

ENANTIOSELECTIVE ADDITION OF WATER
Ulf Hanefeld, Bi-Shuang Chen, Linda G. Otten, and Verena Resch
Technische Universiteit Delft, Delft, The Netherlands **F1**

REDUCTION OF ARYL HALIDES BY CONSECUTIVE VISIBLE LIGHT-INDUCED ELECTRON TRANSFER PROCESSES
Tamal Ghosh, Indrajit Ghosh, Javier I. Bardagi and Burkhard König
Institute of Organic Chemistry, University of Regensburg, Germany **F2**

TEMPO-MEDIATED *IN SITU* FORMATION AND TRAPPING OF UNSTABLE NITRONES: SYNTHESIS OF *N*-CARBAMOYL/ACYL ISOXAZOLINES
Andrea Gini, M. Segler, O. García Mancheño
Institute for Organic Chemistry, University of Regensburg, Germany **F3**

STEREOSPECIFIC SYNTHESIS OF α AND β FUNCTIONALISED P-CHIRAL TERTIARY PHOSPHINE - BORANES
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D-MEDICINAL CHEMISTRY

E – NATURAL PRODUCT CHEMISTRY

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H – POLYMER CHEMISTRY

I – MATERIALS

J – PHYSICAL ORGANIC CHEMISTRY

K – OTHER AREAS

DIRECT PREPARATION OF PYRROLIZIDINES USING IMINES AND ISONITRILES

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ABSTRACTS

AWARD LECTURES

CATALYTIC ELECTROPHILIC CYCLOPROPANATION WITHOUT DIAZO COMPOUNDS: DE NOVO MECHANISTIC DESIGN AND A HISTORICAL TWIST

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We report mechanistic studies aimed at a catalytic, electrophilic cyclopropanation of unactivated olefins without diazo compounds, especially without diazomethane. The reaction would replace the Simmons-Smith cyclopropanation, which is super-stoichiometric in metal. Mass spectrometric experiments on electrosprayed organometallic complexes lays the groundwork for computational studies, using DFT methods, which then proceed to development of synthetic methodology under realistic solution-phase conditions. The new reactions designed and discovered in this work provide a further basis for mechanistic studies; we show an iterative cycle of discovery, investigation, and improvement of catalytic cycles.

CATALYTIC REARRANGEMENTS AS TOOLS FOR BOND FORMATION

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The turn of the century brought about a pressing need for new, efficient and clean strategies for the chemical synthesis of biorelevant compounds. Our group has studied the use of various molecular rearrangements and atom-economical transformations as particularly appealing means towards the streamlined synthesis of complex small molecule targets.[1,2,3]

In this lecture, we will present an overview of our research in these areas and how they provide efficient solutions for total synthesis as well as platforms for the discovery of unusual reactivity.

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RECYCLING IN ASYMMETRIC CATALYSIS

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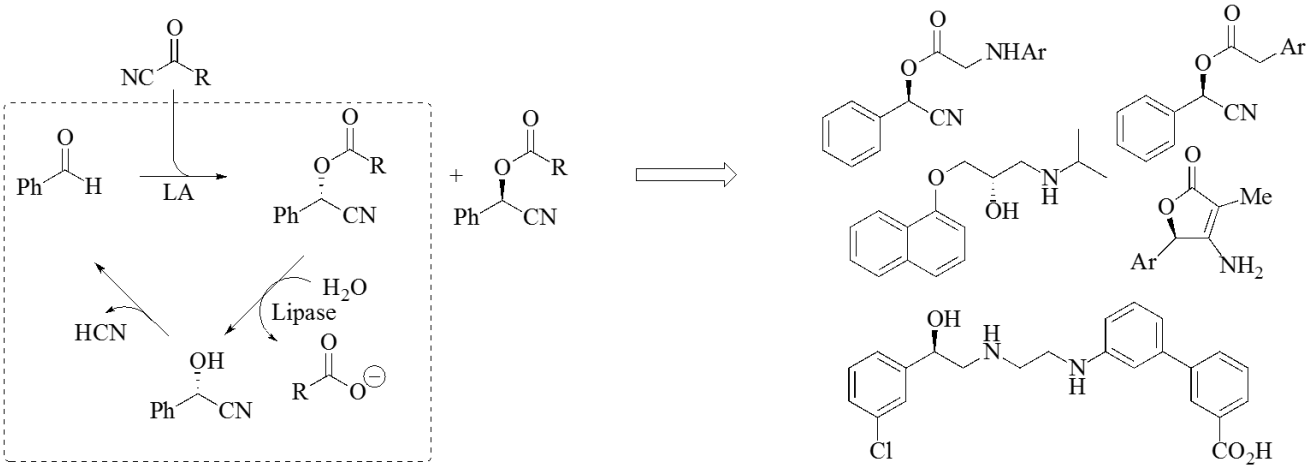
Recycling of the undesired product enantiomer from an enantioselective reaction to achiral starting material is an attractive option for improving the enantiomeric purity of the product. Although the principle of microscopic reversibility states that the reverse reaction cannot favor reaction of the *S*-enantiomer in case the forward, product-forming, reaction favors formation of *R*, chemical energy input via influx of a sacrificial reagent with high chemical energy and the removal of a compound with lower energy may serve as the driving force for a cyclic process.

We have developed minor enantiomer recycling procedures driven by thermodynamically favoured transformation of acyl cyanides to carboxylate (Scheme)[1] as well as of methyl cyanoformate to carbon dioxide.[2] The reactions are characterized by steadily increasing yields and enantiomeric ratios. The procedures have been applied to the synthesis of compounds which have been difficult to obtain with high enantiomeric purity by conventional methods.[3]



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PLENARY LECTURES

PREPARATION AND REACTIVITY OF ACYCLIC TRISUBSTITUTED ENOLATES

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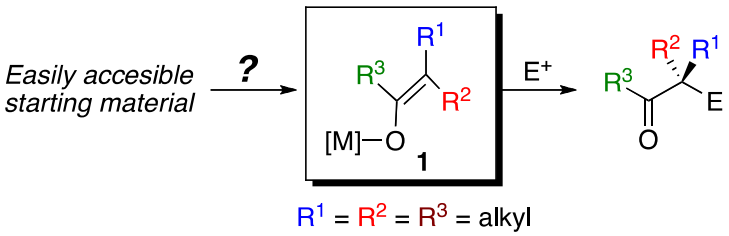
The field of stereoselective synthesis has witnessed tremendous advances over the past half-century providing access to a very large variety of sophisticated molecular fragments with very high diastereo- and enantioselectivity. In this rapidly changing field, initial strategies for single carbon-carbon bond-forming event per chemical steps are now days evolving into new approaches leading to the creation of more than one bond particularly for the synthesis of complex cyclic systems (domino and cascade reactions). However, when structural complexity of the target molecules increases, only very few methods maintain their efficiency. One of the elements that invariably increase the difficulty is the presence of quaternary carbon stereocenters in acyclic systems. This challenge is further exacerbated if more than one stereogenic center is created in the final adducts. Therefore, the preparation of these desired sub-structures with heightened levels of efficiency leads usually to a single carbon-carbon bond-forming event per chemical step between two components. Taking into consideration the significance of enolates as valuable intermediates in asymmetric organic synthesis, one can evaluate the consequence to develop an efficient method to the direct access of trisubstituted metal enolates **1**, in a single-pot operation from common starting materials, as a new route to the formation of the desired quaternary carbon stereocenters. This lecture will describe our approach to the formation of trisubstituted metal enolates.



$R^1 = R^2 = R^3$ = alkyl

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FULLY SYNTHETIC CARBOHYDRATE VACCINES

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Most pathogens including bacteria, fungi, viruses and protozoa carry unique glycans on their surface. Currently, several vaccines against bacteria are marketed very successfully. Since many pathogens cannot be cultured and the isolation of pure oligosaccharides is extremely difficult, synthetic oligosaccharide antigens provide now a viable alternative. Based on the automated synthesis platform,[1] that has now been completely overhauled [2-3] and commercialized.[4] In addition to their function as antigens, synthetic oligosaccharides serve as tools to create monoclonal antibodies, and to establish glycan microarrays to map vaccine epitopes.[5] Diagnostic and preventive approaches against a host of bacteria, fungi, and parasites are being pursued. [6,7]

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PEPTIDES AS MOLECULAR INTERACTORS

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The breakthrough concept that proteins function as a contact network rather than as independent individuals is not only one of the most important advances in our comprehension of living systems, but also translates to a new era in drug discovery. The few reported examples of diseases caused by "impolite" protein social behavior certainly represent only the tip of the iceberg. Therapeutic intervention through molecules designed to selectively modulate the strength and specificity of protein-protein interactions (PPIs) is becoming a reality. This will not only feature molecules with inhibitory capacity: equally or even more interesting are those compounds which can rescue pre-established interactions or structures whose loss results in disease.

In this context, peptides are destined to play a major role as therapeutic agents. My laboratory is contributing to speeding up this process. On the one hand, we devote efforts to studying the molecular details and dynamics of the events that occur during molecular recognition at protein surfaces. We succeeded to design and synthesize peptides able to modulate these recognition events either permanently or in response to light. On the other hand, we are discovering and designing peptides able to cross biological barriers. Our aim is to use these peptides as shuttles for targeting therapeutic agents to organs, tissues, or cells, with a special emphasis on drug delivery to the brain.

PPIs are the result of an ensemble of exquisitely regulated molecular recognition events that take place at protein surfaces. Inspection of protein-protein interfaces allows distinguishing two categories of PPIs: domain-domain and peptide-mediated PPIs.[1] Relatively rigid peptides and peptidomimetics have proved to be very efficient inhibitors of this last class of interactions. In this presentation, recent results from our group related to the use of peptides to modulate PPIs will be discussed. This include, among others: *i)* the recent development of cell-permeable photoswitchable PPI inhibitors, that opens the way to manipulating a specific PPI locally and in a time-controlled manner using illumination patterns [2,3]; *ii)* the application of the retro-enantio approach to obtain a peptide capable of overcoming the blood–brain barrier,[3,4]; and *iii)* the use of peptides to modulate the dynamic behavior of prolyl oligopeptidase (POP), a large 80 kDa protease relevant as therapeutic target in schizophrenia.[5]

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CONTROLLING SUPRAMOLECULAR ASSEMBLIES WITH PROLINE-RICH SCAFFOLDS

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Self-assembly and selective recognition events involving proteins are critical in nature for the function of numerous different processes, for example, catalysis, signal transduction or the controlled formation of structural components such as bones. My group is intrigued by the question whether also peptides with significantly lower molecular weights compared to proteins can fulfill functions for which nature evolved large macromolecules. Specifically we ask whether peptides can serve as effective asymmetric catalysts,[1] templates for the controlled formation of metal nanoparticles,[2] hierarchical supramolecular assemblies,[3] synthetic collagen based materials,[4] or tumor targeting vectors.[5]

The lecture will focus on the development of pH responsive collagen and illustrate the value of distance-controlled molecular templates for the development of supramolecular assemblies.

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CONTROLLING BIOLOGICAL FUNCTION WITH PHOTOPHARMACOLOGY

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Light can be used to control biological events with unmatched temporal and spatial precision. A case in point is optogenetics, which is currently revolutionizing neuroscience. Optogenetics relies on natural photoreceptors that typically employ retinal as the chromophore. Recently, the incorporation of synthetic photoswitches, such as azobenzenes, into naturally “blind” receptors has been explored as well. These molecules can bind covalently or non-covalently to a wide variety of proteins, including ion channels, GPCRs, enzymes, molecular motors, and components of the cytoskeleton, effectively turning them into photoreceptors. As such, photoswitchable molecules add another dimension to pharmacology. I will discuss the advantages and disadvantages of photopharmacology and its potential in biology and medicine, in particular with respect to restoring vision and fighting cancer.

CONCEPTS AND CATALYSTS FOR ORGANIC SYNTHESIS

F. Dean Toste

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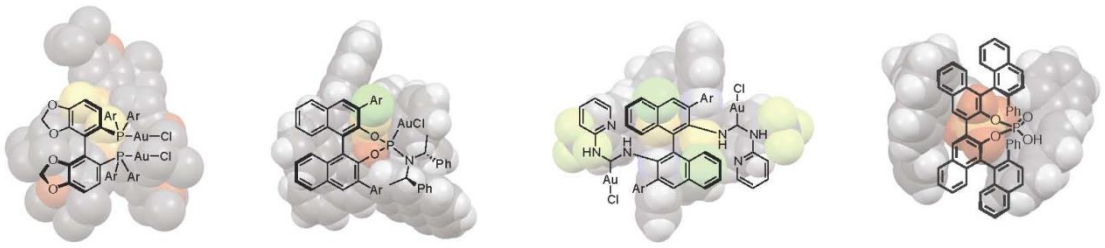
This lecture will emphasize a reactivity driven approach to development of electrophilic catalysts for addition, rearrangement, cycloaddition and coupling reactions of C-C multiple bonds. More specifically, the application of cationic gold(I) complexes,[1] chiral counterions[2] and chiral acids[3] in enantioselective transformations initiated by π-activation will be discussed. Particular attention will be devoted to the mechanistic hypotheses[4] that form the basis for catalyst discovery and the development of new reactions.



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REAGENTS IN CATALYSIS: MECHANISM, DESIGN AND CONTROL

Guy C. Lloyd-Jones

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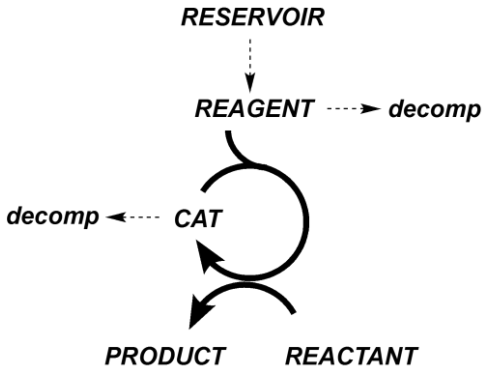
The liberation[1] and delivery of reactants from precursor reagents will be the major topic of the presentation. This will feature selected examples from mechanistic studies into the catalysis of C-C bond forming reactions[2-5] using strategic combinations of isotopic labelling, NMR, kinetics, mass spectrometry calorimetry, computation, X-ray crystallography, and small-angle neutron scattering. What has emerged from these studies, and been of particular interest to us, is the way in which a variety of subtle chemical and physical changes and unanticipated consequences of these changes can conspire to facilitate a useful reaction, or to inhibit undesired ones. A recurring theme is that the *controlled* delivery[3] or release[4,5] of reactants can be a key part of the success of the overall chemical process.



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ORGANIC ELECTRONICS FOR CHEMICAL SENSING

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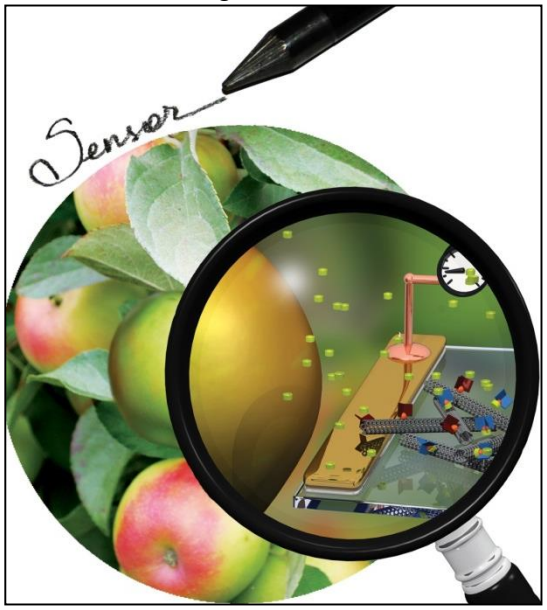
This lecture will detail the creation of ultrasensitive sensors based on electronically active conjugated polymers (CPs) and carbon nanotubes (CNTs). A central concept that a single nano- or molecular-wire spanning between two electrodes would create an exceptional sensor if binding of a molecule of interest to it would block all electronic transport. The use of molecular electronic circuits to give signal gain is not limited to electrical transport and CP-based fluorescent sensors can provide ultratrace detection of chemical vapors via amplification resulting from exciton migration. Nanowire networks of CNTs provide for a practical approximation to the single nanowire scheme. These methods include abrasion deposition and selectivity is generated by covalent and/or non-covalent binding selectors/receptors to the carbon nanotubes. Sensors for a variety of materials and cross-reactive sensor arrays will be described. The use of carbon nanotube based gas sensors for the detection of ethylene and other gases relevant to agricultural and food production/storage/transportation are being specifically targeted and can be used to create systems that increase production, manage inventories, and minimize losses.



FROM BIORENEWABLE RESOURCES TO HETEROCYCLES

Carlos A. M. Afonso

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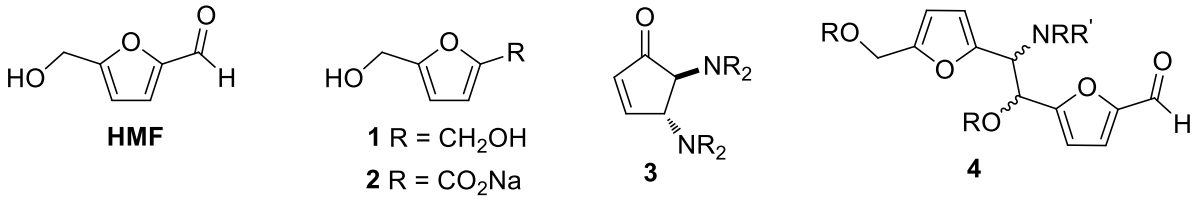
Due to the reduction of fossil resources for energy consumption and platform chemicals for different purposes, several building blocks derived from renewable resources such as ethanol, glycerol, lactic acid, furfural, succinic acid, levulinic acid, are already in use or considered with potential importance in the near future.[1] Among them, 5-hydroxymethyl-furfural (HMF) has been considered a very promising intermediate building block due to its potential rich chemistry that allows different transformations such as to biofuels, polymer monomers, levulinic acid, adipic acid, caprolactam and caprolactone and many other more specific molecules.[2] In line with our interest in the valorization of natural resources[3] and heterocyclic chemistry[4] will be described recent achievements from this laboratory on C-H insertion of acetamide,[5] production of HMF,[6] transformation of HMF and furfural to several building blocks via Cannizzaro reaction **1,2**,[7] amine condensation-rearrangement-cyclization **3**,[8] homo Mannich reaction of trienamine/iminium-ion pair **4** and Friedel-Crafts reaction.[9] In addition, will be presented some biological activity of the synthesized heterocycles and selection guidelines for human exposure of furfural-related compounds.[10]



Acknowledgments: FCT for financial support (PTDC/QUI-QUI/119823/2010, PTDC/QUI-QUI/119210/2010) and ERANET-LAC (ELAC2014/BEE0341).

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INVITED LECTURES

GREEN ARYLATIONS WITH DIARYLIODONIUM SALTS

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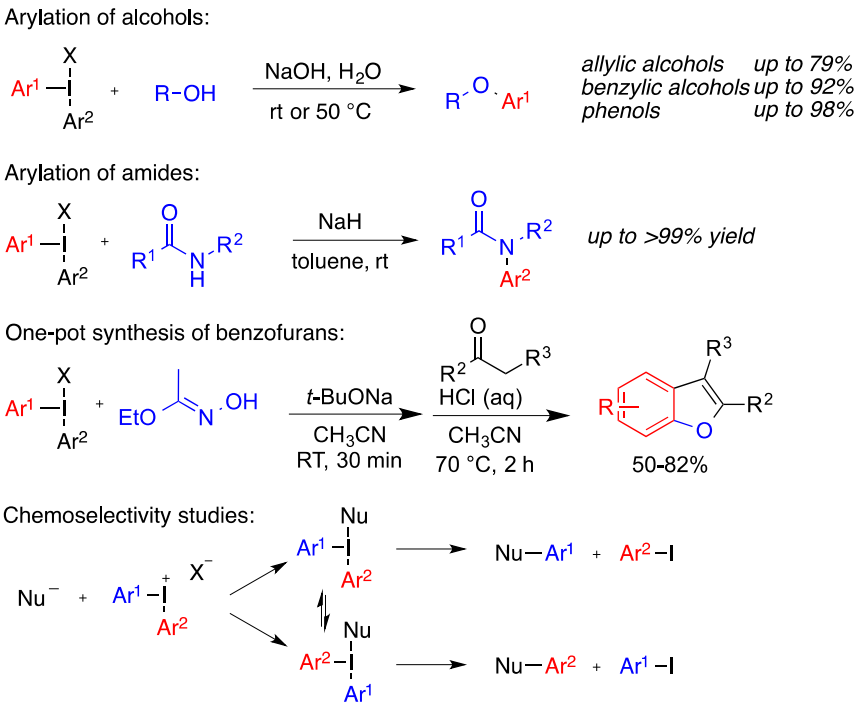
Diaryliodonium salts have recently gained considerable attention as environmentally benign, reactive and selective electrophilic arylation reagents with a variety of nucleophiles.[1] The lack of efficient synthetic routes towards diaryliodonium salts has previously limited their application in organic chemistry. We have recently developed several one-pot syntheses of diaryliodonium triflates, tosylates and tetrafluoroborates.[2] These complimentary routes provide facile access to a wide range of both symmetric and unsymmetric salts with various functional groups.

We have applied these electrophilic arylation agents in arylation of oxygen, nitrogen and carbon nucleophiles under mild and metal-free conditions, providing facile routes to aryl ethers, aryl esters, aryloxyamines, *N*-arylated amides and α-aryl nitroalkanes.[3] We have also developed a metal-free one-pot route to benzofurans, allowing facile access to several biologically important compounds.[4] The chemoselectivity in reactions with unsymmetric diaryliodonium salts will also be discussed.[5]



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SYNTHETIC TOOLS TO STUDY PROTEIN AND DNA MODIFICATIONS

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DNA is the storage of genetic information in Nature. Transmission of the genetic information from the parental DNA strand to the offspring is crucial for the survival of any living species. The entire DNA synthesis in DNA replication is catalyzed by DNA polymerases and depends on their ability to select the canonical nucleotide from a pool of structurally similar building blocks. Human cells express 17 DNA polymerases that have diverse functions and properties. Their coordination remains enigmatic.

The aim of our research is to gain insights into the complex mechanisms of DNA replication and its coordination through application of synthetic molecules with tailored functions and properties. I will report insights into how DNA polymerases faithfully recognize their template,[1] new approaches to study the orchestration of human DNA polymerases by mimicry of posttranslational protein modification,[2] and nucleotide signalling molecules.[3]

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NEW OPPORTUNITIES FOR THE STEREOSELECTIVE DEAROMATIZATION OF INDOLES

Marco Bandini

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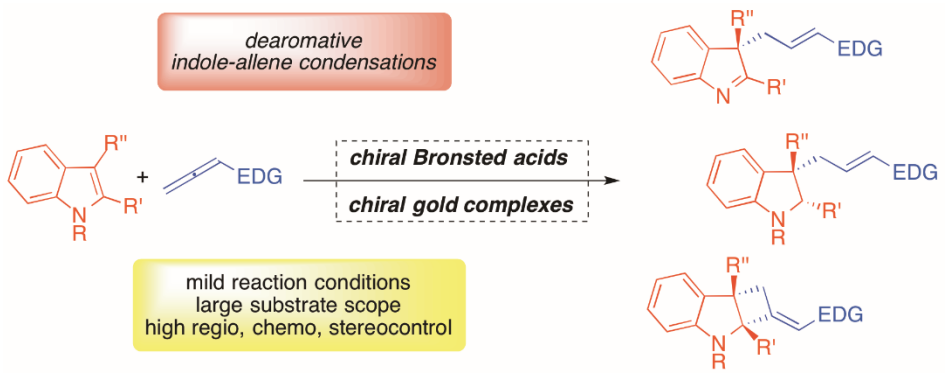
Dearomative synthetic processes of readily available indolyl cores represent a reliable synthetic route to a wide portfolio of polycyclic fused aza-heterocycles, with potential applications in medicinal chemistry and agrochemistry.[1a] In this context, the concomitant creation of new stereogenic centers inspired the development of new stereoselective methodologies based on metal and metal-free approaches.[1b]

Our ongoing interest on the chemical *decoration* of the indole periphery[2] by means of catalytic tools, prompted to elect the intermolecular condensation of electron-rich heteroarenes and activated allenes (*i.e.* allenamides, aryloxyallenes) as a valuable synthetic shortcut towards a chemical diversity/complexity within alkaloid chemistry.[3]

The well-known isolobal analogy often interconnecting [Au(I)] species and the proton enabled the development of several chemo-, regio- and stereoselective catalytic methodologies aiming at the synthesis of densely functionalized indoline as well as indolenine scaffolds (Figure).[4]



An extensive survey across the realized stereoselective dearomatizing protocols along with detailed mechanistic investigations (DFT, NMR) will be presented in the communication.

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MULTICOMPONENT REACTIONS: ADVANCED TOOLS FOR SUSTAINABLE ORGANIC SYNTHESIS

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Multicomponent reactions (MCRs) receive increasing attention because they address both diversity and complexity in organic synthesis. With these one-pot reactions diverse sets of relatively complex structures, especially heterocycles, can be generated from simple starting materials. In many MCRs (e.g. the Ugi reaction), isocyanides are important building blocks. Recently, isocyanides have found also application as versatile C1 building block in palladium catalysis. These reactions offer a vast potential for the synthesis of nitrogen containing fine chemicals. In this presentation, the development of novel atom- and step efficient Pd-catalyzed reactions involving isocyanide insertion will be presented. Further, in order to address stereoselectivity issues connected to certain MCRs, biocatalysis offers unique opportunities. Recently, we have developed several methods based on the enzymatic desymmetrization of meso-pyrrolidines using a monoamine oxidase N (MAO-N) from Aspergillus niger optimized by directed evolution and its combination with highly diastereoselective Ugi-type three-component and Ugi-Smiles reactions. In this presentation we highlight several aspects of this chemistry in the context of heterocycle synthesis with applications in green chemistry and pharmaceuticals.

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MODERN PHARMACOLOGY: MAGIC BULLET & COMBINATORIAL APPROACHES. MECHANISMS OF ANTIGEN DEGRADATION

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The different ways how antigens may be degraded by antibodies (abzymes) and proteasome will be discussed (Belogurov et al, BioEssays, 2009,FEBS Lett.,2012 JBC, 2014). Covalent catalysis is a highly evolved enzymatic trait that poses a significant challenge for artificial enzyme design. Here we describe an immunoglobulin variable fragment obtained by mechanism-based, irreversible covalent reaction (reactibody), which emulates cooperative functionality, for catalysis (Reshetnyak et al. JACS, 2007, Smirnov et al PNAS, 2011). Specific phosphonylation at a single tyrosine within the variable light chain framework was confirmed in an IgG construct. High resolution crystallographic structures of unmodified and phosphonylated Fab displayed a novel 15 Å-deep, two-chamber cavity at the interface of VH and VL, with nucleophilic tyrosine at the base of the site (Smirnov et al. ChemBiol.Interact, 2013) The X-Ray structures of phosphorus –metabolizing “reactibodies”, intermediates and mutated forms will be analyzed Ponoarenko et al. Acta Crystallogr.D). The concept of QM/MM “Immunoglobuline maturation” will be described. The peculiarities of autoantigen degradation via proteasomal pathway will be emphasized. The vast majority of cellular proteins are degraded by the 26S proteasome after their ubiquitination. Here, we report that the major component of the myelin multilayered membrane sheath, myelin basic protein (MBP), is hydrolyzed by the 26S proteasome in a ubiquitin-independent manner both in vitro and in mammalian cells (Kuzina et Bi.omed Res Int. 2014). As a proteasomal substrate, MBP reveals a distinct and physiologically relevant concentration range for ubiquitin-independent proteolysis. Enzymatic deimination prevents hydrolysis of MBP by the proteasome, suggesting that an abnormally basic charge contributes to its susceptibility toward proteasome-mediated degradation. To our knowledge, our data reveal the first case of a pathophysiologically important autoantigen as a ubiquitin-independent substrate of the 26S proteasome Belogurov et al. FASEB J., 2015). We recently showed that myelin basic protein (MBP) is hydrolyzed by 26S proteasome without ubiquitination Beelogurov et al.JBC, 2014) The previously suggested concept of charge-mediated interaction between MBP and the proteasome led us to attempt to compensate or mimic its positive charge to inhibit proteasomal degradation. We demonstrated that negatively charged actin and calmodulin (CaM), as well as basic histone H1.3, inhibit MBP hydrolysis by competing with the proteasome and MBP, respectively, for binding their counterpart. Interestingly, glatiramer acetate (GA), which is used to treat multiple sclerosis (MS) and is structurally similar to MBP, inhibits intracellular and in vitro proteasome-mediated MBP degradation. Therefore, the data reported in this study may be important for myelin biogenesis in both the normal state and pathophysiological conditions. Combinatorial approaches were used to search for potential inducer of autoimmune neurodegeneration at MS (Gabibov et al., FASEB J, 2011). The MBP –derived peptides where shown to cure EAE in SJL/J mice (Belogurov et al. FASEB J., 2013). These peptides encapsulated in liposomes passed the IIa phase as a potential drug of MS.

ADVANCES IN BIOCONJUGATION: NEW TWISTS ON OLD REACTIONS

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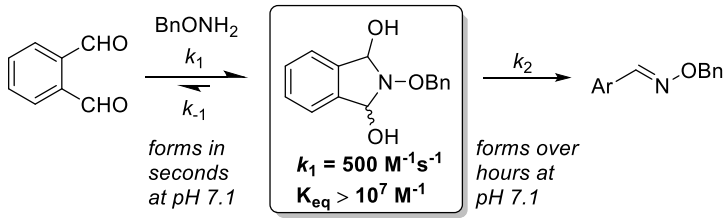
One of the open challenges in chemical biology is to identify reactions that proceed with large rate constants at neutral pH. We have recently discovered that the reaction of O-alkylhydroxylamines with dialdehydes proceed at pH 7.2 with rates of 500 $M^{-1}s^{-1}$.[1] The key to these conjugations is an unusually stable cyclic intermediate, which ultimately dehydrates to an oxime (see graphic). The rate constant for dialdehydes has set a new standard in oxime condensations; but more importantly, the mechanistic insight gleaned in the study of dialdehydes has led us to develop even faster reactions ($k > 10^4$ $M^{-1}s^{-1}$) with the potential for broad application in bioconjugation.[2] I will discuss our initial findings and how our mechanistic analysis has guided us to create exciting new variations on the venerable oxime condensation.[3]



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DESIGN, SYNTHESIS AND STUDY OF PHOSPHOLIPASE A_2 INHIBITORS AS TOOLS AND NOVEL MEDICINAL AGENTS

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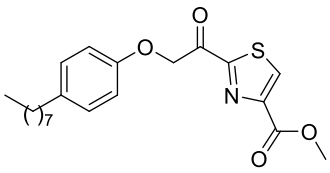
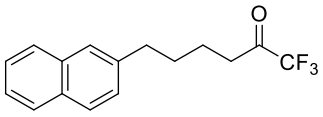
Phospholipase A_2 (PLA_2) enzymes catalyze the hydrolysis of the *sn*-2 ester bond of glycerophospholipids producing free fatty acids, including arachidonic acid, and lysophospholipids. Both products are precursor signaling molecules that are involved in inflammation. The three predominant types of PLA_2 found in human tissues are the cytosolic (such as the GIVA $cPLA_2$), the secreted (such as the GIIA $sPLA_2$), and the calcium-independent (such as the GVIA $iPLA_2$) enzymes. Each PLA_2 type seems to play distinct roles and thus, there is a great interest in developing potent and selective PLA_2 inhibitors as tools and novel agents to treat inflammatory and neurological disorders. A variety of synthetic PLA_2 inhibitors have been developed and some of them reached clinical trials.[1,2]

In our lab, we have developed several classes of novel PLA_2 inhibitors, including 2-oxoamides and thiazolyl ketones targeting GIVA $cPLA_2$, and fluoroketones targeting GVIA $iPLA_2$. Thiazolyl ketone GK470 was found to be a potent inhibitor of GIVA $cPLA_2$, able to suppress the release of arachidonic acid with an IC_{50} value of 0.6 μM in SW982 fibroblast-like synoviocytes.[3] In a prophylactic and a therapeutic collagen-induced arthritis model, GK470 exhibited anti-inflammatory effects comparable to the reference drug methotrexate and enbrel, respectively. The binding mode of a fluoroketone inhibitor to the active site of GVIA $iPLA_2$ has been studied by a combination of molecular dynamics and deuterium exchange mass spectrometry, providing a new tool for the design of more potent GVIA $iPLA_2$ inhibitors.[4] We have recently shown that administration of fluoroketone FKGK18 to non-obese diabetic mice significantly reduced diabetes incidence, reflected by improved glucose homeostasis, and β-cell preservation.[5] In this presentation, we will review the inhibitors developed in the past in our lab and we will discuss our most recent novel PLA_2 inhibitors targeting GIVA $cPLA_2$ and GVIA $iPLA_2$.



GK470



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Acknowledgments: This research has been co-financed by the European Union (European Regional Development Fund - ERDF) and Greek national funds through the Operational Program ‘‘Competitiveness and Entrepreneurship’’ of the National Strategic Reference Framework (NSRF) - Research Funding Program: “Phospholipases A_2 inhibitors: Developing a drug pipeline for the treatment of inflammatory neurological disorders”.

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NATURAL BIOASSAY-GUIDED ISOLATION OF SESQUITERPENES WITH RARE CARBON SKELETONS FROM MARINE ANIMALS

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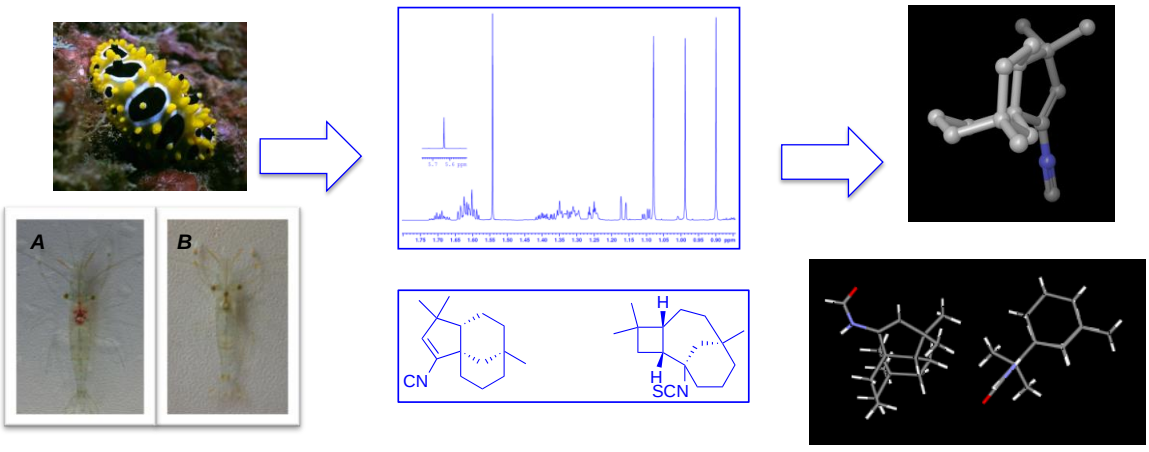
Natural product researchers, armed with a suite of 2D NMR methods and knowledge of biosynthetic pathways, can usually deduce the planar structure of a complex natural product without difficulty. The more complex task of assigning stereochemistry (that is relative and absolute configuration) presents more of a challenge, especially when small quantities of material are available. In this talk, I will describe how a marine chemical ecology study on colour and chemical defense in marine mollusks[1] led us to the isolation of tricyclic isothiocyanato- or isocyanosesquiterpenes with the rare caryolane or clovene skeletons,[2] and of a diterpene isonitrile with an unusual carbon skeleton. NOESY data run at 900 MHz, together with detailed conformational analysis informed by molecular modeling and DFT calculations, and ^{1}H-^{1}H coupling studies enables assignment of individual configurations. The antimalarial and antifungal activities of selected metabolites have been explored.



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PALLADIUM CATALYSIS IN SEQUENTIAL AND OXIDATIVE TRANSFORMATIONS: WHERE ARE WE?

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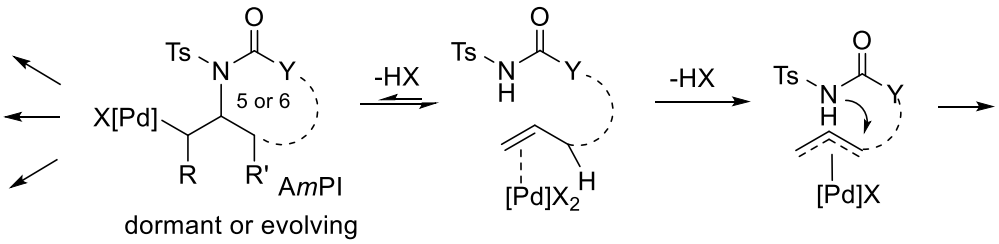
Unsaturated amine derivatives can cyclize under Pd-catalysis according to different mechanistic paths, whose control is a challenging task.[1] In this context, we recently discovered that the oxidative intramolecular Pd(II)-catalyzed amination of unsaturated N-sulfonyl carbamates and carboxamides takes place affording high-energy cyclic (5- or 6-membered) aminopalladated intermediates (A*m*PIs).[2] Such intermediates can subsequently evolve along several different pathways such as distocyclic β-H elimination, oxidative acetylation, carbopalladation, or proxicyclic β-H elimination, as a function of several parameters. Furthermore, in the absence of the above reactivities, the cyclic A*m*PIs are just off-cycle intermediates in equilibrium with the initial substrate, which opens the way to further reactivities such [3,3]-sigmatropic rearrangements or allylic C-H activation of the olefinic substrate.[3] In particular, an in depth DFT study of this latter transformation allowed unveiling its full mechanism.[4] The different routes involved in these intramolecular oxidative cyclization and the factors biasing toward one or the other path will be rationally discussed.



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CARBOPALLADATION CASCADES - NOT ONLY *SYN*, BUT ALSO *ANTI*

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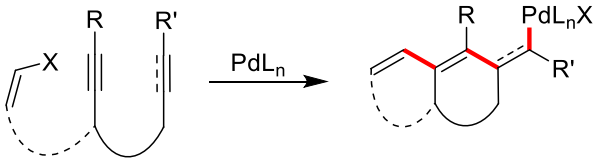
A characteristic feature of carbopalladation reactions is the *syn*-attack of the organopalladium species L_nX[Pd]-R on the reacting π-system.[1] Such a step results in compounds bearing Pd and R on the same side of the originating alkene moiety. Embedded into longer domino sequences complex structures are efficiently obtained by a repetition of this *syn*-carbopalladation step. In this way, linear oligoynes were cyclized in a dumbbell-mode and led to benzene-type structures or higher oligoenes.[1]

We exploited this chemistry to synthesize not only chromans, isochromans[2] and dibenzopentafulvalenes,[3] but also to access the most truncated π-helicenes which only consist of a *Z,Z,Z,..*-oligoene chain that is fixed in an all *s-cis* arrangement.[4] All these domino processes are based on a *syn*-carbopalladation cascade.

However, a carbopalladation cascade involving formal *anti*-carbopalladation steps opens new avenues to create compounds with tetrasubstituted double bonds (Scheme 1). Such a process was realized, and mechanistically and computationally investigated. The synthetic potential was demonstrated for the preparation of various oligocyclic frameworks (*e.g.* highly substituted dibenzofurans and carbazoles).[5]



(R = $CMe_2(OH)$; CMe_3; $SiMe_3$)

Scheme 1. Formal *anti*-carbopalladation reaction embedded in a domino cascade.

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YOUNG RESEARCHERS' INVITED LECTURES

A SWEET TWIST: CONFORMATIONAL BEHAVIOR OF OXOCARBENIUM IONS

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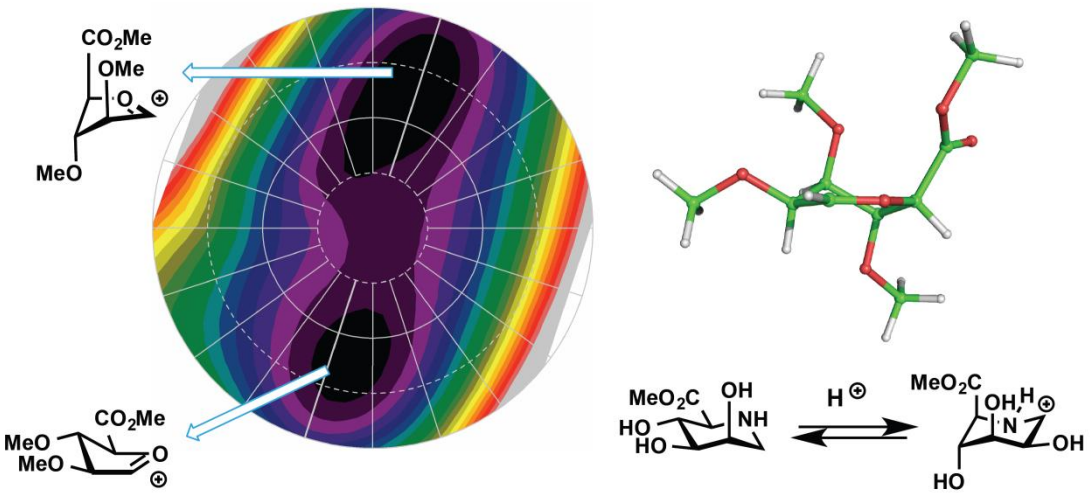
Carbohydrate derivatives bearing a positive charge at C1, such as glycosyl oxocarbenium and iminium ions, take up very different conformations than their non-charged counterparts. To understand the -sometimes striking- reactivity of these species we have to understand their conformational preferences. This lecture will highlight our recent insights into how stereoelectronic substituent effects control the shape of oxocarbenium ions, iminium ions and ammonium ions and how they affect the reactivity and stereoselectivity of these reactive species. These insights will, amongst others, be exploited in the (automated solid phase) construction of challenging 1,2-*cis* glycosidic linkages and stereoselective Ugi reactions.



PHOTOACTIVE MOLECULES AND MATERIALS BASED ON PORPHYRINS AND PHTHALOCYANINES

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Light covers several and important human activities and because of that UN/UNESCO declares 2015 the international year of light and light-based technologies.[1] Indeed, the humanity has been using/exploring/controlling the light for many applications. The use of light covers, if not all, many scientific areas, such as: physics, organic and materials chemistry, catalysis, environment, biology and medicine. For that, natural or artificial photoactive compounds/materials, which can absorb/interact with light, are necessary.

Nature has many examples of photoactive processes, being the photosynthesis probably the most important one. In this context, porphyrins and related compounds constitute a group of natural (photo)active molecules, which play key roles in several vital functions. The possibility to mimic those functions and explore several others, especially when combined with light, have been highly investigated. The decoration of the periphery of the porphyrin macrocycles with different motifs and the selection of their central metals, opens the possibility to fine-tune the physicochemical properties/functionalities of novel molecules/materials to be used in many scientific and technological areas.[2]

In this talk, it will be highlighted some of our recent works on porphyrins, chlorins and phthalocyanines, presenting the used synthetic strategies and some of the obtained results in different areas of research, namely in: i) cancer photodynamic therapy (PDT);[3] ii) photodynamic inactivation of microorganisms (PDI);[4] iii) photoinduced energy- and electronic-transfer materials;[5] and iv) optical (chemo)sensing of pollutants and biomolecules.[6]

Acknowledgements: Thanks are due to the University of Aveiro, FCT (Portugal) and FEDER for funding the projects PTDC/QUI/65228/2006 and PTDC/CTM/101538/2008; CNPq (Brazil) for funding the program “Ciência sem Fronteiras/2012” (4802069445108663); and the European Union for the Marie Curie Initial Training Networks (grant agreement n° 316975).

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METAL-CATALYZED REDUCTIVE CARBOXYLATION WITH CO_2

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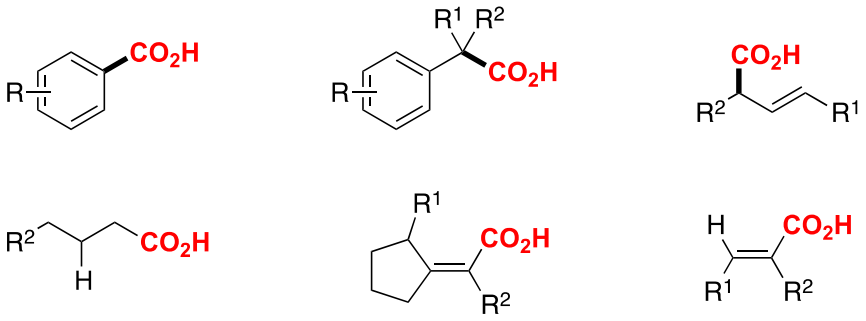
Activation of inert entities has been and continues to be of extreme interest to any organic chemist.[1] This is especially true with activation of atmospheric molecules such as CO_2.[2] The development of operationally-simple and practical catalytic methods for CO_2 fixation would be highly desirable, as many of the current methods involve the use of stoichiometric amounts or air-sensitive organometallic reagents. In the last years, our research group has reported some progress directed towards the catalytic reductive carboxylation of organic matter with CO_2 (Scheme 1).[3] These methods are characterized by their simplicity, wide substrate scope, including challenging substrate combinations with particularly sensitive functional groups and a diverse set of substitution patterns.



Scheme 1. Metal-catalyzed reductive carboxylation with CO_2

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ASYMMETRIC DIFUNCTIONALIZATION OF ENAMIDES VIA HYDROGEN BOND CATALYSIS

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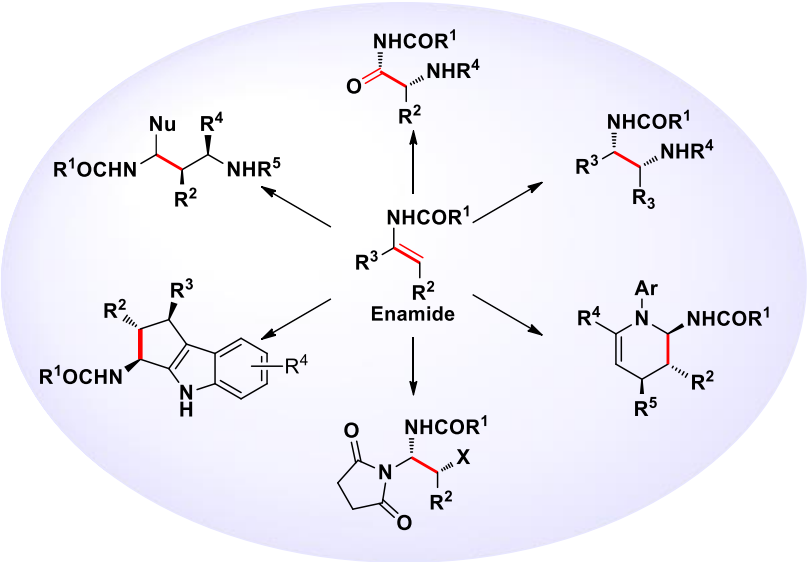
Nitrogen-activated carbon-carbon double bonds, as demonstrated by successful existing works on enamines, have a high potential for the construction of various nitrogen-containing products. In order to expand the application of this class of substrates, we have focused on studying the reactivity of the promising enamide derivatives. Starting from the well-known aza-Diels-Alder reaction, we have gradually been drawn to develop other cycloaddition reactions and more generally an extended range of α,β-difunctionalization methods. This lecture will detail our contribution towards the the development of general approaches toward the synthesis of highly functionalized α,β-substituted amines[1] in the context of an ongoing study towards the synthesis of various biologically active natural and non-natural products.



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ORAL COMMUNICATIONS

ACTIVE PHARMACEUTICAL INGREDIENTS: PURIFICATION SCALE-UP CHALLENGES

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The synthesis, purification and isolation of various Active Pharmaceutical Ingredients (API) developed at Hovione will be discussed. Different cases studies will be discussed and the different challenges involved in taking an innovative drug from discovery to manufacturing.

The added value of introducing Quality by Design (QbD) in the scale-up process and purification step will also be discussed with various examples. In the introduction of QbD the use of process analytical tools (PAT) are of paramount importance to enable process control and reduce operating and holding periods.

In the scale-up of purifications processes different procedures like crystallization, chromatography and reverse-osmosis are required to effectively remove by-products or adjust concentrations of aqueous solutions of various process streams.

DNA AS A SCAFFOLD FOR REACTIONS, CATALYSTS AND PROTECTIVE GROUPS

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In Nature, DNA serves as the storage for genetic information. However, chemists have used nucleic acids in very different contexts to template reactions,[1] as catalysts[2] or as scaffolds for nanoscopic structures.[3] It will be demonstrated how DNA templates a transition metal catalysed reaction. During this reaction a non-fluorescent starting material is converted into a fluorescent product allowing the detection of target DNA down to 10 pM.[4] Instead of templating a dye molecule, it was also possible to use hybridization of ligand-modified oligonucleotides on a target DNA strand to generate an efficient dehalogenation catalyst. Each catalytic site produces several hundred fluorescent compounds enabling nucleic acid detection down to 10 fM.[5] Besides DNA detection, nucleic acids can serve as supramolecular protective groups. These aptameric protective groups block several functionalities in complex natural products like aminoglycoside antibiotics bearing multiple chemically equivalent groups during binding. The chemical functionalities that are not in contact with the aptamer can be transformed enabling the highly chemo- and regioselective derivatization of complex drug molecules in a single synthetic step with excellent conversions.[6] The broad scope of this new paradigm in organic synthesis will be highlighted.

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DIRECT OXIDATIVE SYNTHESIS OF HETEROCYCLES

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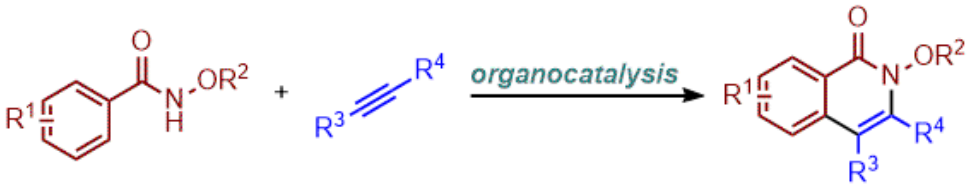
Heterocyclic compounds constitute the majority of organic compounds. Nitrogen-containing heterocycles are present in many natural compounds, biological probes, chemicals and materials. However, the chemical space which can be occupied by relatively simple bicyclic heteroaromatic compounds has not been fully explored and hundreds of novel molecules still remain to be synthesized. A considerable amount of novel ring systems successfully enter drug space annually. Therefore, the development of novel efficient methods of heterocycle synthesis is highly desired and represents a field of intense investigation.

We developed a novel, highly efficient organocatalytic method for the preparation of isoquinolones by regioselective annulation of *N*-alkoxybenzamide derivatives with readily available alkynes.[1] The desired products formed smoothly at ambient temperature in short times using peracetic acid as oxidant and simple organocatalysts such as iodobenzene.



A novel annulation of arenes with 2-aminopyridine derivatives mediated by a hypervalent iodine reagent was developed.[2] This intermolecular approach was applied to the efficient synthesis of benzimidazole derivatives under metal-free conditions. For the first time, we demonstrated application of the methyl group in methyl arenes as a directing, non-chelating, and traceless group in a highly regioselective cross-annulation.

Recently, we developed a multicomponent route for the synthesis of indoles.[3] In the developed method, alkene trifluromethylation was elegantly demonstrated to provide entry into Fischer indole synthesis. The developed process provides access to the divergent and selective syntheses of trifluoromethylated heterocycles under similar reaction conditions. A comprehensive scope of the developed process and the tolerance of a variety of functional groups were successfully demonstrated.

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BENCHTOP NMR SPECTROSCOPY OF REACTION MONITORING

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The science of organic chemistry looks to build carbon-carbon bonds in a straightforward and repeatable manner. This requires a toolbox of reliable reactions that chemists can use to build a specific molecule. However, these reactions must be tailored to different substrates and different starting materials. This can require a great deal of reaction monitoring and optimization. Typical reaction monitoring mechanisms include quenching an aliquot and monitoring reaction progress with thin layer chromatography (TLC), and/or gas chromatography-mass spectrometry (MS). Nuclear Magnetic Resonance Spectroscopy (NMR), however, can be beneficial as it provides more information about the specification and relative quantity of the reaction components. Herein we describe the use of benchtop NMR Spectroscopy to monitor a variety of reactions, from simple small molecule to polymerizations. This monitoring can be done through traditional sampling techniques or through the online NMR spectroscopy.

PERFLUORARYL AZIDES: PRE-ACTIVATED DIPOLE IN CYCLOADDITIONS

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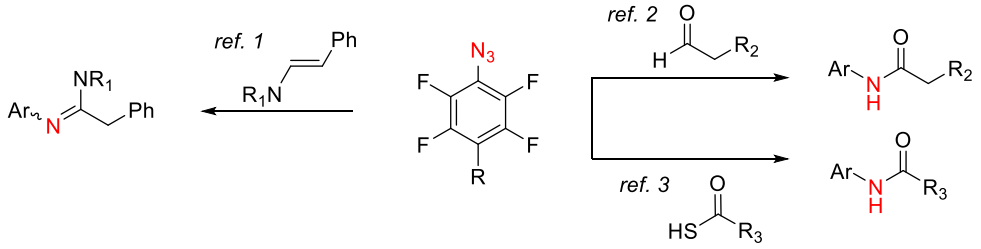
Perfluoraryl azides constituted a special class of dipole owning to highly electron-deficient activation.[1] They react with enamines at room temperature without any catalysts to form 5-aminotriazolines which rearrange to stable amidines, whereas phenyl azide yields isolable triazolines.[1] Reaction of these activated azides with aldehyde yielded amides efficiently under near-neutral conditions at room temperature.[2] In addition, perfluoroaryl azides in thioacid/azide amidations also displayed high reactivity comparable to sulfonyl azides.[3] Those cycloaddition-initiated transformations proved efficient with fast and mild reaction conditions, which are highly attractive to a wide range of applications including bioconjugations, surface functionalization, and nanomaterial synthesis.[4]



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PETASIS BORONO-MANNICH REACTIONS IN GLYCEROL

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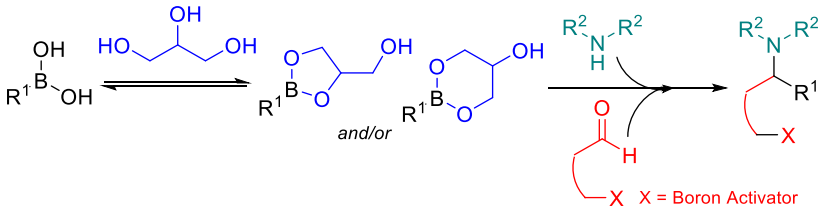
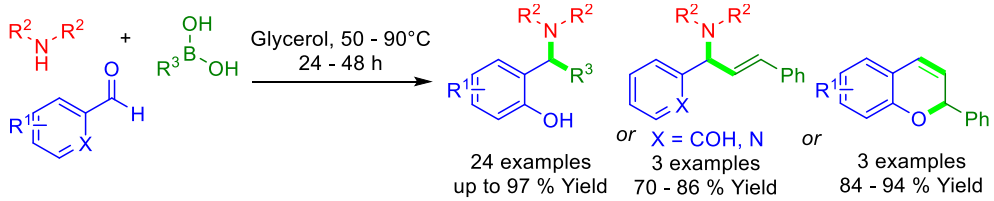
The Petasis borono-Mannich (PBM) reaction, a multicomponent reaction of boronic acids, aldehydes/ketones and amines, is a remarkable tool for preparation of complex molecules in a single step from readily available starting materials.[1]
Glycerol is an abundant, biodegradable, cheap, non-toxic, and highly hydrophilic solvent, composed of a strong hydrogen bond network. It has low vapor pressure, high-boiling point, high dielectric constant and a polarity value similar to DMSO or DMF. Glycerol is a side product in the production of biodiesel, representing ca. 10 wt% of the total output and its worldwide production could have reached 2 million tons in 2010. In 10-15 years it is expected that biodiesel production from algae will account for 37 % of the worldwide production. If so, this may result in a twenty-fold oversupply of glycerol in the upcoming years. Besides its widely spread use in industries like cosmetic, pharmaceutical, food or textile, new uses of glycerol are desirable in order to solve the surplus production issue.[2]
After the previous reports on the use of water as solvent in the PBM reaction[3] and the comparable reactivity of boronic acids and boronic esters in such reaction, it was envisioned that by mixing a boronic acid in glycerol, the corresponding glycerol boronic esters could be formed and subsequently react to provide the PBM product in this peculiar medium (Scheme 1).



Scheme 1

The results on the use of glycerol as an effective medium for the Petasis borono-Mannich reaction will be presented.[4] Alkylaminophenols containing tertiary amines, allyl derivatives, 2-substituted pyridines as well as 2*H*-chromenes, can be prepared in glycerol in good yields (Scheme 2). Crude glycerol derived from biodiesel production was successfully tested in this procedure. A comparative mechanistic study of the reaction, accounting for the possible formation of glycerol-derived boronic esters seems to be competitive to the one where the free boronic acid is considered.



Scheme 2

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BROOK REARRANGEMENT AS A TRIGGER FOR THE RING-OPENING OF CYCLOPROPANES

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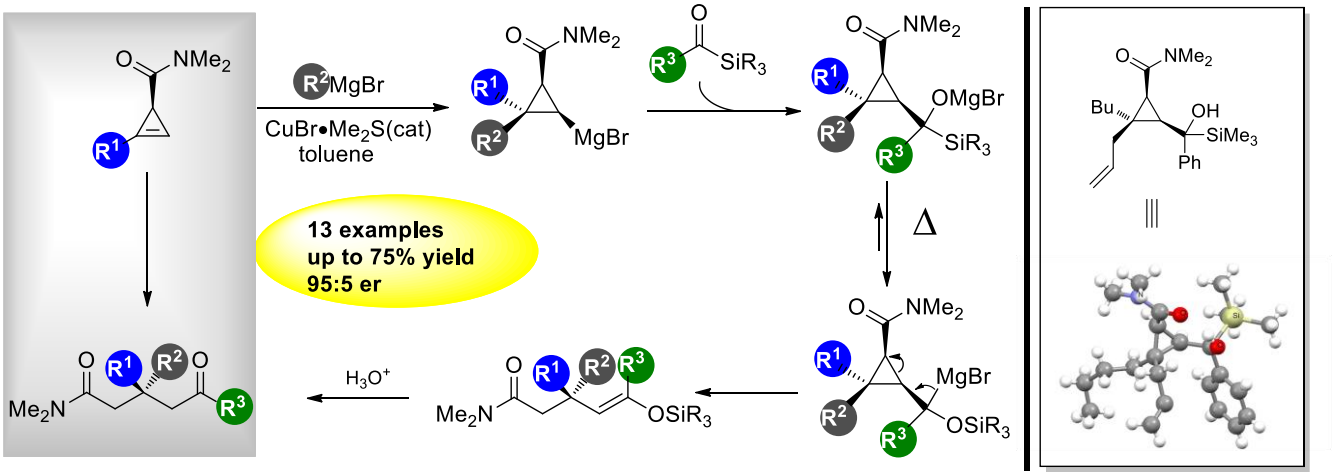
In organic synthesis, it has been a long-standing objective to construct valuable molecules from simple starting materials. In this context, over years our group has developed several efficient stereo- and enantioselctive strategies for C-C bond forming process in a single pot operation.[1] Herein, we disclose a tandem diastereoselective carbometallation of cyclopropene, nucleophilic addition to acylsilane, Brook rearrangement and selective ring-opening of cyclopropane process in one pot operation. With this method, a variety of linear amides fragments bearing all-carbon quaternary stereogenic centres can be prepared in good yields form easily available cyclopropenyl derivatives. Enantiomerically enriched example and mechanistic proposal are also presented.



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APPLICATIONS OF INTRAMOLECULAR THIYL RADICAL REACTIONS IN SYNTHSIS

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Thiosugars are carbohydrate analogues where one or more oxygen atoms are substituted with sulfur in both furanoside and pyranoside structures. Due to the unique conformational and electronic properties conferred by the presence of the sulfur atom, these compounds offer fascinating prospects in medicinal chemistry as glycosidase inhibitors and they have been shown to demonstrate potent biological activity as antiviral, antidiabetic and anticancer compounds.[1] A number of synthetic routes have previously been reported for the synthesis of thiosugars but free-radical cyclisation strategies have not been widely investigated for their preparation.[2]

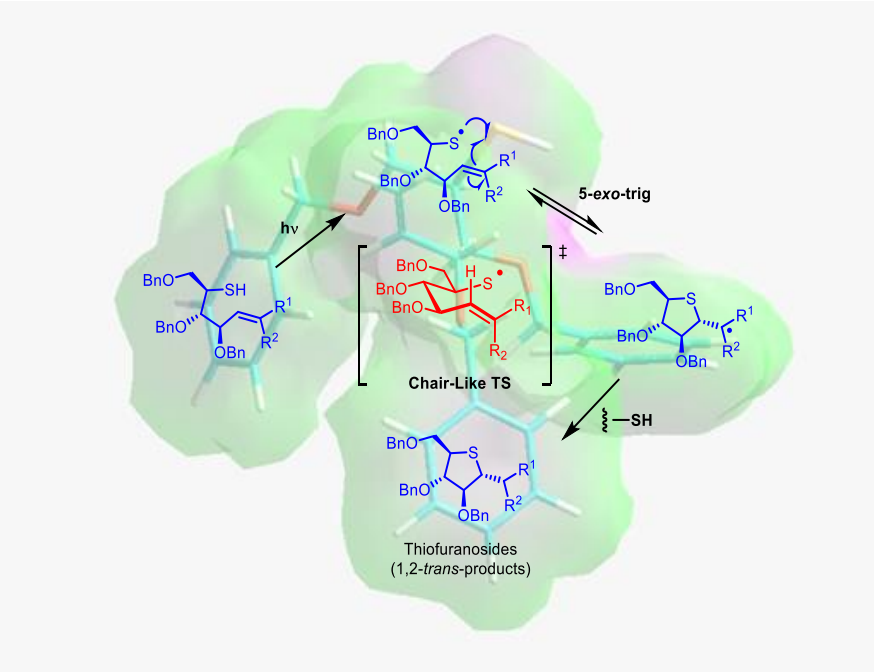

Figure 1. 5-*exo*-trig cyclisation pathway for the preparation of *C*-linked thiosugars

We have developed a highly efficient synthetic methodology to access novel thiosugars by employing intramolecular 'thiol-ene' cyclisation reactions.[3,4] Both 5-*exo* and 6-*endo* cyclisation pathways have been investigated to access a range of novel thiosugar constructs. Cyclization reactions occur in high yield with excellent regio- and diastereoselctivity.

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BOND FORMATION AND INTERACTIONS IN *PERI*-DISUBSTITUTED NAPHTHALENES

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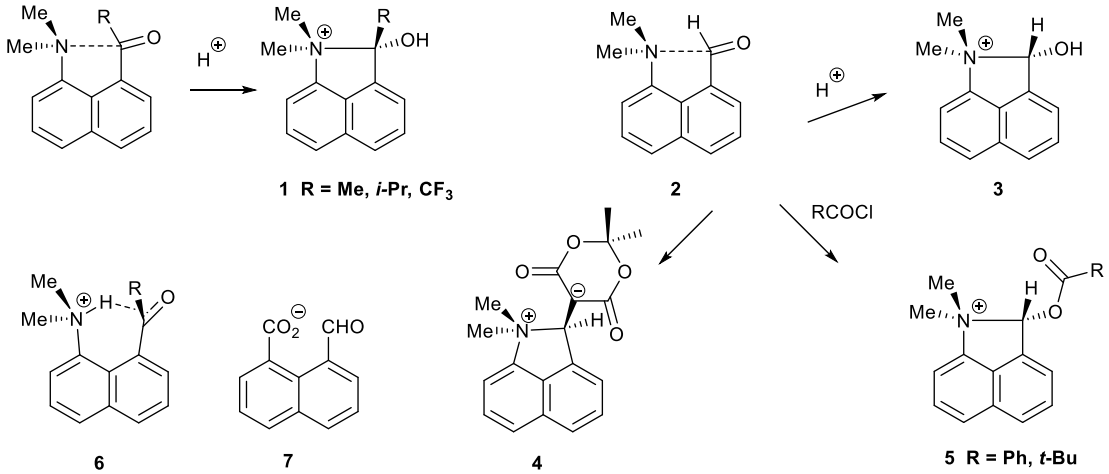
The interactions between electrophilic and nucleophilic functional groups placed at the *peri*-positions of a naphthalene ring, measured by X-ray crystallography, have been investigated as examples of incipient through-space bond formation with particular examples involving amines, ethers or thioethers with carbonyls, polarized alkenes and alkyne groups.[1,2] This system is particularly good since through-space interactions usually outweigh the possible conjugative interactions with the naphthalene system. Furthermore, the degree of bond formation can be probed by charge density measurements and solid-state NMR studies.

Here we report the structures of systems such as **1, 3** and **5** with a much higher degree of C-N bond formation formed by reaction between a dimethylamino group and an aldehyde or ketone promoted by protonation or acylation of the carbonyl oxygen atom. In this respect this *peri*-arrangement of an amino and carbonyl functionality could be considered as a “through space” amide. C-N bond lengths lie in the range 1.624-1.669 Å for **1** and **3** but 1.566-1.568 Å for **5**, which reflects the inability of an oxygen lone pair in **5** to overlap with the C-N anti-bonding orbital. Protonation of the phenyl or *t*-butyl ketone leads a different situation **6** where the protonated amine hydrogen bonds to the carbonyl pi electron density. Solid-state NMR studies will be presented which characterize these two modes of interaction. The power of charge density analysis to characterize bond formation will be illustrated by contrasting results from the aldehyde **2** and the zwitterion **4**, the latter formed by spontaneous reaction between a dimethylamino group and a polarized alkene.

Initial studies will be described on salts of anion **7**, in which the nucleophilic centre is a negatively charged oxygen atom, and which show either O^----C=O or H---CO_2^- interactions in the solid state.



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SELECTIVE MODIFICATION OF UNPROTECTED OLIGOSACCHARIDES

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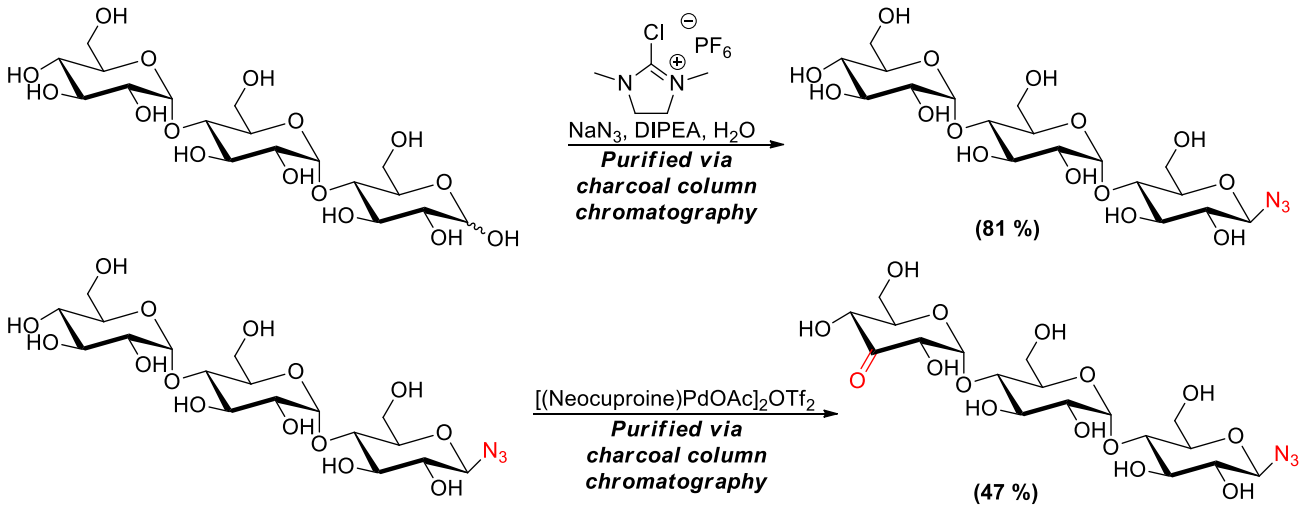
Selective modification of unprotected carbohydrates is a relatively unexplored area, with the exception of the modification of the primary hydroxyl group and the anomeric center. Such modifications on oligosaccharides are scarce and furthermore seldom involve one of the secondary hydroxyl groups. In the field of chemical biology, where often more complex carbohydrates are employed, selective modifications are highly desired. Recently, in our group we have developed an effective procedure for the regioselective oxidation of mono- and disaccharides.[1] With this method, we can selectively oxidize the C3 hydroxyl group on the terminal glucose residue in maltose and cellobiose. The formed ketone moeity opens up a whole range of further modifications of these carbohydrates. We envisioned that we could apply the same method to modify higher oligosaccharides. A boundry in applying our method for oligosaccharides lies in the fact that the carbohydrates have to be non-reducing to yield products which are easier to identify/characterize. For the preparation of non-reducing oligosaccharides we used the approach of Tanaka *et al.*[2] In here the authors show an effective method to yield glycosyl azides. In that report, the obtained products were purified via preprative HPLC, we desired however a more scaleable purification method. Standard silica gel chromatography turned out succesful for glucosyl azide but not for higher oligosaccharides. In search of an effective way to purify oligosaccharides on a preparative scale we studied charcoal column chromatography. Following the work of Whistler *et al.*, we could sequentially elute different carbohydrates by employing a smooth gradient of ethanol/water. With this effective purification method we were able to employ our method for the selective oxidation. With 7.5 mol% of [(neocuproine)PdOAc]$_2$OTf$_2$ full conversion in the oxidation was obtained and we could isolate the oxidized oligosaccharide pure and in good isolated yields. Identification of the oxidation position was carried out using 2D-NMR techniques combined with mass fragmentation studies. In all cases the terminal glucose residue was oxidized on the C3 position.



References:

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COMT INHIBITION AS A TARGET FOR DRUG DISCOVERY

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Over the last 50 years COMT enzyme has become an attractive target for treatment of various peripheral and central nervous system disorders.[1,2] COMT inhibitors prevent the enzymatic *O*-methylation of neurotransmitters as well as of xenobiotic substances and hormones incorporating a catecholic structure (Fig. 1).

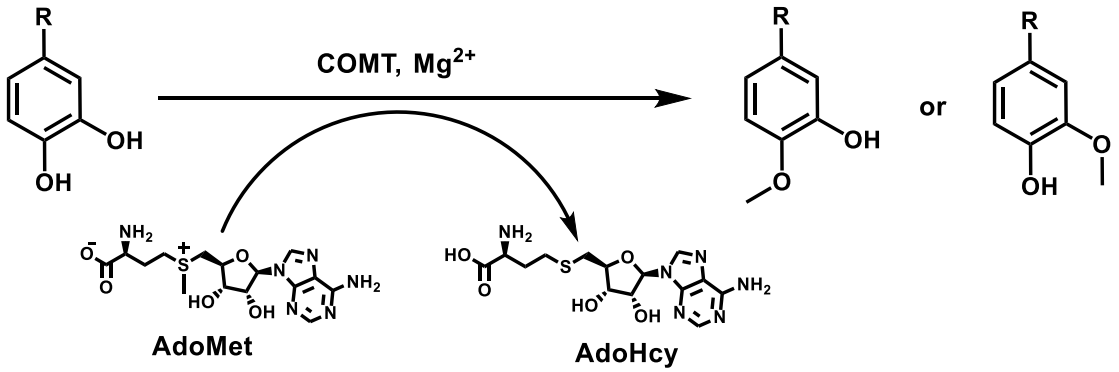

Fig. 1

Dopamine is one of the most common neurotransmitters, involved in many biological functions and several diseases are associated with the dysfunction of the dopaminergic system. Therefore it has been postulated that the clinical use of COMT inhibitors may provide symptomatic relief in patients afflicted with Parkinson´s Disease (PD), restless leg syndrome, schizophrenia, mood disorder, depression, bipolar disorder, edema formation state, gastrointestinal disturbances, substance dependency (e.g. opiate and tobacco addiction) and other dopamine deficiency-related diseases such as attention deficit disorders (ADDs) and attention deficit hyperactivity disorders (ADHDs). The sole clinical application of COMT inhibitors thus far is their co-administration with an amino acid decarboxylase (AADC) inhibitor plus L-DOPA (biological precursor of dopamine) for the symptomatic treatment of PD. However, the aforementioned wide range of possible medical applications of COMT inhibitors has helped to maintain the keen interest of several research groups in development of clinically effective and safe COMT inhibitors. The talk will focus on the medicinal chemistry of COMT inhibitors, how their physicochemical properties are understood to exert influence over their pharmacoligal properties. and discusses the clinical benefits of the most relevant COMT inhibitors.

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CHEMOSELECTIVE ACCESS TO HIGHLY SUBSTITUTED BUTENOLIDES VIA A RADICAL CYCLIZATION PATHWAY: MECHANISTIC STUDY, LIMITS AND APPLICATION

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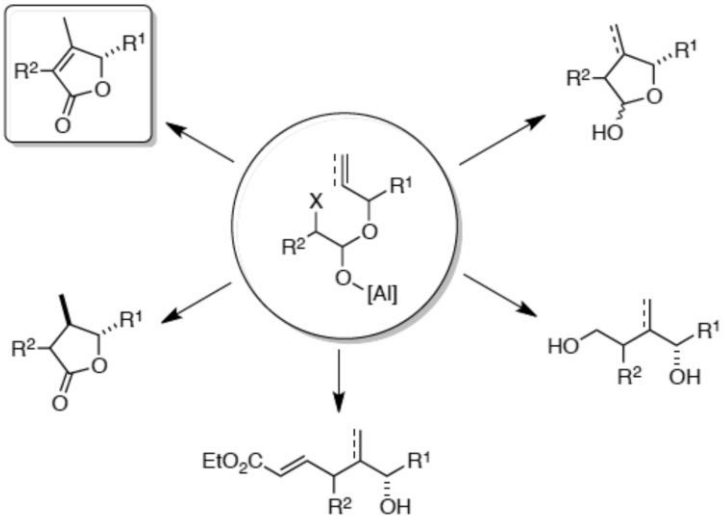
The introduction of trialkylboranes as a source of alkyl radicals represents a significant advance in the field of radical chemistry as it allows initiation of radical chain processes at a very low temperature.[1] Besides the beneficial effect to the selectivities of radical reactions (including chemoselectivity), the possibility to carry out reactions at –78 °C also offers the opportunity to extend the scope of precursors to include thermally unstable intermediates. Some years ago we developed a new approach to gamma-lactols and methylene-gamma-lactols based upon the reduction alpha-bromo esters with DIBAL-H, followed by the radical cyclization of the resulting aluminium acetal intermediates.[2,3] The aluminium acetals resulting from the cyclization process could engage in further functionalization in situ, as illustrated by the Oppenauer-type oxidation to give the corresponding lactones[4] and butenolides.[5] Mechanistic studies (NMR analysis and molecular modelling) gave us insights into the reaction mechanism.



Compared to the approach involving classical conditions for the radical cyclization of alphabromoesters (high temperature, high dilution and slow addition techniques), the cyclization of aluminium acetals proved to be highly chemoselective. Our recent results will be described, and the efficiency of the methodology will be illustrated by the short total syntheses of naturally–occurring butenolides.

References:

[1] C. Ollivier, P. Renaud, *Chem. Rev.* **2001***, 101,* 3415-3434.
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SYNTHESIS OF SUGAR PHOSPHATES ANALOGUES OF AGROCINOPINE A : INSIGHTS IN THE BINDING MODE OF THE PROTEIN ACCA OF AGROBACTERIUM TUMEFACIENS

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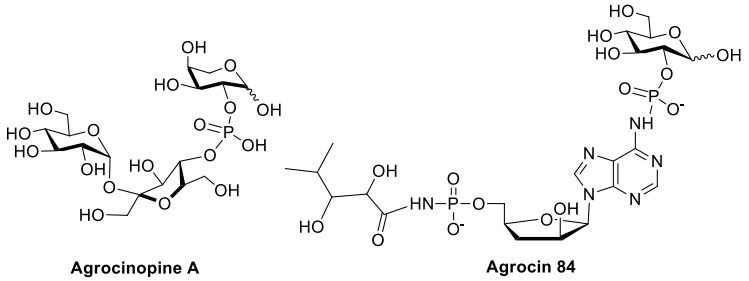
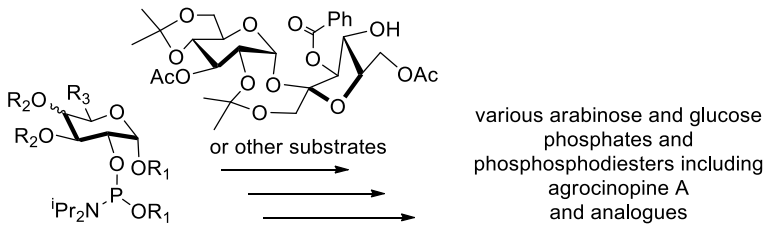
Agrocinopine A is a phosphodiester of sucrose and L-arabinose produced by plant cells modified by *Agrobacterium tumefaciens*. Transported by the PBP protein AccA, it serves as nutrient for the bacteria. Interestingly, the natural antibiotic agrocin 84 which is constructed with a nucleosidic backbone is also able to bind this protein. In the frame of the SENSOR ANR consortium led by biologists in Gif-sur-Yvette, one aim was to establish the binding mode of these compounds through crystallographic investigations of AccA in the presence of its usual or unusual ligands and to propose hypotheses on the minimal scaffold able to be recognized by AccA. To do so, samples of the non-commercially available agrocinopine A and some of its analogs were required, leading us to define to design a strategy offering access to agocinopine A itself as well as to diverse analogues.



The synthetic sequence relies on the synthesis of an adequately protected sucrose and its reaction with a phosphate precursor bearing a L-arabinose substituent. Using an alternative phosphinylation reagent compared to the only few previously reported syntheses of agrocinopine A [1,2] and by carefully isolating all intermediates, a series of new agrocinopine A derivatives, bearing different protecting groups has been synthesized. Agrocinopine A bearing a 3–O-benzoate group on the fructose moiety, which was found to also bind the protein though in a different manner, was investigated more closely. Several analogues, namely L-arabinose-2-phosphate and L-arabinose-2-isopropylphosphate and D-glucose-2-phosphate were also prepared. The communication will focus on the synthesis of this series of compounds and their detailed structural identification and briefly show the results of the structural investigations.



References:

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AMPLIFICATION OF ENANTIOSELECTIVITY DURING ORGANOCATALYZED DESYMMETRIZATION OF *MESO* DIOLS

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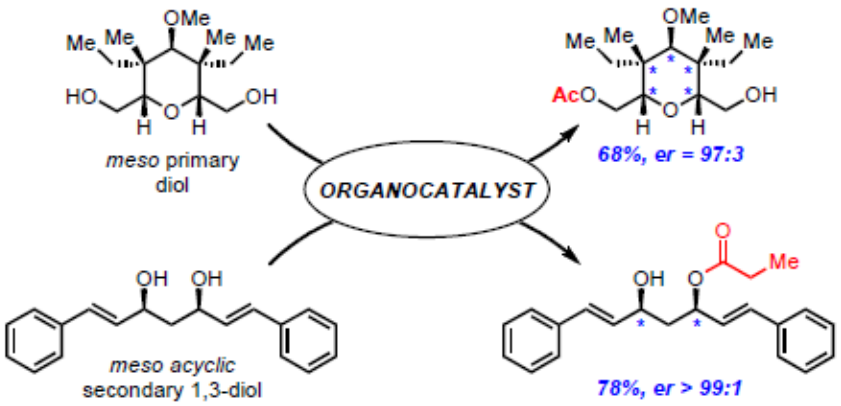
The desymmetrization of *meso* compounds is a powerful strategy to obtain complex chiral building blocks bearing multiple stereogenic centers using a single enantioselective transformation. We recently explore the possibility to combine this strategy with the enantioselective organocatalyzed acylation in two cases. The first one is the desymmetrization of *meso* primary diols usually employed as substrates in biocatalyzed acylation. We found that the Fu's catalyst with planar chirality was able to break the symmetry of precursors bearing all-carbon quaternary stereocenters.[1] The second case concerns the desymmetrization of *meso* acyclic secondary 1,3-diols, an important pattern in natural product. We established a general method to obtain chiral monoester with high level of enantioselectivity, which was successfully applied in the total synthesis of (−)-Diospongin A.[2]



We observed in both cases an amplification of the enantioselectivity due to the synergistic combination of a desymmetrization and a *chiroablative* kinetic resolution leading to the production of a small amount of meso diester. The organocatalyst converts the minor enantiomer of the chiral monoester, obtained after the step of desymmetrization, in the achiral diester leading to improve the enantiopurity of the monoester.

References:

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A NEW CONTRIBUTION TO NITRO SUGAR CHEMISTRY: TRANSFORMATION OF 3-*O*-BENZYL-5,6-DIDEOXY-1,2-*O*-ISOPROPYLIDENE-5-*C*-(METHOXYCARBONYL)- 6-NITRO-α-D-GLUCOFURANOSE INTO HIGHLY CONSTRAINED β-AMINO ACIDS AND SEVEN MEMBERED β-IMINO ACIDS

Amalia M. Estévez, Marcos A. González, Rosalino Balo, Juan C. Estévez, and Ramón J. Estévez*

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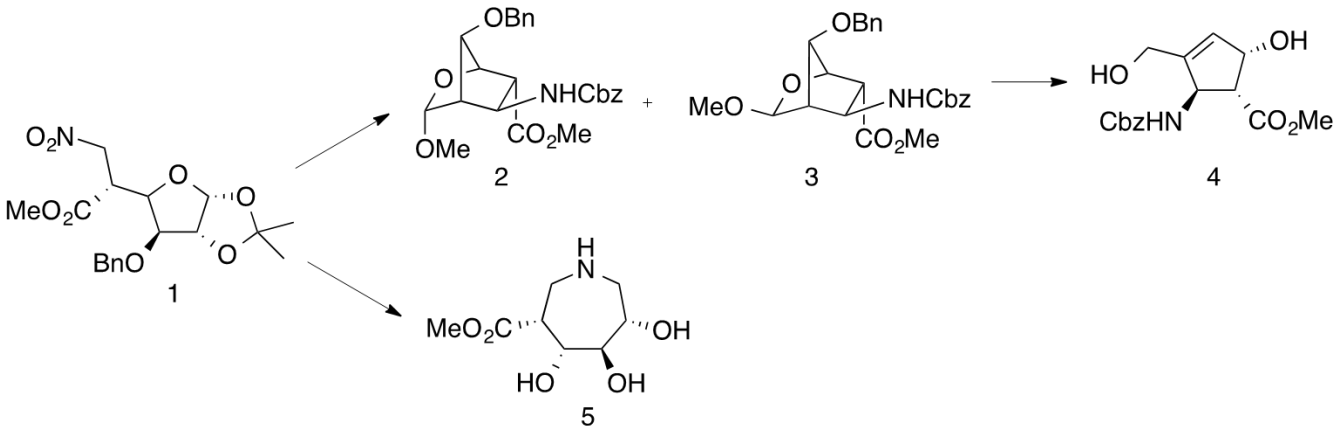
Nitro sugars are powerful synthetic materials that combine the synthetic potential of sugars and the chemical versatility of nitro compounds for the formation of carbon–carbon bonds prior to conversion of the nitro group into a range of other functionalities.[1] 2-Substituted 3-nitropropanoic acids were showed to act as inhibitors against carboxypeptidase A (CPA), and as useful synthetic intermediates for the transformation of nitro olefins into β-amino acids.[2]

We have previously described a transformation of 2-C-glucosyl-3-nitropropanoic acid **1** and its C-5 epimer into the first reported polyhydroxylated cyclohexane β-amino acid and into a rancinamycin analogue, respectively.[3,4]

As a new contribution to the nitro sugar facilitated synthesis of complex β-amino acids, here we present a new synthesis of 2-*C*-glucosyl 3-nitropropanoic acid **1** and its transformation into the highly constrained β-amino acids **2**, **3** and **4** and the seven membered β-imino acid **5**.



Scheme 1

Interest in this chemistry lies on the novelty of compounds **2**, **3** and **4**, and on the pharmacological potential of compounds **5** and their derivatives.

References:

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NATURAL CHIRAL ORGANIC SALTS FOR ASYMMETRIC CATALYSIS

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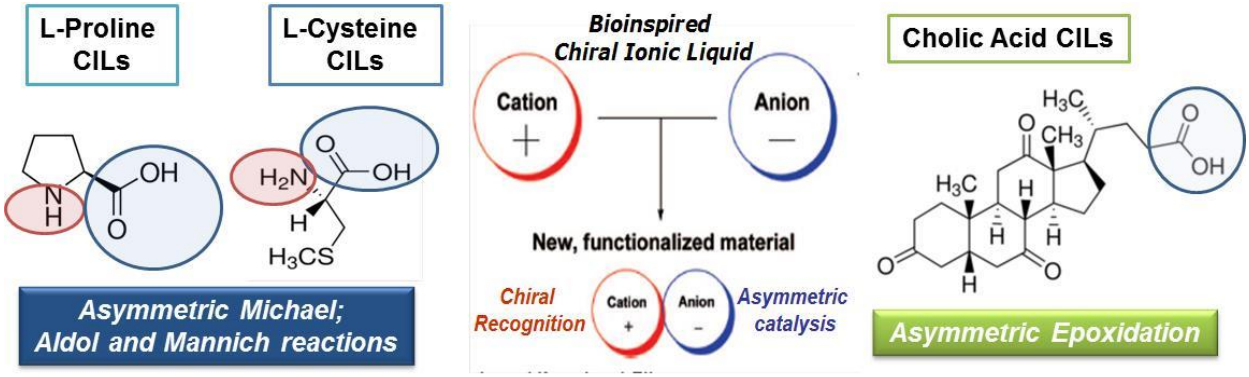
Natural Chiral organic salts and chiral Ionic Liquids (CILs) can be useful as organocatalysts, chiral ligands or chiral reaction media of different asymmetric catalytic processes.[1, 2] Nowadays, the discovery of chiral molecules as novel catalysts remains to grow as a wide range of small organic molecules, including aminoacids and sugar derivative moieties. Recent examples showed the possibility to use chiral salts or ILs as efficient organocatalysts or chiral ligands for Asymmetric Aldol and Michael additions as well as Sharpless dihydroxylation of olefins, among others.[3-5]
In this context, novel Bioinspired chiral ionic liquids (BioCILs) or organic salts based on L-cysteine and L-proline derivatives as well as monosaccharide, oligosaccharide and cholic acid derivatives have been developed.[6, 7]



All novel BioCILs are prepared using efficient and sustainable synthetic methods and their potential as chiral organocatalysts in asymmetric direct aldol, Michael additions, Mannich and epoxidation reactions have been evaluated. For many cases, pure chiral products in good to excellent yields and enantiomeric excesses comparable or higher than conventional systems can be achieved.
The chiral reaction media including BioCILs can be recycled and re-used by efficient sustainable methodologies. For most promising catalytic processes, supercritical carbon dioxide is tested as cleaner extraction method.

Acknowledgements: This work was supported by Fundação para a Ciência e Tecnologia (PEst-C/EQB/LA0006/2013, RECI/BBB-BQB/0230/2012, PTDC/CTM/ 103664/2008, PTDC/CTM-NAN/120658/2010 projects and postdoctoral fellowship GVSMC - SFRH/BPD/72095/2010).

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BISMUTH TRIFLATE-CATALYSED CYCLOISOMERISATIONS INVOLVING ALLENES

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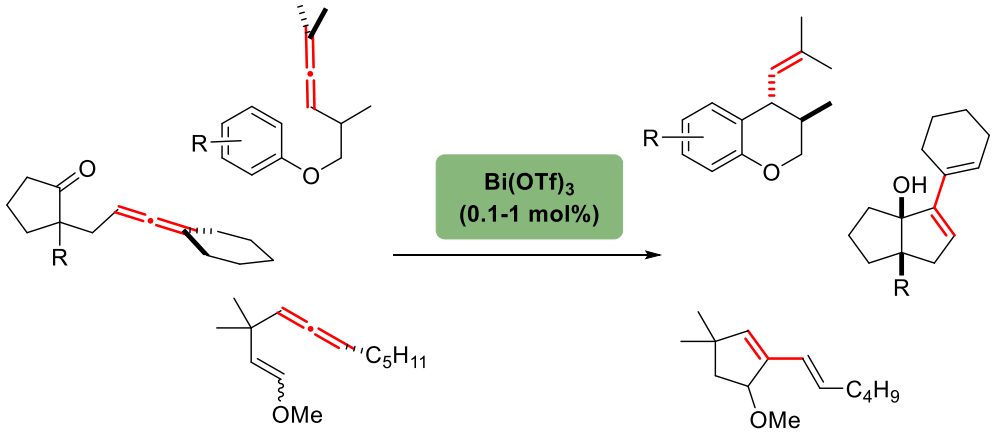
The development of catalytic, efficient and mild synthetic methods to create C-C bonds remains an important topic in the field of organic chemistry. Our group has been involved during the past years in the design of cycloisomerisation reactions catalysed by metal triflates and metal triflimides. These cyclisations are usually based on the activation of substituted olefins and found some applications in fragrance chemistry.[1] Among the metallic species used to perform these cycloisomerisations, the corresponding triflate salt of non-toxic bismuth has proven to be a very active catalyst. Some new transformations catalysed by $Bi(OTf)_3$ of various polyunsaturated systems containing an allene or a conjugated-diene moiety such aryl-allenes[2], keto-allenes[3] and enol ether-allenes[4] will be presented.



These methodologies based on cationic cyclisations represent a convenient approach towards (poly)cyclic compounds through C-C bonds formation under mild reaction conditions. The scope of these reactions as well as the limitations and some of the mechanistic aspects will be discussed.

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BIOSYNTHETIC MECHANISM OF LANOSTEROL: CYCLIZATION

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The remarkable cyclization mechanism of the formation of the 6-6-6-5 tetracyclic lanosterol (a key triterpenoid intermediate in the biosynthesis of cholesterol) from the acyclic 2,3-oxidosqualene catalyzed by oxidosqualene cyclase (OSC) has stimulated the interest of chemists and biologists for over a half century. We will report the 2-D QM/MM MD simulations that clearly show that the cyclization of the A-C rings involves a nearly concerted, but highly asynchronous cyclization, to yield a stable intermediate with "6-6-5" rings followed by the ring expansion of the C-ring concomitant with the formation of the D-ring to yield the "6-6-6-5" protosterol cation. The calculated reaction barrier of the rate-limiting-step (~22 kcal/mol) is comparable to the experimental kinetic results. Furthermore all previous experimental mutagenic evidence is highly consistent with the identified reaction mechanism.

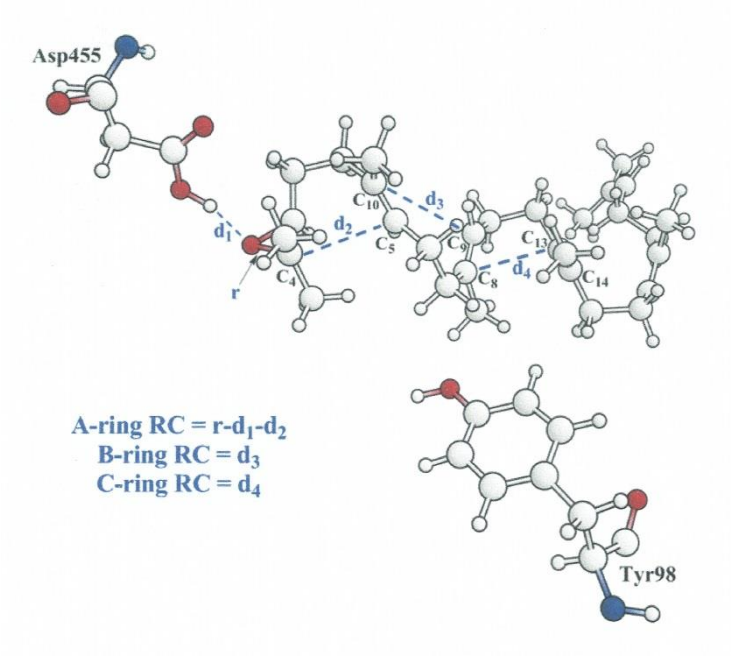

Figure 1. The definition of the reaction coordinates and the QM subsystem

TOTAL SYNTHESIS OF CLAVOSOLIDE A

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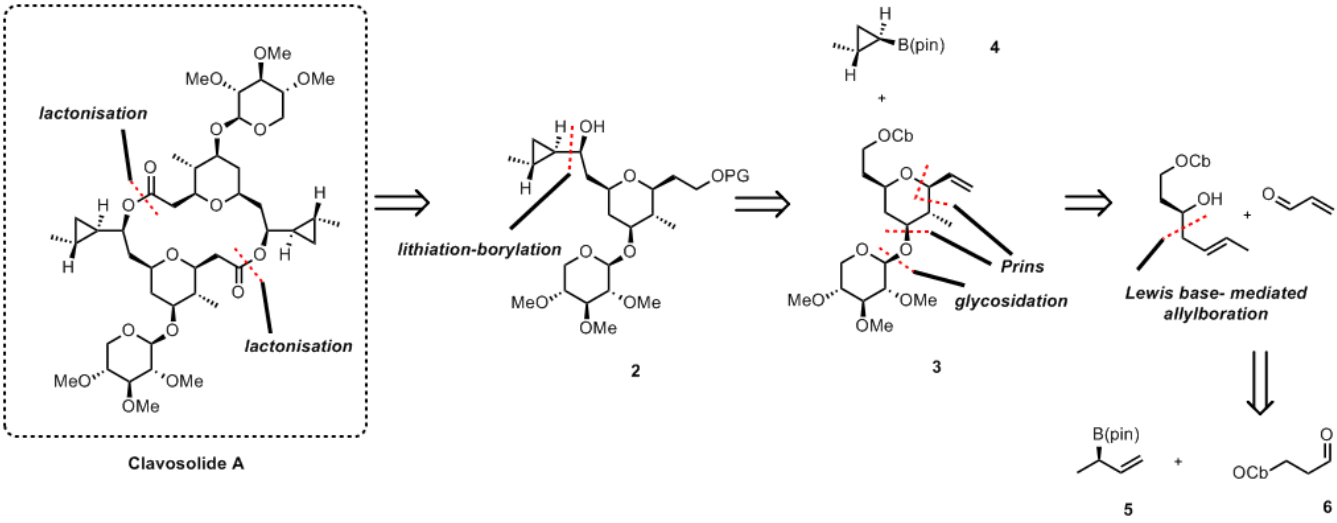
The clavosolides are a family of marine diolide glycosides isolated from extracts of the marine sponge *Myriastra clavosa*, collected in the Phillipines.[1] The unique architecture of this sponge metabolite has attracted considerable interest from the synthetic community – with the first total synthesis described by Willis *et al.*[2] Herein we present a short and highly convergent synthesis towards Clavosolide A, with a "one pot" Lewis-base mediated allylboration-Prins reaction and lithiation-borylation as the key steps.



Clavosolide A is first disconnected through the ester linkages to give the key intermediate **2.** Tetrahydropyran **2** is formed in the forward direction by the enantioselective lithiation of the primary carbamate **3**, followed by its trapping with boronic ester **4** and subsequent 1,2-metallate rearrangement.[3] Carbamate **3** is synthesised by Lewis base-mediated allylboration to form (*E*)-homoallylic alcohol, with control of olefin geometry,[4] followed by a highly stereoselective Prins reaction[5] to form the densely substituted tetrahydropyran core in a single step from the boronic ester **5** and the aldehyde **6**. The xylose moiety is attached in a diasteroselective manner through a glycosidation reaction using a neighboring group participation strategy. This methodology allows the synthesis of this intriguing natural product in just 11 steps in the longest linear sequence, far shorter than any synthesis currently reported.

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GOLD-CATALYZED POST-UGI HETEROANNULATIONS AND DOMINO REACTIONS

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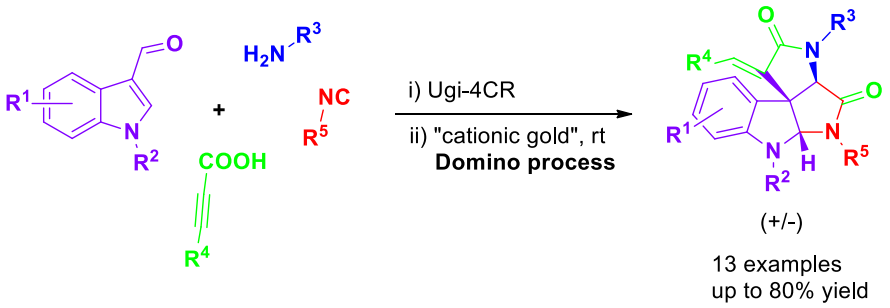
Gold catalysis is one of the fast growing research topics of modern organic chemistry. In this context, gold-catalyzed carbocyclization and heteroannulation strategies have recently attracted much attention due to the selective and efficient activation of the C-C triple bond towards a wide range of nucleophiles. Moreover, the combination of multicomponent reactions with gold catalysis, gives access to complex molecular architectures in few steps, as compared to traditional multistep processes.[1] We will comment on our recent findings in this field. A concise route to indoloazocines[2] via a sequential Ugi/gold-catalyzed intramolecular hydroarylation[3] will be presented. A diversity-oriented approach to spiroindoles via a post-Ugi gold-catalyzed diastereoselective domino cyclization[4] will be described (Scheme), as well as a regioselective approach for the synthesis of pyrrolopyridinones and pyrroloazepinones employing a gold(I)/platinum(II) switch.[5] Employing dual σ/π activation, cationic gold efficiently catalyzes the regioselective tandem cyclization of N-propynylbutynamides via C_{sp3}-H funtionalization to give cyclopentapyridinones.[6]



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THE VERSATILITY OF GOLD(I)-CATALYSIS APPLIED TO THE TOTAL SYNTHESES OF (–)-NARDOARISTOLONE B AND LUNDURINE C

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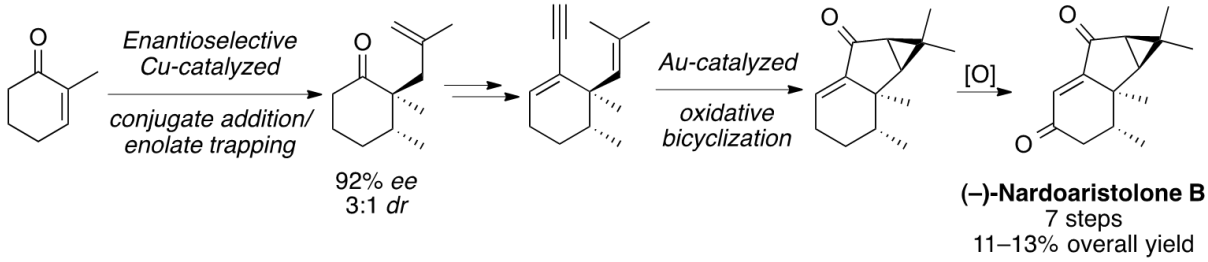
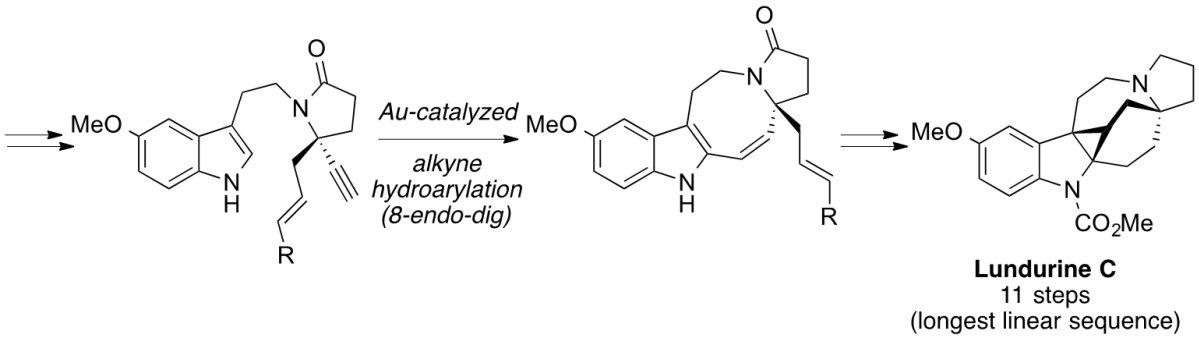
The breadth of reactions catalyzed by electrophilic gold(I) complexes and salts[1] and the versatility of intermediates accessible through these transformations have been utilized to develop expedient and efficient total syntheses of the natural products (–)-nardoaristolone B and lundurine C. Notably, the first enantioselective synthesis of nardoaristolone B has been accomplished implementing for the first time an oxidative gold(I)-catalyzed cyclization of 1,5-enyne in the context of total synthesis, in 7 steps and 11–13% overall yield (Scheme 1).[2]



Scheme 1. First enantioselective total synthesis of (–)-nardoaristolone B.

Furthermore, with a distinct strategy, an intramolecular gold(I)-catalyzed hydroarylation of alkyne has proved successful to efficiently prepare the polycyclic core of the lundurines and complete the synthesis of lundurine C. Our 11-step longest linear synthetic sequence provides a rapid entry towards this architecturally complex natural product and related analogues (Scheme 2).



Scheme 2. Total synthesis of lundurine C.

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SUSTAINABLE GOLD CATALYSIS: SYNTHESIS OF NEW SPIROACETALS

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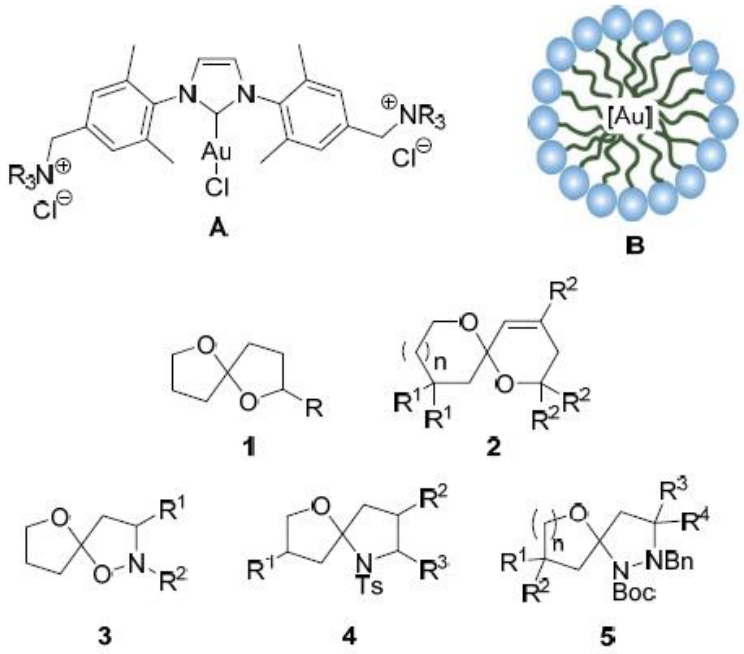
Spiroacetals appear in a wide range of natural products and biologically active molecules. Consequently, there is a high demand for efficient methods to synthesize these privileged scaffolds. Among these, transition metal-catalyzed cyclizations of suitable unsatured substrates are gaining importance. In particular, several examples for the gold-catalyzed spiroacetalization of acetylenic diols and related substrates have been disclosed recently.[1] Here, we describe the application of *recyclable* gold catalysts to spiroacetalizations in *water* as bulk reaction medium. For example, treatment of acetylenic diols with ammonium-salt-tagged NHC-gold complexes of the type **A** affords saturated [O,O]-spiroacetals of the type **1**,[2] whereas the use of gold catalysts in nanomicelles (**B**) provides unsaturated spiroacetals **2** from acetylenic triols by dehydrative spirocyclization.[3] Recently, we have extended the spirocyclization to new types of [O,O]- and [N,O]-spiroacetals (*e.g.*, **3**-**5**), which are of interest as new molecular scaffolds in medicinal chemistry.[4]



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BIOMIMETIC SYNTHESIS OF CHLORINATED MEROTERPENOIDS FROM STREPTOMYCES BACTERIA

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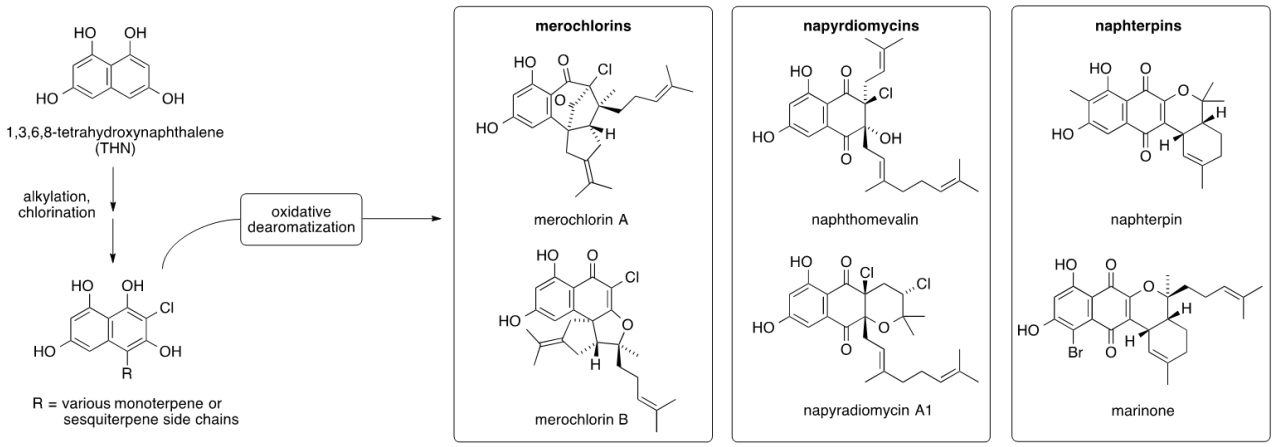
Streptomyces bacteria possess complex secondary metabolism that is responsible for the production of over two-thirds of clinically useful antibiotics of natural origin. In this project, we are interested in studying the organic chemistry of three families of related *Streptomyces* natural products – the *merochlorins*, the *napyradiomycins* and the *naphterpins*. We propose that all of these unusual halogenated meroterpenoids are biosynthesized from 1,3,6,8-tetrahydroxynaphthalene (THN) via predisposed cascade reactions initiated by oxidative dearomatization. We have used our biosynthetic proposals to inspire concise synthetic approaches to all three natural product families.[1]



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O_2-MEDIATED RADICAL DEHYDROGENATIVE AMINATION REACTIONS

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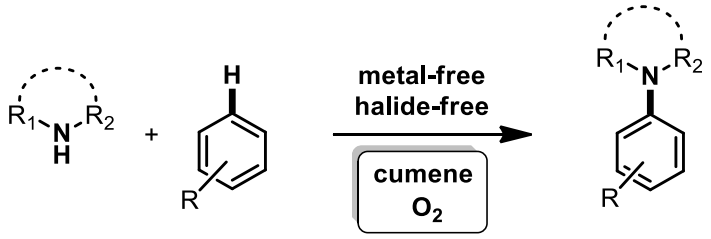
One of the key advantages of the direct aromatic functionalization strategy is the absence of pre-activation steps at the C-H aromatic position. Thus, molecular complexity can be achieved in a single chemical step. A large disadvantage however, aside from the C-H regio-selectivity issue, resides in the often necessary pre-activation or pre-oxidation of the coupling partner such that it becomes sufficiently reactive for the coupling reaction to occur.



The direct dehydrogenative construction of C-N bonds,[1-2] a strategic connectivity in organic synthesis which is classically approached through Cu catalyzed cross-coupling chemistry, has been achieved between unprotected phenols and a series of cyclic anilines, without resorting to any kind of metal activation of either substrates, and without any halide. The resulting process relies on the exclusively organic activation of molecular oxygen and the subsequent oxidation of the aniline substrate. This allows for the coupling of ubiquitous phenols, thus furnishing amino-phenols in a most atom-economical and most sustainable dehydrogenative amination method. This new reactivity concept, relying on the intrinsic organic reactivity of cumene in what is seen as a modified Hock activation process of oxygen, is expected to have a large impact for the formation of C-N bonds.[3] These results and resulting future perspectives will be discussed.

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FLASH COMMUNICATIONS

ENANTIOSELECTIVE ADDITION OF WATER

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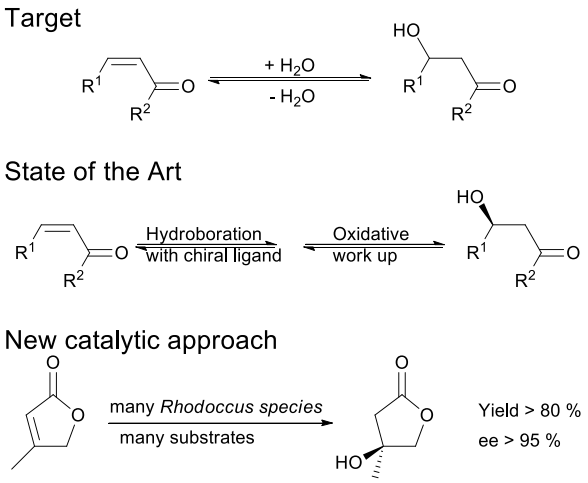
Water is a very bad nucleophile and notoriously unreactive. Its direct addition to double bonds is therefore a major challenge in chemistry. The Michael addition of water is catalyzed by amino acids and some amines, however it is very slow and yields are often low in this reaction. [1,2] Very few examples of enantioselective Michael additions of water have been described and most of them are enzyme catalyzed. These enzymes, hydratases, however suffer in most cases from a very narrow substrate scope. Indeed some only accept one single substrate.



Rhodococcus species have the ability to catalyze the Michael addition of water to many substrates. [3,4] This activity has now been explored and remarkable activities and enantioselectivities have been found. It seems that a wide range of related *Rhodococcus* species can catalyze these reactions. These straightforward to use catalysts can easily be recycled and used many times. Moreover they catalyze the reaction in the reagent water, leading to a very environmentally benign reaction with an excellent atom economy. Thus the classical stoichiometric hydroboration and subsequent oxidative work up can be replaced by a single catalytic step.

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REDUCTION OF ARYL HALIDES BY CONSECUTIVE VISIBLE LIGHT-INDUCED LECTRON TRANSFER PROCESSES

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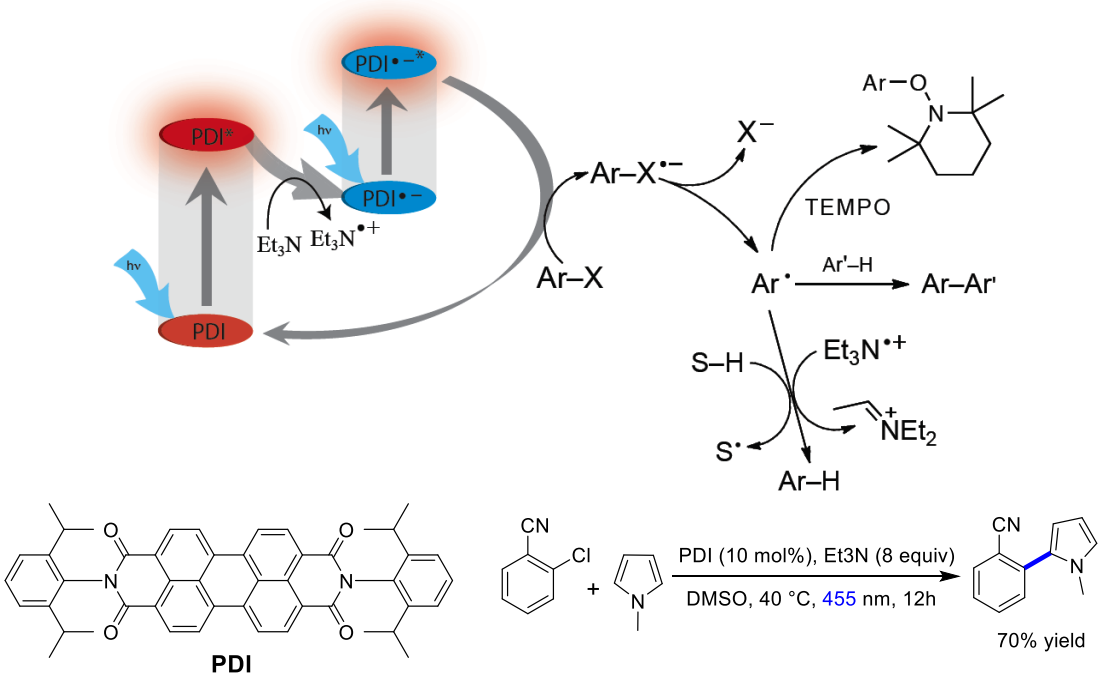
Biological photosynthesis uses the energy of several visible light photons for the challenging oxidation of water, whereas chemical photocatalysis typically involves only single-photon excitation. Perylene bisimide is reduced by visible light photoinduced electron transfer (PET) to its stable and colored radical anion.We reported that subsequent excitation of the radical anion accumulates sufficient energy for the reduction of stable aryl chlorides giving aryl radicals, which were trapped by hydrogen atom donors or used in carbon-carbon bond formation. This consecutive PET (conPET) overcomes the current energetic limitation of visible light photoredox catalysis and allows the photocatalytic conversion of less reactive chemical bonds in organic synthesis.[1]



A recent application is the generation of highly reactive aryl radicals, which are useful arylating reagents in synthesis, by photoinduced electron transfer (PET) from photoredox catalysts to suitable precursors followed by bond scission.[2,3] Our approach is to overcome the limitations of visible light–mediated chemical photocatalysis by using the energies of two photons in one catalytic cycle. However, compounds that are less reactive (e.g., aryl bromides and chlorides) due to a more negative reduction potential, higher carbon-halide bond dissociation energy, and a different, stepwise cleavage mechanism[4] are not accessible by this process using typical photocatalysts and, more importantly, visible light.Our approach is inspired by the Z scheme of biological photosynthesis, which has already been used in water photooxidation[5] but, surprisingly, has not yet been applied in organic synthesis.

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TEMPO-MEDIATED *IN SITU* FORMATION AND TRAPPING OF UNSTABLE NITRONES: SYNTHESIS OF *N*-CARBAMOYL/ACYL ISOXAZOLINES

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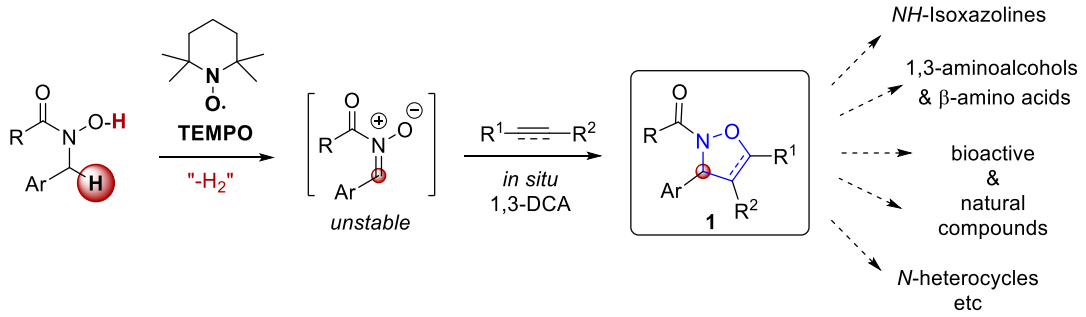
4-Isoxazolines (**1**) are valuable heterocycles used as versatile building blocks for the preparation of biological active compounds such as α-aminoacids, aminoalcohols or alkaloids.[1] Although several methods for their synthesis have been described, the main and most used strategy to obtain the 4-isoxaline core is the 1,3-dipolar cycloaddition (1,3-DCA) between isolated stable N-alkyl and N-aryl nitrones and a dipolarophile, such as an alkene or an alkyne.[1] This leads to isoxazolines with unremovable or difficult to cleavage groups at the nitrogen in the presence of the N-O bond, which significantly limits the scope of this methodology. Thus, the use of intrinsic unstable nitrones bearing easily removable electron-withdrawing groups such as acyl or carbamoyl units is still highly desirable.[2]

Herein, we present a new and convenient synthesis of N-carbamoyl and N-acyl 4-isoxalines. Based on our experience on oxidative C(sp^3)-H coupling reactions with TEMPO derivatives as mild oxidants,[3] an efficient TEMPO-mediated *in situ* formation and trapping of unstable nitrones from benzyl, allylic and alkylic hydroxylamines has been developed. Moreover, an unexpected mechanism with this nitroxide radical oxidant will also be discussed.[4]



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STEREOSPECIFIC SYNTHESIS OF α AND β FUNCTIONALISED P-CHIRAL TERTIARY PHOSPHINE - BORANES

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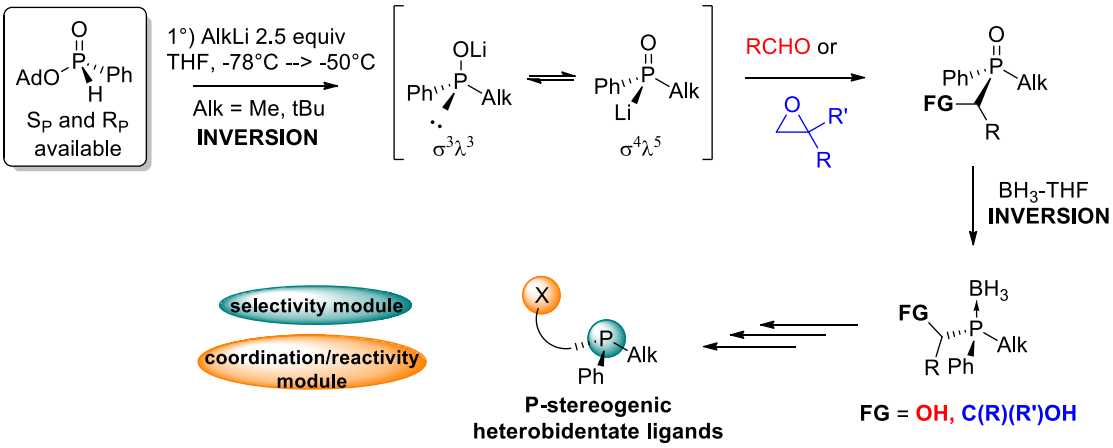
Chiral phosphines are efficient sources of chirality in many transition-metal catalyzed transformations,[1] as well as being powerful organocatalysts themselves.[2] While most of the phosphine ligands used in asymmetric transition-metal catalysis have a chiral backbone, the ones bearing the chiral center at phosphorus (P-stereogenic phosphines) have known tremendous increase of interest. Indeed, in some cases, P-stereogenic phosphines were found to be superior ligands (both in terms of reactivity and enantioselectivity) than their chiral-backbone phosphine counterparts.[3]



In this context, we have developed a new synthetic pathway towards the preparation of phosphorus-based bidentate ligands where the chirality is held by the phosphorus atom. Our synthesis relies on the use of chiral H-adamantyl phosphinate precursor which can be functionalized[4] in a very straightforward manner by one-pot addition of organolithium compound / electrophilic trapping. The corresponding phosphine oxides are then reduced by borane in a stereospecific fashion to allow the formation of functionalized phosphine-borane,[5] which are precursors to potential P-stereogenic bidentate ligands.[6]

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DIRECT CATALYTIC CROSS-COUPLING OF ORGANOLITHIUM COMPOUNDS

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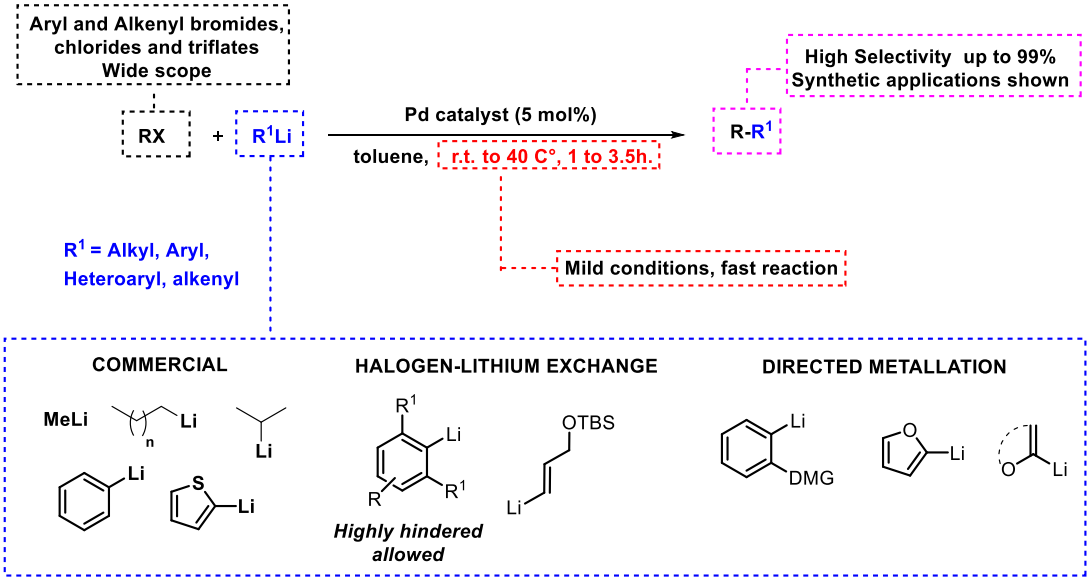
The development of new catalytic methodologies for carbon-carbon bond formation continues to be a major challenge in organic synthesis. Cross-coupling reactions, in particular palladium-catalyzed processes, are among the most important current methods for C-C bond formation.[1-2] A tremendous effort has been dedicated in the last 40 years to expand the scope of these methodologies and many organometallic reagents as Grignard, zinc, boron, tin and silicon reagents were identified as suitable partner in this reactions. Organolithium reagents in contrast have been scarcely considered due to the difficult control of their reactivity. Considering the importance of organolithium compounds, a procedure to directly employ this reagent in Pd-catalyzed cross-coupling reactions is highly desirable.
Herein we report a general methodology for the cross-coupling of organolithium reagents with aryl (pseudo)halides that proceeds under mild conditions and in short time (Scheme 1).[3-6] The observed high efficiency of organolithium in cross-coupling also prompted us to exploit them in the challenging synthesis of highly hindered tri- and tetra-*ortho*-substituted biaryls.[7]



Scheme 1. Direct catalytic cross-coupling of organolithium compounds

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2,4,6-TRIARYLPYRROLO[2,3-*d*]PYRIMIDINES BY SUZUKI COUPLING AND C-H ARYLATION REACTIONS

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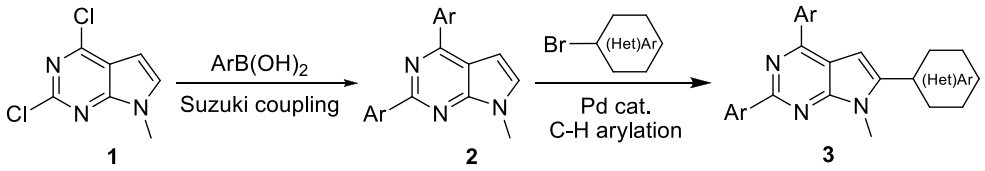
Pyrrolo[2,3-*d*]pyrimidine ring system (7-deazapurine) represents an important pharmacophore in drug discovery and many its derivatives bearing multiple substituents at the carbon atoms of the heterocycle display valuable biological effects. On the other hand, the pyrrolo[2,3-*d*]pyrimidine-core based oligoarylenes exhibit strong UV-blue fluorescence and are promising candidates as fluorescent functional materials.[1] Therefore, development of efficient and economic methods for the synthesis of arylpyrrolo[2,3-*d*]pyrimidines is a worthwhile goal. Methods for the preparation of 4,5-, 4,6-diaryl- and 4,5,6-triarylpyrrolo[2,3-*d*]pyrimidines have been recently established,[2] however, synthesis of 2,4,6-triarylpyrrolo[2,3-*d*]pyrimidines is still explored insufficiently. Herein, we report on the sequential assembly of aryl groups onto the pyrrolo[2,3-*d*]pyrimidine core as a useful method for the construction of pyrrolopyrimidine extended *π*-systems. The synthetic strategy for the introduction of aryl groups to afford 2,4,6-triarylpyrrolo[2,3-*d*]pyrimidines is based on a combination of the Suzuki cross-coupling and direct C-H arylation reactions.



1 2 3

The developed protocols allow a wide library of the title compounds to be generated. The methods are compatible with many valuable functional groups. The C-H arylation reaction works well with aryl bromides bearing both, electron-donating and electron-withdrawing substituents. Reasonable yields of the target compounds **3** were also obtained with sterically encumbered aryl bromides.
Scope and limitations of the arylation reactions will be discussed.

Acknowledgement: This research was funded by a grant (No. MIP-027/2013) from the Research Council of Lithuania.

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ORGANOCATALYZED SYNTHESIS OF HETEROCYCLES: THE MELDRUM'S ACID APPROACH

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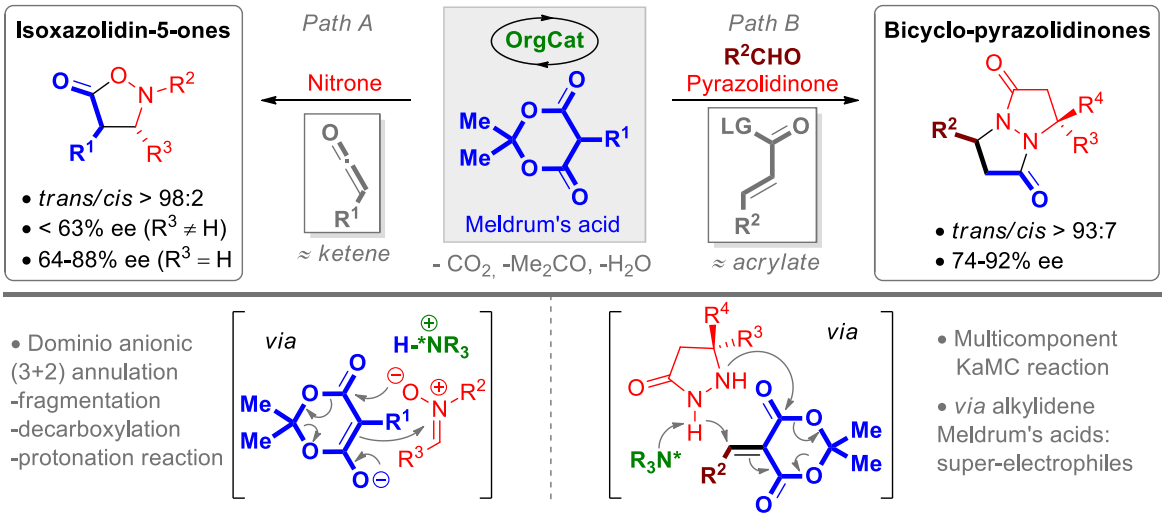
The search for efficacious catalytic construction of chiral bio-relevant heterocyclic architectures is still a fascinating endeavor for chemists intending to explore new chemical spaces and to develop a more sustainable organic synthesis. In this context, we investigated novel/underexplored chemical reactivity of **Meldrum's acid (MA)**, a cheap and readily available starting materials.[1] Based on organocatalytic processes, we intended to capitalize both upon the unique acidity (pK_a = 4.8 in water) and electrophilicity of **MA** derivatives.[1,2]



First of all (*Path A*), it was found that Meldrum's acid anion smoothly reacts with **nitrone** dipoles via a key **(3+2) annulation** followed by a domino fragmentation-decarboxylation-protonation reaction to furnish **isoxazolidinones**; useful precursors of bio-relevant β-amino acids after the facile *N-O* bond cleavage.[2a-b] Interestingly, Meldrum's acid behaves as a user-friendly ketene equivalent along this overall process. Next (*Path B*), it was recently shown that in situ formed alkylidene Meldrum's acid derivatives turned out to be useful acceptors of aza-Michael reaction leading to **biclyclo-pyrazolidinones**; possible precursors of cyclic peptides.[2c] This constitutes an original asymmetric multicomponent reaction (**MCR**) involving a domino Knoevenagel-aza-Michael-Cyclocondensation sequence (**KaMC**). All these reactions were allowed by means of dedicated achiral and enantiopure Brønsted base organocatalyst (**R_3N***) and only releases a molecule of acetone, CO_2 and H_2O upon soft conditions (exclusion of air not required, temp. < 40°C). A story of this chemistry will be told.

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POSTERS

A – SYNTHESIS

USE OF SUBSTITUTED PHENYLACETONES IN ORGANIC SYNTHESIS

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In relation of our studies on the utility of substituted 1-tetralones for the synthesis natural products, we have observed that the substituted phenylacetones can also be selected as staring material for natural products. The use of the commercially available phenylacetones **1** and **2** in organic synthesis will be discussed in this symposium. The phenylacetone **1** was converted to 3-methoxy-4-aminopropio-phenone **3** in four steps (Wolff-Kishner reduction, nitration with copper (II) nitrate, oxidation with PCC in benzene and reduction with Pd/C (10%) and ammonium formate). The condensation of **3** with dimethylacetylene dicarboxylate **4** followed by the cyclization of the resulting compound with PPA afforded the kynurenic acid derivative **5** in 60% yield.

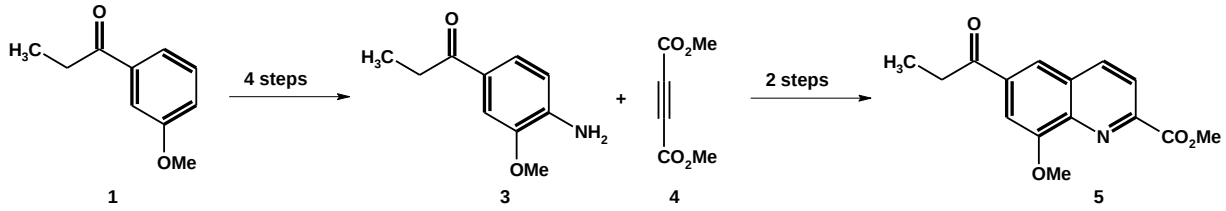

Figure 1

The phenylacetone **2** was converted to benezenesulfonyl derivative **6** in three steps (reduction with $NaBH_4$, bromination with NH_4Br, H_2O_2, AcOH, sulfonyl derivative with $PhSO_2Cl$, Py). The conversion of **6** to α-asarone **7** was accomplished in two steps (dehydration with NaH, DMF, rt, substitution with copper(I) bromide, NaOMe ,DMF). No trace of oily β-asarone **8** was detected.

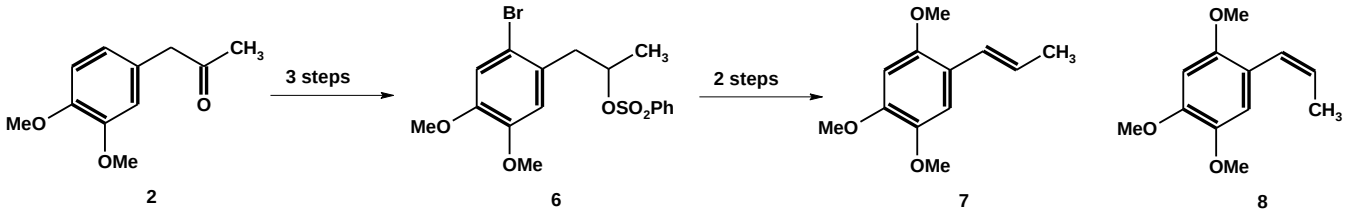

Figure 2

The kynurenic acid and its derivatives exhibit a broad biological activities in neurodegenerative disorders (Alzheimer's, Perkin's disease, retinal damage, etc). α-Asarone, a substance of potent hypolipidemic activity, is mainly found in plant growing in Southwestern Mexico. It is found to have sedating, neuroleptic, spasmolytic and antiulcerogenic activity.

NEW PATHWAY FOR HETEROCYCLES SYNTHESIS: COMBINING CARBONYLATION AND NUCLEOPHILIC SUBSTITUTION

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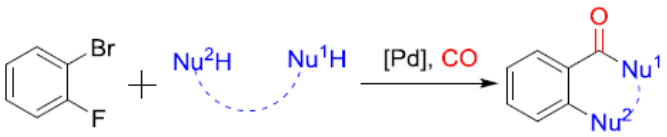
Transition metal-catalyzed carbonylation reactions have already become a powerful tool box in modern organic synthesis.[1] On the other hand, nucleophilic substitution is a fundamental class of organic reactions in which nucleophile attacks the positive charge of an atom to replace a so-called leaving group (electrophile) and forms a new chemical bond. Remarkably, no transitional metal catalyst is involved in nucleophilic substitution which is a big advantage in carbonylation reaction as no CO insertion will occur here. Hence, by the combination of carbonylation and nucleophilic substitution will definitely offer new options for heterocycles synthesis. With this idea in mind, we developed several novel methodologies for the synthesis of carbonyl containing heterocycles. Quinazolinones, isochromenones and isoquinolinones were prepared selectively with high efficiency.[2] The advantage of these procedures have been proved as well.



Offers new pathway for heterocycle synthesis!

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NOVEL PYRAZOLE METAL COMPLEXES: SYNTHESIS AND REACTIONS OF TRISSPIRO(3*H*-PYRAZOL-3-ONE) DERIVATIVE

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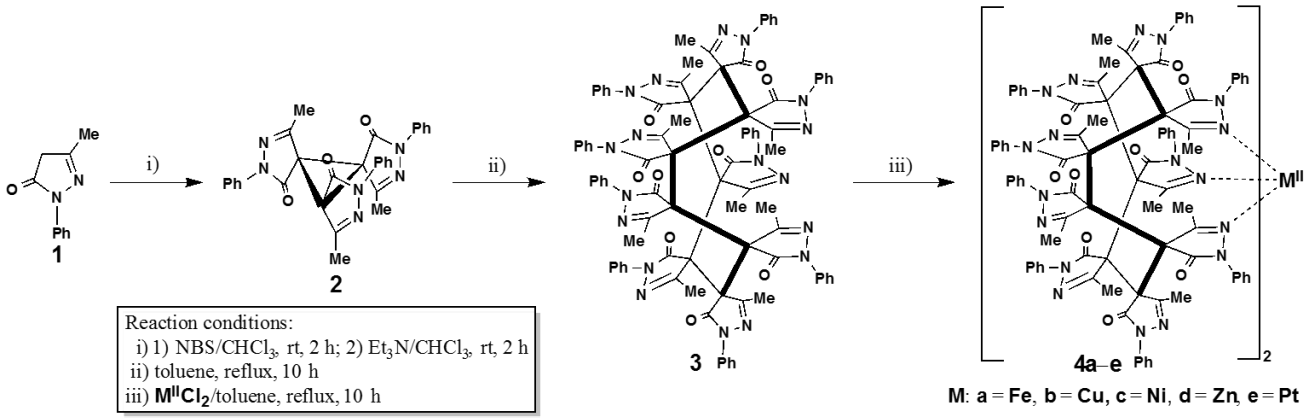
As a part of systematic investigation of synthesis and biological activities of pyrazole metal complexes,[1] a novel series of bis[nonakisspiro(3*H*-pyrazol-3-one)] metal complexes were synthesized. The cleaving agents of nucleic acid have attracted extensive attention due to their potential applications in the fields of molecular biological technology and drug development.[2] Simple metal complexes have been successfully employed to accelerate the rate of double-stranded DNA hydrolysis and those metal complexes with intrinsically high affinity for DNA are the most effective reagent.[3]In this view, the design of small complexes that can bind to DNA becomes more and more important. In connection with our current research interests in the synthesis and reactivity of pyrazole derivatives, we have reported the synthesis of pyrazole tin(IV) complexes.[4] In this work, we wish to report the preparation of novel bis[nonakisspiro(3*H*-pyrazol-3-one)] metal complexes.

The reaction of 3*H*-pyrazol-3-one **1** with NBS in the presence of Et_3N gave the trisspiro(3*H*- pyrazol-3-one) **2**. Thermal treatment of **2** in boiling toluene caused radical polymerization to afford the nonakisspiro(3*H*-pyrazol-3-one) **3**. Compound **3** was reacted with metal(II) reagents, such as iron(II) chloride, copper(II) chloride, nickel(II) chloride, zinc chloride, and platinum(II) chloride, to provide the corresponding bis[nonakisspiro(3*H*-pyrazol-3-one)] metal complexes **4a**-**e**. Newly synthesized compounds **2**□**4** were tested *in vitro* for their DNA cleavage activity. Furthermore, **2**-**4** were evaluated for their antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae*.



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SYNTHESIS AND REACTIONS OF 4-ACYLOXY-3*H*-PYRAZOL-3-ONES: BIOLOGICAL ACTIVITIES OF NOVEL SYNTHESIZED COMPOUNDS

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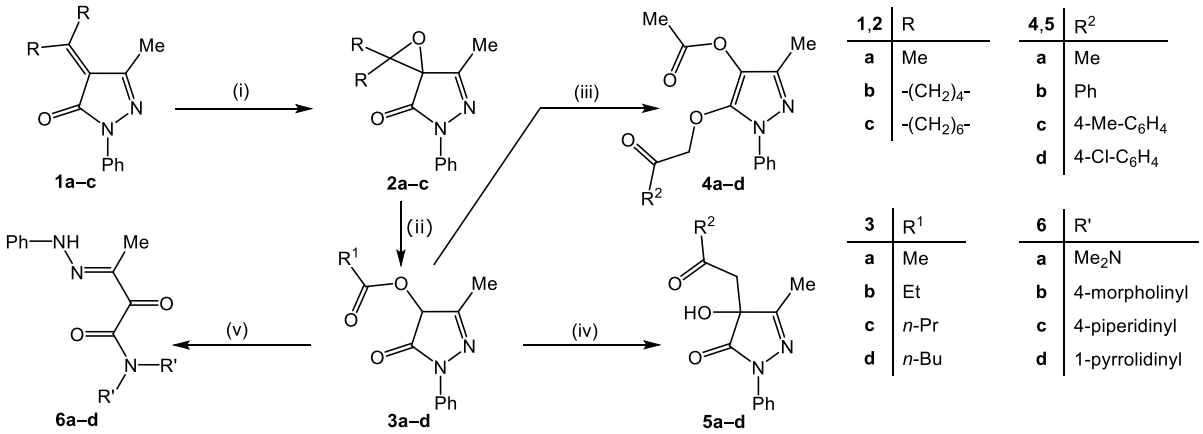
Five-membered nitrogen-containing heterocycles have received intensive research interests because they constitute an important class of natural and unnatural products, which display biological activities, and are important as precursors in the synthesis of many biologically active compounds.[1] Among them, the pyrazol-3-one and pyrazole motifs are attractive targets due to their widespread potential biological activities.[2] On the other hand, hydrazones have also been a useful scaffold in medicinal chemistry for many years.[3] In this work, we have demonstrated a novel convenient approach to spiroepoxide-3*H*-pyrazol-3-ones **2a-c** and 4-acyloxy-3*H*-pyrazol-3-ones **3a**-**d**. Moreover, we have developed a divergent synthesis of 1*H*-pyrazole-4,5-diols **4a**-**d**, 4-hydroxy-3*H*-pyrazol-3-ones **5a**-**d**, and phenylhydrazones **6a**-**d** from 4-acyloxy-3*H*-pyrazol-3-one **3a**.

4-Alkylidene-3*H*-pyrazol-3-ones **1a**-**c** were reacted with *m*-chloroperbenzoic acid in the presence of potassium carbonate to give the corresponding **2a-c**. Treatment of **2a** with acid anhydride in the presence of boron trifluoride diethyl etherate led to the corresponding **3a**-**d**. The reactions of **3a** with α-chloroketones, ketones, and/or secondary amines gave the corresponding **4a-d**, **5a**-**d**, and **6a**-**d**. Furthermore, novel synthesized compounds were tested *in vitro* for their DNA cleavage activity and evaluated for their antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae*.



1,2	R
a	Me
b	-$(CH_2)_4$-
c	-$(CH_2)_6$-

4,5	R^2
a	Me
b	Ph
c	4-Me-C_6H_4
d	4-Cl-C_6H_4

3	R^1
a	Me
b	Et
c	*n*-Pr
d	*n*-Bu

6	R'
a	Me_2N
b	4-morpholinyl
c	4-piperidinyl
d	1-pyrrolidinyl

Reaction conditions: (i) *m*-CPBA, K_2CO_3, $CHCl_3$, 0–5 °C, 1 h; (ii) $(R^1CO)_2O$, $BF_3{\cdot}OEt_2$, $CHCl_3$, r.t., 12 h; (iii) $ClCH_2COR^2$, NaH, DMF, r.t., 12 h; (iv) $MeCOR^2$, Et_3N-H_2O, r.t., 12 h; (v) $R'_2NH{\cdot}HCl$, Et_3N, THF, reflux, 2 h or R'_2NH, Et_3N, THF, 80 °C, 1 h.

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SYNTHESIS AND ANTIOXIDANT ACTIVITY OF SOME BIOLOGICAL ACTIVE COMPOUNDS ARISING FROM [3+2] CYCLOADDITIONS USING SULPHUR SUBSTITUTED AZOMETHINE YLIDES AND NITRILE OXIDES

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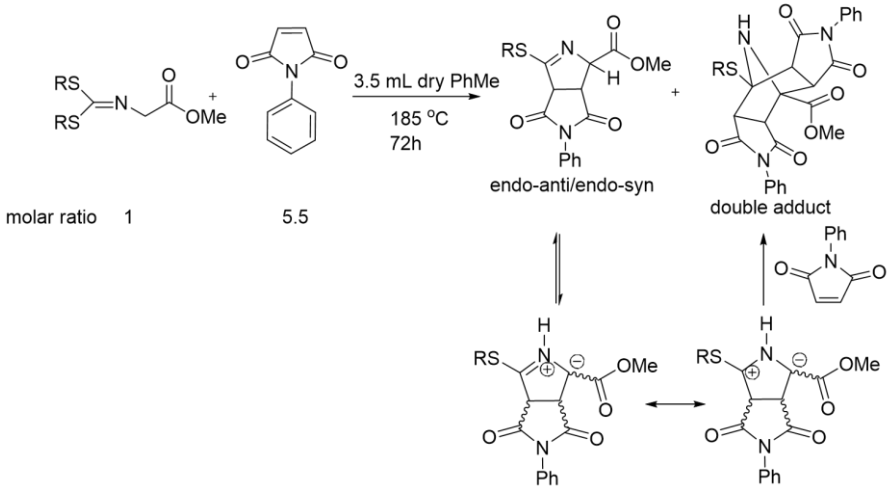
(This work is dedicated with respect to the memory of Associate Prof. YiannisElemes)

The cycloaddition reactions are among the powerful tools for ring construction in organic synthesis [1]. Azomethine ylides and nitrile oxides are reactive 1,3-dipoles, giving rise to a variety of five-membered heterocyclic compounds which have synthetic applications in heterocyclic and natural product chemistry [2]. We report here on the isolation of 5H-dihydro-pyrrolo derivatives from the cycloaddition of a series of *N*,*N*-[bis-methylsulfanyl]-imines of glycine esters to *N*-phenylmaleimide, in good yields under neutral conditions at high temperatures, and their full spectroscopic characterization [3]. The second part of the work includes the addition of nitrile oxides to fragrance and flavor compounds such as (R)/(S)-Limonene, carveol, carvone, and alpha-terpinene. The new isoxazoline and dihydro-pyrrolo compounds have been screened for scavenging ability against the free radical 2,2-diphenyl-1-picryl-hydrazyl (DPPH) and chelating activity on ferrous ions.



Aknowledgements: We gratefully acknowledge financial support of this work by the Amasya University Scientific Research Projects Coordination Department (Project No FMB-BAP14-054/14-086).

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[3+2] CYCLOADDITIONS OF UNSATURATED *N,N'*-BISTRICYCLIC IMIDES

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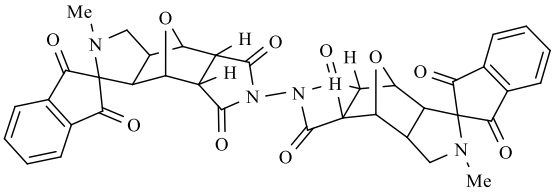
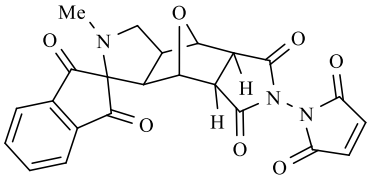
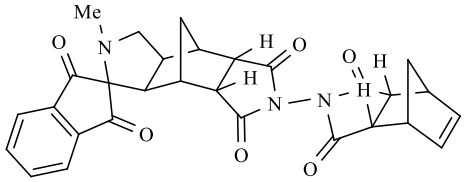
A huge number of biological activities have been conferred to heterocycles and they play a important role as both pharmaceutical and agrochemical products [1]. Imide moiety is an integral part of structures of various important molecules such as fumaramidmycin, granulatimide, isogranulatimide, rebeccamycin, and thalidomide. These molecules are reported to exhibit wide variety of biological activities such as antitumor, anti-inflammatory, and antimicrobial [2]. In addition, *N*-substituted imides, such as maleimides isohematinic acids and especially bicyclic and tricyclic derivatives such as tandospirone derivatives [3] are known for their broad spectrum of pharmacological properties, thus showing antibiotic, fungicidal, analgesic, anxiolytic and cytostatic effects.

The 1,3-dipolar cycloaddition reaction of azomethine ylides to alkenes is one of the most important and elegant methods for the construction of nitrogen-containing five-membered ring compounds. For this reason, we focused on the [3+2] cycloaddition reactions with azomethine ylide to obtain fused spiro-1,3-indandionolylpyrrolidine compounds to have more potentially biologically active molecules available. Spiro compounds are well known to possess varied pharmacological activities and hence their synthesis has always been a challenge and an attraction to organic chemists [4].







Aknowledgements: We gratefully acknowledge financial support of this work by the Yildiz Technical University Scientific Research Projects Coordination Department (Project No. 2011-01-02-KAP03).

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DIRECT ASYMMETRIC ALDOL REACTION FOR THE SYNTHESIS OF SUGARS

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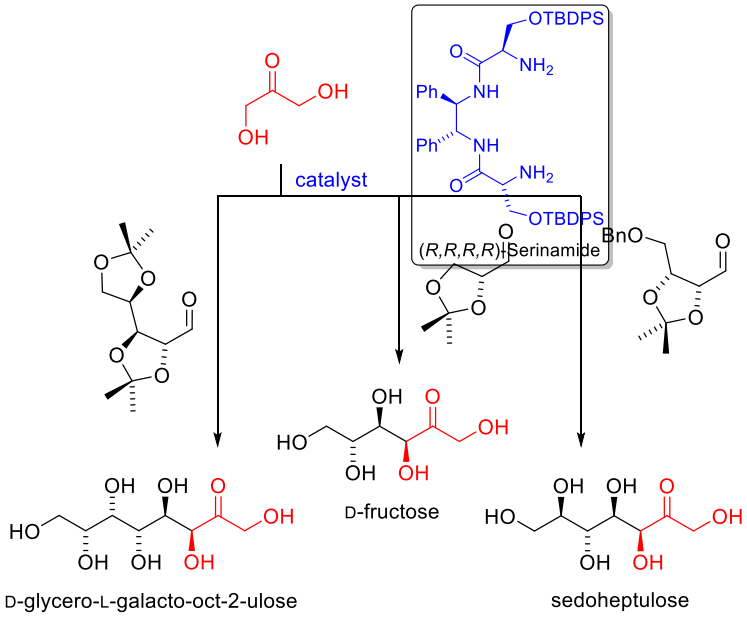
The chemistry of carbohydrates has been extensively developed for over a century. While many synthetic methods based on orthogonally protected sugar precursors have been developed, examples of a direct *de novo* approach from simple carbonyl precursors is still limited.[1] Especially the synthesis of higher-carbon sugars, an important group of monosaccharides that take part in various biochemical processes, still needs improvement.

Recently we have developed a straightforward synthesis of *syn*-configured ketohexoses in a direct aldol reaction of unprotected dihydroxyacetone and both (*R*)- or (*S*)-glyceraldehyde acetonides in the presence of water.[2] Herein, we report a broader application of that methodology for the synthesis of naturally occurring higher-carbon sugars.



In the key step the direct aldol reaction of dihydroxyacetone and D-erythrose catalyzed by serine-based organocatalyst promotes the reaction to yield natural heptose - sedoheptulose (D-*altro*-hept-2-ulose). The synthesis of naturally occurring octose - D-*glycero*-L-*galacto*-oct-2-ulose was accomplished when D-xylose was used. The reactions proceed with very high yields and diastereoselectivities.

Acknowledgements: Financial support from the Polish National Science Centre (grant number NCN 2011/03/B/ST5/03126) is gratefully acknowledged.

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N-TRIFLUOROMETHYLTHIOLATION OF SULFOXIMINES

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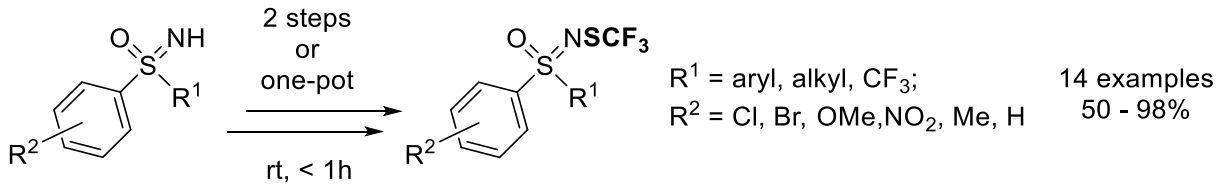
Fluorinated moieties are important in organic syntheses,[1] and they find various applications in biologically active compounds.[2] Hence, their incorporation into molecules became an indispensable strategy for the development of drugs and crop protecting agents. The trifluoromethylthio group (SCF_3) received increasing interest in medicinal chemistry[3] due to its high lipophilicity.[4]

Sulfoximines, the mono-aza analogues of sulfones, contain a modifiable imine nitrogen. Changing the *N*-substituent can lead to a change of physical properties such as the solubility and lipophilicity of the respective molecule.[5] Therefore, sulfoximines have attracted attention as drug candidates[6] and as crop protection agents.[7]

The combined advantages of the sulfoximidoyl moiety and the favorable effects induced by a trifluoromethylsulfenyl substituent are of special interest.

Herein, we present the syntheses of various *N*-SCF_3 functionalized sulfoximines representing a new class of substrates for potential bioactive compounds.



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IMPORTANCE OF SULFORAPHANE, AN ANTI-CANCER COMPOUND, AND ITS SULFOXIMINE ANALOGS

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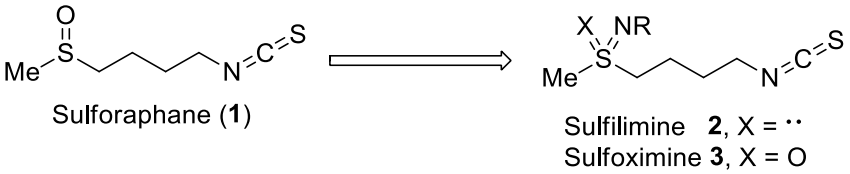
In 1992, Zhang et al.[1] isolated for the first time a small molecule, Sulforaphane (**1**), which derived from the hydrolysis of glucosinolates present in *Brassica* vagetables, especially broccoli.[2] Since then, the biological activities of this compound were deeply investigated. In fact, Sulforaphane plays a fundamental role in the prevention of several kinds of cancer,[3] for instance inhibiting Phase I enzymes, inducing Phase II enzymes, modulating apoptosis, and showing anti-inflammatory effects.[4]

It was also proven that the configuration of the sulfoxide in **1** can be relevant in the stimulation of detoxifying enzymes.[5] Motivated by the importance of this moiety on the biological properties of Sulforaphane, we decided to investigate in detail the influence of the oxidation state of the sulfur atom. Here, we present the synthesis of Sulforaphane analogs, where the sulfoxide is replaced by sulfilimidoyl (**2**) and sulfoximidoyl (**3**) functionality. Studies about the biological activities of these derivatives are still ongoing and have shown promising preliminary results.



Sulforaphane (**1**)

Sulfilimine **2**, X = ••
Sulfoximine **3**, X = O

References:

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THE IRON-CATALYZED ACYLATIVE DEALKYLATION OF *N*-ALKYL SULFOXIMINES

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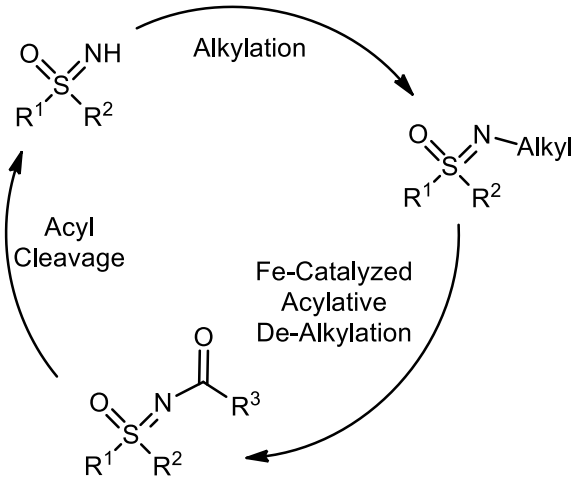
Sulfoximines, the mono-aza analogues of sulfones, are of special interest for application in medicinal chemistry as well as crop protection.[1] In contrast to sulfones, sulfoximines have an imine-nitrogen that can be modified to improve physical properties, for example solubility.[2] Whilst the synthesis of *N*-methyl sulfoximines can be achieved under classical Eschweiler-Clarke conditions,[3] the alkylation using more complex groups has proved more challenging. Recently, our group developed two methods to prepare *N*-alkylated sulfoximines[4] that led us to further explore the chemistry of *N*-alkylated sulfoximines.



Herein, we present an iron-catalyzed dealkylative acylation of *N*-alkyl sulfoximines. This methodology allows to prepare, starting from the *N*-alkylated sulfoximines, a broad variety of *N*-acyl sulfoximines and *N*H-sulfoximines. The first step of the reaction process is a Polonovski-type dealkylation of the *N*-alkylated sulfoximine, generating a reactive intermediate which is trapped either by an aldehyde or an anhydride to form the *N*-acyl sulfoximine. In a second step the acetyl-group can be cleaved under acidic conditions to form the *N*H-sulfoximine.

This methodology now enables the use of alkyl moieties as a nitrogen protecting group that tolerates various reaction conditions, allowing the syntheses of more complex sulfoximine derivatives.

References:

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ASYMMETRIC GRIGNARD SYNTHESIS OF TERTIARY ALCOHOLS

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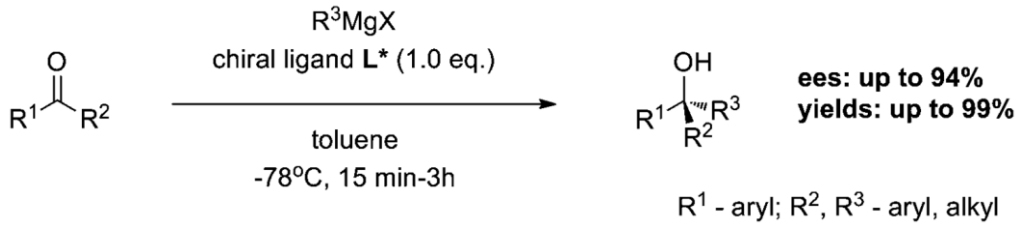
Chiral tertiary alcohols constitute an important class of biologically active molecules.[1] Most conveniently they can be prepared by a stereoselective addition of organometallic reagents to ketones. Among organometallics, the Grignard reagents present the widest scope and greatest versatility. However, stereoselective synthesis of tertiary alcohols by direct 1,2-addition of Grignard reagent to ketones is extremely challenging and most of the successful cases involve transmetallation using transition metals.[2] To best of our knowledge, only a single case was reported to date where high enantioselectivity was obtained in the absence of metals other than magnesium.[3]

The challenges of asymmetric Grignard synthesis of tertiary alcohols lie in: the reduced enantioface discrimination between the prochiral sides of a ketone (as compared to an aldehyde), competitive non-stereoselective reactions, low yields due to enolization/reduction side reactions, and dynamic processes originating from the Schlenk equilibrium.[4]



We focused our research on development of a general methodology of 1,2-addition of Grignard reagents to arylalkyl ketones in the presence of a new class of chiral ligands. By using stoichiometric amounts of readily available enantiopure ligand **L***[5] it was possible to prepare tertiary alcohol products with high enantioselectivities (up to 94%) and high yields (up to 99%). The method was found to be general for a range of ketones and Grignard reagents. The chiral ligand **L*** can easily be recycled from the crude reaction mixture.

References:

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[4] B. Bieszczad, D.G. Gilheany, manuscript in preparation
[5] A patent application is pending: upon its projected publication in May 2015 the structure of the ligand **L*** can be revealed.

SPIRANES SYNTHESIS VIA THIOL-MEDIATED ACYL RADICAL CYCLIZATION

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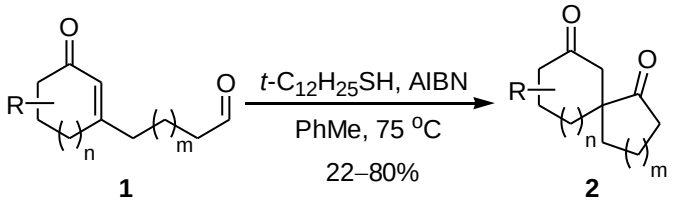
Many natural products with the spiro core are known and they have showed significant biological activities. Therefore, our aim was to develop a general and efficient method for preparing such type of molecules.[1] Herein, we would describe a thiol-mediated acyl radical cyclization to access spiro compounds. Enone-aldehydes **1** were subjected to *tert*-dodecanethiol and AIBN[2] at 75 °C in toluene and various spirocyclic γ-diketones **2** in good yields were obtained. The ring size of the spiro compounds can be easily controlled either by using different cyclic enones or by altering the length of the side chain. The synthetic details will be discussed.



1 **2**

References:

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THIOPHENYL GROUP DIRECTING SYNTHESIS OF γ-HYDROXYBUTENOLIDES VIA FURAN PHOTOOXYGENATION

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γ-Hydroxybutenolide motifs appear in a variety of bioactive natural products and there are continuous efforts for uncovering new methodologies for their synthesis. Studying the photooxygenation (reaction with singlet molecular oxygen, $^1O_2$) of 2-thiophenyl-substituted furans in methanol, we found[1] that they cleanly and within a few minutes of reaction time, lead to γ-hydroxybutenolides (Figure 1). The carbonyl group of butenolide is in the position of the former C-S bond. The fate of thiophenyl moiety is to form diphenyl disulfide, indicative of decomposition of the initially formed [4+2] endoperoxide via an O-O bond radical scission forming thiophenyl radical and the hydroxybutenolide. As 2-thiophenyl furans can be easily synthesized, the current protocol is highly compelling for the regiocontrolled and clean synthesis of γ-hydroxybutenolides from photooxygenation of suitable furan[2]precursors.

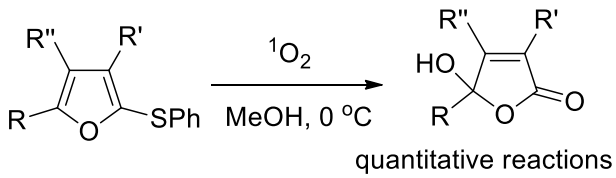

Figure 1: Synthesis of γ-hydroxybutenolides from singlet oxygenation of 2-thiophenyl-substituted furans in methanol.

References:

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TWO SYNTHETIC APPROACHES TO MULTIPHOTOCHROMIC COMPOUNDS FOR OPTICAL PROCESSORS

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A.S. Tatikolov,[b] P.P. Levin,[b] L.D. Popov [c]

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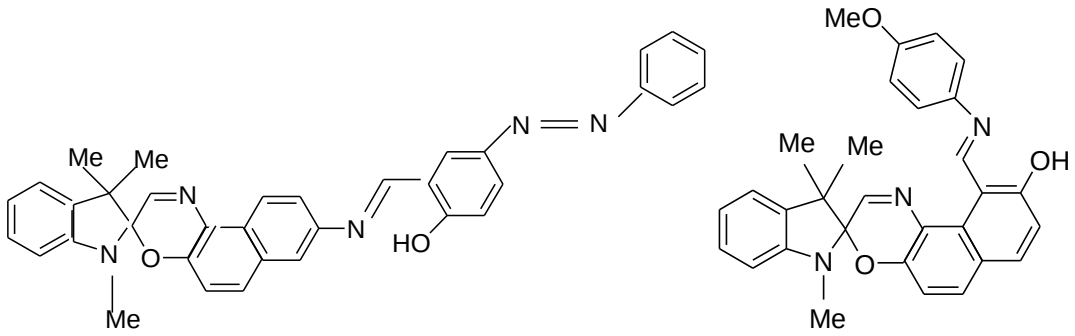
In recent years, bi- and multiphotochromic systems are widely studied due to their practically attractive properties. One of their potential applications is a new generation of materials for molecular electronics, such as molecular switching devices, molecular logic gates. In this context, first important feature in the design of such systems is a different photochemical behavior of constituent elements.
Two different synthetic ways are presented to obtain two series of hybrid compounds on the base of spyronaphthoxazine fragment and substituted salicylideneimine one.



1 type 2 type

Photolysis products were detected using pulse photolysis technique in toluene and methanol solutions. Nitrogen and dye lasers were used for excitation with radiation wavelengthes 337 and 430 nm. Both compounds demonstrate strong dependence of photochemical behavior on a fragments combination mode, wavelength of excitation and solvent nature [1].

Aknowledgements: This work was financially supported by the Presidium of the Russian Academy of Sciences (Program No. 8).

References:

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SYNTHESIS OF FLUORESCENTLY LABELED GLYCOSPHINGOLIPIDS FOR BIOPHYSICAL INVESTIGATIONS

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Glycosphingolipids (GSLs) represent an essential structural component of mammalian cell membranes. They consist of a ceramide moiety with an *N*-acetylated sphingosine group. Either simple monosaccharides or more complex oligosaccharides can be linked to the primary hydroxyl group of the sphingosine as carbohydrate head group (Figure 1).[1]

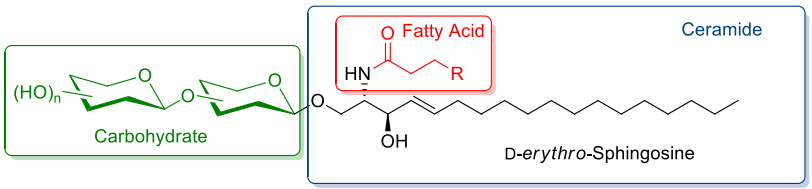
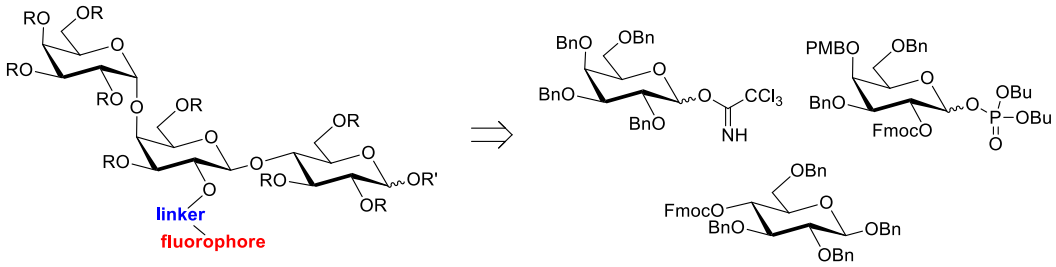


Figure 1. General structure of glycosphingolipids.

After being underestimated for a long time, research over the past decades proved that GSLs are involved in many physiological processes, such as their involvement in cell adhesion/recognition processes or the modulation of signal transduction. Overexpression, redistribution and degradation are associated with several diseases.[1] However, their role in many cellular processes is not yet fully understood.

GSLs are not distributed homogeneously in the membrane. It is postulated that they form semi-ordered lipid microdomains, so called lipid rafts.[2] The synthesis of fluorescently labeled GSLs would enable a direct proof of their localization in artificial membranes and their phase behavior and lateral mobility could be analyzed. Herein, we report recent advances in synthesizing fluorescently labeled derivatives of globotriaosylceramide (Gb_3) for biophysical investigations. The fluorophore shall be installed at the carbohydrate head group in such a way that typical properties of the GSL remain unaffected (Scheme 2). Within this synthesis, the selective installation of the fluorescent dye is the most challenging endeavor. The monosaccharide building blocks depicted in Scheme 1 were identified as suitable precursors for this purpose.



Scheme 1. Retrosynthetic analysis of fluorescently labeled globotrioses (R = protecting group).

References:

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DESIGN AND STEREOSELECTIVE SYNTHESIS OF SECONDARY STRUCTURE MIMETICS WITH PPII HELIX CONFORMATION

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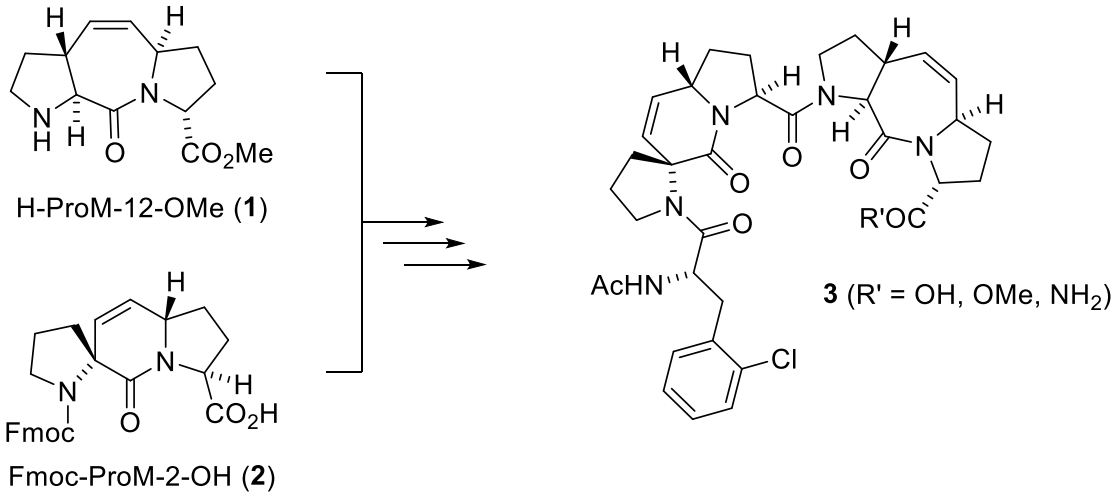
Interactions of proteins containing proline-rich motifs (PRMs) with so called proline-rich motif-recognizing domains (PRDs) are widely utilized by nature and are involved in several relevant processes such as tyrosine kinase receptor signaling, endocytosis, cytoskeletal rearrangements, transcription, and splicing. In recent years, some PRDs were identified as putative therapeutical targets that can possibly be addressed by synthetic small molecules.[1]

Aiming at the development of polyproline type II helix (PPII) secondary structure mimetics for the modulation of proline-rich motif mediated protein-protein interactions[2], new conformationally rigidified diproline mimetics (ProM-2) and (ProM-12) were designed by bridging the two pyrrolidine rings of either a L-Pro-L-Pro or a L-Pro-D-Pro unit through a Z-vinylidene moiety.



The main goal of our work is the development of small drug like molecules such as (**3**) which resemble a section of a PPII helix and act as specific interface inhibitors replacing natural PRM ligands from their respective PRDs.

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[1] L. Ball, R. Kühne, J. Schneider-Mergener, H. Oschkinat *Angew. Chem. Int. Ed.* **2005**, *44*, 2852 – 2869.
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[3] R. Opitz, M. Müller, C. Reuter, M. Barone, A. Soicke, Y. Roske, K. Piotukh, P. Huy, M. Beerbaum, B. Wiesner, M. Beyermann, P. Schmieder, C. Freund, R. Volkmer, H. Oschkinat, H.-G. Schmalz, R. Kühne *PNAS* **2015** (in press).

SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF HEXACYCLINIC ACID

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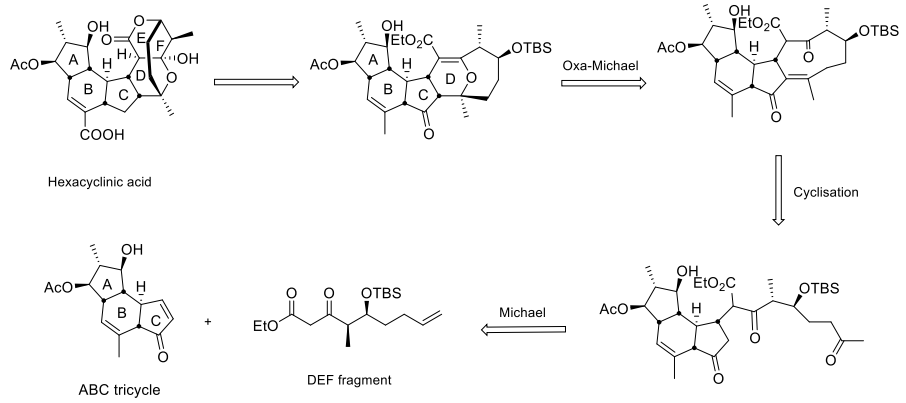
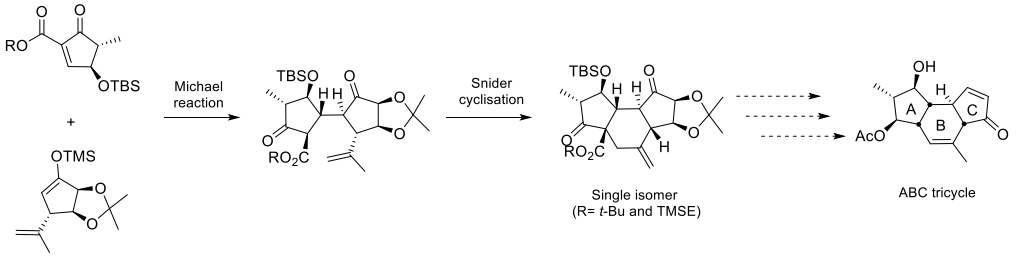
Hexacyclinic acid is a polyketide that was isolated for the first time in 2000 by Zeeck *et al.* [1] from *Streptomyces cellulosae* and has shown interesting cytotoxic activities. The retrosynthesis envisaged by the group involves an oxa-Michael reaction to close the D ring, formation of a nine-membered ring and a Michael reaction between the ABC tricycle and the DEF fragment (Scheme 1).



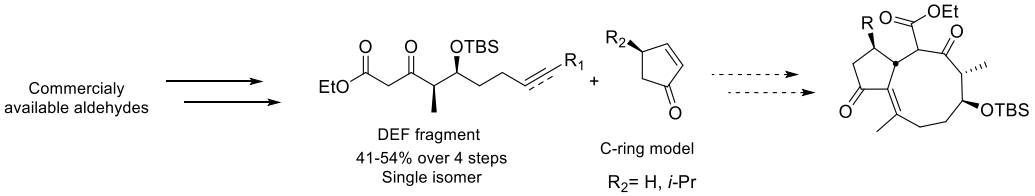
(Scheme 1)

Advanced intermediates in the synthesis of the ABC tricycle have been successfully synthesised using a route previously developed by the group. This pathway involves a diastereoselective Michael reaction followed by a radical cyclisation (Scheme 2). [2]



(Scheme 2)

We developed a synthetic route for a CDEF model and we are currently investigating the formation of the nine-membered ring, the key step of our synthesis (Scheme 3).



(Scheme 3)

References:

[1] R. Hofs, M. Walker, A. Zeeck, *Angew. Chem. Int. Ed.* **2000**, *39*, 3258-3261.
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PALLADIUM-CATALYZED ENANTIOSELECTIVE DECARBOXYLATIVE ALLYLATION: A STRAIGHTFORWARD METHOD TO ACCESS OPTICALLY ACTIVE SPIROIMINES

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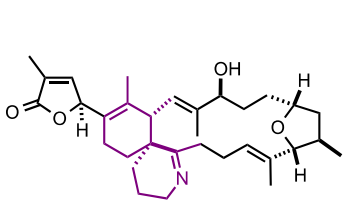
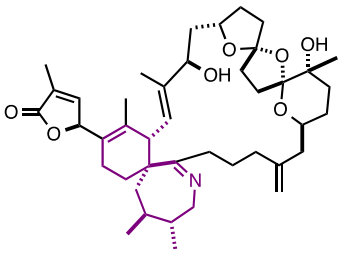
Institut de Chimie des Substances Naturelles, CNRS, Bâtiment 27, LabEx Lermit, Avenue de la terrasse, 91198 Gif-sur-Yvette, matt.rambla@cnrs.fr

Gymnodimine A **1** (GYM A) and 13-desmethyl spirolide C **2** (SPX C) belong to a class of complex marine phycotoxins, produced in small amount by microorganisms.[1] These toxins are then transferred and concentrated into shellfishes to finally end up into fishes and humans, causing intoxication due to consumption of contaminated seafood. Recently, it was shown that GYM A and SPX C are potent antagonists of nicotinic acetylcholine receptors (nAChRs) with limited selectivity toward a subtype of nAChRs.[2-3]

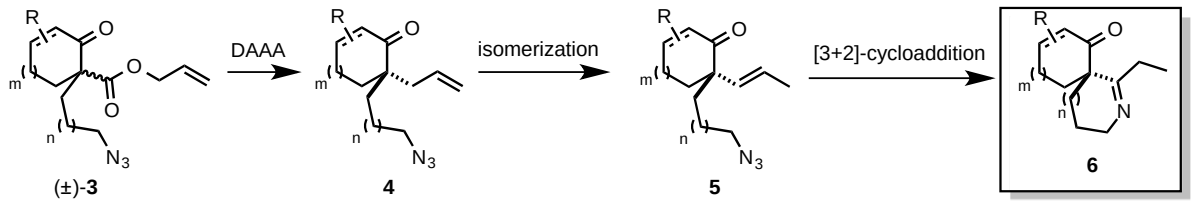


Gymnodimine A **1**



13-desmethyl spirolide C **2**

We report herein a straightforward enantioselective synthesis of analogues of the spiroimine core of GYM A and SPX C.[4] We developed a three-step sequence that includes a Pd-catalyzed decarboxylation of azido β-ketoester (±)-**3** to set the stereochemistry of the quaternary carbon atom. Then isomerization of the allyl moiety of **4** followed by azide-alkene [3+2]-cycloaddition of **5** furnished optically active spiroimines **6**.



References:

[1] L. Mackenzie, *Seafood New Zealand* **1994**, *2*, 47-50.
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DIASTEREOSELECTIVE HYDROXYMETHYLATION OF CYCLIC *N-TERT*-BUTANESULFINYLKETIMINES USING METHOXYMETHANOL AS FORMALDEHYDE SOURCE

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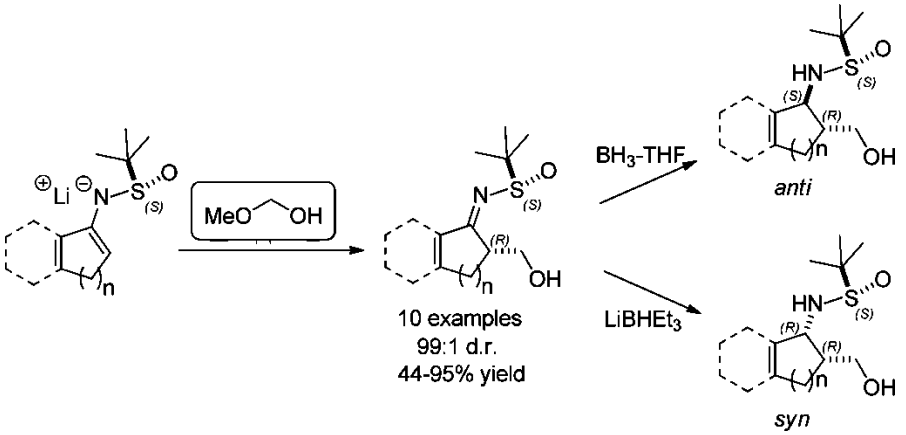
Hydroxymethylation of cyclic (S_S)-*tert*-butylsulfinylketimine-derived lithium enamides with methoxymethanol as a source of anhydrous monomeric formaldehyde affords (S_S,*R*)–α-hydroxymethyl ketimines with excellent diastereoselectivity (99:1 dr). Subsequent diastereoselective reduction of the ketimine moiety from *Re*-face with BH_3-THF provided (S_S,*R,R*)-*N*-sulfinyl-1,3-amino alcohols. Diastereomeric (S_S,*R,S*)-1,3-amino alcohols were also obtained by using $LiBHEt_3$ as the reducing agent. The *tert*-butylsulfinyl chiral auxiliary controls the diastereoselectivity of both hydroxymethylation reaction and subsequent reduction of ketimines. Further studies to expand the scope of aldehydes in the reaction with (S_S)-*tert*-butylsulfinyl ketimines are ongoing in our laboratory.[1]



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SYNTHESIS OF QUATERNARY PROLINE DERIVATIVES BY DIASTEREOSELECTIVE INTRAMOLECULAR ARYLATION OF AMINO ESTER ENOLATES

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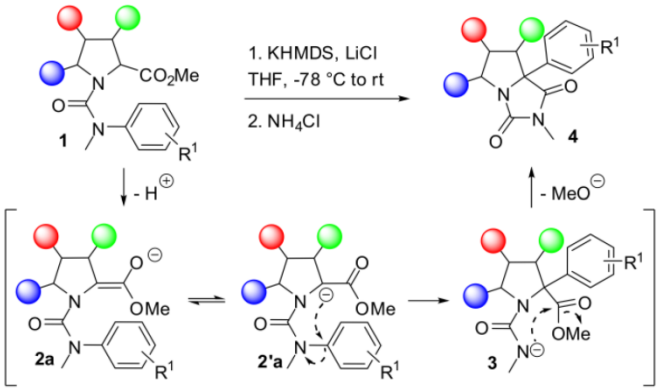
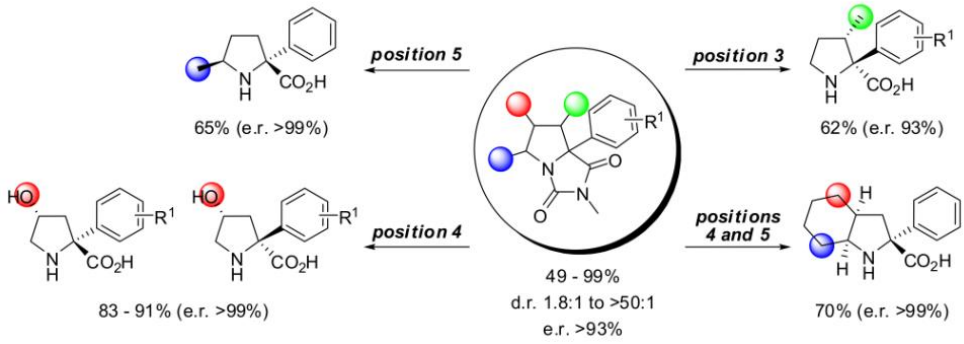
In the last decades, natural and non-natural prolines and their α-quaternary derivatives have become of great interest in many fields, such as peptide chemistry and design of new chiral organocatalysts for asymmetric chemistry. However, although proline ester derivatives are readily alkylated, their α-arylation is still challenging. One solution is to promote intramolecular coupling of an enolate with an arene by tethering them through a urea linkage. This strategy has already proved successful for the arylation of organolithiums.[1]



The deprotonation of urea derivatives of chiral substituted proline analogues leads to hydantoins, *via* a cascade reaction involving intramolecular nucleophilic aromatic substitution and cyclisation, in good yields and high diastereoselectivity (d.r. > 50:1). The hydrolysis of these various hydantoin intermediates generates various quaternary proline derivatives.



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REACTION OF PHOSPHORUS AND PHOSPHORUS-CONTAINING NUCLEOPHILES WITH THE MORITA-BAYLIS-HILLMAN ADDUCTS

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The Morita-Baylis-Hillman adducts (activated allyl acetates and bromides) are useful trifunctional substrates for a range of nucleophilic displacements, additions and rearrangements.[1] Accordingly, they have been exploited as the synthetic platform in multitude transformations, proceeding both in an inter- and intramolecular manner, frequently with a stereoselective induction. The application of the MBH adducts in organophosphorus chemistry has attracted a limited attention. A few types of P-nucleophiles has been studied for substitution of the electrophilic components.[2] In this communication we report the results of our studies on the reactivity of MBH acetates and bromides with hypophosphites, phosphites, phosphinates, and carboxyphosphonate and methylenebisphosphonate carbanions. After hydrolysis multifunctional phosphonic and phosphinic acid products are structurally novel compounds of a biological activity potential.

Acknowledgements: The work is supported by a grant from the Polish National Science Centre (Grant 2013/09/B/ST5/00090).

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[1] D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110,* 5447-5674.
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A POWERFUL STEREOSELECTIVE ENTRY TO 4,5-DISUBSTITUTED PROLINES: APPLICATION IN THE SYNTHESIS OF TRANDOLAPRIL

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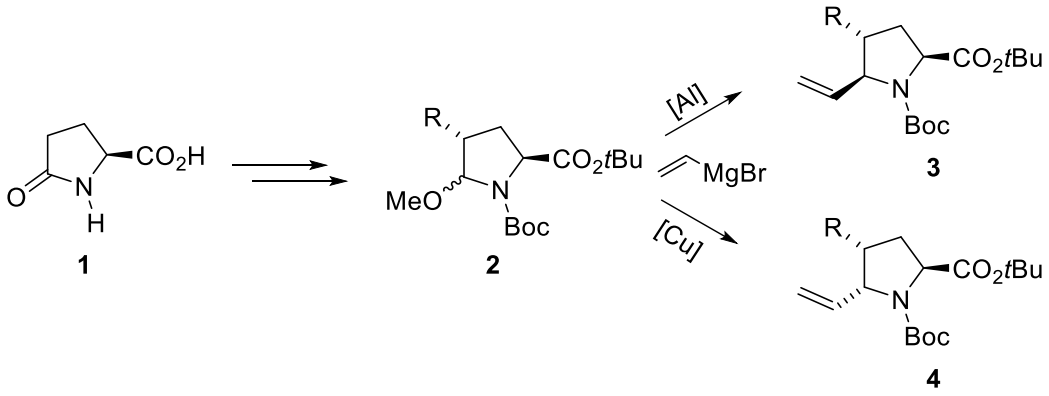
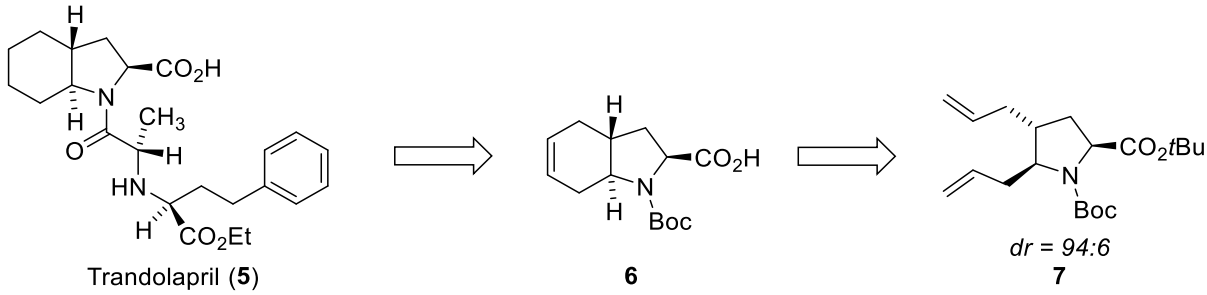
[b] Leibniz Institute for Molecular Pharmacology, Berlin, Germany

In the course of our studies towards the synthesis of proline-based dipeptide mimetics with defined conformation,[1] we have developed a methodology for the stereoselective preparation of proline derivatives starting from pyroglutamic acid (**1**).



This method led to a variety of *trans*-4-substituted prolines (**2**) and allowed the subsequent introduction of a second side-chain, which could be installed with high diastereoselectivity, to afford either the *cis*-(**3**) or the *trans*-isomer (**4**) depending on the metal additive used.[2] The power of the method was demonstrated in an efficient synthesis of the ACE-inhibitor trandolapril (**5**),[3] a synthetic drug used for the treatment of high blood pressure.



Key steps of this synthesis include the formation of a diallylated proline derivative **7** and a Ruthenium-catalyzed ring closing metathesis to the hexahydroindole species **6**.

References:

[1] (a) J. Zaminer, C. Brockmann, P. Huy, R. Opitz, C. Reuter, M. Beyermann, C. Freund, M. Müller, H. Oschkinat, R. Kühne, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2010**, *49*, 7111-7115; (b) C. Reuter, P. Huy, J.-M. Neudörfl, R. Kühne, H.-G. Schmalz, *Chem. Eur. J.* 2011, *17*, 12037-12044; (c) V. Hack, C. Reuter, R. Opitz, P. Schmieder, M. Beyermann, J.-M. Neudörfl, R. Kühne, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2013**, 52, 9539-9543; (d) A. Soicke, C. Reuter, M. Winter, J.-M. Neudörfl, N. Schlörer, R. Kühne, H.-G. Schmalz, *Eur. J. Org. Chem*. **2014**, *29*, 6467-6480.
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A FACILE ACCESS TO DIHYDROBENZO[*b*]PYRIMIDO[5,4-*f*]AZEPINE AND DIHYDRO[1,2,4]TRIAZOLO[4',3':1,6]PYRIMIDO[4,5-*b*]BENZO[*f*]AZEPINE DERIVATIVES

Justo Cobo,*,[b] Lina María Acosta,[a] Alirio Palma,*,[a] Manuel Nogueras[b]

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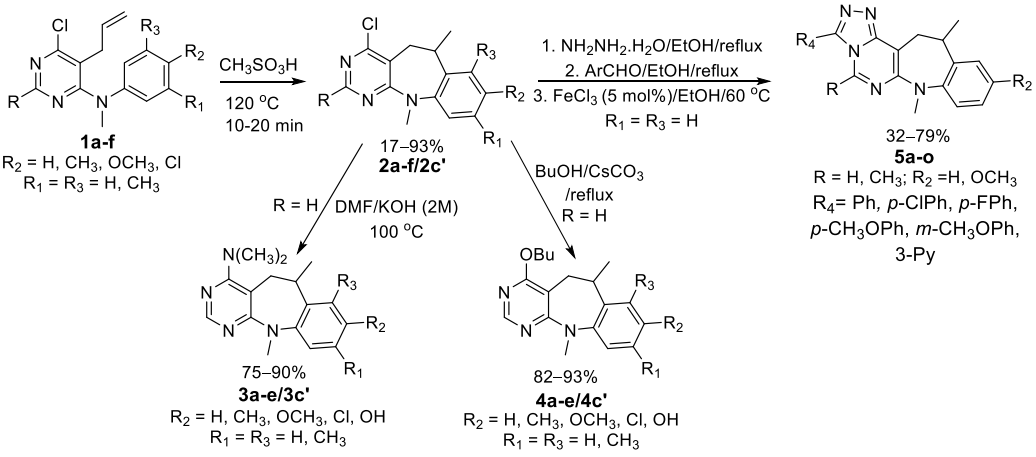
It is well known that pyrimidine derivatives have considerable pharmacological and chemical significance because of their important roles in fundamental biological processes and in pharmaceutical industry.[1] Our work is now focused on the design and synthesis of new dihydrobenzo[*b*]pyrimido[5,4-*f*]azepine derivatives, a tricyclic-pyrimidine system little studied[2], despite of its closely structural similarity to the widely studied dihydrodibenzo[*b*,*f*]azepine system, an heterocyclic nucleus presents in the structure of synthetically developed drugs such as imipramine[3], carbamazepine and oxcarbazepine[4]. In our ongoing research program on the search of new molecules with potential anticancer activity, we report here the easy functionalization of the 6,11-dihydro-5*H*-benzo[*b*]-pyrimido[5,4-*f*]azepine core at C-4 position. The synthetic scheme to prepare compounds **3a-e/3c', 4a-e/4c'** and **5a-o** is depicted below; The procedure involves a nucleophilic aromatic substitution of chlorine atom promoted by different bases over compounds **2**. The preparation of compounds **5a-o** is carried out in three steps, so, the initially formed hydrazines were further subjected to an oxidative cyclocondensation, first in a reaction with different aldehydes and afterwards with ferric chloride as oxidant agent.



Acknowledgements: AP and LMA acknowledge for the financial support due by the Colombian Institute for Science and Research (COLCIENCIAS, grant No 1102-521-28229). JC and MN thank "Centro de Instrumentación Técnica" of Universidad de Jaén and the staff for data collection and supporting. The financial support from the Consejería de Economía, Innovación y Ciencia (Junta de Andalucía) for financial support is thanked.

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STEREOSELECTIVE SYNTHESIS VIA A Zn – BROOK REARRANGEMENT FOLLOWED BY AN ENE-ALLENE CARBOCYCLIZATION REACTION

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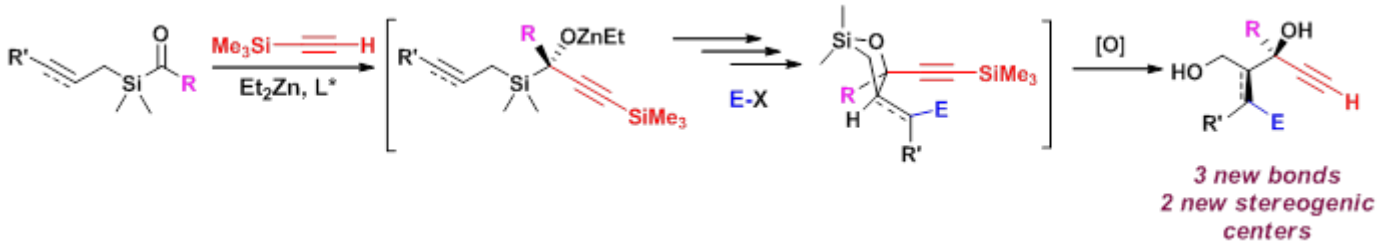
The design of new enantioselective methods for the construction of stereogenic centers is of primordial importance in organic synthesis. Previous research in our group led to the development of new methodologies that create several carbon-carbon bonds and stereogenic centers, including quaternary ones, in a single-pot operation, from acylsilanes 1 and alkynes involving the Zn–Brook rearrangement followed by an ene-allene cyclization.
In this current research we were able to extend this concept to substrates that lead to the construction of alternate stereocenters in acyclic system as described below. In this process, three new bonds and two new stereogenic centers, including a tertiary alcohol are created. The scope and limitations of this new reaction will be described in the poster.



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SYNTHESIS OF HIGHLY FUNCTIONALIZED OXEPANES BY BRÖNSTEDT ACID-MEDIATED CYCLISATION OF 1,2-OXAZINE DERIVATIVES

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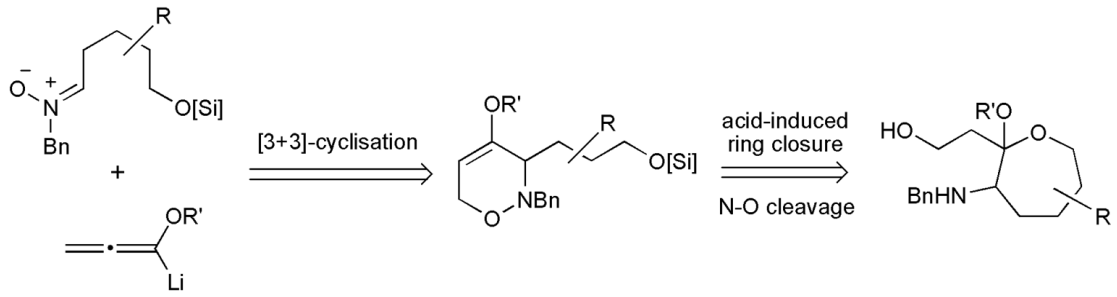
In a series of recent papers lithiated alkoxyallenes have been demonstrated as a versatile building blocks for the construction of numerous heterocyclic systems,[1] including furan and pyran derivatives as well as 7-membered oxacycles of biological importance.[2] Here we report on three-step approach to enantiopure septanoside analogues starting with aldopentose-derived δ-siloxynitrones,[3] which after the reaction with lithiated alkoxyallenes provided key 3,6-dihydro-1,2-oxazine derivatives. Brönstedt-acid induced cyclisation of the latter compounds followed by N-O bond cleavage afforded title oxepanes in high overall yields.



Scheme 1

Aknowledgements: Financial support by the Ministry of Science and Higher Education (Republic of Poland, grant Iuventus Plus no IP2014 017173) is gratefully acknowledged.

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UNEXPECTED REACTIONS OF 3-BROMOOXINDOLE WITH 4-METHOXYTHIOBENZAMIDE AND THIOUREA

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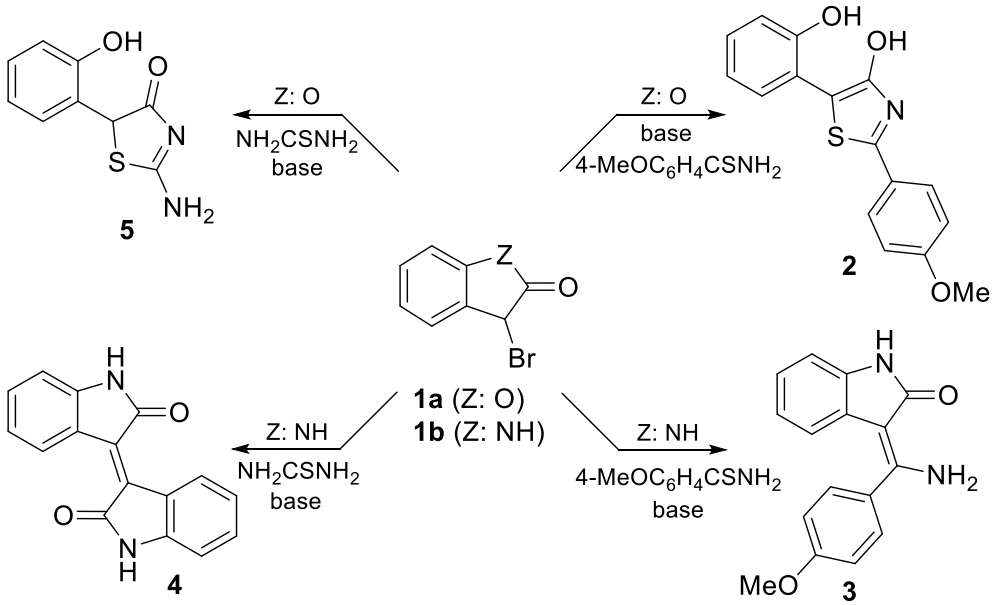
In our previous works we extensively studied the ability of butyrolactam[1] and butyrolactone[2] ring containing a substituted or an unsubstituted isothiuronium side chain in the α-position to undergo ring transformation reactions. In all cases the corresponding substituted 1,3-thiazolidin-4-ones were formed exclusively under mild conditions in aqueous buffer solutions.

In present the reactions of 3-bromo-1,3-dihydro-2*H*-indol-2-one (**1b**) with 4-methoxythiobenzamide and thiourea under mildly basic conditions is studied. While analogous 3-bromo-1-benzofuran-2(3*H*)-one (**1a**) gave the expected 5-(2-hydroxyphenyl)-2-(4-methoxyphenyl)-1,3-thiazol-4-ol (**2**) or 2-amino-5-(2-hydroxyphenyl)-1,3-thiazol-4(5H)-one (**5**) the lactam **1b** reacted with thioamide *via* an unexpected Eschenmoser coupling reaction to give (3*Z*)-3-[amino(4-methoxyphenyl)-methylidene]-1,3-dihydro-2*H*-indol-2-one (**3**). When lactam **1b** is treated with thiourea, isoindigo (**4**) is the only isolated product. The reaction mechanisms, involving formation of α-thioiminium or isothiouronium salts and their base-catalyzed decomposition is also proposed.[3]



It is worth mentioning that product **3** has previously been synthesized using a different synthetic approach showed significant kinase inhibitor activity[4] (IC_{50} = $3.1 \cdot 10^{-6}$). The Eschenmoser coupling reaction of lactam **1b** and its analogs therefore represents a suitable alternative to the existing synthetic approaches.

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NEW APPROACH TO MACROCYCLIC DERIVATIVES WITH SUCROSE SCAFFOLD

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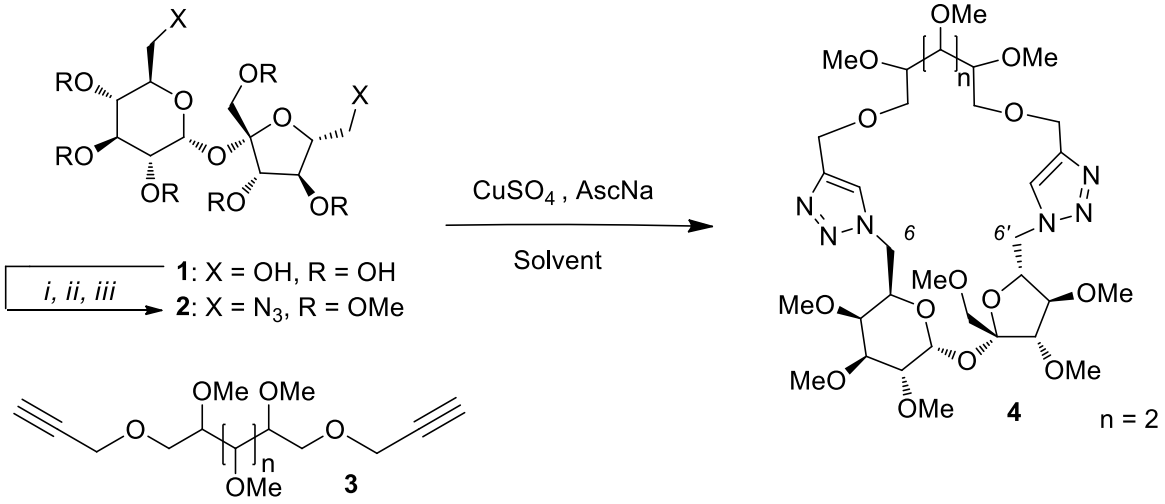
Supramolecular chemistry[1] is very attractive research field, because of the interdisciplinary topics (biochemistry, biology) which deals with the non-covalent 'host – guest' interactions. Although this field is already quite well explored, the search for new classes of macrocycles receptors, being able to distinguish the individual enantiomers of the guest molecules, is still continued.

In our group in the IOC PAS, the search of new class of chiral receptors: crown and aza-crown ether analogues with sucrose scaffold is pursued.[2,3] Several such receptors display interesting complexing properties were already prepared.[2,4] To broaden this field we are now exploring the possibility of the synthesis of sucrose-based receptors in which the terminal positions (C6 and C6') are connected via a long polyhydroxylated carbon linker. Model synthesis of such macrocycle (**4**) was accomplished by reaction of modified sucrose (**2**) with di-acetylene **3** under the 'click' conditions.



i. Ph_3P, CCl_4, Py, 60°C; *ii.* TBAB, CH_3I, KOH, DMF, rt; *iii.* NaN_3, DMF, 120°C

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SYNTHESIS OF NOVEL MACROCYCLIC DERIVATIVES WITH SUCROSE SCAFFOLD

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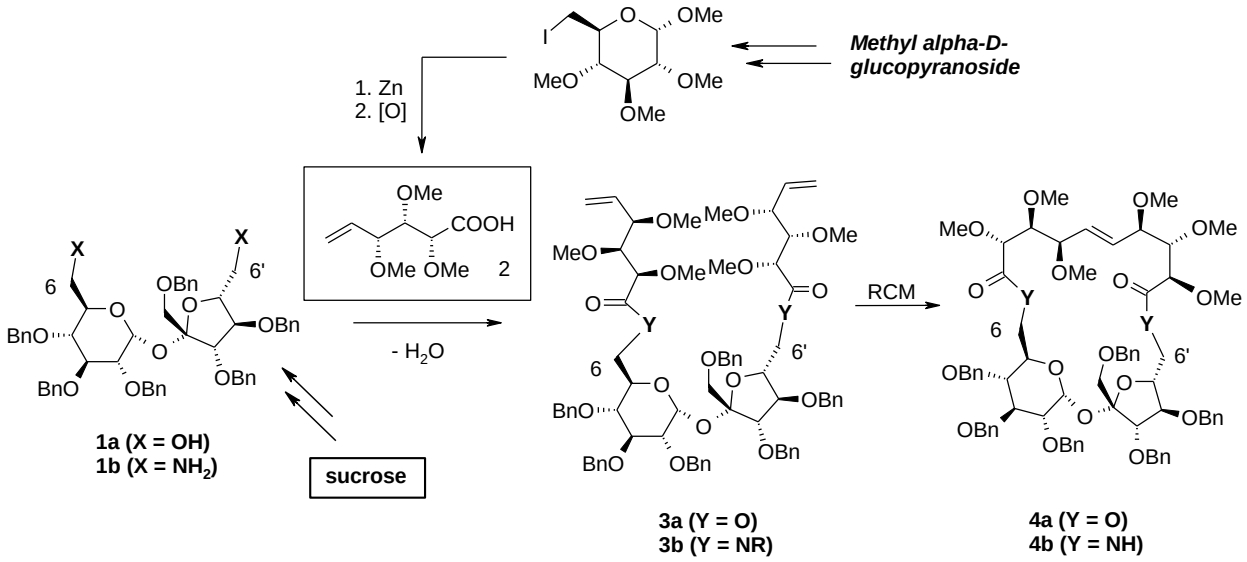
Chiral macrocyclic compounds, because of their wide application in enantioselective recognition, are important targets in organic synthesis.[1] We have proposed several approaches enabling efficient synthesis of sucrose-based macrocycles.[2,3] Encouraged by their promising cation-binding properties, we have designed preparation of novel macrocyclic derivatives of type **4**. This was realized by connection of the terminal positions [C-6 (glucose) and C-6' (fructose)] in known[4] hexa-*O*-benzylsucrose **1a** or 6,6'-diamino-6,6'-dideoxy-hexa-*O*-benzylsucrose **1b** with suitably modified simple sugars. The desired macrocyclic framework was obtained by a ring-closing metathesis of either **1a** or **1b**, which provided olefin **4a** or **4b** as a single isomer with the *E*-geometry across the double bond.



Acknowledgments: The support from Grant of National Science Centre UMO-2012/05/B/ST5/00377 is gratefully acknowledged.

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BOIMPYs – NEW MEMBERS APPROACHING THE BODIPY FAMILY

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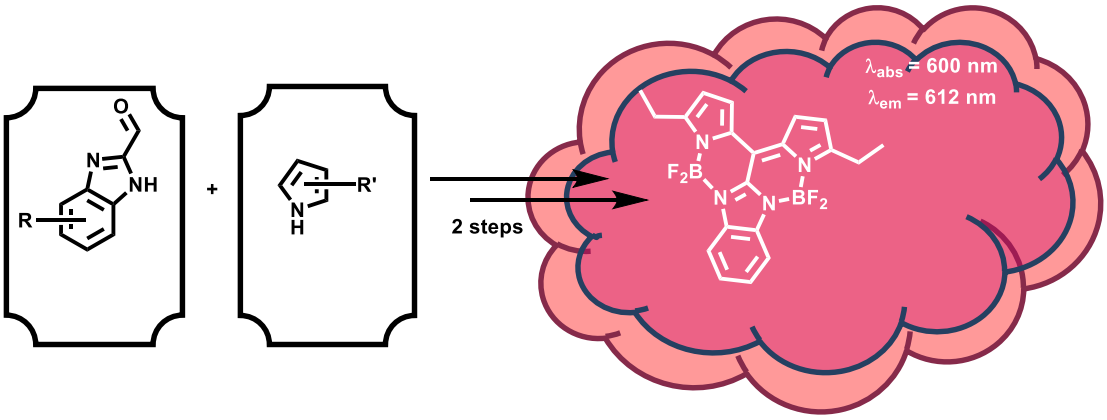
BODIPYs developed into a versatile family of reliable fluorophores occupying wide fields of biological, biochemical and biophysical research areas.[1,2] Their advantageous features are well-known: great photostability, high, solvent independent quantum yields, long wavelength absorption and easy preparation; further developments embark e.g. on improving water solubility[3], channeling the absorbed energy in others ways[4], assembling specific indicators[5], but quite generally, on accessing the less energetic NIR region. In the 90s the latter feature led to the revival of aza-dipyrromethenes as precursors for so called aza-BODIPYs, which captivate due to bathochromic shifts in their absorption properties.[6]
Herein another class of fluorophores was designed to combine even longer wavelength absorptions and short preparation times by equally exploiting the crucial *meso*-position of the native BODIPY core. Bearing a benzimidazole moiety as the central bridging ligand, the name “BOIMPY” appears as an appropriate, catchy term for distinction.
The route to this novel fluorophores is straightforward and relies on the faithful condensation between pyrroles and aldehydes followed by an oxidation-coordination step to furnish BOIMPYs in good yields by a two-step protocol. The substitution patterns can be diverse; the bathochromic advance of approx. 90 nm in comparison to usual BODIPYs can contribute to a facile preparation of NIR-fluorophores.



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SYNTHESIS OF ENANTIOENRICHED 1,2-*TRANS*-DIAMINES USING THE BORONO-MANNICH REACTION WITH *N*-PROTECTED ALPHA-AMINO ALDEHYDES

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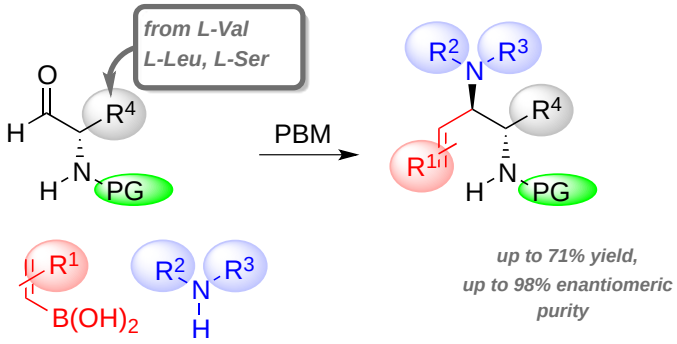
The Petasis borono-Mannich (PBM) process is a powerful method involving the condensation of an aryl or a vinylic boronic acid with an amine and a carbonyl compound.[1] This reaction constitutes one of the most direct and mild methods for preparing geometrically pure allylamines. Usually, the Petasis reaction relies on the presence of a hydroxyl or a carboxylic acid group proximate to the reacting carbonyl group. This allows the activation of the organoboronic acid as an "ate" complex followed by an intramolecular organyl ligand transfer to a transient iminium species.[2] By taking advantage of the directing effect of the α-hydroxyl group of chiral aldehydes,[3] this reaction leads to the corresponding enantiopure □-amino alcohols with an exclusive *anti* diastereoselectivity. The obtained motif β-amino alcohols has been widely utilized as a key step in the synthesis of many bioactive molecules and complex natural products such as polyfunctionalized pyrrolidines, iminosugars, conduramines, *N*-acetylneuraminic acid, or anti-influenza agents. We report here the direct use of *N*-protected α-amino aldehydes as substrates for the Petasis reaction to produce enantioenriched 1,2-diamines with a pure *trans* selectivity (scheme 1). This class of aldehydes is particularly challenging since it is known to be unstable and prone to racemization.



Scheme 1

References:

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THE QUEST OF CONFIGURATIONALLY STABLE CHIRAL ALLYL ZINC COMPOUNDS

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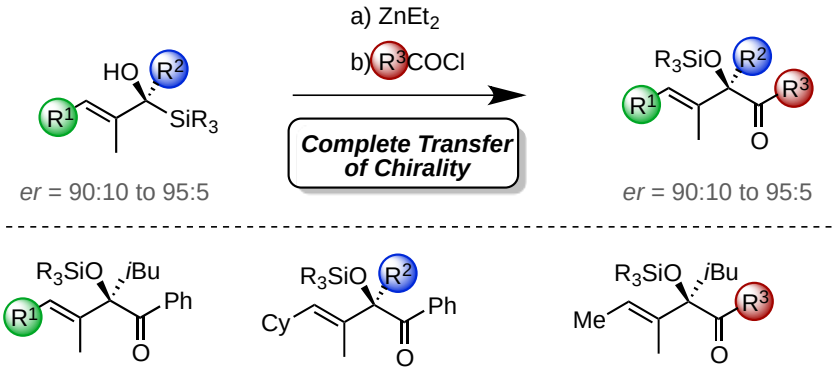
Organometallic species bearing a stereogenic carbon center attached to the metal depict an important class of chiral intermediates. After reaction with different organic electrophiles, a variety of chiral products can be obtained. In this context the preparation of chiral organolithium reagents has been an active research field and led to configurationally stable organometallic compounds, which proved to be of great utility in organic synthesis. The absence of a heteroatom at the α- position led to configurationally unstable organolithium compounds. It is anticipated that organometallic compounds bearing a more covalent carbon-metal bond, such as carbon-zinc bonds, should be configurationally more stable.[1]

Our approach makes use of an unprecedented type of "Allyl Zinc Brook Rearrangement"[2] and subsequent electrophilic trapping of the allyl zinc intermediate. Therefore chiral tertiary allyl alcohols were prepared via an asymmetric copper catalyzed 1,2-addition of Grignard reagents to a variety of acyl silanes.[3] Two major questions arise in the course of this project: 1) Would be the newly formed allyl zinc species configurationally stable? and 2) Would a transfer of chirality occur whilst electrophilic trapping?



R^1 = Me (85%)
R^1 = *i*Pr (80%)
R^1 = Cy (70%)

R^2 = Et (97%)
R^2 = Bu (86%)
R^2 = C_2H_4Ph (82%)
R^2 = $C_3H_6CHCH_2$ (94%)

R^3 = 2-thiophenyl (81%)
R^3 = 4-CF_3-Ph (71%)
R^3 = Naph (74%)
R^3 = OMe (65%)

All reactions provided the corresponding chiral hydroxyketones in high yields and complete transfer of chirality (>99%). Electron rich as well as aliphatic acyl chlorides furnished only poor yields (< 20%) and unclean crude mixtures. In addition to acyl chlorides also methyl chloroformate could successfully be converted into the respective ester (65%), which opens the route to a broader variety of substrates. Further electrophiles as well as mechanistic studies are under current investigation.

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CHIRAL MODULAR CATALYSTS BEARING PYRIDINES AND PHENANTHROLINES. SYNTHESIS AND APPLICATION IN ENANTIOSELECTIVE REACTIONS

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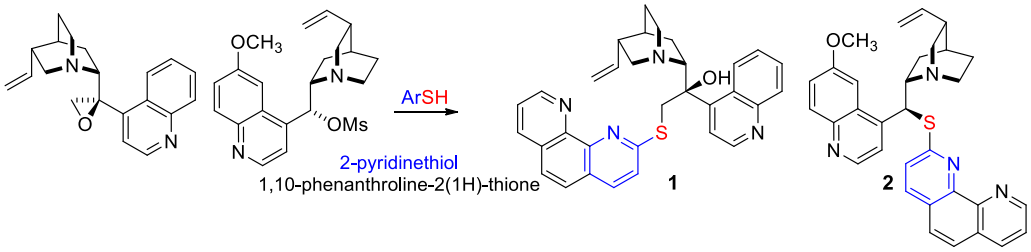
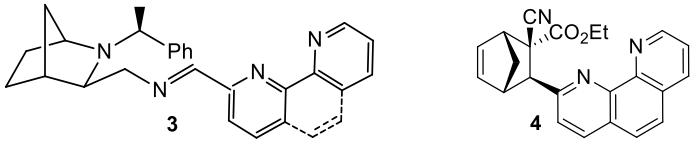
Many enantioselective reactions are simultaneously facilitated by a nucleophile/Brønsted base and a Lewis acid. Thus, an effective catalyst should have both functionalities properly located within its structure. Based on this idea, in order to create an additional Lewis acid center, we introduced to various chiral motifs the complexing moieties of pyridine and 1,10-phenanthroline.

As a first chiral scaffold we adopted *Cinchona* alkaloids, itself being privileged catalysts.[1] We have recently reported diastereoselective Corey-Chaykovsky 9-epoxymethylation of *Cinchona* alkaloid 9-ketones.[2] The regio- and stereoselective ring opening of the epoxide resulted in the simple synthesis of the respective modular catalysts, such as **1**.[3] We developed the synthesis of new C9 sulfur-containing *Cinchona* derivatives **2** with the pyridine and phenanthroline moieties.[3]



Another class of chiral frameworks constituted chiral 2-azanorborn-3-yl derivatives. Also these compounds were conjugated to the respective metal-complexing fragments (**3**).



Furthermore, a series of the Diels-Alder reaction products with the metal complexing moieties (pyridine or 1,10-phenanthroline) was obtained. These rigid chiral compounds (e.g. **4**) were deracemized and examined directly as the modular parts of chiral catalysts.

The effectiveness of the devised modular catalysts in the model Cu-catalyzed Henry, Zn-catalyzed aldol, and Pd-catalyzed Tsuji-Trost reactions was examined and the outcomes will be discussed.

Acknowledgement: This project was funded by the National Science Centre, Cracow, Poland (Grant DEC-2013/09/B/ST5/03410)

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THIENO-FUSED HETEROCYCLES VIA THERMOLYSIS OF 1-(THIOPHEN-2-YL)-1*H*-TETRAZOLES

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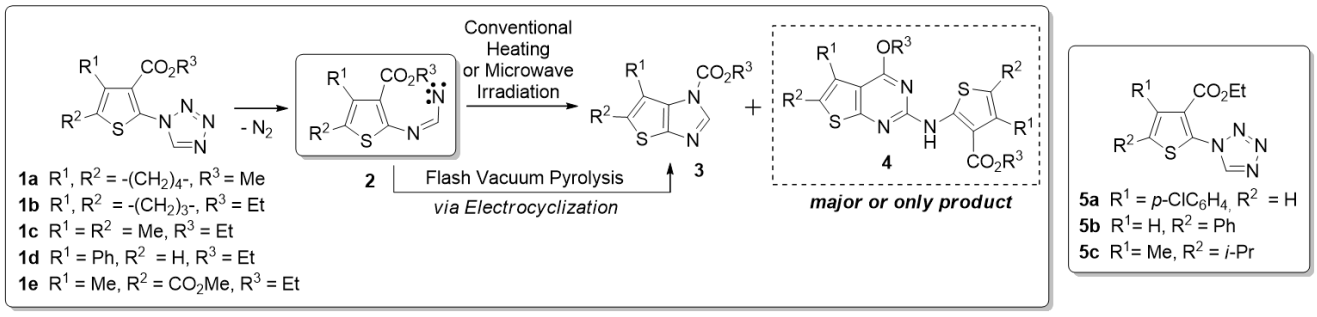
Tetrazoles are important and versatile building blocks in synthetic chemistry.[1-3] Among their reactions, the thermal ones represent an important example of the synthetic utility of these nitrogen heterocycles.[4] Currently we are interested in exploring thermal reactions of monosubstituted 1-heteroaryl-1*H*-tetrazoles as a route to thieno[2,3-*d*]pyrimidines and thieno[2,3-*d*]imidazoles. Recently, we reported the first results on the thermal reactivity of 1-(thiophene-2-yl)-1*H*-tetrazoles.[5] The solution thermolysis of 1-(thiophene-2-yl)-1*H*-tetrazoles **1** under conventional heating and microwave irradiation afforded the unexpected new thieno[2,3-*d*]pyrimidines **4** incorporating two thiophene rings which were obtained as major or only product. The synthesis of these heterocycles was rationalized considering the initial nitrogen elimination to generate imidoylnitrene **2** followed by rearrangement to the corresponding carbodiimide and subsequent cyclization triggered by the nucleophilic attack of the in situ generated 2-aminothiophene. Under flash vacuum pyrolysis or solution thermolysis 1-(thiophene-2-yl)-1*H*-tetrazoles **1** also gave thieno[2,3-*d*]imidazoles **3** via formal insertion into a C-C bond of the corresponding imidoylnitrene intermediate.

Thieno[2,3-*d*]pyrimidines are an important class of compounds in Medicinal Chemistry characterized by a broad spectrum of biological activities, including antibacterial, antiviral and antitumoral. Due to the interesting potential of this class of compounds, the scope of the thermolysis of 1-(thiophen-2-yl)-1*H*-tetrazoles as an approach to new thieno[2,3-*d*]pyrimidine derivatives was extended to new derivatives (e.g. 1*H*-tetrazoles **5**). Thus, in this communication we report our recent research on the thermal reactions of 1-(thiophen-2-yl)-1*H*-tetrazoles. Preliminary results of the biological evaluation of thieno[2,3-*d*]pyrimidines **4** as antitumoral agents will also be presented.



Scheme 1. Thermolysis of 1-(thiophen-2-yl)-1*H*-tetrazoles.

Acknowledgments: Thanks are due to B.Sc. student Juliane S. Rocha for carrying out some of the experimental work and FCT (Centro de Química de Coimbra through the project UID/QUI/00313/2013 and CEMDRX through the project PEst-C/FIS/UI0036/2014) for financial support.

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COMBINATION OF THE S_N^H REACTION, SUZUKI CROSS-COUPLING AND PHOTOCYCLIZATION AS A VERSATILE STRATEGY FOR CONSTRUCTION OF NEW POLYCYCLIC SYSTEMS ON THE BASIS OF THE PYRIMIDINE SCAFFOLD

Ekaterina M. Cheprakova,[a,b] Egor V. Verbitskiy,[a,b]* Gennady L. Rusinov,[a,b] Oleg N. Chupakhin,[a,b] Valery N. Charushin[a,b]

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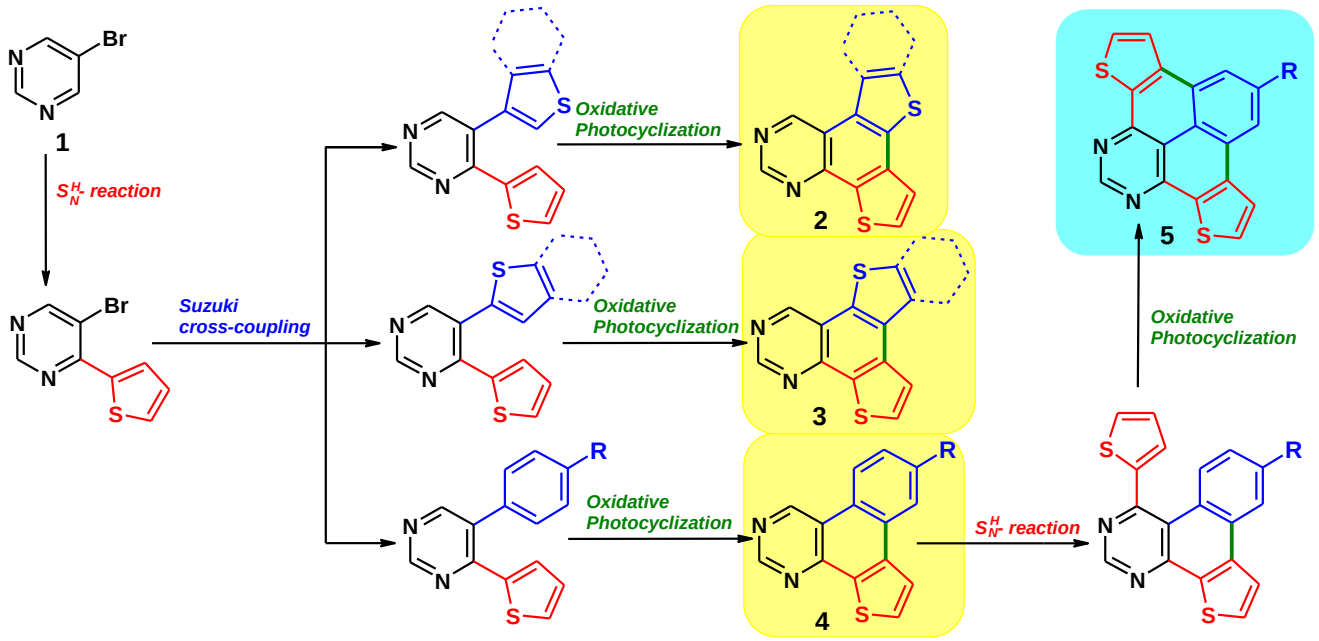
A convenient synthetic route to novel thienoacene **(2** and **3)** systems, 5-R-1-thia-9,11-diaza-cyclopenta[*l*]phenanthrenes **(4)** and 8-R-benzo[*g,h*]dithieno[2,3-*e*:3',2'-*j*]perimidines **(5)** bearing the fused pyrimidine ring has been advanced. A commercially available 5-bromopyrimidine **(1)** was used as the starting material to obtain various polycyclic systems through nucleophilic aromatic substitution of hydrogen (the S_N^H reaction), the Suzuki coupling, and oxidative photocyclization. The redox and optical measurements for some new compounds have been performed. The data obtained show usefulness of dithienoquinazoline [1] and azapyrene systems in organic electronic applications.



Acknowledgments: This work was financially supported by the Russian Foundation for Basic Research (research projects No. 13-03-96049-r_ural_a, 13-03-12434 ofi_м2, 14-03-01017-A, 14-03-00479-A and 14-03-31040-mol_a), the Council on Grants at the President of the Russian Federation (Program of State Support for Leading Scientific Schools of the Russian Federation and Young Scientists, Grant MK-3939.2014.3).

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1,2-BIFUNCTIONALIZATION OF ARYNES

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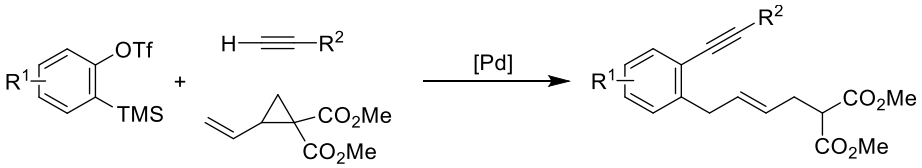
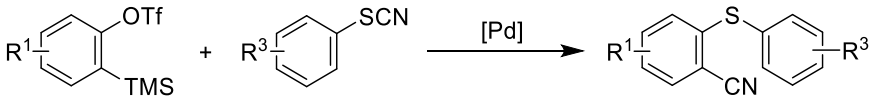
Aryne chemistry has become an important pillar for the facile 1,2-bifunctionalization of arene units in recent years. The aryne precursor 2-trimethylsilylphenyl triflate can be functionalized under mild reaction conditions via cycloaddition reactions or multicomponent reactions.[1]

During our work on aryne chemistry, we discovered a palladium-catalyzed three-component coupling of arynes with terminal alkynes (as nucleophile) and vinyl cyclopropane dicarboxylate (as electrophile). This process represents the first example of aryne chemistry combined with the ring-opening of vinyl cyclopropanes (Scheme 1).[2]



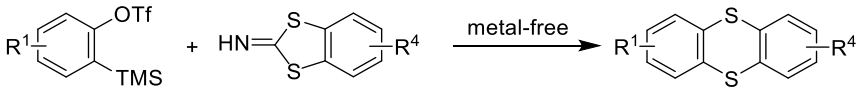
Scheme 1. Palladium-catalyzed three-component coupling involving arynes.

Another palladium-catalyzed reaction dealing with arynes allows the activation of carbon-sulfur bonds of aryl thiocyanates to generate new C–S_{Ar} and C–CN bonds in one step. The aryne mediated S–CN bond cleavage of thiocyanates provides a straightforward access to 1,2-thiobenzonitriles (Scheme 2).[3]



Scheme 2. Sulfur-carbon bond cleavage of thiocyanates and reaction with arynes.

Moreover, we developed a broadly applicable transition metal-free methodology for the synthesis of thianthrene scaffolds. For this purpose, readily available amphiphilic dithioloimines containing one negatively and one positively charged sulphur were transformed using aryne chemistry (Scheme 3).[4]



Scheme 3. Facile metal free access to thianthrenes.

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SUBSITUTED PERYLENEIMIDE ACIDS: REGIOSELECTIVE SYNTHESIS AND PROPERTIES

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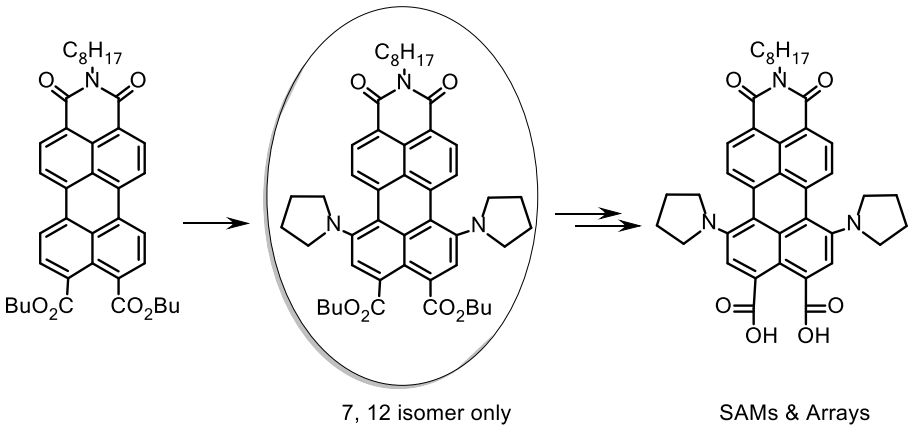
Perylene dyes are one of the most versatile and robust chromophores known to be thermally and photophysically stable. The functionalization of the perylene core at *peri*-, *bay*- and *ortho*-positions greatly influences the solubility, electronic and morphological properties of the dyes.[1-2] The current work presents a way towards highly regioselective synthesis of perylenemonoimide anhydrides and dicarboxylic acids where isomerically pure 7-pyrrolidinyl or 7, 12-dipyrrolidinyl derivatives are synthesized in satisfactory to good yields. The amination proceeds through a radical anion mechanism and can be tuned at will to obtain either mono or bis-substitued perylenes.[3] The synthesized PMI diesters were then converted into PMI dicarboxylic acids via a ring closing-opening strategy in good to excellent yields.[4]



Scheme 1. Regioselective synthesis of PMI acids

The electrochemical and photo physical properties of these compounds were studied both experimentally and computationally in detail and self-assembling monolayers (SAMs) were prepared over ZnO films and TiO2 nanoparticles. The results of the studies suggest that these compounds can be good candidates for their potential use as sensitizers in DSSCs and related applications.

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THE SYNTHESIS AND OPTICAL PROPERTIES OF POLYCYCLIC IMIDAZO[1,2-*a*]PYRIDINE ANALOGUES

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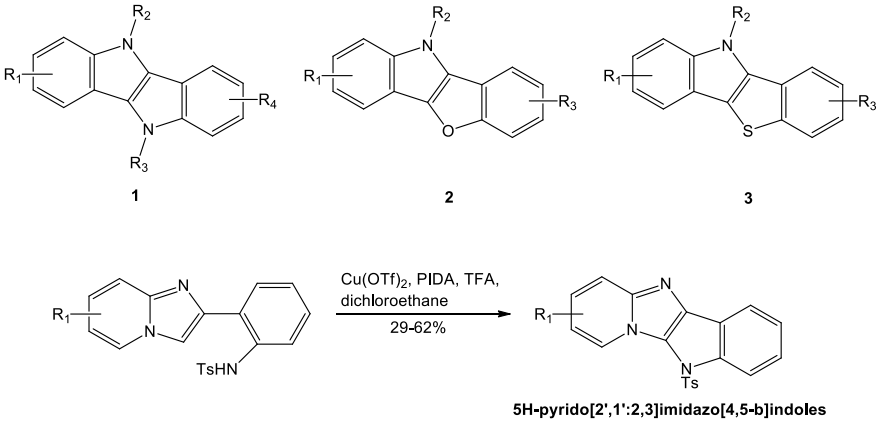
Imidazo[1,2-*a*]pyridines are a group of very important heterocycles possessing strong and diverse biological activity. Their structural motif can be found in several marketed drugs, such as anxiolytic alpidem, necopidem and saripidem and in drugs used for the treatment of insomnia and brain disorders (zolpidem). Their antiviral, antiparasitic, antibacterial, anti-inflammatory, analgesic and antipyretic properties are also well documented, as well as the ability to inhibit β-amyloid formation. Besides the pharmacological importance, imidazo[1,2-*a*]pyridines exhibit interesting optical properties. Not surprisingly, methodology of their synthesis has attracted significant attention in the last decade.

In the advent of interest in ladder type aromatic heterocycles, we reasoned that π-expanded imidazo[1,2-*a*]pyridines being analogues of recently explored systems such as indolo[3,2-*b*]indoles, can offer new opportunities once the efficient synthetic methodology is developed. Indolo[3,2-*b*]indoles (**1**), benzofuroindoles (**2**) and benzothioindoles (**3**) were recently reported as highly active sex steroid hormone receptor modulators and anticancer agents and were also investigated in optoelectronics. Only three synthetic methodologies leading to our targeted 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles were reported: Cadogan cyclization,[1] multicomponent Bienaymé reaction followed by *N*-arylation[2,3] and ionic liquid promoted cyclization of *N*-methylisatin and 2-aminopyridine.[4] The synthesis of the library of pyridoimidazoindoles and the analysis of the relationship between their structure and spectroscopic properties might open a door for their future optoelectronic applications.

Herein, we propose novel strategy towards this class of nitrogen containing heterocycles, with key step involving oxidative C-H bond amination of easily available 2-(2-aminophenyl)imidazo[1,2-*a*]pyridines by the use of copper (II) triflate, trifluoroacetic acid and (diacetoxyiodo)benzene. The obtained library of π-expanded imidazo[1,2-*a*]pyridines was for the first time fully characterized spectroscopically. Prepared compounds strongly absorb UV light exhibit fluorescence in the 415 – 461 nm region.[5]



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SYNTHESIS OF LUPANE SAPONINS FROM ACETYLATED GLYCOSYL DONORS

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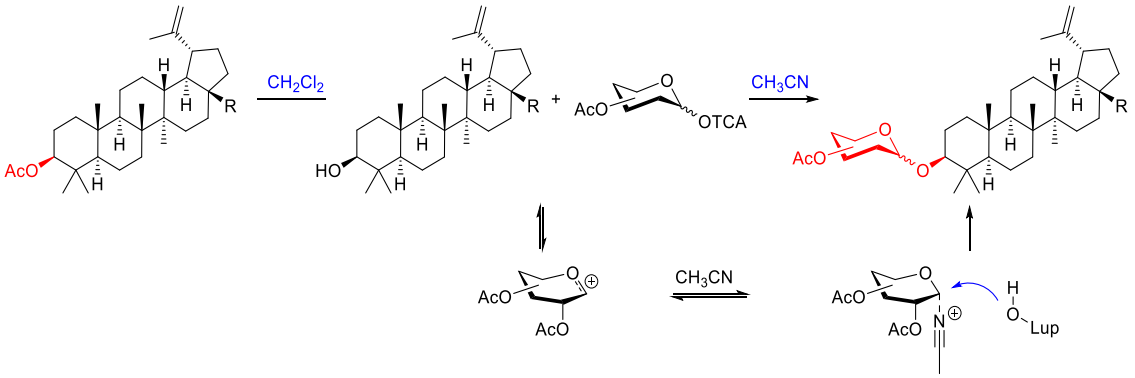
Acetylated Schmidt donors are cheap and versatile starting materials for the synthesis of glycoside bond. Acetyl migration from donor to acceptor molecules is, however, usually observed during their reaction with lupane-type triterpenes as shown in sheme below.[1,2] As a result, acetylated triterpenes are isolated as main, and sometimes only products instead of the expected glycosides. We found that in the presence of acetonitrile, reaction of acetylated Schmidt donors with lupanes affords the required saponins in high yield. In this communication, we will present detailed results on the use of peracetylated Schmidt donors in the synthesis of lupane saponins.[3]



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INVESTIGATION OF PROMOTOR SYSTEMS FOR EFFICIENT ACTIVATION OF GLYCOSYL HALIDES

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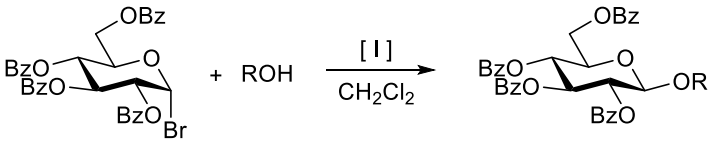
New efficient procedures for activation of glycosyl halides are in high demand. The Koenigs-Knorr reaction has been the paramount coupling reaction between saccharides for more than a century.1 However in this and related procedures glycosyl halides are generally activated by toxic and expensive metals salts, which most commonly contain silver or mercury.2 As a result, we envisioned to use inexpensive halogen electrophiles as promotors.

Here a protocol for efficient activation of highly disarmed glycosyl bromides using an iodine source for activation is described as an alternative to the metal salts commonly used in the Koenigs Knorr glycosylation. The disarmed donor used in all initial investigations is 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide, since it is stable and easy to handle. We have been able to successfully glycosylate different monosaccharide acceptors using the protocol developed in good yield and reasonable reaction times.



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COHERENT-SYNCHRONIZED OXIDATION OF PYRIDINE WITH NITROUS OXIDE TO 2,2- AND 2,3-DIPYRIDYL

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In the present work, we report the results of the coherent-synchronized oxidation experiments of pyridine with nitrous oxide to 2,2- and 2,3-dipyridyl.The reaction was performed in the flow quartz reactor of according methods in [1-3], construction of which ensured the entry of nitrous oxide vapors into zone by a quartz tube, separately from pyridine. By another quartz tube preliminarily heated pyridine in a gaseous state is feeded. The volume of the reaction zone made up 5.5 cm^3. The reaction products were analyzed chromatographically. The qualitative determination of the reaction products composition was performed by chromatomass-spectroscopic method: Agilent Technologies (Germany).

Coherent-synchronous oxidation of pyridine with nitrous oxide was studied in a wide range of process parameters: pyridine feed rate - 0,948 ml/h -1,896 ml/h, nitrous oxide feed rate 250 –750 ml/h. The reaction was carried out at various temperatures between 530 and 600^0C.
The reaction is carried out in the temperature range 530-600^0C. Experimental studies have shown that the oxidation reaction of pyridine with nitrous oxide proceeds to form 2,2- dipyridyl and 2,3-dipyridyl. Small amounts were detected 2.2': 6'.2" terpiridil to 4.6 wt.%, 2.2- oxidipyridyl to 2.09 wt.%. As a positive factor it should be noted that observed stable formation of 2,2-dipyridyl and 2,3-dipyridyl in all experiments.

As result of our studies, it was found that coherent-synchronized oxidation of pyridine with nitrous oxide leads mainly to the formation of 2,2-dipyridyl and 2,3-dipyridyl in a yield of 21.4 wt.% and 22.9 wt.%, respectively.

Experimental investigation was carried out with a view to of establishing the kinetic laws of the process of the homogeneous process of pyridine with nitrous oxide.

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EFFICIENT TOOL FOR ORGANIC REACTIONS: PREPARATION OF BUILDING BLOCKS

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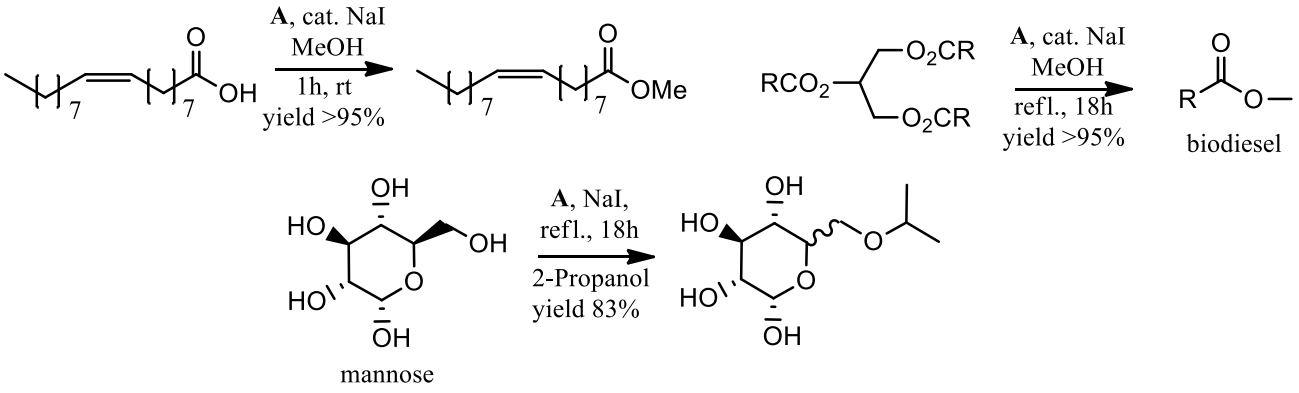
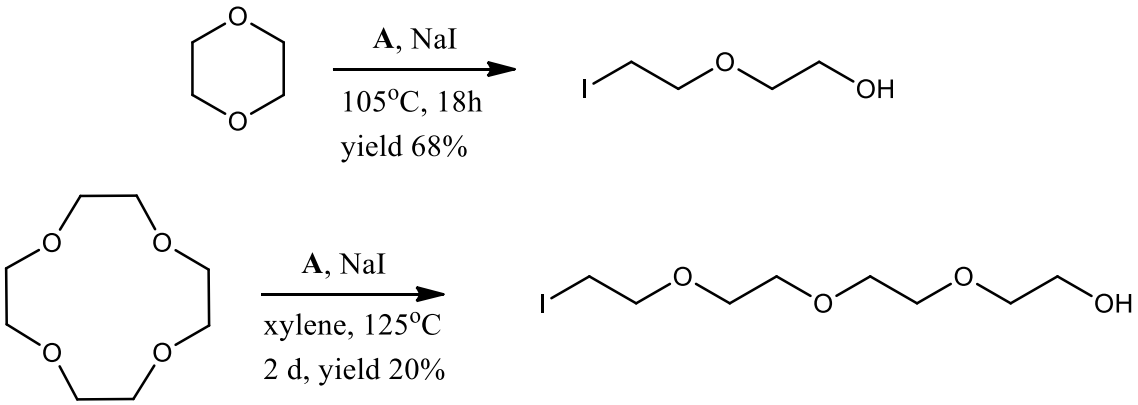
We have recently reported a powerful tool to perform organic addition and substitution reactions.[1] The reported tool enables e.g. effective esterifications under very mild conditions, transesterification of used cooking oil to produce biodiesel and selective substitution of primary HO-group over secondary HO-groups in sugar (mannose) without any protection steps. The tool is based on the use of dried Dowex® (**A**) and NaI.[1]



The reported tool also enables to prepare highly interesting building blocks for e.g. medicinal chemistry purposes. Polyethylene units with variable chain lengths are highly important linkers to optimize e.g. physicochemical properties of drug molecules.[2,3] Here we describe some examples to prepare haloalkanols from cyclic ethers, like 1,4-dioxane or even 12-Crown-4 ether.



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DIRECT STEREOSELECTIVE SYNTHESIS OF ENANTIOMERICALLY PURE *ANTI-β*-AMINO ALCOHOLS

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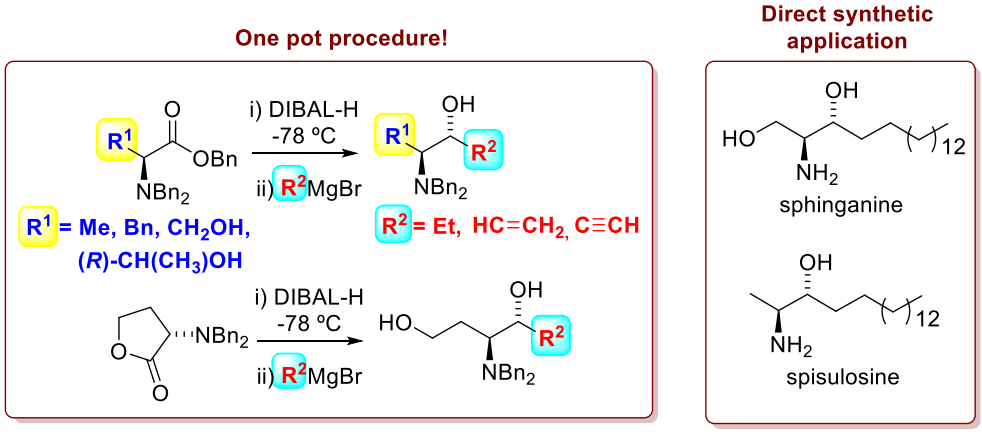
β-Amino alcohols have received much attention in the scientific community due to they can be used as chiral ligands in asymmetric synthesis, as chiral synthons in the synthesis of natural products, as well as in the synthesis of molecules with biological interest. An important class of amino alcohols are the sphingolipids (SLs) represented by sphinganine, which show an *anti*-2*S*-3*R* configuration (Scheme 1). Another relevant group of long-chain amino alcohols are the 1-deoxySLs such us spisulosine (Scheme 1). It was initially a promising antiproliferative agent against diverse human tumor cell lines. However clinical studies were discontinued in phase I. In the literature, there are many SLs reported with antiproliferative activity, and the number is still growing.

Due to, the SLs are associated with bioactive properties, and as part of our interest in the synthesis of nitrogen-containing bioactive molecules. The aim of this work was to develop a more versatile and efficient *one-pot* methodology for the synthesis of functionalized *anti*-β-amino alcohols based on the in situ DIBAL-H reduction of α-(*N,N*-dibenzylamino)benzyl esters to their corresponding aldehyde, followed by the sequential addition of commercially available Grignard reagent. In order to obtain new SLs analogues and test their antiproliferative activity. To demonstrate the versatility of this methodology spisulosine and sphinganine were synthetized in two steps from α-(*N,N*-dibenzylamino)benzyl esters of alanine.[1]



Scheme 1. Scope of *one pot* procedure and synthetic application of natural products.

Aknowledgments: Co-financed by the EU Research Potential (FP7-REGPOT-2012-CT2012-31637-IMBRAIN), the European Regional Development Fund (FEDER), the Spanish MINECO (CTQ2011-28417-C02-01 and Instituto de Salud Carlos III PI11/00840). G.S.-D. thanks the EU Social Fund (FSE) and the Canary Islands ACIISI for a predoctoral grant and the funding granted to Universidad de la Laguna.

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V-SHAPED BIS-COUMARINS: SYNTHESIS AND OPTICAL PROPERTIES

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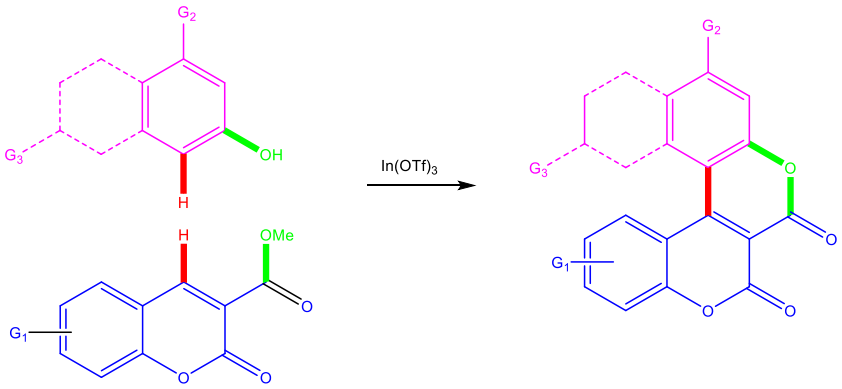
Regardless of the presence in nature and well-documented biological activity, growing interest in the synthesis of new coumarins has mainly been driven by their applications. As a result of strong light absorption, high fluorescence quantum yields, and large Stokes shifts, they have been widely investigated as optical brighteners, fluorescent probes, emitter layers in organic light emitting diodes (OLEDs), *etc*.[1]

Coumarins fused with other aromatic units have recently emerged as a hot topic of research. Their synthesis is partly based on the classical methodologies such as Pechmann reaction or Knoevenagel condensation, but it also sparked the discovery of completely new pathways.[2]

Herein we would like to present the highly efficient procedure for the synthesis of bis-coumarins fused at the pyranone ring. The electron-rich phenols reacted with esters of coumarin-3-carboxylic acids, afforded substituted chromeno[3,4-c]chromene-6,7-diones in the good yields. The reaction is compatible with various functionalities such as NO2, Br, and OMe. Not only benzene derivatives but also dihydroxynaphthalenes are reactive in this reaction. Moreover, the structure of the product can be controlled by adjusting the reaction conditions. Furthermore, a double addition is possible, leading to a horseshoe-shaped system comprised of seven conjugated rings. Compounds with four structurally unique skeletons have been obtained and have been shown to strongly absorb in the violet, blue, and/or green regions of the visible spectrum. Most of them display strong greenish-yellow fluorescence, which can be modulated by both structural changes and the character of the solvents. Again, introduction of an electron-donating group in the chromeno[3,4-c]chromene-6,7-diones caused a significant red shift in both the absorption and emission maxima, and the effect became especially noteworthy in the case of amino substituents.

The broad study consisting of synthetic aspects as well as optical properties of the products will be presented.



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3-METHYLENE-2,4-CHROMANDIONE *IN SITU* TRAPPING

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The reactivity of *ortho*-quinone methides (*o*-QMs) has been exploited in natural product synthesis, total synthesis, medicinal chemistry and biochemistry. The high reactivity of this structural intermediate makes it attractive, in particular for multi-component reactions (MCR).[1] Quinone methides have been hardly ever isolated, due to reactions favored by rearomatization into phenol, acting as the driving force (Figure 1a).

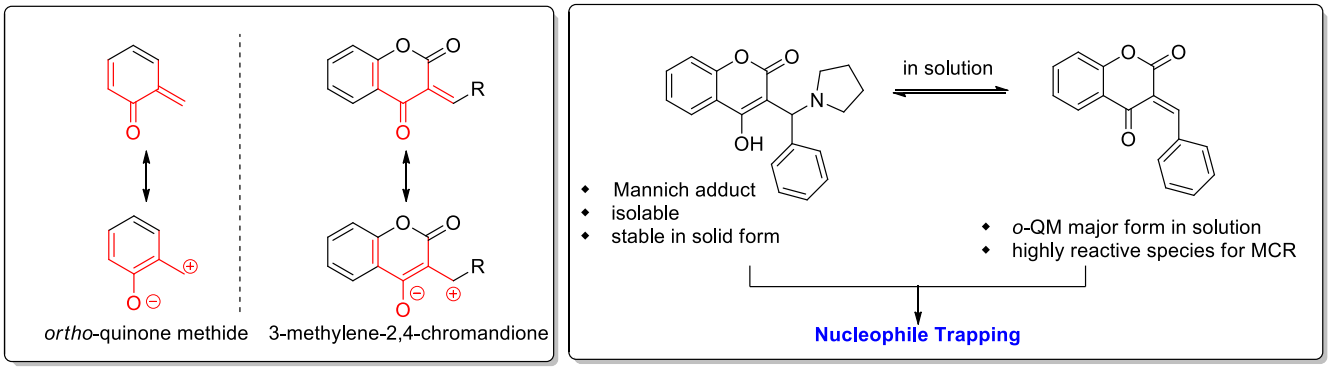

Figure 1. a) Structural analogy with 4-hydroxycoumarin skeleton; b) Equilibrium between Mannich adducts and 3-methylene-2,4-chromandione

Recently, our laboratory reported an effective procedure for C-3 reductive alkylation of 4-hydroxycoumarin by a dehydrogenative oxidation of benzylic alcohols in the presence of tris(triphenylphosphine)ruthenium(II) dichloride (5 mol%), KOH (0.2 eq) in ^{tert}amyl alcohol under microwave irradiation at 140°C in 2 hours.[2] Supposed mechanism is described as a first step of activation of the alcoholic substrate by metallo-catalyzed dehydrogenative oxidation, followed by a Knoevenagel condensation / reduction sequence (restitution of hydride or H_2 by the metal depending on its nature). All these steps proceeded under one pot conditions with a single catalytic species. The Knoevenagel adduct (3-methylene-2,4-chromandione) displaying similar structural analogy (Figure 1a) with more classical *o*-quinone methide, is a versatile substrate for MCR.[3] The approach developed in the laboratory is to trap the 3-methylene-2,4-chromandione highly reactive intermediate in a solid-state stable Mannich adduct. In solution, the equilibrium is more favourable for the *o*-QM adduct which upon treatment with various nucleophilic species can react in excellent yields (Figure 1b). This communication aims to describe our recent efforts developed for trapping this intermediate by different nucleophiles (including simple reduction methods).[4]

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NEW FUNCTIONALIZED METHYLENEBISORGANOPHOSPHORUS ACIDS AND THEIR DERIVATIVES AS PERSPECTIVE LIGANDS AND BIOACTIVE SUBSTANCES

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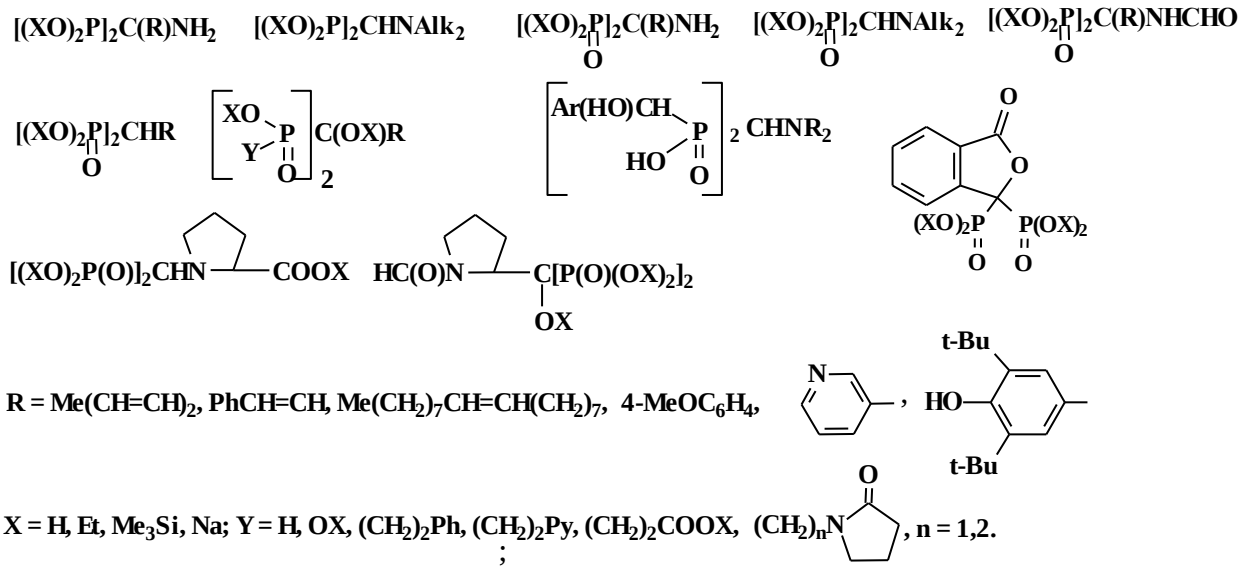
Functionalized methylenebisorganophosphorus acids and their derivatives are of great interest as effective chelating ligands and perspective bioactive substances with various properties. These acids are well-known analogs of hydroxy or amino carboxylic acids and natural pyrophosphates. We have developed the organosilicon-based synthesis of new functionalized bisorganophosphorus acids and their derivatives including heterocyclic, aromatic and unsaturated fragments as well as hydroxyl, amino, and carboxyl groups using as starting compounds the trimethylsilyl esters of several trivalent phosphorus acids and functionalized alkenes, aldehydes, imines, and various derivatives of carboxylic acids.[1] The obtained trimethylsilyl esters of bisorganophosphorus acids easily react with methanol or sodium methylate in methanol yielding the new water soluble bisorganophosphorus acids or their salts which are presented here.



The obtained functionalized methylenebisorganophosphorus acids with various unsaturated, aromatic and heterocyclic fragments containing hydroxyl, amino or amido groups are promising polydentate ligands and organophosphorus biomimetics of natural pyrophosphates and hydroxy or amino acids as well as effective antioxidants and cytoprotectors with the multifactor activity.[2]

Acknowledgements: This work was supported by Russian Foundation for Basic Researches, grants 14-03-00001 and 15-03-00002.

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SYNTHESIS OF HIGHLY FUNCTIONALIZED DECALINS FROM GLUCOSE

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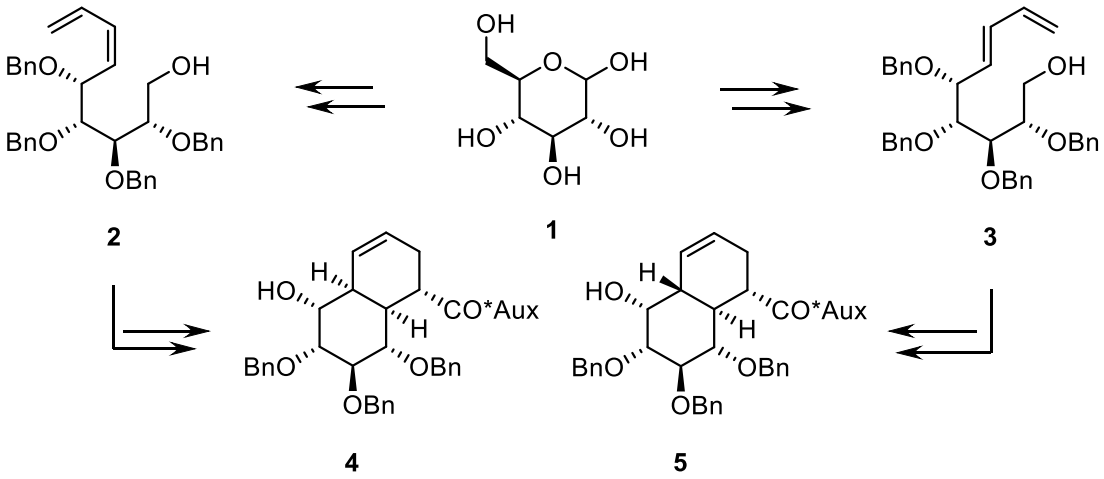
Some of polyhydroxylated bicyclic derivatives can act as inhibitors of glycosidases; in optically pure form such compounds can be conveniently prepared from sugars.[1] The important category of these bicycles is represented by derivatives with a decalin skeleton.[2] Synthesis of this system is relatively underexplored, since most of the reported methods lead to racemic products.

We have proposed a stereoselective route to optically pure, highly functionalized *cis*-decalins *via* the intramolecular Diels-Alder reaction of sugar derived trienes.[3] Configuration at the ring junction is dependent on the configuration across the internal double bond of the precursor; the *E*-diene gives the *cis*-decalin. We reason that the *Z*-isomer should cyclize to *trans*-decalin. Our standard methodology, however, provides only the *E*-dienes.[3]



Now we propose the methodology which allows to obtain dienes with either *E*- or *Z*-configuration across the internal double bond as shown by a transformation of D-glucose (**1**) into dienes **2** and **3**. The key step involves an allyltitanation of the appropriate sugar aldehyde followed by the Petersen elimination of resulting *β*-hydroxysilyl moiety. Such elimination, carried out in acidic medium, provided only the *E*-diene, while elimination induced by base yielded the alternative *Z*-diene.
Dienes **2** and **3** were transformed into trienes by PCC oxidation folowed by Horner–Wadsworth–Emmons olefination. This compounds were subjected to intermolecular Diels-Alder reaction catalyzed by Et_2AlCl providing decalins with high selectivity.

Acknowledgments: The support from Grant: POIG.01.01.02-14-102/09 (part-financed by the European Union within the European Regional Development Fund) and Grant from the National Science Centre UMO-2014/13/N/ST5/00554 are gratefully acknowledged.

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MICROWAVE ASSISTED SYNTHESIS OF LAPACHOL ANALOGUES *VIA* QUINONE METHIDE NUCLEOPHILIC ADDITION

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Quinones methides are reactive intermediates found in many areas of chemistry and biology, being renowned for their polar characteristics and high reactivity.[1] These intermediaries have great relevance in organic synthesis one they are able to react with various nucleophiles of biological interest, like alcohols, thiols,[2] nucleic acids, proteins and phosphodiesters. The aim of this work consists in the synthesis of new analogues of lapachol (**1**) from lawsone (**2**) via *O*-Quinone methides (Figure 1).

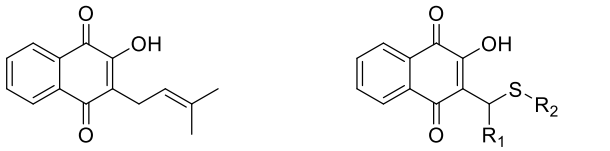
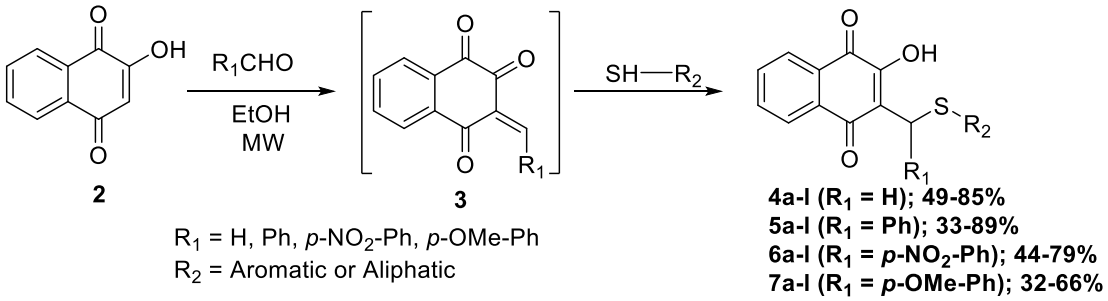


Figure 1. Lapachol (**1**) and analogues

In this methodology, lawsone (**2**) was used as the starting material and, it reacted with different aldehydes via the Knoevenagel condensation, followed by nucleophilic addition of thiols to the *O*-Quinone methide generated *in situ* (Scheme 1).



Scheme 1. Synthesis of lapachol analogues

The reaction studied was performed in EtOH under microwave irradiation (150° C, 20 min.). Applying this protocol, it was possible to prepare 48 new compounds using 12 different thiols as nucleophiles, in moderate to excellent yields (Scheme 1). All reaction products were purified by column chromatography using silica gel and subsequently characterized by conventional spectroscopic techniques.

In summary, in this work we showed that nucleophilic addition in **2** employing thiols proved to be a good alternative for the synthesis lapachol analogues.

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SYNTHESIS AND REACTIVITY OF TRIMETHYL[1,1,2,2-TETRAFLUORO-2-(ARYL)ETHYL]SILANES

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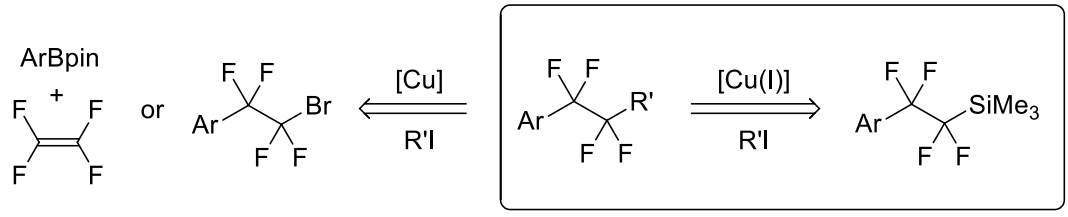
Fluorinated and perfluoroalkylated compounds are of great interest to medicinal chemists and material scientists due to their unique reactivity, stability and bioavailability.[1] The trifluoromethyl group is the most frequently used motif, and trifluoromethylation methodologies have attracted much attention in the last decade.[2] Interestingly, manipulation of the tetrafluoroethyl moiety has been studied less, despite its prevalence in liquid crystals and bioactive targets.[3]

Few methods for the synthesis of bridging tetrafluoroethylene motifs are known. Building-block approaches have been considered, as well as methods relying on the use of highly reactive fluorinating reagents (SbF_4/HF or F_2).[3] Ogoshi and Hu have recently published copper-mediated methodologies, utilizing tetrafluoroethylene or 2-bromo-1,1,2,2-tetrafluoroethyl compounds, respectively, as the source of the tetrafluoroethylene motif.[4]

The Ruppert-Prakash reagent (Me_3SiCF_3) is a powerful and extremely useful reagent for trifluoromethylation.[5] In comparison, its perfluoroalkylated derivatives have been studied less comprehensively. Here, we report the synthesis and reactivity of substituted trimethyl(tetrafluoroethyl)silanes ($ArCF_2CF_2SiMe_3$), a new class of reagents allowing access to a range of disubstituted tetrafluoroethyl compounds.



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DIVERSITY ORIENTED SYNTHESIS OF BIOLOGICALLY ACTIVE IMIDAZOLES

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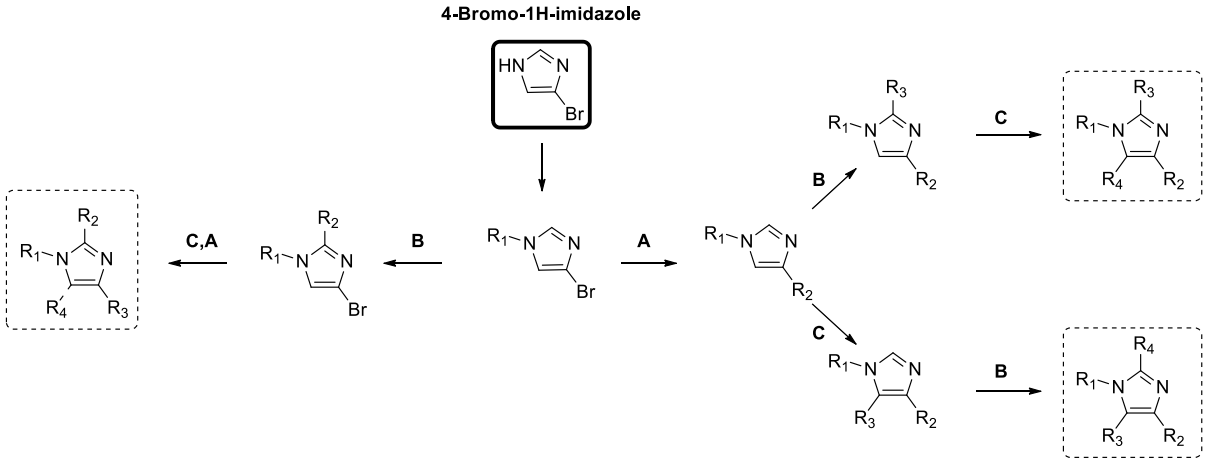
The imidazole scaffold is omnipresent in biological relevant molecules showing a wide range of pharmacological activity.[1] In particularly the 2-aminoimidazole scaffold has attracted increased interest over the last decade due to its emerging biologic activity.[2,3] Several synthetic methodologies towards 2-aminoimidazoles have been reported,[4–7] however the majority of these methods lead to a specific substituent decoration of the 2-aminiomidazole scaffold. Therefore a diversity-oriented approach towards 2-aminoimidazoles and their analogues is desired. This approach should allow late stage modification of different substituent positions depending on the requirements. We have developed a synthesis methodology, presented in Scheme 1, starting from 4-bromo-1H-imidazole based upon 3 set of reactions (A, B and C) which can be performed sequentially to obtain selective functionalization on each position. By altering the order of the reactions the order of functionalization can be controlled and specific late stage modification can be obtained.



Scheme 1. Diversity Oriented Synthesis of Imidazoles.

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REGIOSELECTIVE AMINATION OF PERYLENEIMIDES

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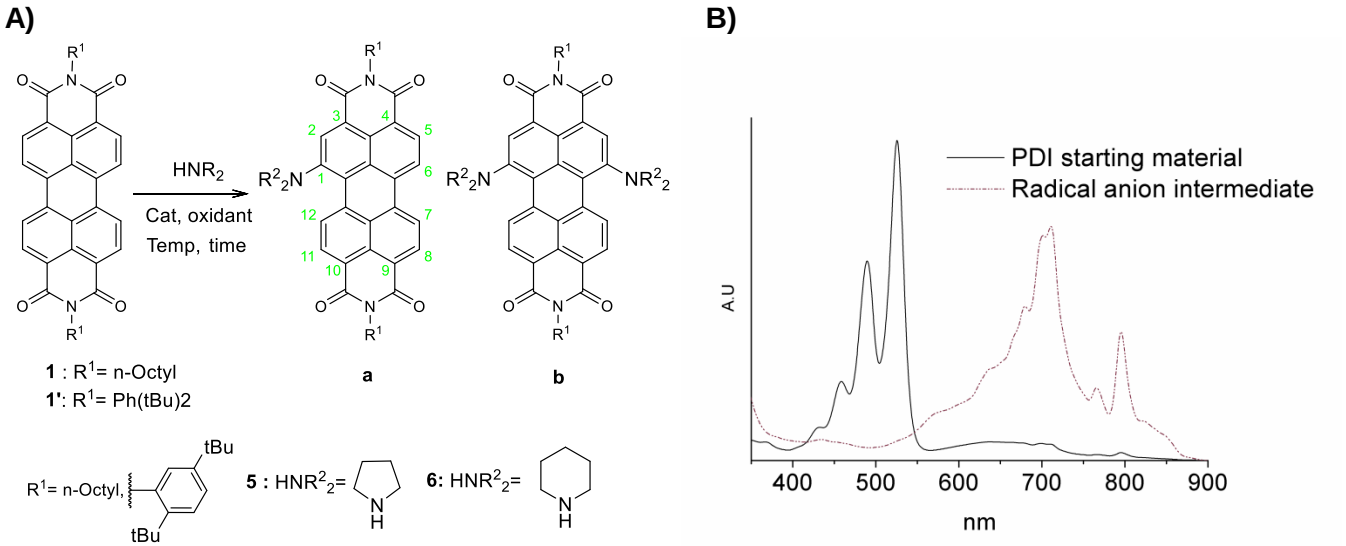
Perylene imides are organic molecule with good thermal and photostability, high fluorescence quantum yields, molar absorptivity and excellent redox properties. [1] Its application in photovoltaics, field effect transistors, biosensors, organic light emitting diodes are well known. [2] Classic functionalization of perylene imides involves bay-region bromination and subsequent replacement of bromines with suitable substituents. However the procedure results in the formation of 1, 6- and 1, 7- isomers which have significantly different photochemical properties. [3] We herewith report the regioselective amination of perylene imides which does not require any leaving group for substitution. The presence of imide cycle is very important for reaction to occur. Reaction proceeds via oxidation of radical anion and amination occurs at mild conditions and with remarkable selectivity. The diimides are exclusively substituted at 1, 6- bay position and monoimides at 7, 12- positions with yields ranging from 20-97%.[4]



A) Regioselective amination of perylenediimide (PDI); **B)** Absorption of PDI and its radical anion intermediate.

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MECHANISTICAL ASPECTS OF THE STEREOSPECIFIC REDUCTION OF HYDROXYMETHYL FUNCTIONALISED PHOSPHINATES AND PHOSPHINE OXIDES

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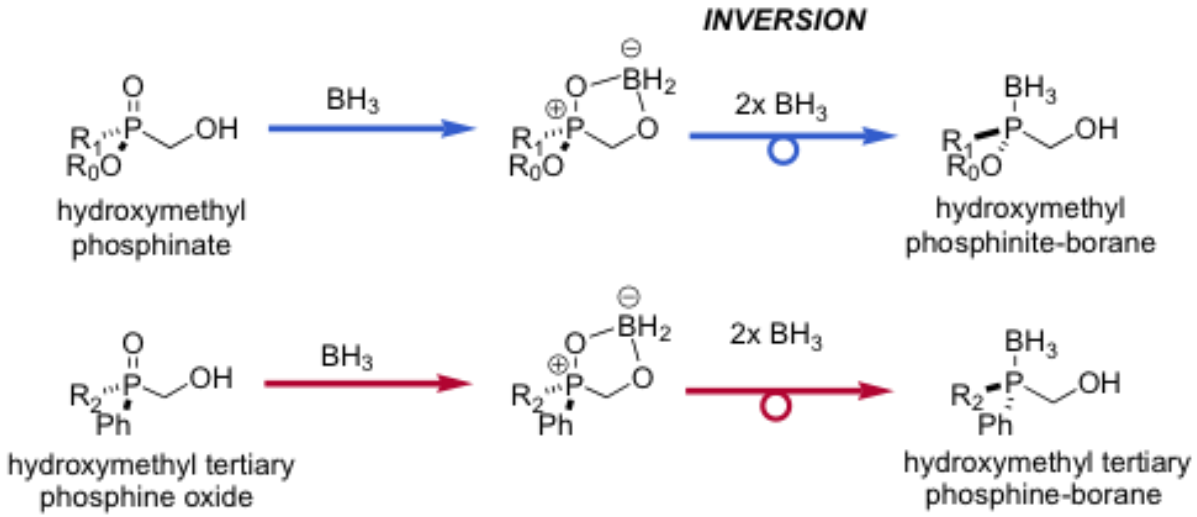
We present recent advances in the understanding of the reduction of optically pure hydroxymethyl functionalised phosphinates or phosphine oxides which represent key intermediates for the preparation of P-stereogenic ligands. Their reduction conducts to P-chiral phosphinites or phosphines. This reaction is not trivial due to the strength of the P=O bond. Many reagents can reduce the P=O bond with inversion or retention of configuration at phosphorus atom.[1] However the relatively high temperature necessary to obtain the desoxygenated compounds in high yield is a major drawback, and moreover, could be prejudicial to the chemo- and the stereoselectivity of the reaction. When the P=O bond bears an alcohol function in proximity, the problem can be circumvented.[2] The reduction can occur stereospecifically with inversion of configuration using BH_3.THF which plays three roles: activating, reducing an protecting agent. Here we present the recent results [3] obtained during the reduction of hydroxymethyl functionalised phosphinates or phosphine oxides, as well as the experimental evidences of the P=O activation by BH_3 through the formation of a 5-membered ring intermediate (Scheme).



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ENANTIOSELECTIVE ORGANOCATALYZED MULTICOMPONENT BIGINELLI- AND UGI-LIKE REACTIONS INVOLVING ISATINS

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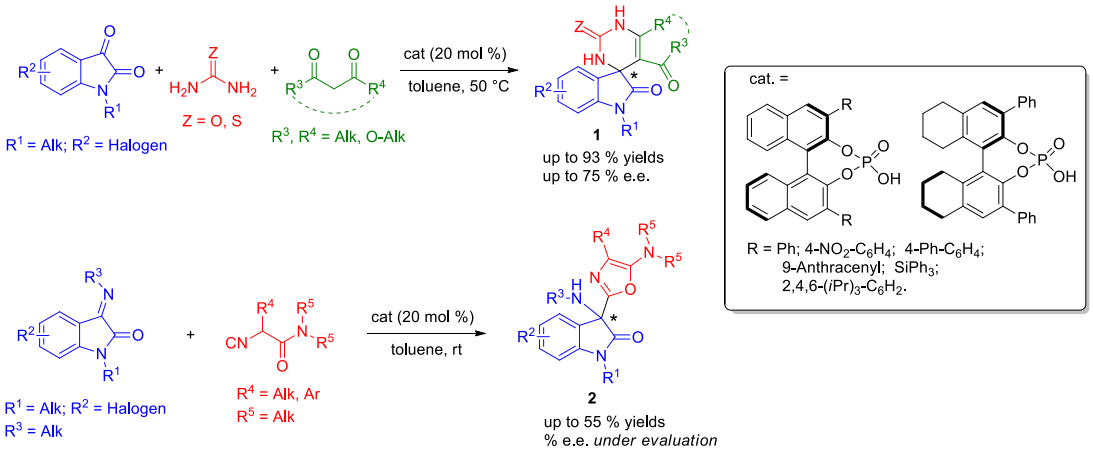
2-Oxindoles, especially those 3,3-disubstituted or spiro-fused to other cyclic frameworks, feature in a large number of natural and unnatural compounds with important biological activities and serve as key intermediates for the synthesis of many kinds of drug candidates.[1] Multicomponent reactions (MCRs) are very efficient tools to quickly prepare pharmacological compounds, and its application in the field of indole-based derivatives has attracted considerable interest owing to its exceptional synthetic efficiency and extensive diversity-generating ability. Even if the application of organocatalytic processes to enantioselective MCRs is still in its infancy, the results reported until now show the possibilities and versatility of this type of strategy, with an elevate level of atom efficiency being reached. In particular, the use of asymmetric MCRs catalyzed by chiral Brønsted acids, mainly BINOL-derived monophosphoric acids, has recently emerged as a particularly robust tool, in the context of asymmetric counteranion-directed catalysis (ACDC).[2]

Going on with our interest in the asymmetric synthesis of 3,3-disubstituted oxindole derivatives and related spiro-compounds,[3] we have developed a project aimed to explore the applicability of organocatalysis, particularly ACDC, to the enantioselective synthesis of isatin-derived 2-oxindoles, by means of multicomponent Biginelli- and Ugi-like reactions. The Biginelli-like reaction, employing isatins as carbonyl components, urea and various β-dicarbonyl compounds, allowed us to obtain a small library of chiral spiro(indoline-pyrimidine)-diones derivatives (**1**) with good yields and moderate enantioselectivity. Post-condensation reactions have been performed, increasing the number of potentially useful compounds. On the other hand, starting from isatin-derived imines and α-isocyanoacetamides, we applied an unprecedented Ugi-like reaction, affording chiral 3-(amino)-3-(oxazol-2-yl)indolin-2-ones derivatives (**2**) with high yields and good enantioselectivity. The assignment of the configuration at the new oxindole C-3 stereocenter through X-ray diffraction of selected compounds, as well as computational studies in order to explain enantioselectivity and stereochemical outcome of both reactions, are currently underway.



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SYNTHESIS OF HYDROXYLATED BIPHENYL COUMARINS AS POTENTIAL BIOACTIVE AGENTS

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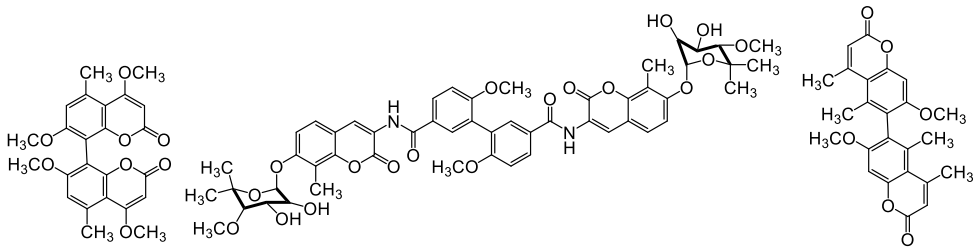
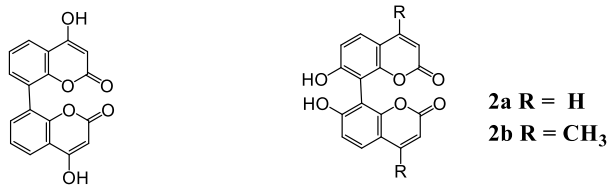
The biphenyl unit is embedded in many structures of bioactive natural products and some of them are present in compounds of high biological relevance like vancomicin and biphenomicins. In our laboratory we have been actively engaged in the synthesis and biological evaluation of hydroxylated natural-like biphenyls.[1a-c] Hydroxylated biphenyls generally manifest higher antioxidant activity and less toxicity than the corresponding monomers.[2a-c] We have considered coumarins, an important class of bioactive compounds widespreaded in various plants. They have been used in various sectors like cosmetics, pharmaceuticals, antioxidants. Some examples are reported in the literature on coumarins bearing biphenylic unit where the biphenyl is fused to coumarin moiety (e.g. kotanin and desertorin)[3a-b] and where a hydroxylated biphenyl acts as a linker between coumarinic units (e.g. **3**).[3c]



kotanin **3** **desertorin**



1 **2a-b**

2a R = H
2b R = CH_3

We have synthetized new biphenylic coumarines by Pechmann condensation reaction starting from C_2 symmetric biphenols using malonic acid or β-ketoesters under different acidic conditions. The dimeric coumarins (e.g. **1**, and **2a-b**) have been fully characterized and the synthesis will be described.

Acknowledgement: “Cluster BIT3G GreenChem-Chimica verde” –D.D. N.257 30/05/12

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TOWARDS THE SYNTHESIS OF β-1,4 THIOTETRAXYLAN

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Xylanase is a family of glycoside hydrolases, which hydrolyses xylosidic linkages in the xylan component of plant cell walls. These enzymes are currently used widely in pulp and paper manufacture, alcohol, brewery and food industries, and the need for these enzymes continuously grows[1,2].

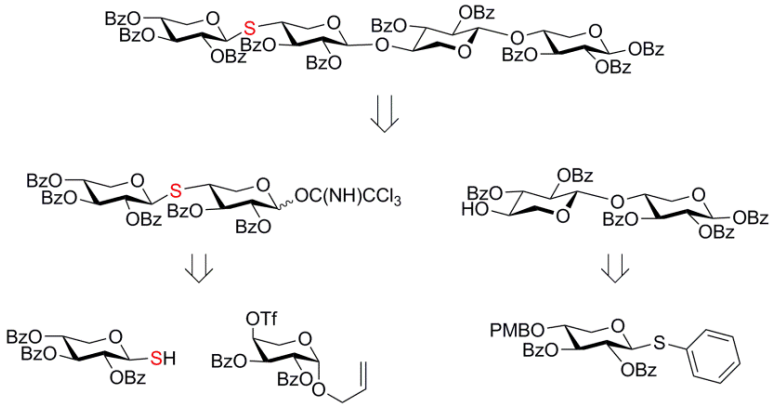

Figure 1. Retrosynthetic pathway

In this project we wish to prepare linear and branched thiooligosaccharides of xylans, which can be used as inhibitors/stable ligands in the determination of the properties and the specificities of the enzymes. In order to synthesize the thiooligosaccharides, we propose in this poster an interesting strategy for making thioglycosides, which is straightforward and easy to perform. The overall synthesis of the thiotetraxylan is based on a 2+2 coupling strategy, which intends to make the synthesis more flexible and suitable for different types of target molecules.

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FORMATION OF STEREODEFINED TRISUBSTITUTED SILYL ENOL ETHERS AS A NEW ROUTE TO CARBON QUATERNARY STEREOCENTERS

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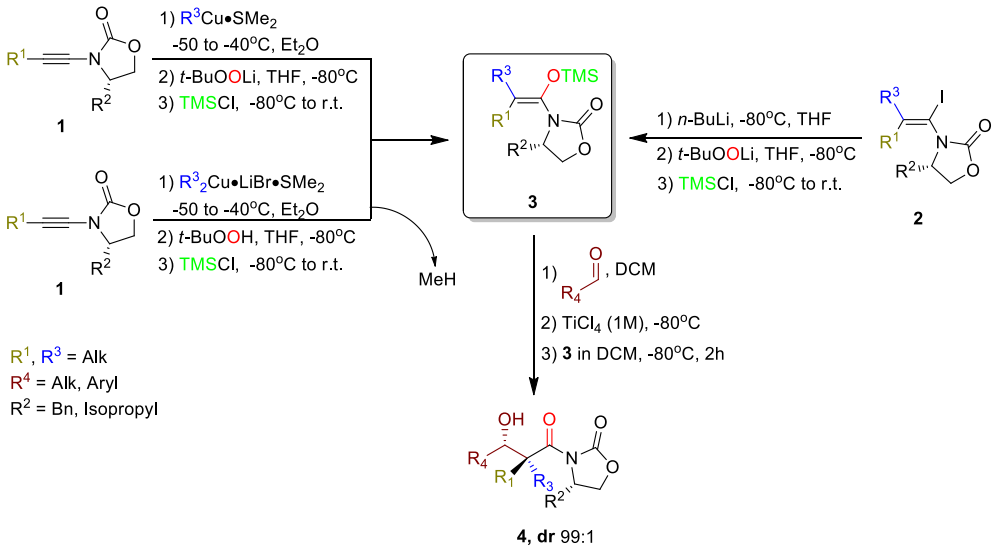
Formation of enantiomerically pure quaternary carbon center α to a carbonyl center remains a challenge in modern synthetic organic chemistry. The aldol reaction could provide an access to such molecular framework if stereodefined trisubstituted enolate could be formed stereoselectively.[1] To solve this problem, we have developed a one-pot method for the generation of stereodefined trisubstituted enolates from simple alkynes by a carbometalation/ oxidation sequence[2] that was subsequently trapped as trisubstituted silyl enol ether **3**. Using the Mukaiyama aldol reaction of these silyl enol ethers with aliphatic and aromatic aldehydes led to the formation of the aldol products possessing the expected quaternary stereocenter in high yield and diastereoselectivity (Scheme 1).[3]



Scheme 1. The Mukaiyama addition with stereodefined trisubstituted silyl enol ether derivatives

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ELECTROPHILE-MEDIATED TRANSFORMATIONS OF PROPARGYLIC SUBSTRATES

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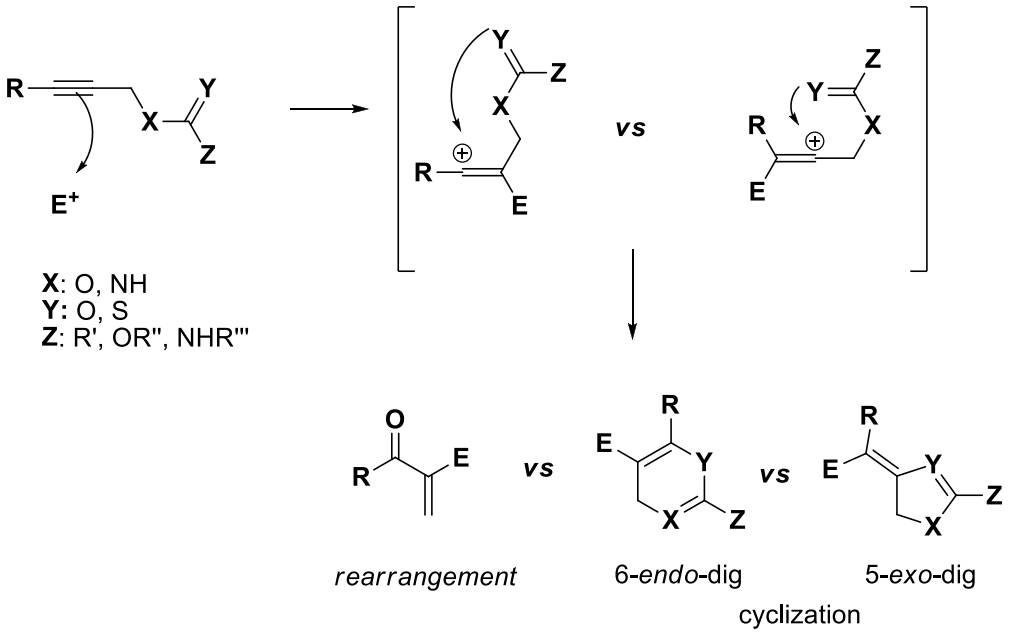
Functionalized propargylic substrates are class of alkynes with useful chemical behavior. Generally, π-acidic transition metal salts are used as catalysts for activation of triple bond and therefore subsequent cyclizations or skeletal rearrangement processes become possible.[1]

In this presentation, we present our recent findings on electrophile-promoted rearrangements of propargylic substrates.[2] We have found that the title compounds being representative of nucleophilic alkynes are able to react with electrophilic reagents forming ionic intermediates. Then a neighboring nucleophilic group participates in stabilization of vinylic carbocations. This reactivity mode gives a precedent for electrophile initiated rearrangements or cyclization reactions and therefore considerably extends the synthetic utility of propargylic substrates (esters, amides, (*thio*)carbamides and carbamates).



The mechanistic aspects of the reactions together with scope and limitations will be discussed.

Acknowledgements: This research was funded by a grant (No. MIP-15016) from the Research Council of Lithuania.

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COUPLING APPROACHES TO UNSYMMETRICAL PHTHALOCYANINE ANALOGUES WITH π-EXTENDED LINKERS BETWEEN DONOR (*N,N*-DIMETHYLAMINO) AND ACCEPTOR MOIETIES

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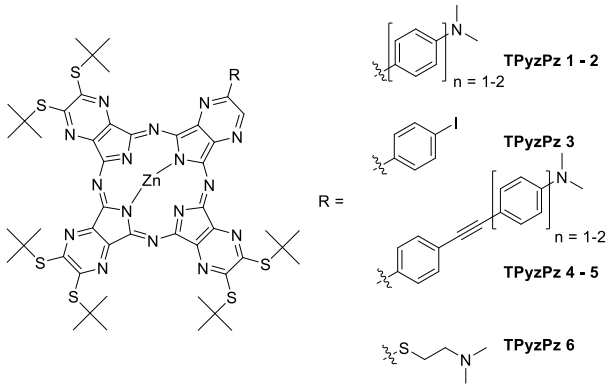
Tetrapyrazinoporphyrazines (TPyzPz) are the most studied class of phthalocyanine aza-analogues with interesting spectral and photophysical properties. Intramolecular charge transfer (ICT) is responsible for quenching of excited states in aminosubstituted TPyzPz [1].. Peripheral amine which is in conjugation with acceptor serves as a donor and the TPyzPz core as an acceptor of the electrons. The process of ICT can be blocked by various factors that can be used for sensoric applications [2]. The aim of this study is to evaluate the effect of the distance between donor and acceptor moiety on ICT efficiency. In general, synthesis of unsymmetrical TPyzPz is based on cyclotetramerization of two appropriate precursors, mostly substituted pyrazine-2,3-dicarbonitriles. In this study, the TPyzPzs with π-extended linkers between donor (*N*,*N*-dimethylamino) and acceptor moiety were prepared. The linkers were presented by one and two 1,4-phenylene units or with two and three 1,4-phenylene units with inserted triple bond. Precursors with one and two 1,4-diphenylene units arised from halogene 5-substituted pyrazine-2,3-dicarbonitriles and pinacol ester boronic acid derivatives under Suzuki-Miyaura coupling condition. Afterwards, these precursors were allowed to react with 5,6-bis(*tert*-butylsulfanyl)pyrazine-2,3-dicarbonitrile using magnesium butoxide as an initiator of the reaction to form TPyzPz **1** – **2** (Figure below). The starting compound for further post-cyclotetramerization modification (i.e, iodo substituted TPyzPz **3**) was prepared from 5-(4-iodophenyl)pyrazine-2,3-dicarbonitrile and 5,6-bis(*tert*-butylsulfanylpyrazine-2,3-dicarbonitrile in the similar way. TPyzPz **4** – **5** (Figure below) were prepared from TPyzPz **3** by the reaction with linkers containing terminal ethynyl group *via* Sonogashira coupling reaction. Finally, the TPyzPz **6** containing donor without conjugation with TPyzPz core was synthesized.



Acknowledgments: The financial support from the GA UK 1182313/2013 is gratefully acknowledged.

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SYNTHESIS OF 2-IMINO-1,3-THIAZINES AND 2-THIOXOPYRIMIDINES

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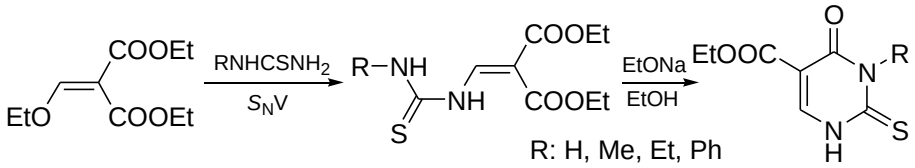
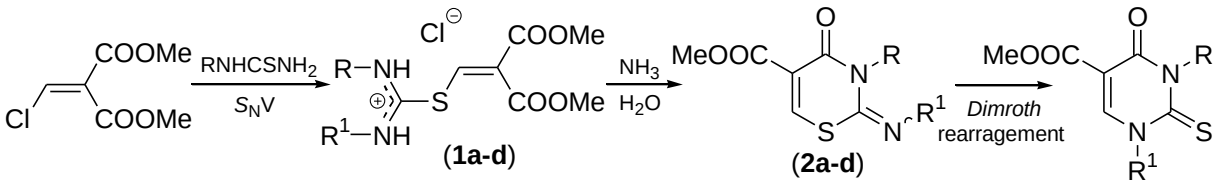
Polarized ethylenes represent suitable starting material for synthesis of various heterocycles.[1]The synthesis of 2-thioxopyrimidines (thiouracils)[2,3] starting from (alkoxymethylidene)malonates and substituted thioureas is known for a long time (Scheme 1) but corresponding isomeric 1,3-thiazines were not published yet.

Therefore we decided to start our synthesis from original isothiuronium salts (**1a-d**) prepared from easily available dimethyl (2-chloromethylidene)malonate and substituted thioureas. These isothiuronium salts were submitted to the reaction with various bases (TEA, aqueous ammonia, sodium methoxide, sodium carbonate) in water, methanol or in biphasic system (chloroform/water) and reaction products were investigated. It was found that strong bases in excess (and sometimes also in equimolar ratio) caused complete decomposition of individual salts to many different product. When equimolar amount or slight excess of weaker base (ammonia) was used then the formation of cyclic product was observed (Scheme 2). In the case of unsubstituted isothiuronium salt corresponding methyl-2-imino-4-oxo-3,4-dihydro-2*H*-1,3-thiazine-5-carboxylate (**2a**) was isolated whereas *N*,*N'*-dimethyl (**1b**), *N*-phenyl (**1c**) and *N*-phenyl-*N'*-methyl (**1d**) isothiuronium salts possessed corresponding 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**3b-d**).



Scheme 1. Described method of preparation of 2-thioxopyrimidines[2,3]



a) R, R^1: H; **b)** R, R^1: Me; **c)** R: H, R^1: Ph; **d)** R: CH_3, R^1: Ph;

Scheme 2. Our method of preparation of 2-Imino-1,3-thiazines and 2-thioxopyrimidines

On the basis of careful NMR measurements it was found that corresponding 2-imino-1,3-thiazines are always formed first which subsequently undergo nucleophile-assisted *Dimroth* rearrangement to give 2-thioxopyrimidines (**3b-d**).

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TOWARDS A SHORT SYNTHESIS OF (*R,R,R*)-α-TOCOPHEROL

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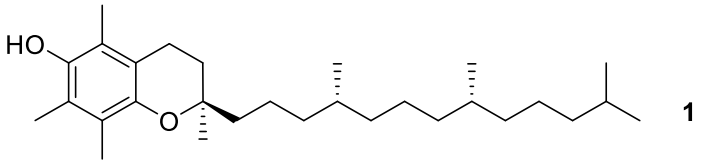
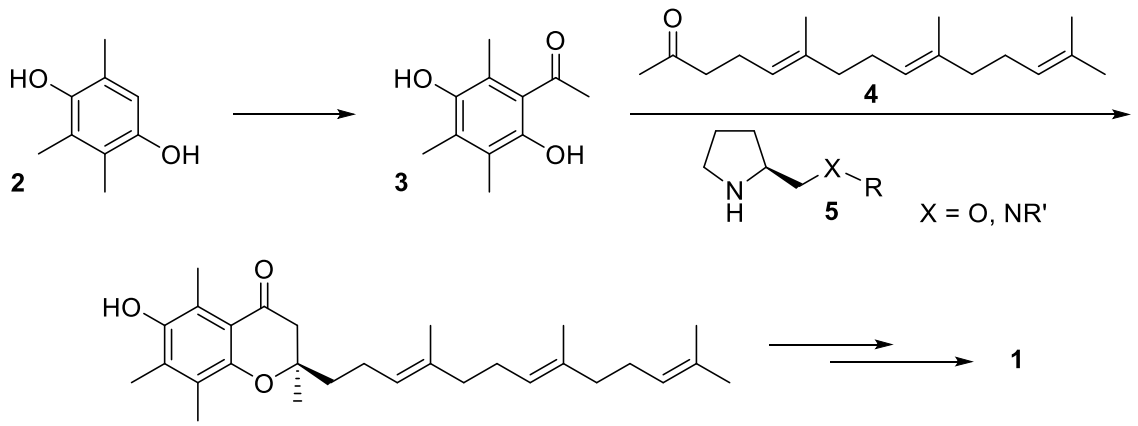
The most bioactive compound within the vitamin E class is (*R,R,R*)-α-tocopherol (**1**). The industrially manufactured product is a mixture of all eight α-tocopherol stereoisomers, as known synthetic approaches to the optically pure (*R,R,R*)-α-tocopherol are lengthy and complicated.[1]



An achiral organocatalytic approach to chromans had been published in 1978 by Kabbe and Heitzer.[2] Tocotrienols were accessible in good yields using 2-acetyl-3,5,6-trimethylhydroquinone (**3**) and farnesyl acetone (**4**) as starting materials. In the present contribution we disclose how we achieved a very short synthesis of optically enriched (*R,R,R*)-α-tocopherol starting from industrially available 2,3,5-trimethylhydroquinone (**2**) and farnesyl acetone (**4**) using chiral organocatalysts having a pyrrolidine backbone such as **5**. After subsequent asymmetric hydrogenation of the side-chain containing unfunctionalized olefins by applying the Pfaltz methodology,[3] we obtained a stereoisomerically enriched (*R,R,R*)-α-tocopherol (**1**) in only four steps and very good yield. We discuss the influences of various reaction conditions, mechanistic studies as well as the limitations of this approach.



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SYNTHESIS AND BIOLOGICAL EVALUATION OF IMINOSUGARS C-GLYCOSIDES AS GlcNAc MIMICS

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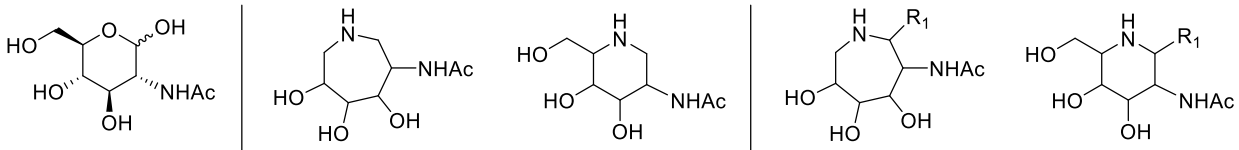
jerome.desire@univ-poitiers.fr

Iminosugars, sugars in which the ring oxygen has been replaced by nitrogen, constitute undoubtedly the most promising class of sugar analogues[1] because their unique glycosidase and/or glycosyltransferase inhibition profile make them promising therapeutics.[2] As a consequence, some iminosugar derivatives are already on the market to treat diabetes or Gaucher disease while others are currently involved in clinical trials to treat cancer, viral infections or genetic diseases such as cystic fibrosis. Introduction of a stable pseudoanomeric substituent produces iminosugar C-glycosides that are usually more potent and selective towards glycosidases compared to the parent iminoalditols, an improved efficacy which can be attributed in part to the information brought by the aglycon moiety.[3]

The main challenge associated with iminosugars C-glycosides is currently the design of efficient and general routes enabling introduction of structural diversity from advanced synthons to accelerate the discovery of biologically relevant molecules.[4] We have developped a powerful strategy towards piperidine iminosugar C-glycosides synthesis based on the alkylation of a seven-membered electrophilic iminosugar and its subsequent ring isomerisation.[5] Surprisingly, except our recent synthetic routes to homoiminosugars derived from *N*-acetyl-D-glucosamine (D-GlcNAc)[6] and one report on the synthesis of iminosugar *C*-glycoside analogues of α-D-GlcNAc-1-phosphate,[7] no general access to iminosugars C-glycosides, as GlcNAc mimics, bearing diversity at C-1 has been described so far.



We will present herein our recent results regarding the synthetic access, the biological and the synthetic potential of six and seven-membered iminosugars C-glycosides in the GlcNAc series.

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SYNTHESIS OF OLIGOSACCHARIDE FRAGMENTS OF RHAMNOGALACTURONAN-II

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A considerable interest in the biology of the plant cell wall has been grown recently, especially in respect to the polysaccharides and polyesters that dominate the dry mass of the walls. This is driven both by a lack of detailed molecular understanding of the structures and their role in plant development, growth and evolution and by the huge potential cell walls have as a source of biomass.[1]

In this project, we are targeting one of the three major structural component of pectin, rhamnogalacturonan-II (RG-II). RG-II is highly conserved between plant species and has been shown to be very important to plant cell wall function.[2] Several research groups have attempted the synthesis of RG-II, focusing on different fragments of the polysaccharide, but none has been successful.[3] Therefore, our goal is to develop synthetic routes for the backbone homogalacturonan that will allow us to introduce branching at a late stage of the synthesis and we will target the C and D side chains specifically (Figure 1).

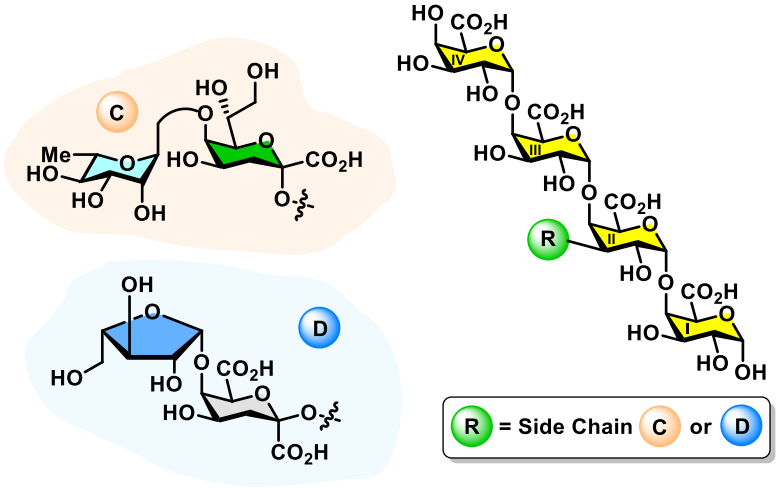

Figure 1. Example of target molecule.

These structures are shorter than the very complex A and B chains and completion of backbone HG with the C and D chains installed will provide valuable knowhow for future research in this area. Furthermore, the target oligosaccharides will be highly valuable in their own right, since such structures have never been synthesized before and will allow us to perform chemical biology studies of RG-II modifying enzymes and to raise antibodies that will facilitate in planta studies of RG-II localization and function.

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SYNTHESIS OF MODEL LIGNIN-CARBOHYDRATE COMPLEXES AND THEIR DEGRADATION VIA GLUCURONOYL ESTERASES

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In the process of biomass degradation, the presence in the plant cell wall of covalent linkages between polysaccharides (hemicellulose) and lignin fragments, so called lignin-carbohydrate complexes (LCCs), has been implied to have a recalcitrant role, complicating the separation of lignin from cellulose and hemicellulose.[1] Among the various LCCs found in nature (benzyl ethers, phenyl glycosides, esters), the ester linkage between 4-*O*-methyl-D-glucuronic acid residues of xylans and lignin alcohols could be subjected to enzymatic degradation and it has been proposed to be hydrolyzed by a recently discovered class of enzymes, Glucuronoyl esterase (GE).[2,3] In other to further investigate the activity and the specificity of GEs, in this work model substrates have been prepared to develop a simple and efficient enzymatic assay.

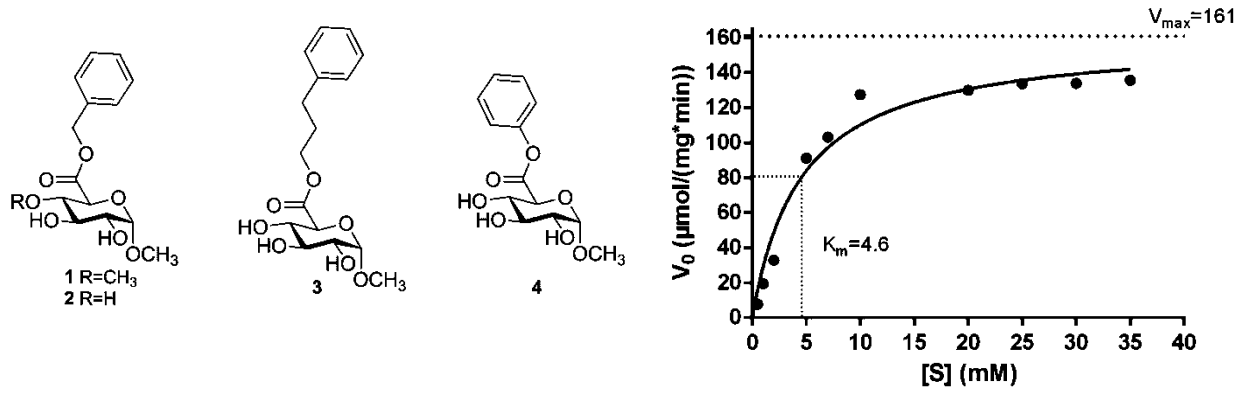

Figure 1

The desired molecules have been obtained in few steps and good yields with a straightforward synthetic pathway, starting from methyl α-D-glucopyranoside. Hence two different GEs, both expressed and purified at Novozymes, have been characterized and the activity evaluated via determination of kinetic parameters (K_m, V_{max}, k_{cat}).[4]

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EFFICIENT DIRECT TRIFLUOROETHYLATION OF INDOLES WITH HIPERVALENT IODONIUM REAGENTS: SCOPE, MECHANISM AND SYNTHETIC OUTLOOK

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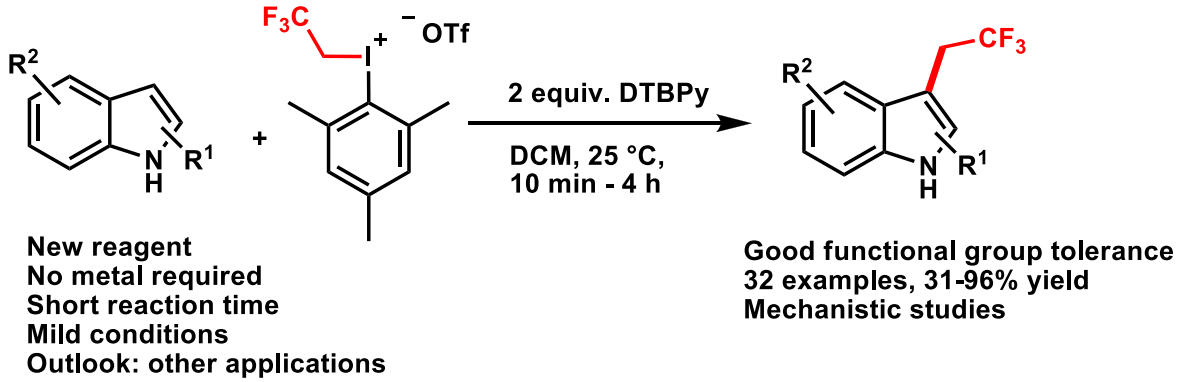
The installation of fluorous functional groups into organic molecules is an important area of research, since the introduction of fluor atom modifies the physical, chemical and biological properties of the compounds. Aromatic and heteroaromatic cores equipped with trifluoromethyl, trifluoromethoxy and trifluormethyltio groups are important compounds in the field of medicinal chemistry, due to their beneficial biological activity. Regarding their synthesis, the efficient introduction of trifluoroethyl group as the desired functional group to aromatic core is still rare.



We designed a new a hypervalent iodonium salt which is efficently applicable as trifluoroethylating agent. With the utilization of the salt we successfully accomplished the trifluoroethylation of indoles in position 3 in a rapid reaction under mild conditions. The reaction works efficiently in the trifluoroethylation of indoles bearing both electron donating and electron-withdrawing substituents. With the help of DFT calculations the mechanism of the reaction was revealed, which explained the importance of the basic additive (2,6-ditertbutylpyridine) in the transformation.[1] Beyond the detailed discussion of this methodology a brief outlook will be provided regarding further application of the salt in the field of transition metal catalyzed C-H activation.

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COORDINATION DIVERSITY IN HYDROGEN BONDED HOMOLEPTIC FLUORIDE-ALCOHOL COMPLEXES MODULATES REACTIVITY

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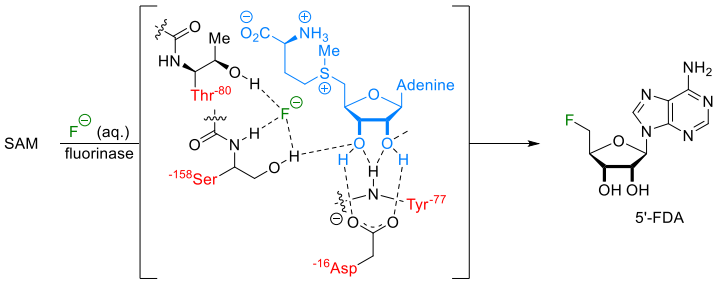
Although highly sought-after, examples of metal-free catalytic nucleophilic fluorinations starting from fluoride are rare. This is rooted in limited solubility of common fluoride salts as well as the high basicity of free fluoride leading to side reactions. Also, solvation through hydrogen bonding affects its nucleophilicity. In the fluorinase enzyme, nature overcomes these problems using carefully positioned hydrogen bond donors in its active site to effect desolvation and control basicity making possible the synthesis of 5´-fluoro-5´-deoxyadenosine from fluoride in aqueous medium (Scheme 1).[1]



Scheme 1

After seminal work by Yonezawa[2] and Kim[3] examining the effect of hydrogen bonding on fluoride's reactivity as well as selectivity, structural studies of hydrogen bonded fluoride complexes remain scarce. In this contribution we will present the structure of 14 complexes of fluoride anion with alcohols of varying steric bulk which were studied by X-ray as well as neutron diffraction crystallography (Figure 1). The structural diversity will be related to differences in reactivity as well as S_N2/E2 selectivity of these fluoride sources as determined on a model reaction. A rationale for the observed trends will be discussed.

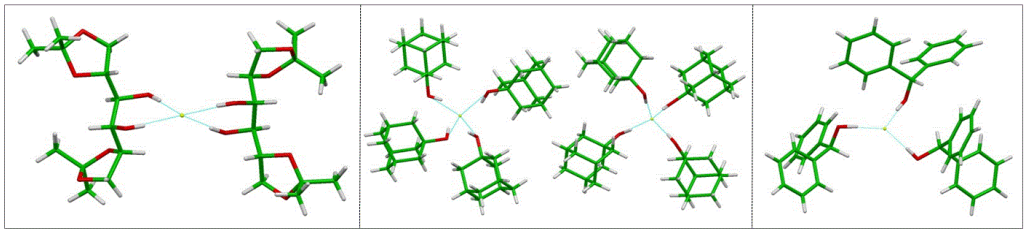


Figure 1

References:

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REACTION OF 3-BROMOCOUMARAN-2-ONE WITH THIOUREAS, THIOAMIDES AND DITHIOCARBAMATES

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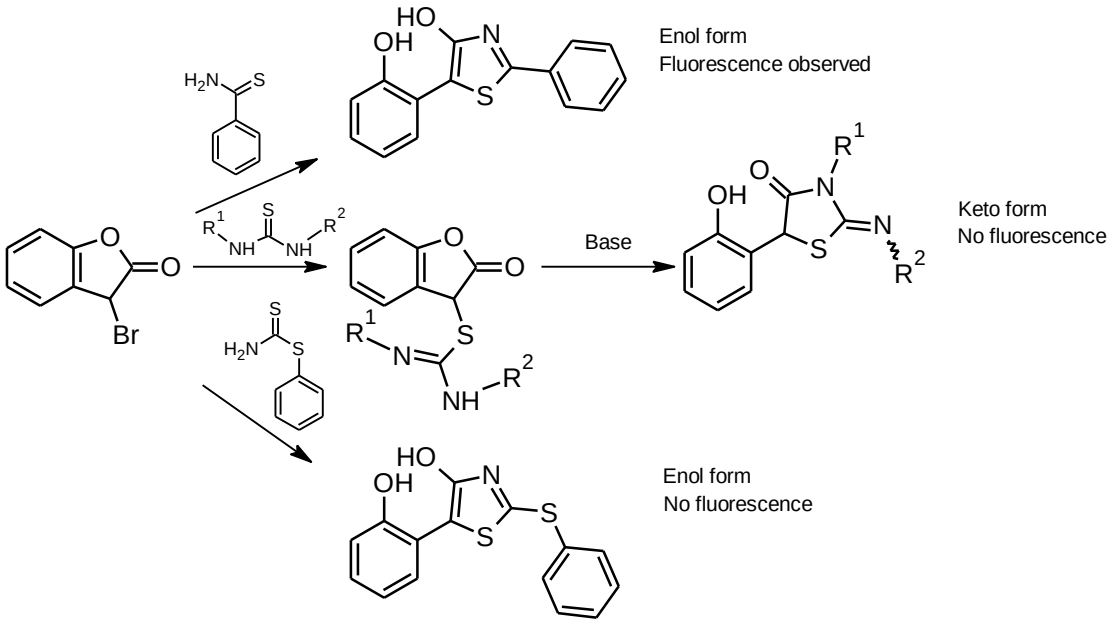
There are two reactive centers in the structure of 3-bromocoumaran-2-one, *i.e.* carbonyl group and carbon atom carrying bromine. 3-Bromocoumaran-2-one therefore easily reacts [1] with thioureas to isothiuronium salts and these salts rearrange to appropriate 2-imino-1,3-thiazolidin-4(5*H*)-ones under mild base conditions. When the aromatic thioamides are used instead of thioureas, the reaction gives 1,3-thiazol-4-oles whose enol tautomeric form was confirmed by ^{1}H and ^{13}C NMR spectra. While the 2-imino-1,3-thiazolidin-4(5*H*)-ones are colorless and they do not display any fluorescence, structurally similar 1,3-thiazol-4-oles form orange solids displaying intense fluorescence in the solution but no fluorescence in solid state. 1,3-Thiazol-4-oles can be easily converted to their anionic forms because of the presence of the two hydroxy groups. Fluorescence of this anionic form is lower in solution but when this anionic form is isolated in solid state its fluorescence is sustained. For comparison dithiocarbamates were also used for synthesis 1,3-thiazol-4-oles from 3-bromocoumaran-2-one. These 1,3-thiazol-4-oles are slightly yellow but any fluorescence in solution or solid state was not observed. Synthesis, structure and behavior of prepared 2-imino-1,3-thiazolidin-4(5*H*)-ones and 1,3-thiazol-4-oles will be discussed in detail.



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SYNTHESIS OF CHIRAL PROMOTERS FOR STEREOSELECTIVE CATALYSIS BASED ON THE 3,3'-BITHIOPHENE SCAFFOLD

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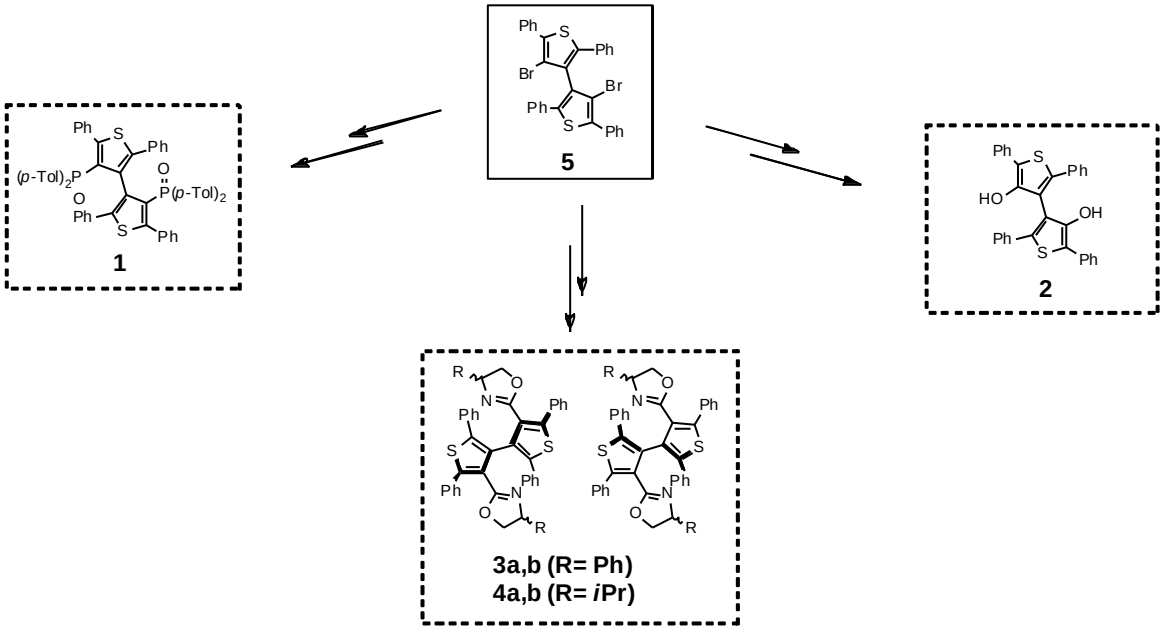
Chiral promoters for stereoselective reactions characterized by a 2,2',5,5'-tetramethyl-3,3'-bithiophene atropoisomeric scaffold exhibit high stereoselection levels, both as complexes of transition metals (bis-oxazolines[1] and bis-phosphanes[2]) and as organic catalysts (bis-phosphane oxides[3]). The good results achieved with these chiral mediators prompted us to prepare a new family of chiral analogues characterized by a 2,2',5,5'-tetraphenyl-3,3'-bithiophene core. We considered an interesting task to investigate the effects of the different steric and electronic properties on the catalytic activity and the stereoselection ability of the new mediators.

The key intermediate for the synthesis of all the new chiral compounds **1**, **2**, **3** and **4** is the 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene (**5**), as reported in the scheme:



The synthesis and the chemical and chiroptical characterization of all new compounds are reported.

The preliminary results obtained employing the bis-phosphane oxide **1** as organocatalysts and the behavior of bisoxazolines **3** and **4** as ligands of different transition metals (Zn, Cu, Pd) are discussed.

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FUNCTIONALIZATION OF PHOTOCHROMIC DITHIENYLMALEIMIDES

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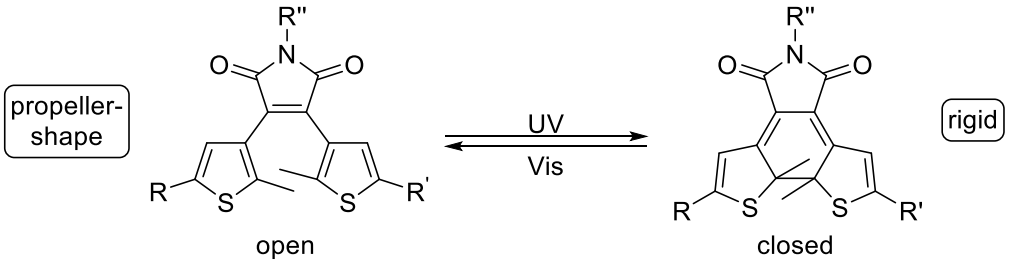
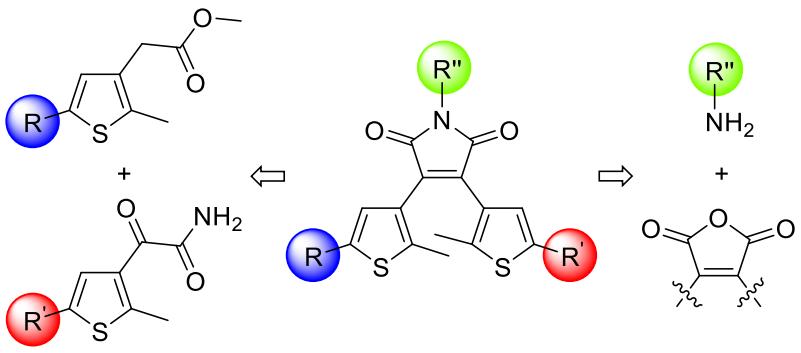
The incorporation of photochromic molecules in biological systems as light dependent triggers has become a valuable tool for the study of many important cellular processes and pathogeneses.[1] Dithienylethenes (DTEs) were successfully applied as light-controllable inhibitors for various enzymes.[2-4] The increased hydrophilicity and biocompatibility of dithienylmaleimides compared to other classes of DTEs makes them more favorable for biological applications. They can reversibly be switched between an open and closed photoisomer by irradiating with light of an appropriate wavelength.[5]



Synthetic routes for the functionalization of photochromic dithienylmaleimides at three different positions are reported: at each of the thiophene moieties and the maleimide nitrogen.[6] A Perkin-type condensation of two thiophene precursors is used as the key step to assemble the maleimide core, which allows the synthesis of non-symmetrically substituted dithienylmaleimides, such as photochromic amino acids. A different approach to the maleimide core is provided by the reaction of a dithienylmaleic anhydride with amines or hydrazides leading to maleimide protected dithienylmaleimides and photochromic labeled natural amino acids. The photochromic properties of the new photoswitches were investigated showing reversible photochromism in polar organic solvents.



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AN EFFICIENT ONE-POT SYNTHETIC APPROACH TO PYRROLO[4,3,2-de]QUINOLINONES

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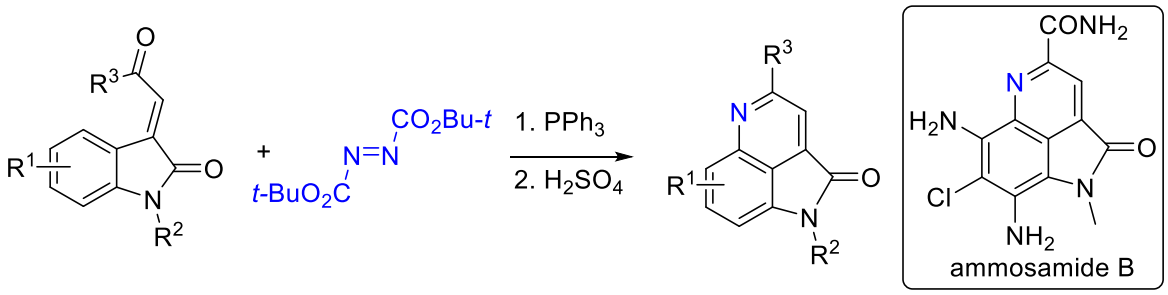
Pyrrolo[4,3,2-de]quinoline core is a characteristic substructure found in a number of natural products which often exhibit a wide range of biological activities.[1] For example, an array of newly discovered marine alkaloids ammosamides[2] with such fused cyclic skeleton possess attractive bioactivities including significant cytotoxicity against human HCT-116 colon carcinoma and moderate inhibitory potency against human quinone reductase. They are also thought to modulate tubulin and actin dynamics through myosin binding.[3] Promising biological activities of those natural products have stimulated much interest from organic chemists and biologists. However, the lack of efficient and practical methods for preparation of diverse pyrrolo[4,3,2-de]quinolines somehow retards exploring their potential application as pharmaceutics. Recently we developed a novel annulation reaction between 3-alkylidene oxindoles and Huisgen zwitterions which provided an efficient and convenient access to functionalized pyrrolo[4,3,2-de]quinolinones. By this method, we also demonstrated a concise total synthesis of marine alkaloid ammosamide B (Scheme 1). Herein we present the synthetic details.



Scheme 1

Acknowledgement: The authors thank the National Natural Science Foundation of China (grant no. 21272119; 21472096; 21121002) for financial support.

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HIGHLY DIASTEREO- AND ENANTIOSELECTIVE SYNTHESIS OF CHIRAL HYDROCHCOUMARINS VIA ORGANOCATALYZED CASCADE MICHAEL ADDITION-TRANSESTERIFICATION OF AZLACTONES AND 2-((*E*)-2-NITROVINYL)PHENOLS

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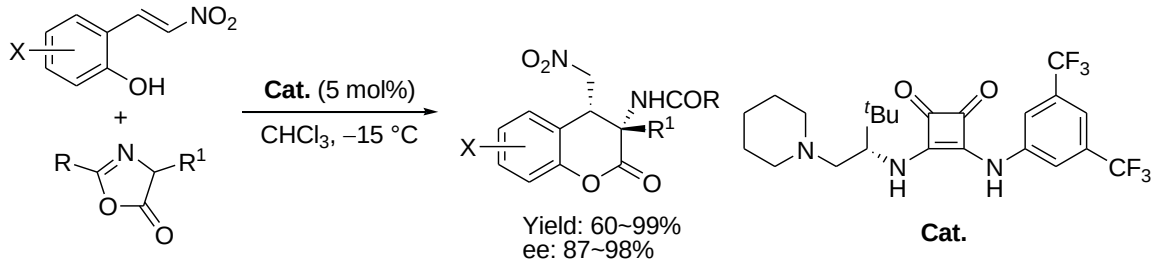
Hydrocoumarin is a privileged structural motif presenting in many biologically active compounds which exhibit antioxidant, antifungal, and anti-inflammatory activities.[1] Despite their high relevance as biologically active compounds, however, the methodology for the asymmetric synthesis of nonracemic hydrocoumarins have been rarely explored.[2] Therefore, it is desirable to develop novel methodologies for the synthesis of chiral hydrocoumarins, which could potentially lead to this type of compounds with enhanced pharmacological features. As part of our ongoing studies on organocatalyzed asymmetric cascade reactions,[3] we wish to describe herein the highly stereoselective cascade Michael addition-transesterification of azalactones and 2-((*E*)-2-nitrovinyl)phenols catalyzed by a bifunctional tertiary amine-squaramide organocatalyst.



Acknowledgement: We are grateful to the National Natural Science Foundation of China (No. 20972070, 21121002), the National Basic Research Program of China (973 program 2010CB833300), Program for New Century Excellent Talents in University (NCET-11-0265) for generous financial support for our programs.

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SYNTHESIS OF CHIRAL SULFONIMIDOYLALKYL NAPHTHOLS BY BETTI CONDENSATION UNDER SOLVENT-FREE CONDITIONS

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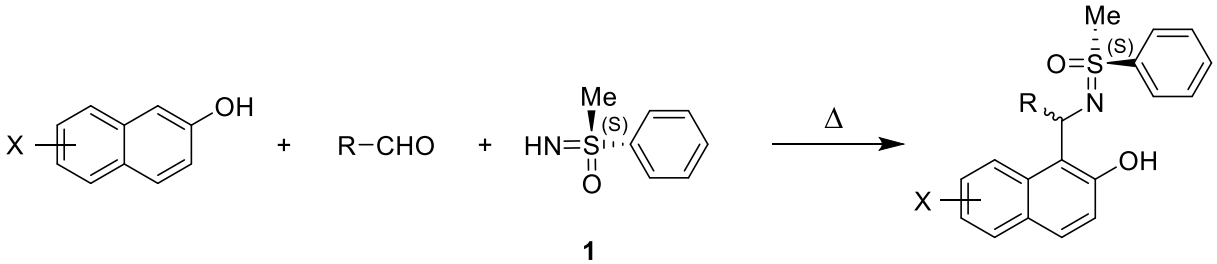
The classic “Betti reaction” is known as a Mannich-type condensation between 2-naphthol, benzaldehyde and ammonia. As a multicomponent reaction (MCR) it offers a simple one-pot procedure and quick access to a large number of complex compounds by variation of the three reactants. Subsequently, various naphthol analogues, aldehydes and nitrogen sources [such as primary or secondary amines, amides or (thio-)ureas] have successfully been applied.[1] To date, sulfoximines[2] such as **1** have never been investigated in this type of process.

Herein, we present the application of (chiral) sulfoximines in the Betti-type condensation with aldehydes and naphthol derivatives. The developed process features an environmentally friendly setup (no solvent, mild reaction temperature, reactants in almost ideal stoichiometry and water as only by-product) and gives rise to a broad range of products **2** in uniformly high yields. The products are stereogenic at sulfur and carbon and in nearly all cases the diastereomers were fully separated by column chromatography. The absolute configuration of one of the sulfonimidoylalkyl naphthols was determined by X-ray crystallography which allowed unambiguous identification of all stereogenic centers.



1 **2**

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THE SYNTHESIS OF PHOSPHONONAPHTHALENES VIA DIELS-ALDER REACTION

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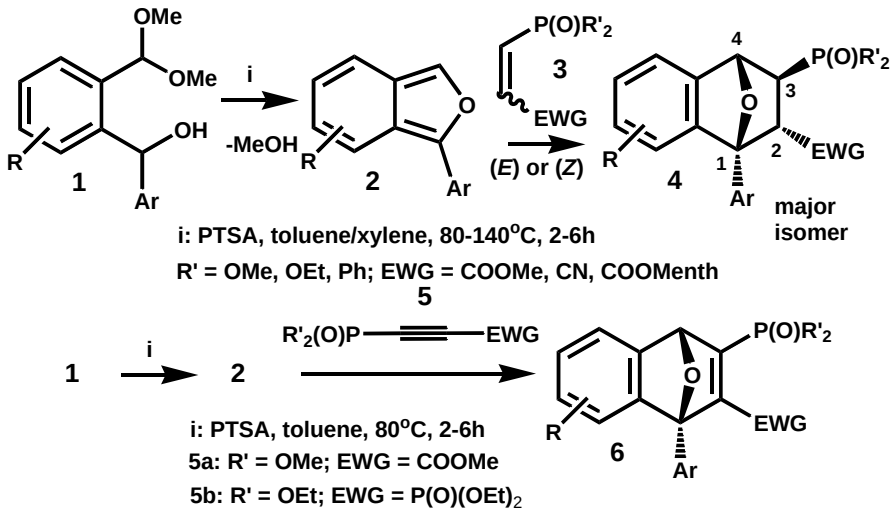
We proposed new approach to the synthesis of functionalised 3-phosphono-1-aryl-1,2,3,4-tetrahydronaphthalenes with generally high yields starting from simple substrates. Regioselectivity of cycloadditions (the key step) is controlled by more electron withdrawing group (EWG) of dienophiles. We observed that activating groups (EWG) occupy "*endo"* and *"ortho"* position to the most electron donating substituent (aryl) in the corresponding major cycloadducts. There are only a few reports on cycloaddition reactions between isobenzofurans and alkenyl/alkynyl phosphonates/phosphine oxides.[1] The simple and readily available diarylomethanols **1** in the presence of catalytic amounts of acid (eg.: *p*-TSA) generates isobenzofurans **2** which react with phosphorylated dienophiles **3** to give cycloadducts **4** – 3-phosphono-1,2,3,4-tetrahydronaphthalenes. The ratio of *endo/exo* isomers varies from 2.5:1 to 8.0:1 depending of nature of substituents in substrates. In the cycloaddition reaction were observed small amounts of "*meta"* products too. The ratio of *ortho/meta* isomers was about 5:1. Cycloaddition reaction with dienophile having triple bond - **5a** produce unsaturated adduct **6a** (3-phosphono-1,4-dihydronaphthalene). Subsequent hydrogenolysis of **6** give us only one isomer (*ortho* and *exo* 3-phosphono-1,2,3,4-tetrahydronaphthalene). Analogous **5b** (bis(diethoxyphosphoryl) acetylene) give us product **6b** with two phosphoryl group.



The proposed approach will be utilized in total syntheses of biologically active compounds possessing 1-aryl-1,2,3,4-tetrahydronaphthalene skeleton which belong to lignan family.

Acknowledgements: This work was supported by The National Science Centre under Grant no UMO-2012/05/B/ST5/00738.

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HYPERVALENT IODINE REAGENTS: A NOVEL AND EFFICIENT METAL FREE METHOD FOR THE OXIDATION OF *N*,*N*-DISUBSTITUTED HYDROXYLAMINES TO NITRONES

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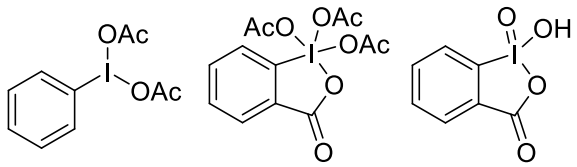
Hypervalent iodine reagents such as diacetoxyiodobenzene (DIB, **1**), Dess-Martin periodinane (DMP, **2**) and *o*-iodoxybenzoic acid (IBX, **3**) are commercially available oxidizing agents widely employed in the oxidation of several organic functional groups (Figure 1).[1] However, to the best of our knowledge, no examples of their use in the oxidation of hydroxylamines have been reported to date. Searching for novel and convenient metal-free methods for the synthesis of nitrones, useful intermediates for the obtainment of alkaloids and other nitrogen containing products,[2] we envisaged in hypervalent iodine reagents suitable candidates.



1, DIB **2**, DMP **3**, IBX

Figure 1

We present herein our results on the oxidation of several *N*,*N*-disubstituted hydroxylamines (cyclic, acyclic, symmetric, non symmetric) to the corresponding nitrones, by hypervalent iodine oxidants **1**-**3** (Figure 2).

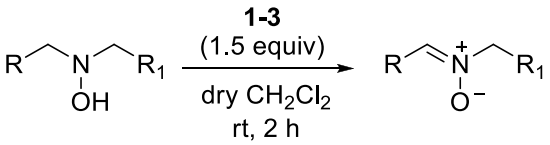


Figure 2

The procedure is very simple and user friendly and affords the target compounds with high efficiency and regioselectivity, highlighting IBX as the reagent of choice due to the higher yields obtained and the possibility to avoid, in most cases, any separation technique . Moreover, IBX presents uncommon potentiality for the regioselective oxidations of non symmetric hydroxylamines especially in the preferential formation of aldo- vs. keto-nitrones, for which a remarkable increase in regioisomeric ratio for this transformation was shown in comparison to the most common oxidants. A mechanistic hypothesis of the oxidation of hydroxylamines with IBX, supported by collected spectroscopic evidences, will be also discussed.

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FROM π-EXPANDED COUMARINS TO π-EXPANDED PENTACENES

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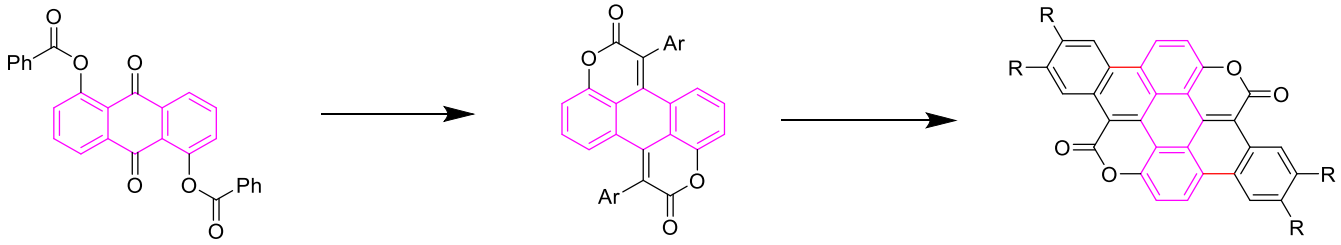
The synthesis of two novel types of π-expanded coumarins has been developed.[1] Modified Knoevenagel bis-condensation afforded 3,9-dioxa-perylene-2,8-diones. Subsequent oxidative aromatic coupling or light driven electrocyclization reaction led to dibenzo-1,7-dioxacoronene-2,8-dione. Unparalleled synthetic simplicity, straightforward purification and superb optical properties have the potential to bring these perylene and coronene analogs towards various applications.



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SYNTHESIS OF PHOTOACTIVATABLE FATTY ACIDS FOR THE FUNCTIONNAL AND STRUCTURAL STUDY OF THE MITOCHONDRIAL MEMBRANE UNCOUPLING PROTEIN UCP_1

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Uncoupling protein 1 or UCP_1 is a mitochondrial membrane protein that uncouple the respiratory chain from ATP synthesis by allowing the passive diffusion of protons, from the intermembrane space (where protons are accumulated) to the mitochondrial matrix. *In vivo*, the protein is activated by the fatty acids (FAs) and inhibited by puric nucleotides. Several hypotheses concerning the interaction of UCP_1 with its ligands and the mechanisms of the protons transport have been established during the last two decades[1-6]. More recent works[7] contributed to elucidate the mechanisms of protons transport but the FAs binding pocket within UCP_1 remained unknown.

Our aim is to determine how protons transport is regulated by UCP_1 and what is the peptidic sequence involved in FAs binding. To achieve this goal we designed FAs derivatives to cross-link them to UCP_1 by using photochemistry[6].

Various photoactivatable lauric acid derivatives were synthetized by introducing the probe (aliphatic or aromatic azido group, aliphatic or aromatic diazirine, benzophenone) at various position along the fatty chain.

The yielded photoactivatable FAs were incubated, in a first preliminary step, with liposomes in order to assess the effect of the position of the probe on the FAs fatty tail on liposomes proton permeability. We found that having the probe close to the carboxylic function drastically increased the proton permeability on liposomes.

Initial activity tests on UCP_1-containing liposomes have shown that few of the synthetized derivatives are fully able to activate the protophoric activity of UCP_1, opening the way to determine the aminoacids involved in the FAs binding pocket by mass spectroscopy analysis.

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CATALYTIC REGIOSELECTIVE OXIDATION OF AMINOGLYCOSIDE ANTIBIOTICS

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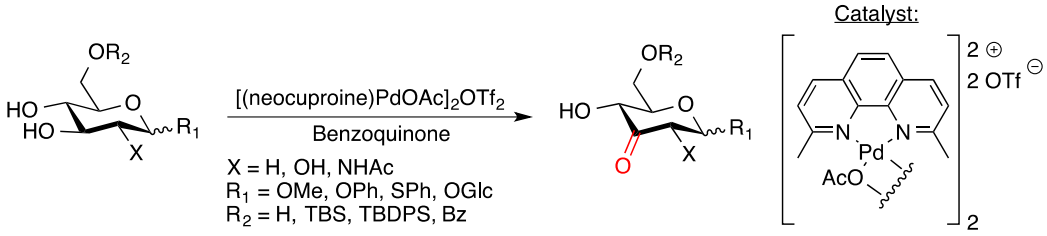
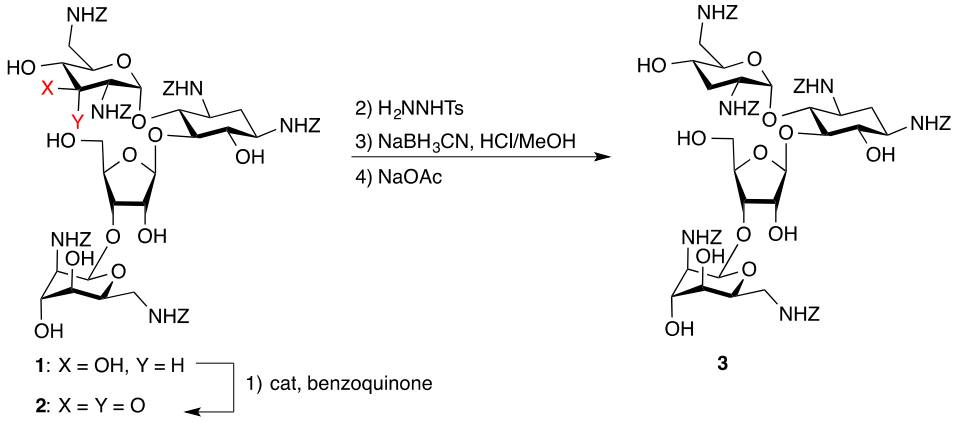
Since the discovery of streptomycin by Waksman in 1944, aminoglycoside antibiotics have been applied successfully in the treatment of bacterial infections and diseases. By binding the bacteria's 16S rRNA in the codon-decoding A-site, the codon-anticodon pairing is hampered, resulting in mistranslation and cell death.[1] Unfortunately, by developing aminoglycoside modifying enzymes, bacteria have found a way to chemically modify and deactivate aminoglycoside antibiotics. One class of these aminoglycoside modifying enzymes comprises the aminoglycoside *O*-phosphotransferases (APHs), which selectively phosphorylate the aminoglycoside antibiotic at the 3' position.[1] Removal of the 3' hydroxy should prevent deactivation of the aminoglycoside by APHs.



Scheme 1. Catalytic regioselective oxidation of glycosides.

Recently, our group reported the catalytic regioselective oxidation of mono- and disaccharides at the 3 position, without using laborious protection and deprotection steps (Scheme 1).[2] We envisioned that the synthesis of 3'-deoxy aminoglycoside antibiotics could be realized in a concise manner using the oxidation methodology reported by our group. As a proof of principle, Cbz protected neomycin B (**1**) was regioselectively oxidized to 3'-keto Neomycin B (**2**) (Scheme 2). Formation of the corresponding tosylhydrazone followed by the reductive removal of the tosylhydrazone moiety using a two step methodology developed by Nair *et al*.[3] resulted in 3'-deoxy neomycin B (**3**). With **3** in hand we are going to evaluate its activity on different resistant bacterial strains.



Scheme 2. Regioselective oxidation and reduction of neomycin B.

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INTRAMOLECULAR THIOL-YNE CYCLISATION REACTIONS FOR THE SYNTHESIS OF THIOGLYCALS

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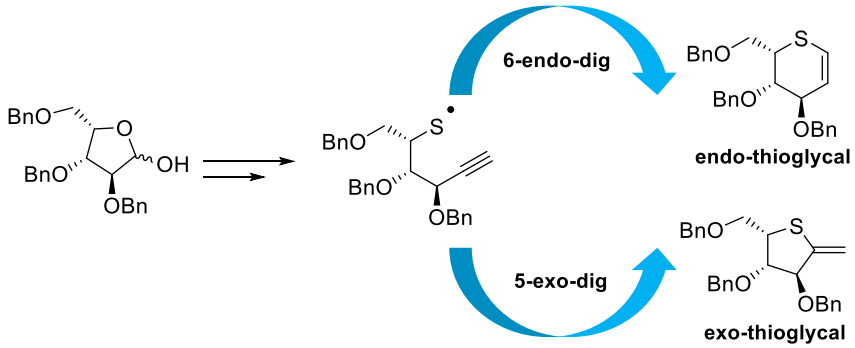
Sulfur containing heterocycles are of particular interesting in medicinal chemistry due to the unique electronic properties of the sulphur atom.[1] In glycoscience, thiosugars have been identified as competitive glycosidase inhibitors and a number of synthetic routes have been developed for their synthesis.[2] The intramolecular thiol-ene reaction has been reported as a facile and efficient strategy for the synthesis of sulfur containing heterocycles, including thiosugars.[3][4] We have demonstrated that the related thiol-yne cyclisation can be employed for the efficient preparation of unusual thioglycals of both D- and L-sugars.



The intramolecular thiol-yne radical cyclisation was investigated using thiol derivatives prepared from tri-*O*-benzylated arabinofuranose. Both D- and L-sugars were investigated under radical cyclisation conditions. The L-sugar gave a mixture of both *exo*- and endo-thioglycal products, however the D-sugar gave exclusively the *exo*-thioglycal. An ionic cyclisation pathway was also investigated for both D- and L-sugars and furnished the endo-glycal products exclusively.

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PHOTOCHROMIC DI-INDOYLETHENES

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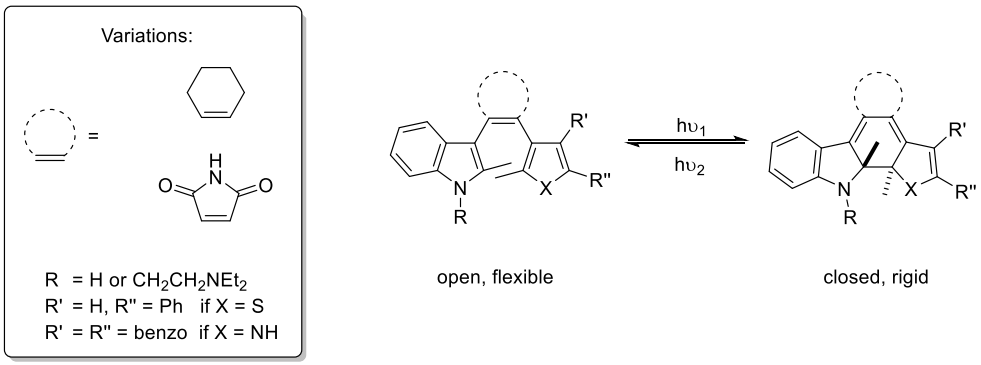
Photochromic compounds have received considerable interest because of their potential use in optical data storage and as investigation tools in biology. Among such compounds, 1,2-diarylethenes containing heterocyclic rings are particularly promising for practical use. The compounds undergo conrotatory electrocyclic reactions yielding the ring-closed isomer. Alteration of the π-conjugated system of diarylethene derivatives through structural rearrangement by photoirradiation can be used to control reactivity, donor-acceptor interactions, magnetic properties and physiological response. Such changes, induced by light, are essential for creation of new materials and devices as well as for molecules of biological relevance.[1-3]
Dithienylethenes (DTEs) are frequently used for the preparation of photochromic compounds as they exhibit fast and almost quantitative photoisomerisation as well as excellent fatigue resistance.[1] However, DTEs require UV light to be ring-closed which can be a crucial drawback especially for the application in a biological environment as it causes cellular damage.[4] Therefore, the investigation of new photochromic materials absorbing light in the visible range is of current interest. One approach is to move to heterocyclic systems as indoles as their absorption range is bathochromic shifted in comparison to the respective thiophenes. In addition, especially indole containing maleimides exhibit a very broad spectrum of biological applications.[4]



In the presented work we hence focus on Di-indoylethenes (DIEs).Both synthetic strategies and photophysical characterization is discussed for several scaffolds.

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NOVEL SYNTHETIC STRATEGIES TOWARDS AZAINDOLES – PROMISING COX-2 INHIBITORS

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Being relatively unexplored, azaindoles have been a recent focus in synthetic research, for its promising pharmaceutical properties due to the similarity with the indole ring. Despite this, azaindoles feature unique electronic properties and a heteroatom as an extra site for binding, as well as to increase solubility[1]. With the existence of four possible positions for the heteroatom, the chance of suitable enzyme binding is increased, improving selectivity and bioavailability.[2] Owing to the electron deficiency of pyridines, methods for indole synthesis cannot be applied as successfully to azaindoles. Regardless, several methods for the preparation of azaindoles have been developed (Figure 1).

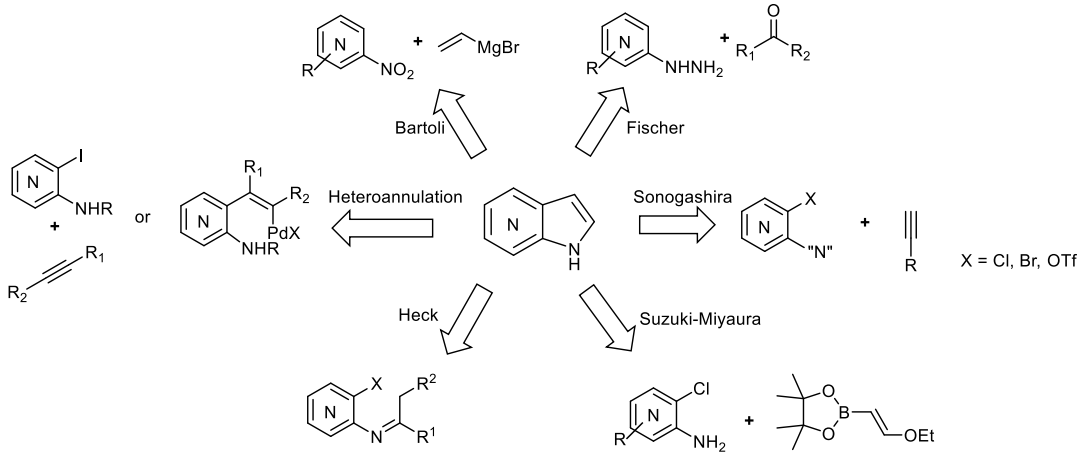

Figure 1 – Synthetic methods for the preparation of azaindoles[3].

We are developing a novel regioselective method to synthesize azaindoles, using haloaminopyridines as readily available starting materials. One of the key steps in our research plan consist of a C-N cross coupling of a properly functionalized aminopyridine with an aromatic vinyltriflate or aromatic halovinyl compound.

Herein we will present the recent developments on a novel synthetic approach towards 5-azaindoles and 7-azaindoles.

Acknowledgements: We would like to thank the Faculdade de Ciências e Tecnologia for the support.

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APPLICATION OF SILA-*ENE* REACTION IN ALLYLSULFOXIDE SYNTHESIS

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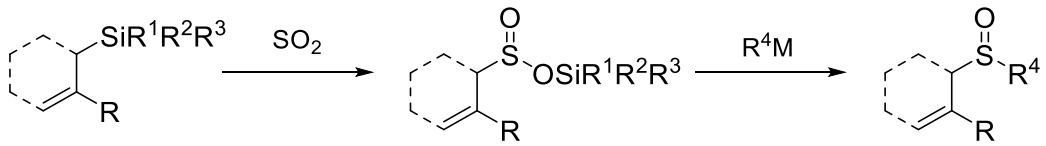
Ene-reaction of allyltrialkyltin, allylgermanes, allylsilanes and enoxysilanes with sulfur dioxide are well known.[1] Our research is focused on application of silyl sulfinates **1** in the synthesis of functionalized sulfoxides **2** (Scheme 1). Application of silyl sulfinates **1** in organic chemistry has been demostrated in different fields, including their transformation into sulfones, sulfonamides, sulfonic esters,[1] in total synthesis of polypropionate antibiotics[2] and as silylation reagents for GC-MS quantative analysis.[3]
Traditional synthesis of sulfoxides **2** includes oxidation of sulfides and C-S bond formation with nucleophilic substitution.[4] Various sulfinyl transfer agents have been used for C-S bond creation, but silyl sulfinates **1** provide a new approach towards sulfoxide **2** synthesis.
In order to optimize the reaction conditions for sulfoxide **2** synthesis we investigated influence of solvent, temperature, organometallic reagent and Lewis acid additive on sulfoxide **2** yield. We have also diversified silyl moiety in sulfinate **1** structure, examining trimethylsilyl- (**1a**), *terc*-butyldimethylsilyl- (**1b**) and triisopropylsilyl sulfinate (**1c**) in order to increase the yields of sulfoxides **2**. The optimal reaction conditions will be discussed and the scope of the method will be demonstrated on aryl-, alkyl-, allyl- and heterocyclic organometallic reagents.



1a $R^1 = R^2 = R^3$ = Me
1b $R^1 = R^2$ = Me, R^3 = *t*-Bu
1c $R^1 = R^2 = R^3$ = *i*-Pr

R = H or Me; R^4 = aryl-, alkyl-, allyl- or heterocyclic.

Scheme 1. Strategy of sulfoxide **2** synthesis.

References:

[1] P. Vogel, M. Turks; L. Bouchez, D. Markovic, A. Varela-Alvarez, J. A. Sordo, *Acc. Chem. Res.* **2007**, *40*, 931-942.
[2] P. Vogel, M. Turks, L. Bouchez, C. Craita, X. Huang, M. C. Murcia, F. Fronquerne, C. Didier, C. Flowers, *Pure Appl. Chem.* **2008**, *80*, 791-805.
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[4] E. Wojaczynska, J. Wojaczynski, *Chem. Rev.* **2010**, *110*, 4303-4356.

ORGANOCATALYTIC APPROACH TO INDOLE TERPENOIDS

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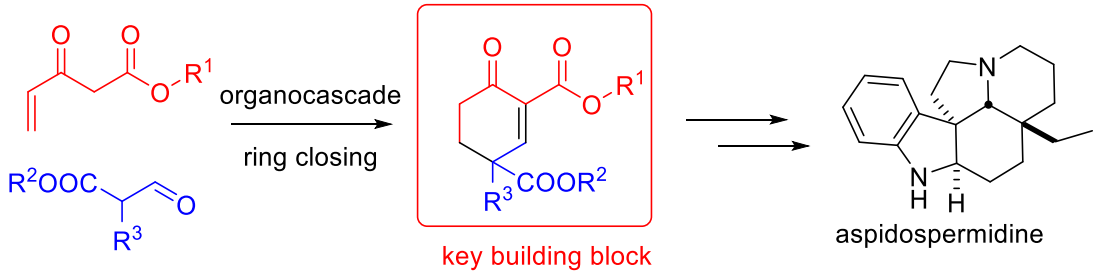
Asymmetric organocatalysis is a powerful method to assemble chiral molecules without using transition metals or harsh reaction conditions. Most of the applied organocatalysts have been synthesized from renewable sources (e.g., amino acids, alkaloids) and used in enantio- and diastereoselective syntheses of complex chiral molecules, which are valuable building blocks. Moreover, this methodology demonstrated the potential in natural product synthesis.[1]
We have developed bifunctional cinchona based thiourea catalysts, which have been used in several asymmetric transformations with high enantioselectivities and yields.[2] Recently, we have applied these bifunctional catalysts in organocascade reactions to assemble densely substituted cyclohexane derivatives.[3] These ring closing reactions are useful methods to synthesize selectively chiral building blocks with quaternary stereocenters.



As part of our synthetic program, we wished to use our cyclohexane intermediates in the concise synthesis of biologically active natural products. We aimed to use our methods in the synthesis of aspidospermidine.[4] Our results in the asymmetric synthesis and transform of various building blocks will be disclosed in the poster.

Acknowledgements: Financial support provided by grants OTKA PD-112268 and János Bolyai Research Scholarship of the Hungarian Academy of Sciences are gratefully acknowledged.

References:

[1] S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan *Nature* **2011**, *475*, 183-188.
[2] B. Vakulya, Sz. Varga, A. Csámpai, T. Soós *Org. Lett.* **2005**, *7*, 1967-1969.
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STEREOSELECTIVE SYNTHESIS OF STEREOTRIADS WITH ORGANOCATALYTIC DESYMMETRIZATION

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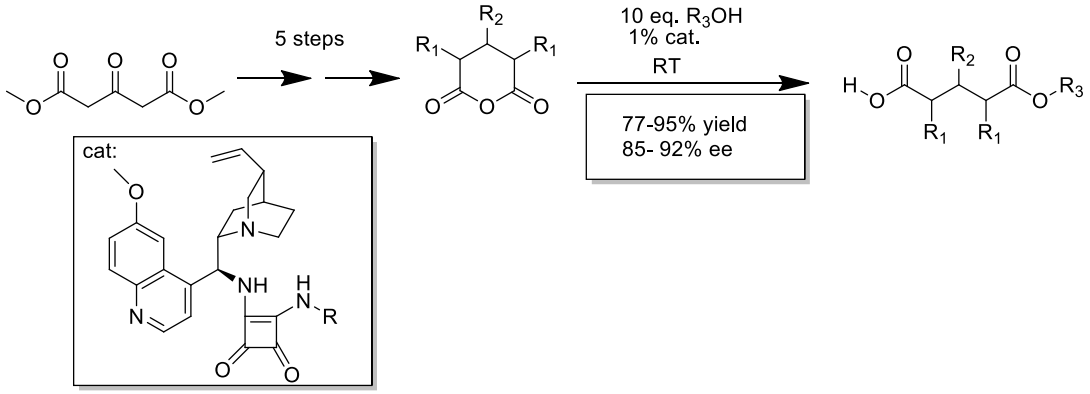
Synthesis of polypropionate polyketides is a challenging endeavour because of their rich and complex stereochemistry.[1,2]To streamline the complexity their synthesis, molecules containing three directly adjacent stereogenic centers – called stereotriads – can be useful. The diastereoselective synthesis of stereotriads is an additional stereochemical problem.

Initiated by this problem, we have developed a synthetic method which enables producing stereotriads with good yields with not only high diastereoselectivity, but also high enantioselectivity. The enantioselective step is the desymmetrization of a trisubstituted glutaric anhydride with using bifunctional squareamide derived organocatalyst.[3]



As part of our synthetic program, we are planning to functionalize these chiral building blocks and use them in the synthesis of complex structures and biologically active, natural products. The synthetic route to these stereotriads will be disclosed in our poster.

References:

[1] R. W. Hoffmann; *Angew. Chem*. *Int. Ed.* **2000**, 39, 2054-2070.
[2] R. W. Hoffmann; *Angew. Chem*. *Int. Ed.* Engl. **1987**, 26, 489-503.
[3] M. D. Díaz de Villegas, J. A. Gálvez, P. Etayo, R. Badorrey, P. López-Ram-de-Víu; *Chem. Soc. Rev*. **2011**, 40, 5564-5587.

BIO-INSPIRED CATALYTIC OXYGENASE CASCADES TO GENERATE COMPLEX SMALL MOLECULES

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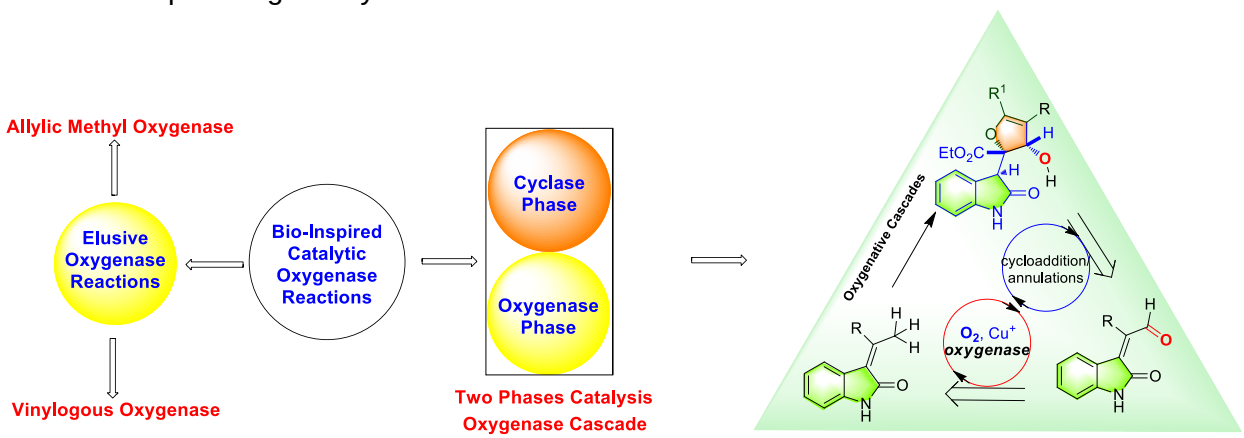
Catalytic, selective and controlled oxidative functionalization of C-H bonds using molecular oxygen as oxidant remains highly desired and equally challenging in the development of synthetic methodologies.[1] Herein we present first Cu(I) catalyzed oxygenative transformation of an allylic methyl group into an aldehyde in 3-methylidene oxindoles. The Cu(I) catalyzed oxygenase reaction used in tandem with a base catalyzed annulation of β-ketoesters with newly generated aldehyde provides the first *oxygenase cascade* synthesis of substituted dihydrofuran appended oxindoles.[2] Furthermore, we developed a vinylogous oxygenation of ketones, which remains an elusive problem in current organic synthesis. We believe that with rising demands for sustainable and environmentally benign synthetic routes to complex molecules, catalytic *oxygenase cascades* that employ O_2 as driving force in a domino or cascade reaction sequence will draw further attention of broader chemistry community and find more applications in green and clean bioinspired organic syntheses.



References:

[1] C. Zhang, C. H. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464-3484.
[2]Y. Wang, J. O. Bauer, C. Strohmann, K. Kamal , *Angew. Chem. Int. Ed.* **2014**, *53*, 7514-7518.

TOTAL SYNTHESIS OF *ENT*-PROGESTERONE AND TRUNCATED ANALOGS

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Steroids occur in Nature exclusively in one enantiomeric form, due to conservative biosynthetic pathways. Clearly defined binding pockets in nuclear receptors distinguish between natural (*nat*-) and enantiomeric (*ent*-) steroids. However, some membrane steroid receptors (e.g. $GABA_A$) are effected by *ent*-steroids, probably through membrane perturbation.[1] We will discuss here a total synthesis of *ent*-progesterone **I** (Fig. 1) to probe the mechanism of action of steroids at the NMDA receptor. The retrosynthesis was planned in respect to explore the minimum binding requirement of these substrates at NMDA receptors. Physiological activities of some neurosteroid congeners will be discussed.

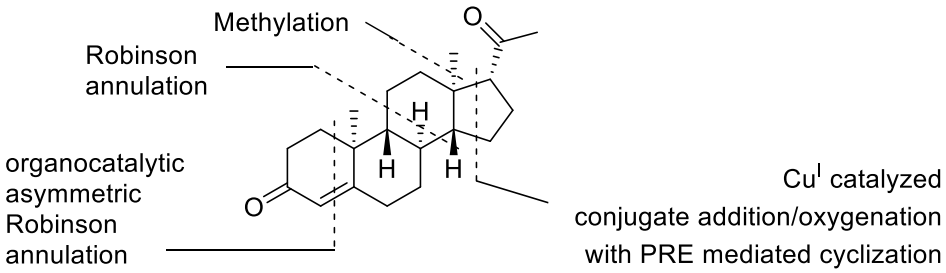

Figure 1. *ent*-Progesterone retrosynthesis

The key step of the synthesis is a novel reaction sequence consisting of Cu-catalyzed conjugate addition and oxygenation. A thermal radical cyclization employing the persistent radical effect (PRE)[2] leads to annulation of the five-membered ring. The synthesis of *ent*-progesterone is accomplished in a total of 15 steps.

References:

[1] D. F. Covey, *Steroids* **2009**, *74,* 557-585.
[2] A. Studer, *Chem. Eur. J.*, **2001**, *7*, 1159-1164.

SYNTHESIS OF OLIGOSACCHARIDES OF THE LINKAGE REGION AS POTENTIAL SUBSTRATES OR INHIBITORS OF GLYCOSYLTRASNFERASES INVOLVED IN THE BIOSYNTHESIS OF PROTEOGLYCANS

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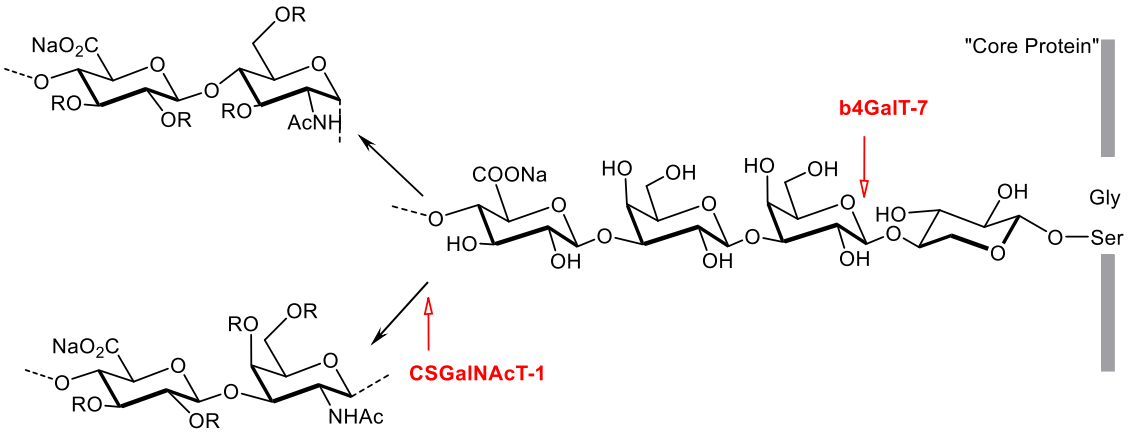
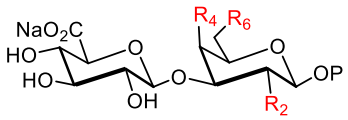
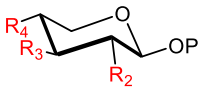
Proteoglycans (PGs) are a family of complex macromolecules characterized by the presence of glycosaminoglycan (GAG) chains covalently linked to a core protein. GAGs play important roles in a plethora of biological processes, such as cell growth and proliferation, embryonic development, and the coagulation cascade. They are also involved in the pathogenesis of several diseases including arthropathies, Alzheimer's disease and cancer. The biosynthesis of PG-GAG chains involves the sequential action of glycosyltransferases (GTs) responsible for the formation of a tetrasaccharide sequence GlcA-β-1,3-Gal-β-1,3-Gal-β-1,4-Xyl-β-O-attached to a L-serine residue of a core protein. This GAG-linkage region serves as a primer for polymerization of two types of GAG chains, heparin/heparan sulfates (Hep/HS) and chondroitin sulfates/dermatan sulfate (CS/DS). While the elongation is in progress, the GAG chains are modified by the cooperative action of multiple sulfotransferases and epimerases to yield the final complex GAG structure. It has been reported that the linkage region may be modified by sulfation or phosphorylation but the exact role of these substitutions in not yet fully understood.



The major goal of our team is to synthesize oligosaccharides of linkage region in order to advance our knowledge in the biosynthetic pathways of GAGs and particularly in the catalytic mechanism of the two human GTs: β4GalT-7 which transfers the first Gal residue and CSGalNAcT-7 which orientates the biosynthesis towards the CS/DS. Synthesis of modified xylosides and GlcA-Gal disaccharides will be presented as well as preliminary enzymatic results.



R2 or R4 or R6 = F or H or SO3Na



R2, R3, R4 = H, OH or F

References:

Saliba, M.; Ramalanjaona, N.; Gulberti, S.; Bertin-Jung, I.; Thomas, A.; Dahbi, S.; Lopin-Bon, C.; Jacquinet, J.-C.; Breton, C.; Ouzzine, M.; Fournel-Gigleux, S. *J. Biol. Chem.* **2015**, *290*, 7658-7670.

1-OXO-1*H*-PHENALENE-2,3-DICARBONITRILE: CHEMICAL STORY OF MISASSIGNED STRUCTURES

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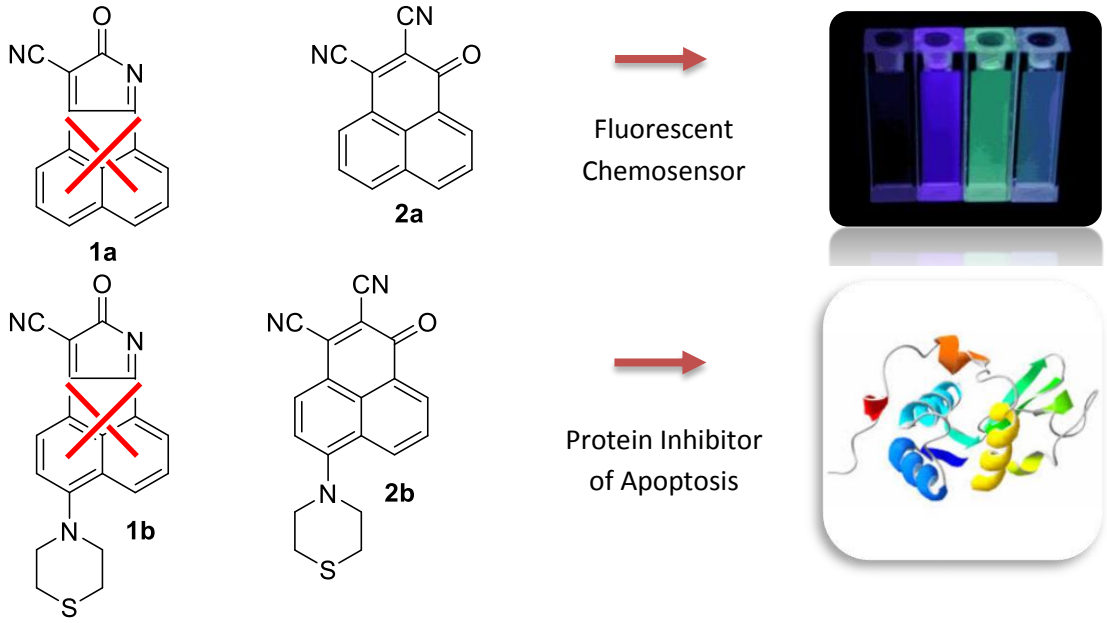
The preparation of substituted and fused polycyclic aromatic compounds and their corresponding heteroaromatic derivatives is an important field of organic chemistry with various applications from medicinal chemistry to materials sciences.

After being prepared for the first time in 2005,[1] the derivatives from 8-oxo-8*H*-acenaphtho[1,2-b]pyrrol-9-carbonitrile **1a** appeared in major publications by describing their great optical properties for fluorescent chemosensor devices.[2] Analogous structures **1b** were also recently reported for their promising effect as potent inhibitors of Bcl-2 and Mc1-1 proteins.[2]



A synthesis of the originally proposed 8-oxo-8*H*-acenaphtho[1,2-b]pyrrol-9-carbonitrile **1a** led to a structural revision, and the product has now been identified as unknown compound 1-oxo-1*H*-phenalene-2,3-dicarbonitrile **2a**. Thorough examinations of the structure and mechanism were investigated and will be discussed along with new chemical transformations.[3]

References:

[1] Xiao, Y.; Liu, F.; Qian, X.; Cui, J. *Chem. Commun*. **2005**, 239-241.
[2] Xiao, Y.; Liu, F.; Chen, Z.; Zhu, W.; Xu, Y.; Qian, X.; *Chem. Commun*. **2015**, 6480-6488.
[3] Lenk, R., Tessier, A.; Lefranc, P.; Silvestre, V.; Planchat, A.; Blot, V.; Dubreuil, D.; Lebreton, J. *J Org. Chem.* **2014**, *79*, 9754-9761.

A FACILE METHOD TO OBTAIN 1-ARYL-1,2,3,4-TETRAHYDROISOQUINOLINES

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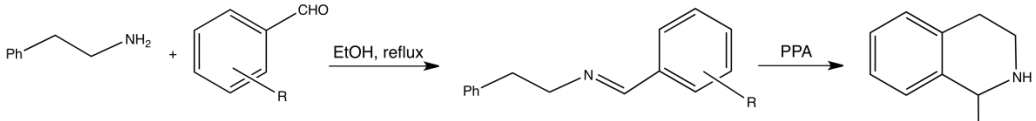
1,2,3,4-Tetrahydroisoquinolines (THIQ) are widely used biologically active compounds. Still, many of the methods currently used for their preparation are expensive or difficult to scale-up. We needed to develop a simple and convenient way to obtain significant quantities of the parent 1-phenyl-THIQ that could also be used to prepare other THIQ. Many compounds of this class have been prepared by acid catalyzed cyclization of the corresponding imines – Pictet-Spengler reaction[1]. Still, polyphosphoric acid has been used mainly to prepare THIQ from imines that undergo cyclization with ease[2], while a detailed study of the synthesis of the parent 1-phenyl-THIQ under these conditions has not yet been performed. Our aim was to adjust the reaction conditions, so that the synthesis could be used to obtain several hundred grams of this compound, and possibly even more. For research purposes, we also needed smaller quantities of substituted 1-aryl-THIQ, so we wished to extend the scope of this reaction.

We found it most convenient to carry out the synthesis in two separate steps (Scheme 1). First, we condensed phenethylamine with several benzaldehydes. Only the unsubstituted imine was obtained in high purity under the usual conditions (room temperature, dehydrating agent $MgSO_4$). Other imines often contained traces of the starting substituted benzaldehyde. We improved reaction conditions and obtained the requisite imines in absolute ethanol under reflux. All imines were essentially pure (GC and NMR), and the yields were quantitative. Further, we carried out cyclization of the imines in polyphosphoric acid (1:2 85% H_3PO_4:P_2O_5 by mass) at 160°C. Reaction half-time was established by GC for six imines (Scheme 1). No considerable side-reactions were detected, the yield of the THIQ was close to quantitative (GC) and still very good after isolation (Scheme 1), and the prepared THIQ were essentially pure, except that they occasionally contained trace of the initial imine. We also used this method to prepare 1-(2-piridyl)- and 1-(1-isoquinolyl)-THIQ. These reactions proceeded faster even at lower temperature, but gave slightly lower yields. Preparation conditions of the unsubstituted 1-phenyl-THIQ were further improved by lowering the concentration of polyphosphoric acid, so that commercial acid could be used, and increasing its amount. Reaction time did not change appreciably, while the yield of the THIQ on 100 g scale remained as high as 90% and it was completely pure (GC and HPLC).



Aldehyde*	Pictet-Spengler reaction half time, min	Yield, %
Benzaldehyde	122	90
2-Bromobenzaldehyde	65	92
3-Bromobenzaldehyde	58	88
4-Bromobenzaldehyde	95	80
4-Chlorobenzaldehyde	135	85
4-Fluorobenzaldehyde	175	75
2-Pyridinecarbaldehyde	**	58
Isoquinoline-1-carbaldehyde	**	62

* Used for imine synthesis
** Not determined

Scheme 1. Synthesis of THIQ

References:

[1] J. Stockigt, A.P. Antonchik, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011***, 50,* 8538-8564.
[2] A.P. Venkov, I.I. Ivanov, *Tetrahedron* **1996**, *52*, 12299-12308.

OXIDATIVE C-C BOND CLEAVAGE OF KETONE ENOLATES BY NITROSATION

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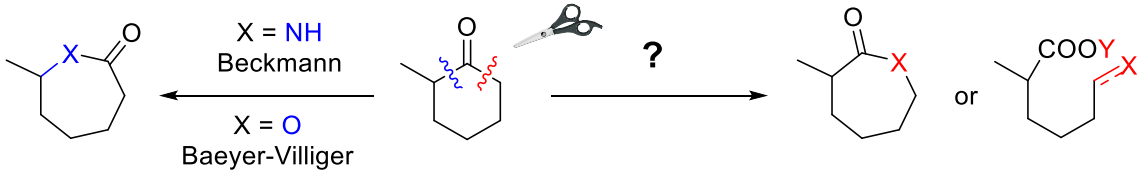
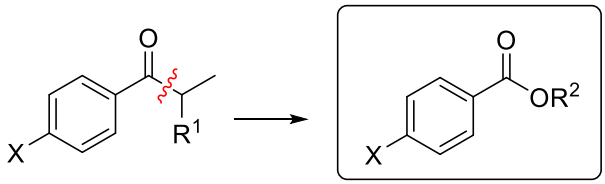
The Beckmann rearrangement and Baeyer-Villiger oxidation represent traditional ways of cleaving the otherwise rather inert C-C bond in ketones. In both cases, the regioselectivity of the reaction is mainly dictated by the substrate, i.e. *E/Z* configuration of oxime in case of the Beckmann rearrangement or relative migratory aptitudes in the case of Baeyer-Villiger oxidation. Since oxidative opening of ketones is a useful synthetic tool,[1] ways of controlling the site of the cleavage are very desirable. The possibility to direct the cleavage to the side of the less substituted carbon (the side of kinetic enolate) would complement the existing methodology.

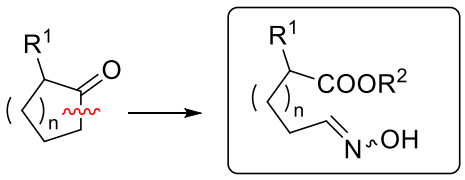


To address this issue, we found that treatment of ketone enolates with alkyl nitrites at low temperature results in facile C-C bond cleavage producing two new carbon termini in different oxidation states, namely ester and aldoxime - thereby simultaneously introducing nitrogen functionality. Aldoximes are versatile synthetic intermediates that can be transformed in one step to primary amines, aldehydes, nitriles or nitrile oxides.



X = H, F, OMe
R^1 = H, Me
R^2 = *t*-Bu, *n*-Bu, *i*-Am, *i*-Bu

66 - 99 %



R^2 = *i*-Am, *n*-Bu
R^1 = H, Me
n = 2

69 - 82 %

The practical aspects and scope of this transformation will be discussed on examples of various alkyl aryl ketones, cyclic and linear aliphatic ketones as well as reactivity of different metal enolates in combination with linear and branched alkyl nitrites.

References:

[1] J. Le Paih, J. C. Frison, C. Bolm in *Modern Oxidation Methods* (Eds.: J. E. Bäckvall), Wiley-VCH, Weinheim, **2004**, pp. 265-275.

SELF-ASSEMBLING CORROLES

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[b] Istituto per la Sintesi Organica e la Fotoreattività (ISOF), CNR, Via P. Gobetti 101, 40129 Bologna, Italy
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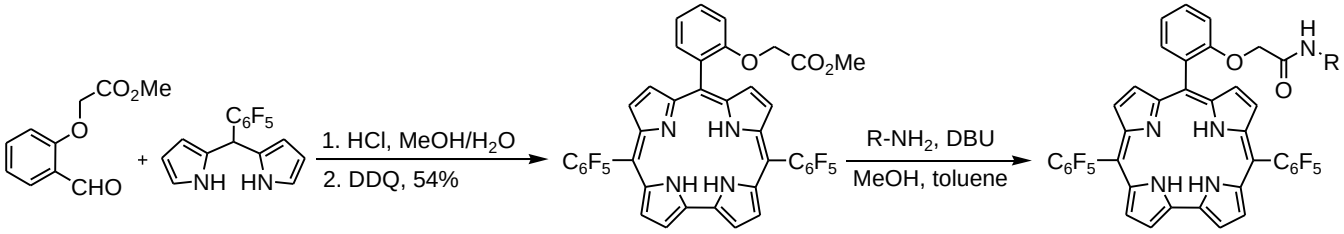
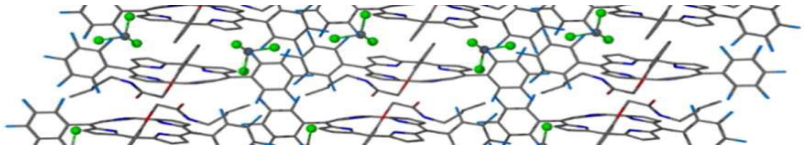
Self-assembly as a strategy towards creating large, highly organized structures from relatively simple building blocks is an attractive goal and the design of organic compounds with the ability to adopt specific compact conformations continues to be a flourishing area of research.[1] Many *meso*-substituted A_4-porphyrins do self assemble and Balaban and co-workers have proved that porphyrins possessing the minimum number of vantage points can create large organized assemblies as well.[2] The only known example of self-assembly of corroles has been as the amphiphilic sodium salt.[3] During our work we improved that *trans*-A_2B-corroles bearing $–OCH_2CONHR$ substituents at *ortho* position of the *meso*-phenyl substituent, undergo self organization both in the solid state as well as in solution.



The character of the internal NH at the corroles's core (serving as the hydrogen bond donor) is directly responsible for the strong self-organizing properties of these compounds. When combined with the special nature of the –CONH– group, these donating properties lead to the formation of aggregates in the solid state.



In solution, UV-vis absorption and fluorescence analyses revealed the formation of large aggregates in methanol/water mixtures at a critical water percentage of about 40-50%. The formation of strong intermolecular hydrogen bonds was clearly visible in crystallographic structures as well as in ^{1}H NMR spectra as strong upfield shifts of the amide-arm signals. The nature of hydrogen-bonded assembly can be regulated *via* the presence of an additional hydrogen-bond acceptor at the amide arm, opening interesting perspectives for the applications for the reported corroles.

References:

[1] J. S. Park, E. Karnas, K. Ohkubo, P. Chen, K. M. Kadish, S. Fukuzumi, C. W. Bielawski, R. W. Hudnall, V. M. Lynch and J. L. Sessler, *Science*, **2010**, *329*, 1324.
[2] T. S. Balaban, M. Linke-Schaetzel, A. D. Bhise, N. Vanthuyne, C. Roussel, C. E. Anson, G. Buth, A. Eichhöfer, K. Foster, G. Garab, H. Gliemann, R. Goddard, T. Javorfi, A. K. Powell, H. Rösner and T. Schimmel, *Chem.--Eur. J.*, **2005**, *11*, 2267.
[3] S. Nardis, D. Monti and R. Paolesse, *Mini-Rev. Org. Chem.*, **2005**, *2*, 355.

MODULAR SYNTHESIS OF HEPARAN SULFATE OLIGOSACCHARIDES

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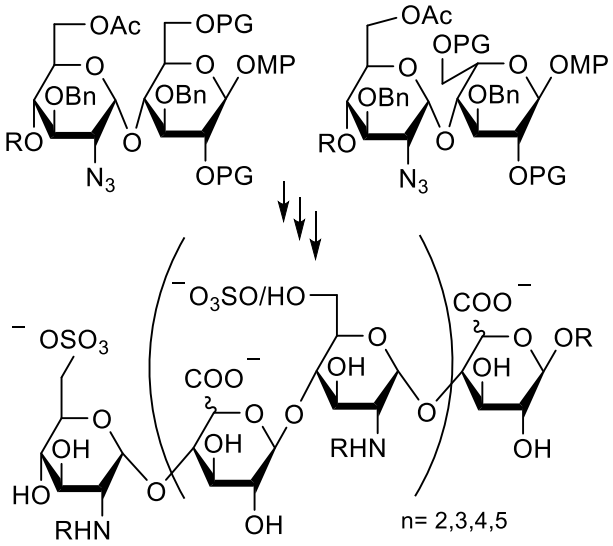
Heparan Sulfates (HS) are a class of sulfated polysaccharides which function as dynamic biological regulators of the interactions of diverse proteins.[1] Chemical synthesis of defined oligosaccharide structures represents a challenging but powerful approach to understand the structure-activity relationships of the complex sulfation patterns present in HS.

We have developed a novel generic method for the synthesis of HS oligosaccharides applied to the production of a library of 16 hexa- to dodecasaccharides targeted at BACE1 (β-site APP cleaving enzyme 1) inhibition.[2,3] In vitro activity assays using FRET peptides identified several compounds as potent non-coagulant inhibitors of β-secretase with potential for the development as leads for the treatment of Alzheimer's Disease through lowering of Aβ-peptide levels.[3,4]



In an effort to broaden the applicability of this synthetic methodology, we present here the use of additional protecting groups, enabling the synthesis of more complex and specifically sulfated or *N*-substituted HS oligosaccharides.

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METAL-FREE α-ARYLATION OF NITROALKANES USING DIARYLIODONIUM SALTS

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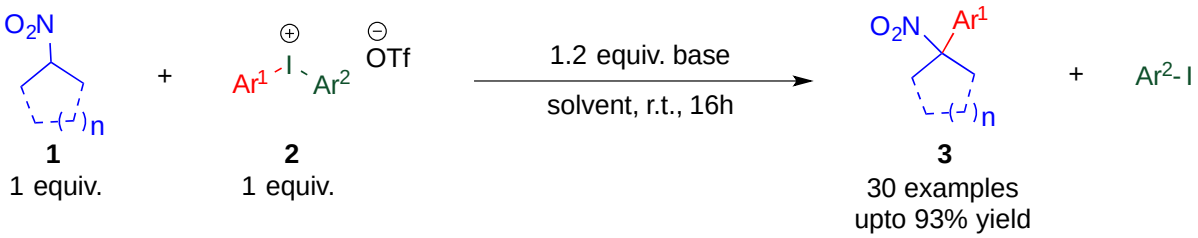
Nitroalkanes are synthetically important structural intermediates that have been used in total synthesis of natural compounds,[1] and the nitro group can be transformed into numerous other functional groups.[2] Unlike theα-arylation of carbonyl compounds such as ketones, esters, and amides, fewer protocols are known for the α-arylation of nitroalkanes. These include Pd–catalyzed α-arylation; or stoichiometric use of organolead(IV), organothallium(III), or organobismuth(V) reagents, which are all toxic metals.

Hypervalent iodine compounds have recently received substantial attention as mild, and nontoxic reagents in organic synthesis. Diaryliodonium salts were used for the α-arylation of carbonyl compounds, as well as for the *O*-arylation and *N*-arylation.[3] Herein we communicate a metal-free protocol for the α-arylation of nitroalkanes using diaryliodonium salts. Diaryliodonium salts were used for this purpose in the early sixties, but the limited scope of these reactions and the need for preformed alkalinitronate encouraged us to find a more efficient and user-friendly protocol.



Scheme 1. Metal-free α-arylation of the nitroalkane using the diaryliodonium salts

We have optimized the reaction and it was found that no excess of reagents is required and the reaction can be carried out at room temperature (Scheme 1). The yields are excellent independent of the ring size of the cyclic nitroalkanes. Both electron donating and electron withdrawing groups on the aryl ring of the iodonium salt afforded excellent yield in the α-arylation reactions. Similar to the cyclic nitroalkanes, the acyclic nitroalkanes were also successfully arylated in excellent yields.

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STEREOSELECTIVE SYNTHESIS OF NATURAL PRODUCT INSPIRED COMPOUND LIBRARY OF TETRAHYDROINDOLO[2,3-*a*]QUINOLIZINES

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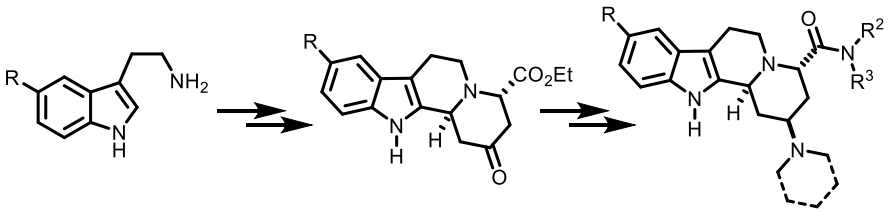
In the process of drug discovery, the hit and lead structures are discovered by high throughput screening (HTS) campaigns of different compound libraries.[1] Often, library synthesis efforts are driven by the availability of inexpensive substrates or synthesis routes which result in heavily compromised structural features of molecules and yield, for instance relatively flat heterocycles.[2] Such compound collections may fail to provide interesting starting points for drug discovery research.[3] Hence there is always a need for synthesis protocols towards novel core-structures or scaffolds to build a compound collection. Natural products (NP) have been an important source of drug discovery, with many useful drugs developed from plant sources. Bioactivity screening of NP derivatives and NP-derived compounds has become a feasible strategy for hit and lead identification in early phase of drug discovery.[4] In NP-inspired synthesis approach[5], not only the relative positions and nature of substituents around a NP-scaffold can be varied but also different relative stereochemistry patterns can be generated covering a broader chemical space of a particular structural class. In order to enrich the compound collection being developed in the consortium European Lead Factory (ELF)[6] with natural product based structural motifs, we set out to develop synthetic access to indole alkaloids inspired tetrahydroindolo[2,3-*a*]quinolizine scaffold and a compound collection based on this framework. Here we present the stereoselective synthetic access to a compound collection of tetrahydroindolo[2,3-*a*]quinolizine molecules.



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1,5-OR MIGRATION / CYCLIZATION: APPLICATION TO THE TOTAL SYNTHESIS OF SESQUITERPENES

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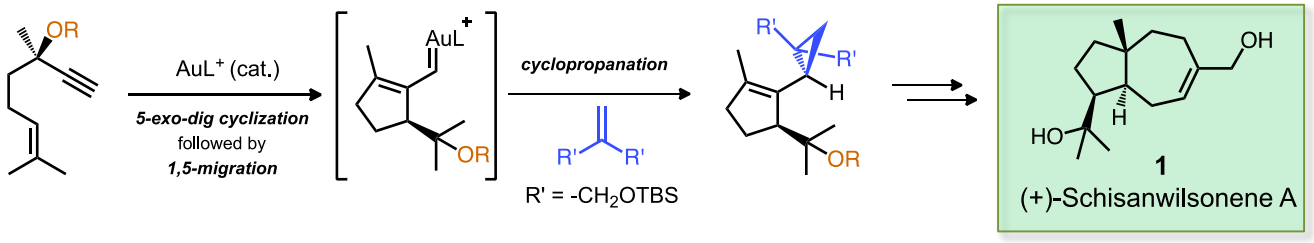
As part or a program aimed at the synthesis of natural sesquiterpenes, we targeted (+)-schisanwilsonene A (**1**) which was isolated from *Schisandra wilsoniana*, a medicinal plan indigenous to southern China.[1] This natural product has shown to be a potent antiviral agent against the hepatitis B displaying higher activity than current over-the-counter drugs (e.g. *Epivir-HBV* or *Zeffix*).

In 2013 we reported the first total synthesis of **1**, where the key reaction sequence 1,5-migration / cyclization was catalyzed by gold.[2] Nevertheless, partial racemization and low yield in the Au-mediated reaction was obtained as a result of a competitive 1,2-shifting of the –OAc migrating group.
Now we are looking for new routes that improve the former features of the synthesis. Preliminary results show –OPNP (*p*-nitrophenoxy) is a promising migrating group: the use of starting material bearing –OPNP prevents racemization (SM = 89% *ee* in the starting material leads to 89% *ee* in the product), and enhances remarkably the chemical yield (78-80%).
Further improvements will be presented in the near future.



Acknowledgments: We thank MICINN (project CTQ2010-16088/BQU), MINECO (Severo Ochoa Excellence Accreditation 2014-2018, SEV-2013-0319), the European Research Council (Advanced Grant No. 321066), and the ICIQ Foundation for support.

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THE CHITIN JOURNEY: FROM A NATURAL POLYMER TO RELEVANT OLIGOSACCHARIDES

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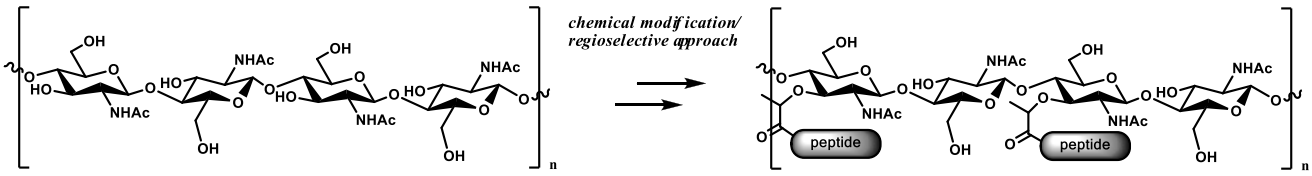
The biological importance of glycostructures made them popular targets in modern synthetic chemistry, in particular those incorporating *N*-acetyl-D-glucosamine (NAG) units. The urgent need of these compounds in pure form and in significant amount has implied vast synthetic efforts.

Usually oligosaccharides are constructed through sugar monomers manipulation, which implies time-consuming protection/deprotection steps and wild glycosylation reactions. Thus, in the last years, several approaches have been developed to attain complex glycostructures.[1] However, it has been demonstrated that glycosylation using NAG derivatives as glycosyl donors is still a difficult task.[2]

Our group has been also involved in the synthesis of glycostructures based on NAG units,[3] more specifically on the assembly of small fragments of bacterial peptidoglycan which will allow the identification of key interactions that determine their recognition by the host. Since these structures are composed of NAG and *N*-acetylmuramic acid (NAM) units connected *via* a β-1,4 linkage, it was envisaged that chitin could be used as an interesting starting material due to its particular structure – a linear (β1-4)NAG polymeric chain. This biopolymer provides a new dimension to attain the desired glycostructures by a reversed synthetic approach: the use of a high molecular weight biopolymer to attain a smaller molecule, as an alternative to classical glycosylation methods.

Herein, we report our recent advances on the synthesis of a biologically important NAG-NAM fragment associated with expression of bacterial resistance to different antibiotics and with a variety of host/bacteria interactions.[4] Taking advantage of our preliminar work on chitin manipulation, it is reported its chemical modification and an attractive regioselective approach to construct the NAG-NAM structure.



Chitin — Peptidoglycan fragments ($n < 5$)

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SYNTHESIS OF COMPLEX N-GLYCAN MIMICS VIA POLYGLYCOSYLATION USING CATALYTIC IRON(III) TRIFLATE

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Glycosylation is ubiquitous in nature and more than half of proteins are glycosylated. Glycan chains of glycoproteins are involved in numerous biological events.[1] Well-defined N-glycans are essential tools in glycobiology. Isolation from nature is possible but challenging and the quantities obtained are rather small.[2] Chemical synthesis can be used to obtain larger quantities but is time-consuming because of the structures complexity (Figure). Fast transformations are still required in order to work out new synthetic strategies.

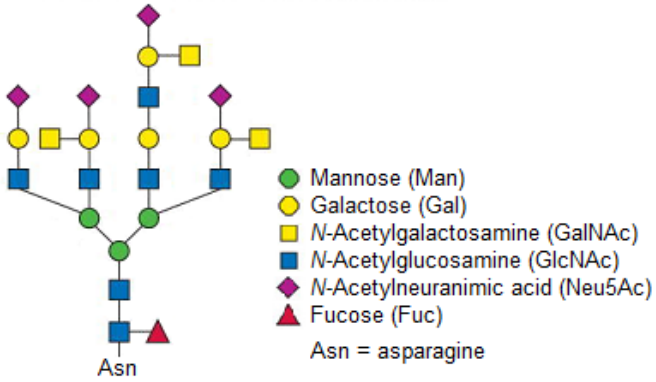
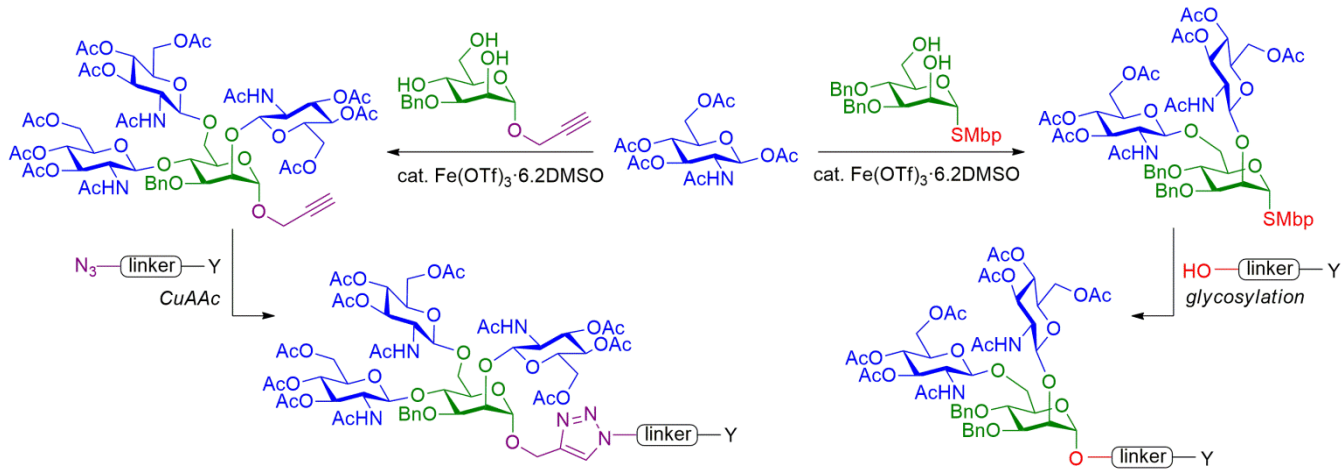


Figure. Structure of a complex N-glycan

Efficient and highly selective glycosylation with peracetylated β-*N*-acetylglucosamine donor, using iron(III) triflate under microwave conditions, has been described by our group.[3] Various disaccharides were rapidly obtained in good yields. We will report the use of these conditions to synthesize a number of branched structures of *N*-acetylglucosamine units on a mannosidic core, which are present in each complex N-glycan. The polyglycosylation was achieved with complete β-selectivity (Scheme). The synthesis of this kind of motifs has been described in several steps with moderate overall yields.[4] Depending on the anomeric group, the oligosaccharides were finally engaged in another glycosylation reaction or in a CuAAc click reaction to introduce a functionalized linker.



Scheme 1. Synthesis of complex N-glycan mimics

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EFFICIENTLY SYNTHESIS OF COUMARIN-CHALCONE HYBRID COMPOUNDS

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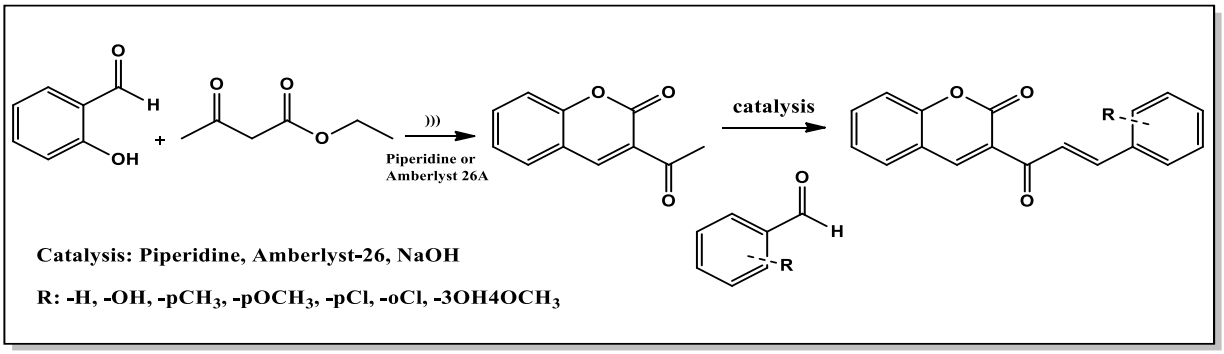
Coumarins, heterocyclic compounds having oxygen, occur naturally in a number of plants. They are isolated from various plants or obtained synthetically, in the commercial uses. Coumarin derivatives are especially important in medicine due to variety of biological activity. Furthermore, their applications range in perfume, food, plastic and dye industries[1].

Chalcones are an important class of organic compounds being studied over the years and reported to possess wide spectrum of biological properties[2] such as antibacterial[3], antifungal[4], antimalarial[4], antitumor[4,6,8], anti-inflammatory[5], anticancer[5,7,8], antitubercular[3,4], and anti-oxidant[4,7,8] activities.Chalcone also used to regulate the cholesterol levels, reduces blood pressure and blood sugar, reduces allergy and sinus problem, improve vision and memory, aids sleep, suppresses gastric acid secretion[3,4,6,7,8]. As a potent antioxidant, it helps to protect the organ from destructive free radical and shows the ageing process[4,7,8].

In this study, we synthesized 3-acetylcoumarin, which is going to be used for synthesis of chalcone, with traditional method and ultrasonic vibration. In the second step this coumarin compound reacted with benzaldehyde derivatives and three different catalysts. The effect of catalyst amount on the coumarin-chalcone hybrid yield was also investigated. The seven desired chalcone derivatives were obtained with from moderate to excellent yield (40-92%) after 2-5 hours reaction time.



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ORGANOCATALYTIC DEVELOPMENT OF CHIRAL BUILDING BLOCKS

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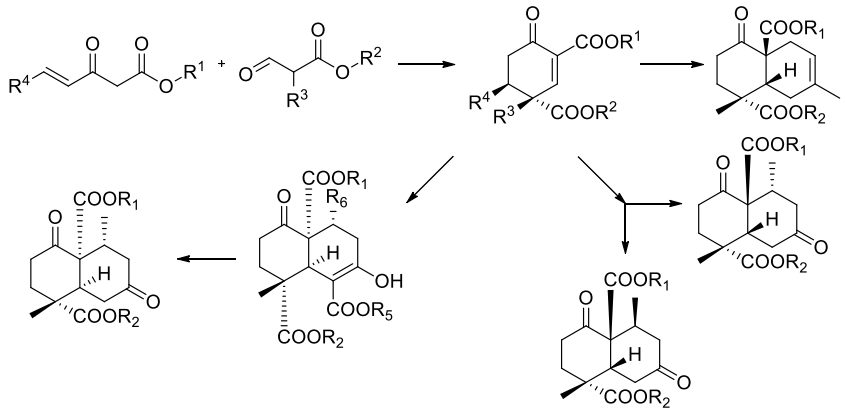
Our aim has been to develop chiral building blocks, which can be utilized as key intermediates in the synthesis of terpenoids. The terpenoids can be recognized in many molecules derived from natural sources. Moreover, they show potent biological activity and can be used in the pharmaceutical and perfume industry as well. [1]

Our major focus has been the synthesis of an appropriately decorated decalin rings which are common motives in terpenoids. We envisioned a new chiral building block having a quaternary stereocenter that can be prepared by an organocatalytic tandem reaction of Nazarov's reagent.



With the cyclohexene derivative in hand, two ring closing reactions were probed for the preparation of the *cis*-decalins which were the anionic Deslongchamps annulations with a Nazarov's reagent and the Diels-Alder reaction.[2,3] The result of this synthetic work, the diastereoselectivity of the process will be outlined in this poster.

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EPIMERIZATION OF TERTIARY, ALKYL-SUBSTITUTED STEREOGENIC CENTRES VIA A RADICAL PATHWAY

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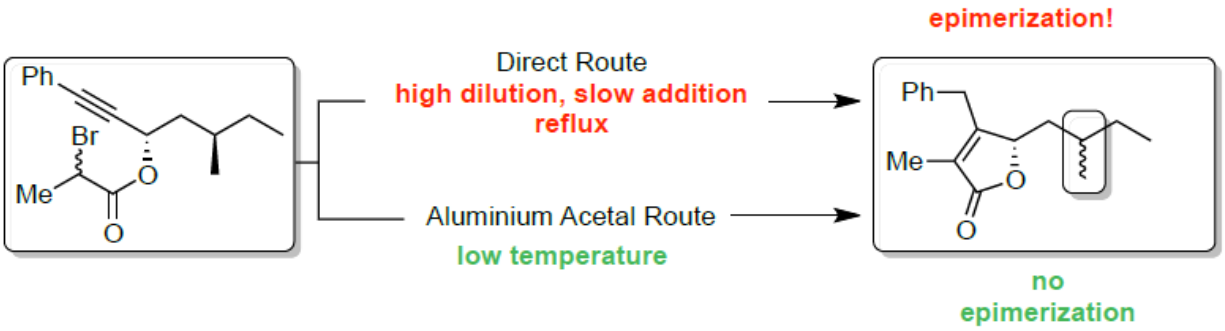
Polysubstituted butenolides were obtained in good to high yields from alpha-bromoesters derived from propargyl alcohols via a one-pot reaction involving the radical cyclization of alpha-bromo aluminium acetals,[1,2] followed by the oxidation of the resulting cyclic aluminium acetals in an Oppenauer-type process[3] and migration of the exocyclic C=C bond into the alpha,beta-position. A comparison with the direct cyclization of alpha-bromoesters at high temperature and under high dilution conditions is described. Deuterium-labelling experiments allowed us to uncover "invisible" 1,5-Hydrogen Atom Transfers (1,5–HATs) that occur during these cyclization processes, and the consequences of the latter in the epimerization of stereogenic centres.[4]



Compared to the classical approach, the cyclization of aluminium acetals proved to be highly chemoselective. Our recent results in this field will be discussed herein.

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PYRIDINE – HETEROCYCLES: PREPARATION AND USES

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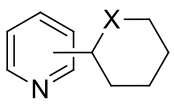
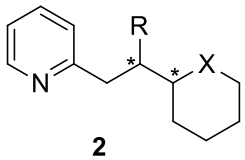
Molecular architectures based on the combination of both a pyridine ring and an additional saturated heterocycle such as piperidine or tetrahydropyran represent challenging targets in organic synthesis. Despite increasing reports dealing with the applications of such patterns, their preparation suffers from a lack of generality. We focused our attention on pyridyl-heterocycles patterns **1** or with an ethylene-based spacer linking both heterocycles **2**.



1



2

X = O, NH

The use of a Prins cyclization as a key step allowed us very short preparations and a large structural scope of **1** and **2**. The Prins reaction most often required a minimum of 3 equivalents of acid, which is quite important in regard of the Lewis acids generally used, quite expensive and generating problems of purification and wastes. In this context, an additional hurdle to overcome could arise from the use of pyridine derivatives as substrates due to potential neutralization or complexation of the pyridine nucleus with the acid requested for the reaction. The resolution of these inconvenients will be discussed.[4]

Such structures can be found in alkaloids[1] and synthetic bioactive molecules.[2] Further, these bisheterocyclic molecules have been recently shown to be efficient ligands in transition-metal promoted transformations.[3] The use of our targets **2** as organo- and metallocatalyst will be described.

References:

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MECHANOCHEMICAL RITTER REACTION: A RAPID APPROACH TO FUNCTIONALIZED AMIDES AT ROOM TEMPERATURE

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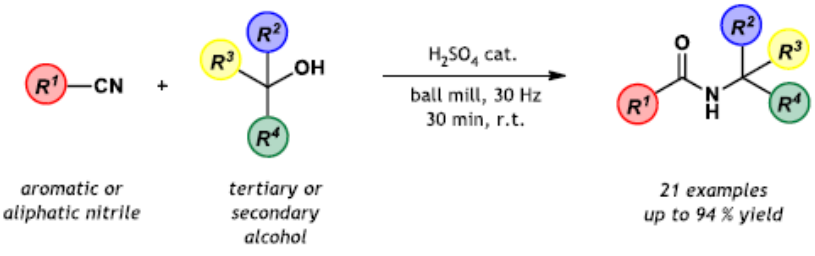
We report a general procedure for Brønsted acid catalysed mechanochemical Ritter reaction under mild conditions: room temperature, short reaction time, and a solvent-free or low-solvent environment. The versatility of the protocol was veryfied through a wide substrate scope investigation, including functionalized nitriles, as well as secondary and tertiary alcohols.[1]

The Ritter reaction is an organic reaction that allows formation of amides from a carbocation precursor (tertiary alcohol or substituted olefin) and a nitrile using a strong acid catalyst. Although the Ritter reaction found its application in drug, and natural product and natural product-like syntheses, the traditional use of stoichiometric amounts of strong corrosive acids at elevated temperatures and long reaction times limit its wider application. Moreover, harsh reaction conditions confine functional group variety.

Mechanochemistry has been recognized as one of the most successful modes of solvent-free synthesis. Mechanochemical reactions, usually performed in ball mills, are now present in all fields of chemistry, and their application in organic synthesis is increasing. Recently, it has been shown that conditions produced by a ball mill could be compared to those produced when performing the same reaction at elevated temperature in a solution, though the temperature in the vial remains virtually ambient.[2] Hence, the activation energy of the Ritter reaction could be overcome during ball milling.

The hypothesis was proved valid, as the Ritter reaction was successfully performed in a ball mill in 30 min at room temperature utilizing sulfuric acid catalyst. The reaction is tolerant of a wide range of functionalized nitriles, as well as secondary and tertiary alcohols, generating amides in up to 94 % isolated yield. In most examples, recrystallization was sufficient purification method. The reaction proceeds in a solvent-free environment with equimolar amounts of reagents, however, in several cases liquid-assisted grinding with nitromethane was required.

Developed procedure offers a rapid approach to functionalized amides, and may find application in the synthesis of complex frameworks and natural product analogues comprising sensitive functional groups.



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4-SUBSTITUTED-4-ALKYNYL 2-OXAZOLINES VIA THE RITTER REACTION

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Oxazolines are important building blocks for the synthesis of chiral ligands, natural products and other materials. In addition, oxazolines can be readily transformed to amino alcohols and amino acids.

The Ritter reaction has been used to prepare oxazolines from epoxides and diols. Importantly, the substrates for the Ritter reaction should have a group, which stabilize the intermediate carbocation.[1] [2] [3]

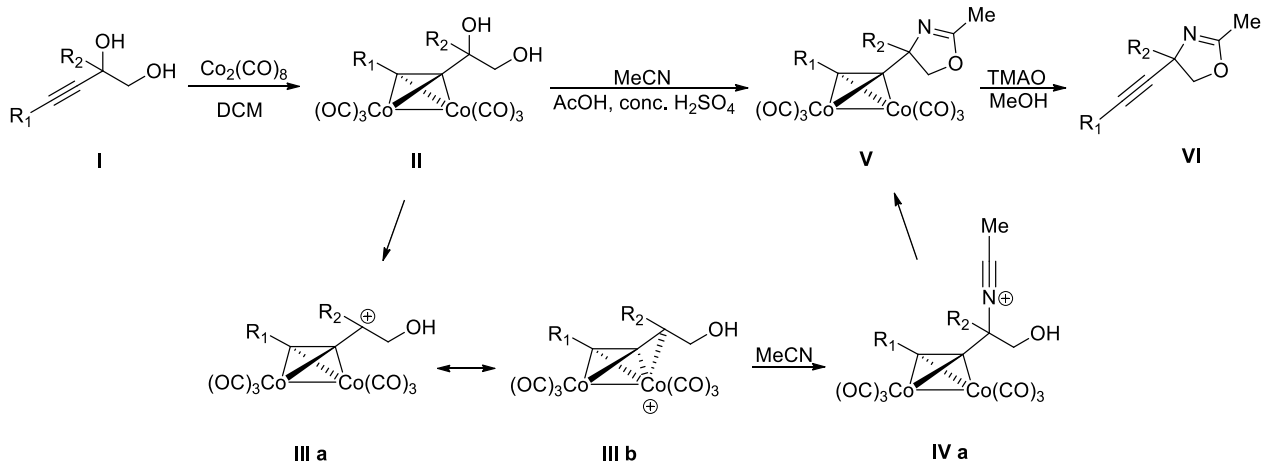

Figure 1

In our poster, we present a new method for the synthesis of 4-alkynyl oxazolines **VI** from $Co_2(CO)_6$ complexed alkynyl diols **II** and acetonitrile via the Ritter reaction (Figure 1). It was found that Co complex with alkyne is crucial for the successful reaction. This can be attributed to the formation carbocation at the *α*-position of the alkyne **IIIa** stabilized by delocalization of positive charge into $Co_2(CO)_6$ (mesomeric structure **III b**). Attack of nitrile to carbocation results in the formation of iminium ion **IV a,b**, which cyclizes to oxazolines **V**. Finally, the oxidative destruction of Co complex provides alkynyl 2-oxazoline **VI**.

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SYNTHESIS OF NITROARENES USING DIARYLIODONIUM SALTS

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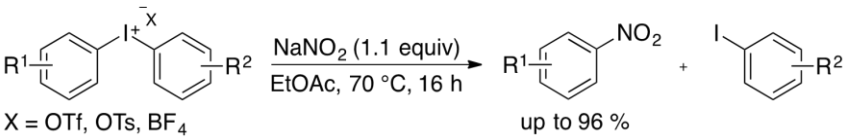
Aromatic nitro compounds are key intermediates in the synthesis of many dyes, plastics and explosives.[1] Nitrations are commonly performed via an electrophilic aromatic substitution (EAS) between an arene and a nitronium ion. This method suffers from the limitations of EAS reactions, including regioselectivity issues and reactivity problems for electron-deficient arenes. Furthermore, unforgiving conditions are necessary, supporting the need for more selective and milder protocols.[2] Buchwald and co-workers have developed a high-yielding protocol for *ipso*-nitration of aryl chlorides, triflates and nonaflates using palladium catalysis.[3] However, this protocol suffers from a limited scope and the use of metal catalysts. Recently, Goswami and co-workers published a metal-free alternative that nitrates arylboronic acids using a nitro radical.[4] While this procedure is mild and has a broad scope, it requires an excess of reagents and the use of boronic acids.

Our group has used electrophilic hypervalent iodine reagents, diaryliodonium salts, to arylate several different *C*-[5] and *O*-nucleophiles[6]. We now wish to extend this methodology to include *N*-arylation, for the regiospecific, metal-free synthesis of nitroarenes.

By employing sodium nitrite together with diaryliodonium salts, we have achieved an efficient synthesis of nitroarenes under mild conditions (Scheme 1). The reaction uses the sustainable solvent ethyl acetate and requires no excess of reagents or inert atmosphere.



Scheme 1. The optimal conditions used in the nitration of diarylionium salts.

The reaction has a broad scope; bulky or sterically hindered arenes, electron withdrawing and donating groups and halogen substituents are allowed and deliver the nitroarene in good to excellent yields. Heteroaryl groups, such as pyridine, are also tolerated and give the nitrated product in high yields.

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ENANTİOMERS OF 1-ACETYL-2-THİOHYDANTOİN DERİVATİVES

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Although there are publications on the synthesis and structural evidence of 1-acetyl-2-thiohydantoin derivatives from optically active amino acids [1-2], there is no information about the enantiomeric purity of the products. We attempted to investigate whether 1-acetyl-2-thiohydantoin derivatives synthesized as a single enantiomers or as racemates using (S)-TFAE and (1*R*,2S)-(-)-ephedrine as chiral auxilaries and enantioselective HPLC with Chiralpak IC column at 7 ^{o}C and found out that the syntheses produced racemic mixtures.

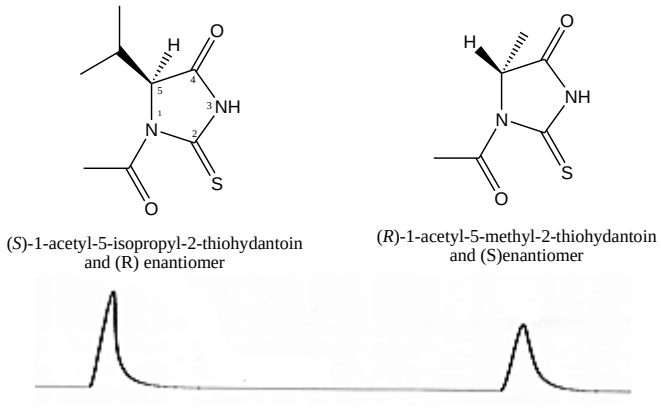

Figure 1. The HPLC chromotogram of 1-acetyl-5-isopropyl-2-thiohydantoin on Chiralpak IC showing the presence of R and S enantiomers.

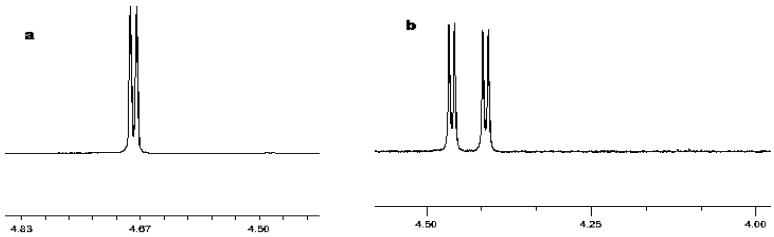

Figure 2. ^{1}H NMR peaks of CH proton at C-5 of 1-acetyl-5-isopropyl-2-thiohydantoin in the (a) absence of chiral auxiliary (b) presence of chiral auxiliary (1R, 2S)-(-)-ephedrine.

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THE EFFECT OF THE SUBSTITUENT ON PROLINE-CATALYZED ALDOL REACTIONS

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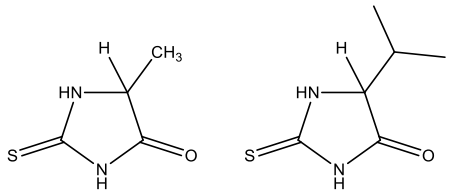
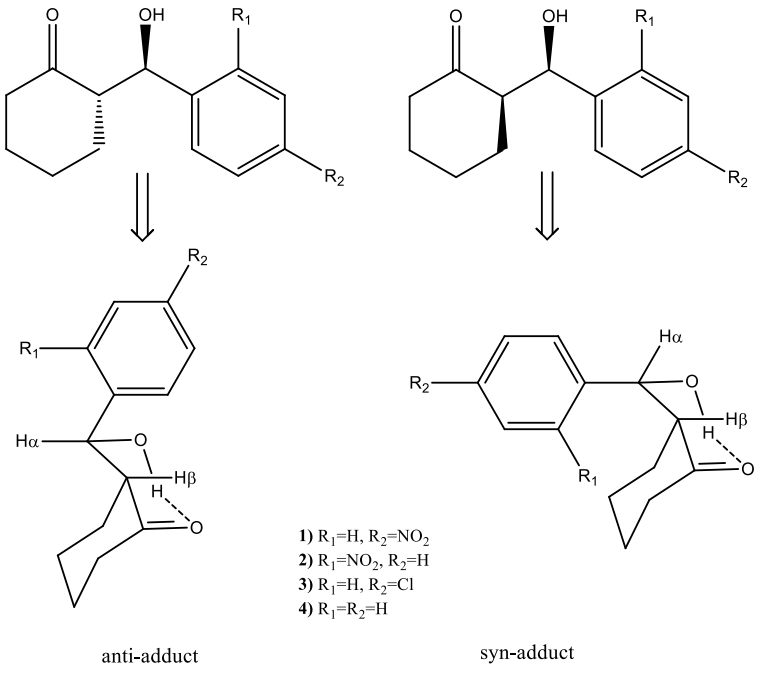
Environmentally friendly synthesized 5-substituted thiohydantoins (Scheme 1)[1] were used as additives in proline-catalyzed aldol reactions of cyclohexanone with different aldehydes lacking α-H. The formation of the diastereomeric products (*anti-* & *syn-*) (Scheme 2) was proved by using difference in the coupling constants in ^{1}H NMR and the enantiomeric ratios were determined by HPLC with a chiral stationary phase. It was observed that the position and the type of the substituent have an effect on the diastereoselectivity.



Scheme 1. The synthesized 5-substituted thiohydantoins



Scheme 2. The adducts in proline-catalyzed aldol reaction

References:

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SELECTIVE DEPROTECTION OF α-HYDROXYBENZYL ETHER BY AN INTRAMOLECULAR HYDROGEN ATOM TRANSFER

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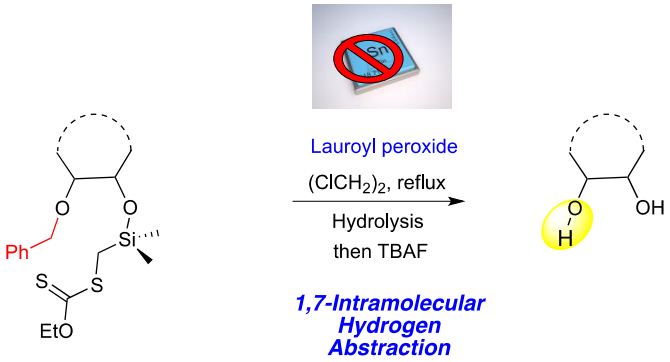
The synthesis of biologically active molecules from carbohydrates derivatives requires the preparation of suitably protected monomers. The one-pot regioselective protection of hydroxyl groups represents an important strategy for the preparation of these molecules.[1] However, the selective deprotection of this function could represent an interesting alternative method. The benzyl ether is one of the most widely used protecting group due to its easy formation, stability under various conditions and the numerous deprotection methods. Hence, several methods of de-*O*-benzylation of perbenzylated saccharides[2] have been reported in the literature. Most of these approaches are however incompatible with thioglycosides[3] which represent a major building block in oligosaccharides synthesis. For this purpose, we have developed a tin-free regioselective radical de-*O*-benzylation, which is based on an unusual 1,7-intramolecular hydrogen transfer.[4] We will report here the extension of our methodology to non glycosidic structures with NMR evidence on the mechanism.



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STABLE TETRAHEDRAL INTERMEDIATES DURING ENAMIDINE FORMATION REACTIONS

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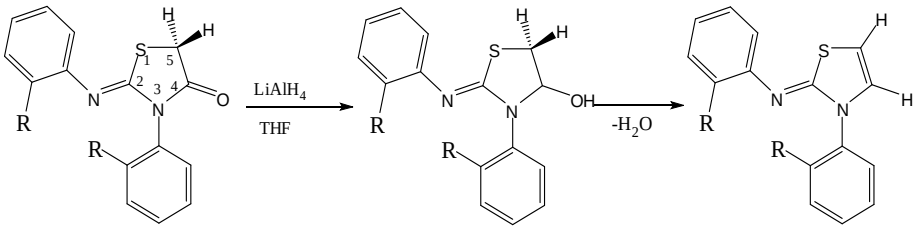
Imine conjugated hemiaminals (**2a-d**), which are tetrahedral intermediates during enamidine formation reactions, have been isolated as stable compounds from $LiAlH_4$ reductions of the corresponding 2-arylimino-3-aryl-thiazolidine-4-ones[1] (**1a-d**) and identified by ^1H NMR. In solution, the hemiaminals have been found to slowly convert to the corresponding enamidines (**3a-d**) with time (Figure 1). The first order rate constants for the conversion processes have been determined by time dependent ^1H NMR analyses. The half-life times of the hemiaminals were found in the range of 2.5 days to >5 months. The hemiaminals owed their ease of formation mainly to the imine conjugation of the amide nitrogen N3 which is expected to give a ketone character to the amide carbonyl by shifting the lone pair of electrons on the amide nitrogen towards the imine side. The stabilities of the hemiaminals were due to the amidine conjugation of the hemiaminal nitrogen and partly due to an intramolecular H-bonding interaction for the *o*-methoxyphenyl derivative.



1a. R=OCH_3
1b. R=H
1c. R=CH_3
1d. R=benzo

2a. R=OCH_3
2b. R=H
2c. R=CH_3
2d. R=benzo

3a. R=OCH_3
3b. R=H
3c. R=CH_3
3d. R=benzo

Scheme 1. Synthesis of the compounds **2a-d** and **3a-d.**

References:

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SYNTHESIS OF BICYCLIC TERPENOID FRAGMENTS FROM A CHIRAL BUILDING BLOCK

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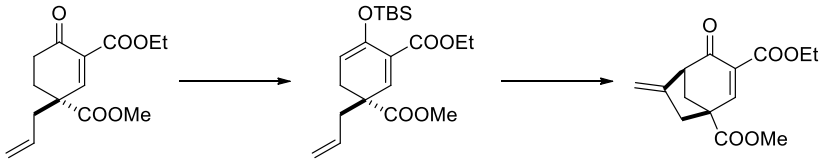
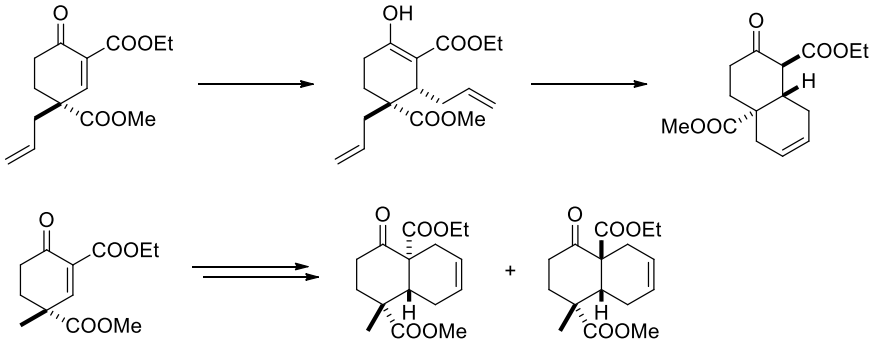
Recently, we have developed a chiral cyclohexene building block which can be used as an intermediate in terpenoid total synthesis. This compound can be synthetized from easily available starting materials (the well-known Nazarov reagent and an α-formyl carboxylate) in an enantioselective Michael-aldol tandem reaction catalyzed by *cinchona* alkaloid based organocatalyst. The building block contains two esther groups and an electron-deficient olefin bond providing possibility for further functionalisation.

Our aim was to synthetize two general structural moiety from the these building blocks. The bicyclo[3.2.1]octane ring system is a key fragment of the *Isodon* terpenoid family. We have developed a palladium catalyzed route to prepare this motif using the silyl enol ether of the allyl substituted cyclohexene derivative.[1]



Additionally, novel routes to assemble *trans* decalin skeleton will be outlined. Hosomi-Sakurai allylation of the building block resulted a diallyl compound diastereoselectively.[2] By subsequent ring closing metathesis reaction we obtained the desired product in moderate yield. Additionally, a four-step pathway have been developed relying on a double-allylation- metathesis sequence.



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NUCLEOPHILIC RING OPENING OF SMALL SIZE *N*-HETEROCYCLES IN LIQUID SULFUR DIOXIDE

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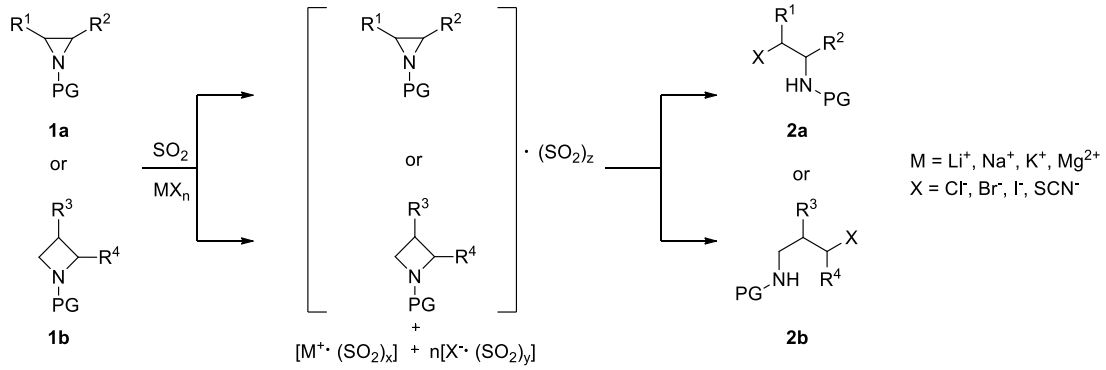
Aziridine and azetidine moieties are important small ring N-heterocycles in organic synthesis due to their biological and pharmacological properties and synthetic potential as a building blocks.[1] Modifications of these aza-heterocycles can lead to the formation of various classes of compounds, such as heterocycles,[2] alkaloids [3] and non-natural amino acids.[4] The reactivity of aziridines and azetidines strongly depends on variation of ring substituents, activation of nitrogen atom and ring strain. Due to the latter, the most common transformations of these heterocycles are the nucleophilic ring-opening reactions (NRORs). NRORs have been exhaustively described in excellent reviews.[5]

Halogen nucleophiles can be introduced under acidic conditions (e.g.: with HCl).[6] Another source of halogen nucleophiles are metal halides. However, there are only a few precedents of ring opening using halides MXn.[7]



Here we present a new synthetic process of aziridine and azetidine NRORs with metal halides and other nucleophiles in liquid sulfur dioxide. The use of sulfur dioxide in organic synthesis has recently seen a renaissance [8]. Reactions were carried out in three temperature modes. The efficiency of each aziridine or azetidine ring opening reaction was monitored in several solvents in parallel experiments: SO2(liq.), DMSO, MeCN, TFE. We have used I and II group metal halides as a nucleophile source.
The obtained results showed that the aza-heterocycles NRORs in liquid sulfur dioxide occurs noticeably faster and cleaner than in other solvents.

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STUDIES TOWARDS MODIFIED CHITOSAN: A NEW APPROACH TO NAG-NAM

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[b] Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Av. Da República (EAN), Oeiras, Portugal

Peptidoglycan (PGN) is the major component of the bacterial cell wall, and is composed of alternating β-(1,4) linked *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) residues, cross-linked by short peptide bridges (Figure 1). PGN is recognized by invertebrate and vertebrate innate immune system (IIS) and is capable of inducing an innate immune response.[1] Due to the biological relevance of PGN several research groups have contributed to the development of muropeptide synthesis.[2] Our research group have been dedicated to the preparation of glucosamine building blocks and NAG-NAM disaccharides.[3]

During our research on PGN recognition by molecular patterns on IIS,[1] we came across with the structural similarity of chitin/chitosan and the carbohydrate skeleton of bacterial PGN, murein.[3c] Thus we have embarked on the synthesis of PGN of different molecular weight from chitosan, through selective chemical modifications of the naturally abundant biopolymer.

Herein we will present our recent developments on the quest for an artificial bacterial PGN, starting with commercial chitosan through chemoselective modifications and enzymatic recognition.

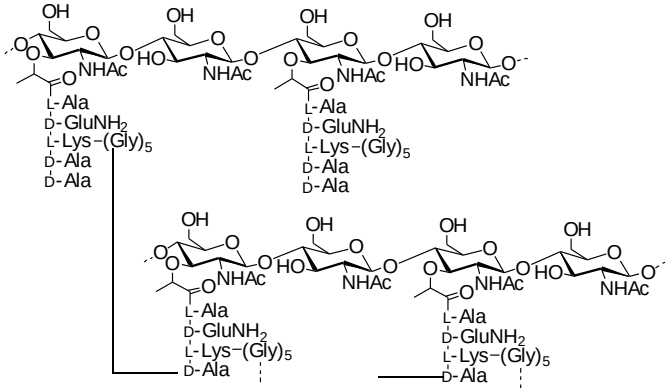

Figure 1. Structure of the *S. aureus* peptidoglycan (a Lys-type PGN).

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SYNTHESIS OF NEW MYCOBACTERIAL SULFOGLYCOLIPID ANALOGUES, RELATED TO *MYCOBACTERIUM TUBERCULOSIS*

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Some natural sulfoglycolipids, metabolites found in *Mycobacterium tuberculosis*' cell wall, as well as synthetic analogues, were recently identified as new antigens able to control mycobacterial infection[1] and appeared to be promising additive candidates for the development of a new and efficient vaccine against tuberculosis.[2] These metabolites are acylated and sulfated α,α-D-trehalose derivatives, esterified at C2 by palmitic acid and at C3 by a chiral polydeoxypropionic chain (Figure 1).

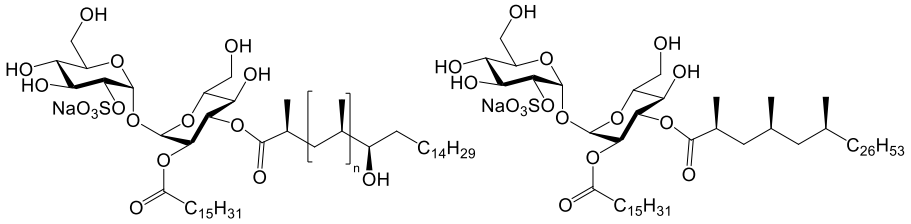

Figure 1. Natural sulfoglycolipids (**1**) and a synthetic analogue (**2**)

In order to evaluate the influence of chain length and sulfated moiety on the immune response, we focused on the synthesis of new analogues of sulfoglycolipids. In our approach (Figure 2), *O*-sulfated glucose unit was replaced by diverse mimetic units and acylated intermediates were prepared starting from D-glucose using selective functionalizations, including a tandem regioselective protection.[3] The analogues' synthesis presented will include an access to long chiral polydeoxypropionate chains using Myers' alkylation and cross metathesis olefination as key steps.[4]

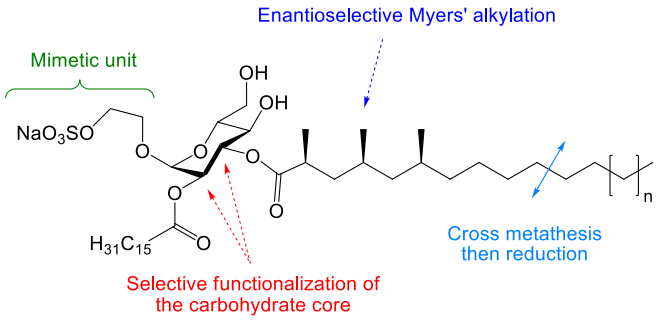

Figure 2 : Approach to new sulfoglycolipid analogues

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SYNTHESIS AND FUNCTIONALIZATION OF TRIAZOLOPYRIDOPYRIMIDINES

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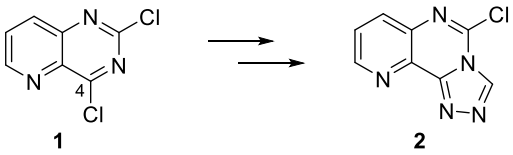
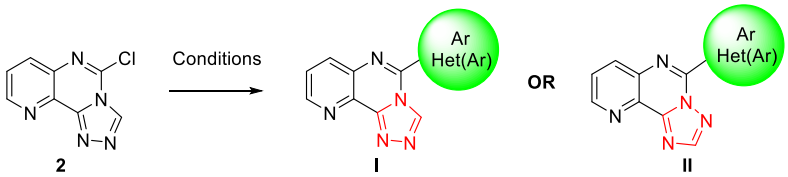
Pyridopyrimidines are interesting pharmacophores for the construction of biologically active compounds. Very recently, our laboratory reported the synthesis of two new dual PI3K/mTOR inhibitors which incorporated this scaffold having nanomolar enzymatic and cellular activities.[1] This current work is based on the reactivity of a molecule synthesized in Orleans several years ago: 2,4-dichloropyrido[3,2-*d*]pyrimidine (1).[2] Regioselective substitution of the first chlorine atom in position *C*-4 was possible to give, in only two steps, pyrido[2,3-*e*][1,2,4]triazolo[4,3-c]pyrimidine (2) in good yield.



1 **2**

Molecules with a fused pyrido[3,2-*d*]pyrimidine/1,2,4-triazolo ring are very rare and poorly described in the literature. We wished to explore the reactivity of derivative 2 in Suzuki-Miyaura and Sonogashira coupling reactions in order to increase molecular diversity and chemical space around this innovative platform.

During our investigation, we judiciously used a 1,2,4-triazolo isomerization (Dimroth rearrangement)[3] to elaborate two novel platforms using the sole and unique starting material 2. We have found that by correctly choosing the reaction conditions both the substituted 1,2,4- and the 1,3,4-triazolopyridopyrimidine ring I and II systems can be selectively obtained in good to excellent yields.



2 **I** **II**

Acknowledgements: This work was supported by the National Cancer League (Grand-Ouest), the Region Centre, the Canceropole Grand Ouest (strand "valorization of marine products in oncology") and the LABEX Synorg [ANR-11-LABEX-0029] for the Master fellowship of AL.

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NOVEL APPLICATIONS OF SULFUR DIOXIDE IN ORGANIC AND ANALYTICAL CHEMISTRY

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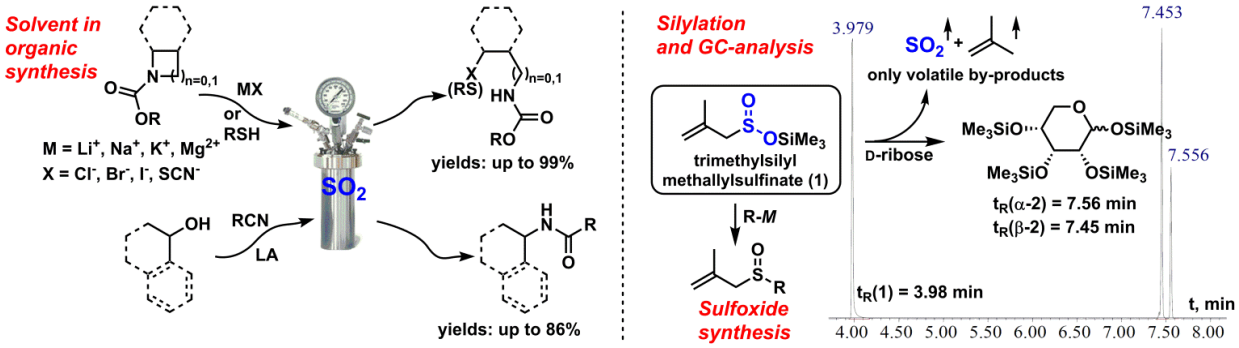
Sulfur dioxide, which is a gas at ambient conditions, reveals a rather long liquid range: it boils at -10 °C and freezes at -75.5 °C. Most importantly, SO_2 condenses easily by compression due to its high critical temperature (157.35 °C, 7.88 MPa) and its phase diagram predicts only ~10 atm pressure at 60 °C in a closed reactor.[1] Sulfur dioxide has a high dipole moment (1.61 D), therefore it readily can dissolve both organic and inorganic salts. On the other hand, SO_2 has been reported as reaction medium for processes involving carbenium ions.[2]

This has prompted us to search for organic reactions that would profit from their running in liquid SO_2 as a reaction medium.[3] We have discovered that carbamate-protected aziridines and azetidines undergo efficient ring-opening reactions in liquid SO_2 with I and II group metal halides, including NaCl and KBr (Scheme 1). The advantage of this approach is based on the fact that carbamate groups (Cbz, Boc) can be easier removed if required than their well-described sulfonamide counterparts. We have also found application of liquid SO_2 as an interesting solvent for the Ritter reactions.[4] The screening of suitable Lewis acid catalysts and scope and limitations of amidation reaction under these conditions will be discussed.



Scheme 1

Additionally, we have developed a method of derivatization of polyhydroxy compounds via silylation and subsequent GC-analysis by Vogel's silyl sulfinate (**1**) which is obtained in sila-*ene* reaction between methallylsilane and SO_2.[5] This reagent easily transfers the silyl group and forms only volatile by-products: isobutylene and SO_2. Moreover, the reactions of silyl sulfinates with organometallic reagents providing a direct entry in sulfoxide synthesis will be discussed. This opens a novel approach for allylsulfoxide synthesis from allylsilanes *via* the sila-*ene* reaction of the latter with SO_2 followed by addition of Grignard reagents.

The authors thank ESF project Nr. 2013/0007/1DP/1.1.1.2.0/13/APIA/VIAA/024 for financial support.

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SEPARATION OF HELICENE ENANTIOMERS

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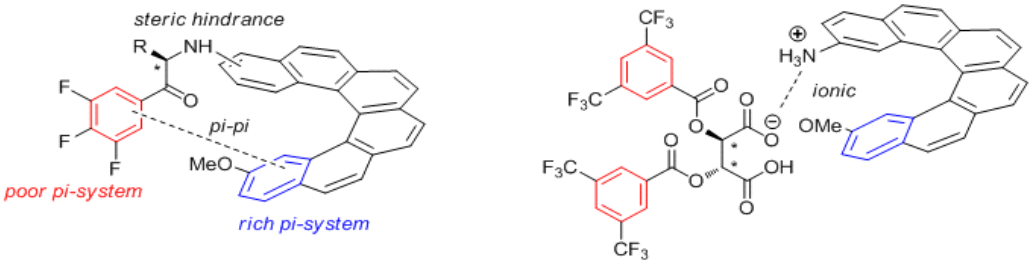
Curious structure of helicenes, inherently chiral *o*-condensed polyaromatic compounds, grants them several interesting properties (e.g. unusually high α value). Our group has developed feasible multigram-scale synthesis of various racemic helicenes[1] and respective derivatives[2]. However, full exploration of their application potential asks for their resolution into pure enantiomers. Furthermore, considering the current price of these materials in racemic form[3], this operation should be preparative, reasonably (in)expensive, quick and efficient – given facts exclude methods based on chromatography with chiral stat. phases.

Our reflections lead us to optimization of "classical" racemate separation methods using preferential crystallizations, precipitations, complex formations, sophisticated solvent systems or temporary helicene derivatizations leading to diastereomeric compounds (resolvable by non-chiral chromatography etc.). Pharmaceutical industry describes many optimized large-scale processes focused on this field, however helicenes do not share structural similarities with common racemic drugs. Inherently chiral PAHs (5+ annulated rings) often exhibit unexpected properties (solubility, reactivity, stability…) and even seemingly trivial operations can represent a challenge in sense of finding the appropriate principle strategies and conditions. To the best of our knowledge, simple resolution of helicenes has not been reported so far.

We are namely focused on formation of helicene diasteremoeric *pi-pi* complexes, covalent derivatives and salts resolvable by convenient preparative methods providing helicene enantiomers. In addition, appropriate merging of interactions (*pi*-electronic, ionic, steric) within scope of one structural pair could further endorse the resolution process (***scheme 1***). Current state of knowledge will be discussed on poster session.



Scheme 1. Examples of diastereomeric pairs potentially leading to conventional racemate resolutions.

Acknowledgements: We appreciate the financial support from the Technology Agency of Czech Republic (no. TA04010082).

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FUNCTIONALIZATION OF QUINAZOLIN-4-ONES *VIA* Pd-CATALYZED MICROWAVE AND COPPER-ASSISTED C-H ARYLATION

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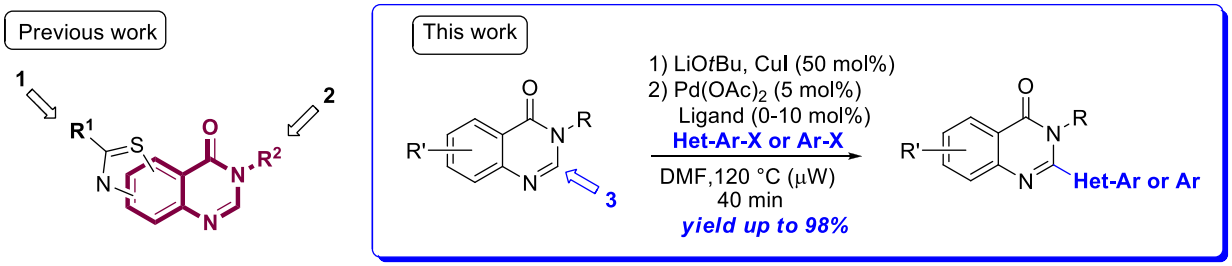
CNRS, IRCOF, 1 rue Tesnière, 76821 Mont Saint Aignan Cedex, France.

Our group is focused on the synthesis of C,N,S- or C,N,O-containing heterocyclic precursors of bioactive molecules able to modulate the activity of kinases involved to some extent in Alzheimer's disease.[1] Previous biological results lead us to intensively study thiazoloquinazolin-4-one backbone especially modulations of positions **1** and **2**. Following our effort for the construction of a broad range of substituted thiazoloquinazolin-4-one derivatives as potential kinase inhibitors,[2] modulating the position **3** was further explored. As an efficient and versatile approach in complex molecules synthesis palladium-catalyzed, C–H functionalization of heteroarenes[3] represents an extremely attractive approach.



We described the first extensive study of palladium-catalyzed direct C-H (hetero)-arylation of quinazolin-4-ones with aryl iodides, bromides and chlorides under microwave irradiation.[4] This innovative methodology tolerates a broad range of heteroaryl and aryl halides substituted by electronically different groups. The scope of substrates was extended to pyridinopyrimidin-4-ones. This method provides an efficient, versatile, and rapid access to *2*-arylquinazolin-4-one backbone and will be extended to our thiazoloquinazolin-4-one derivatives.

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SYNTHESIS AND SPECTRAL CHARACTERIZATIONS OF 2-(2´/3´-CHLORO- AND 2´,4´/3´,4´-DICHLORO-PHENYL)-5-METHYL-1,3-BENZOXAZOLES

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Benzoxazole ring is one of the most common heterocycles in medicinal chemistry. Previous reports revealed that substituted benzoxazoles possess diverse chemotherapeutic activities including antibiotic, antimicrobial, antiviral, topoisomerase I and II inhibitors and antitumor activities[1]. In addition, benzoxazoles are found in a variety of natural products and are important targets in drug discovery and also find applications in material science as photochromic agents and laser dyes[2].

In this study, 2-(2´/3´-chloro- and /2´,4´/3´,4´-dichloro-phenyl)-5-methyl-1,3-benzoxazoles (**1** – **4**, Figure 1) were synthesized by reaction of 2-amino-4-methylphenol with 2/3-chloro-, 2,4-dichloro- and 3,4-dichloro-benzoic acids in polyphosphoric acid media. The compounds were characterized by using analytical data, FT-IR, ^{1}H- and ^{13}C-NMR, ESI-MS and fluorescence spectroscopy.

According to the fluorescence spectral data, **1**, **3** and **4** show dual fluorescence in ethanol whereas **2** presents triple fluorescence. 2-(2´,4´-Dichloro-phenyl)-5-methyl-1,3-benzoxazole (**3**) is the most thermally stable derivative among the compounds; the 2-chloro derivative (**1**) has the lowest thermal stability. Thermal stabilities of the compounds decrease in the following order: **3**>**4**>**2**>**1**. It is observed that the second chloro substituent brings high thermal stability to the compounds.

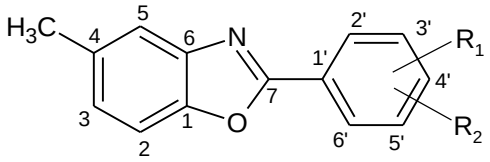

Figure 1. The general formula of the compounds in the study
(**1**, R_1= 2'-Cl, R_2= H; **2**, R_1= 3'-Cl, R_2= H; **3**, R_1= 2'-Cl, R_2= 4'-Cl; **4**, R_1= 3'-Cl, R_2= 4'-Cl)

Acknowledgments: This work was supported by the Scientific Research Projects Coordination Unit of Istanbul University.

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A METATHESIS APPROACH TO BUTENOLIDE-MACROLIDE MOLECULES

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A concise strategy towards the bicyclic butenolide-macrolide core structure of several natural products has been achieved.[1] The macrolide rings ranging from 12- to 16-membered annulated (bicyclic) on to a butenolide moiety have been synthesized with ease employing a relay ring-opening/double ring-closing metathesis strategy (Figure 1). The starting precursors could be assembled through an esterification using cyclobutene carboxylic acid. The potential of this strategy has been further demonstrated by the protecting group free synthesis of (±)-desmethyl manshurolide.[1,2] The strategy has future potential towards the synthesis of bicyclic butenolide-macrolide natural products.

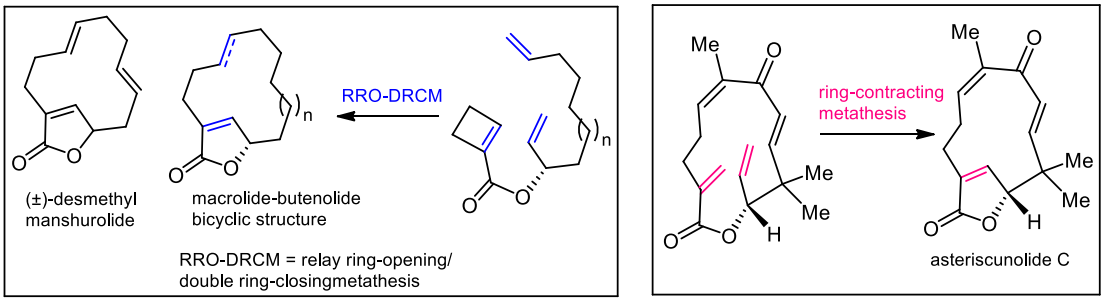

Figure 1. Metathesis approach to butenolide-macrolide molecules.

Similarly, a metathesis approach towards the first stereoselective synthesis of (-)-asteriscunolide[3] has also been developed through a ring contraction strategy[4] (Figure 1).

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TWO-STEP SOLVENTLESS SYNTHESIS OF NUCLEOBASE–DERIVED IONIC LIQUIDS AND THEIR BIOLOGICAL EVALUATION

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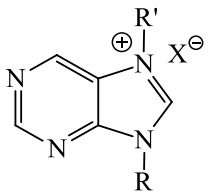
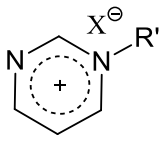
Nucleobase are nitrogen containing five and six membered heterocyclic compounds having potent synthetic and biological applications.[1] Over the years, the nucleobase turned out to be a vital pharmacophor and they are also closely allied with the development of organic chemistry. Therefore, on the basis of literature survey, we have focused on the synthesis of biologically potent nucleobase-derived novel ionic liquids (ILs).Ionic liquids are molten salts that results from the combination of organic cations and various anions with melting point below 100 °C.[2] Ionic liquids have received a significant interest due to their attractive properties such as chemical and electrochemical stability, high ionic density, conductivity, negligible volatility, and low flammability. Owing to this, they are accredited as environmental friendly solvents to conventional solvents and find considerable applicability in organic synthesis and catalysis, chemical engineering, electrochemistry, pharmaceutical chemistry and in polymerization.[3]The physicochemical properties of these ILs, anticipated as "task specific solvents'' can be tailored by altering independently the cationic and anionic moiety with the motive to promote exploration of new compounds preparation, characterization, and applicability of their properties in various physical, chemical, biological and medical fields. Furthermore, the ILs shows biological potency against microorganisms reveals the relationship between cationic moiety and microorganisms.[4] Therefore, our interest in this field is to enterprise and synthesise ILs that contains nucleobase as a cation moiety and to study their biological potency. We have developed a strategy to synthesise a series of nucleobase-derived novel ionic liquids in a safe and controllable manner with different anionic moiety *i.e.* BF_4^-, PF_6^-, NTF_2^-, $AlCl_4^-$,CH_3COO^-, NO_2^-etc.



(I)



(II)

R and R' = C1 - C12 alkyl group ;

X = BF_4^-, PF_6^-, NTF_2^-, $AlCl_4^-$, CH_3COO^-, NO_2^-

The proposed method is high yielding and partially greener because it is a solvent free method and practical due to commercial availability of the starting materials. The characterization of synthesised novel ILs was done by ^1H, ^{13}C NMR, FT-IR, and LC-MS. Methods used to synthesise ILs of high purity, eliminate the use of volatile organic solvents, the severity of reaction which in turn made the preparation of ILs feasible in a rapid and reproducible manner.

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NUCLEOPHILIC RING-OPENING OF BICYCLIC VINYL AZIRIDINES UNDER PHYSIOLOGICAL CONDITIONS

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Aziridines are reactive three-membered heterocycles, used as intermediates in the synthesis of carbocycles with significant biological activity, such as aminocyclopentitols and beta-lactams.[1] An easy and useful procedure for the synthesis of aziridines was reported in 1972 by Kaplan *et al.*, describing the photochemical transformation of pyridinium salts to bicyclic vinyl azridines under basic conditions (Figure 1).[2] The scope and mechanism of the pyridinium ion photohydration reaction has been investigated ever since[3] and the aziridine product studied in several reactions such as nucleophilic ring-opening,[4,5] and used as a precursor in the total synthesis of important natural products.[3,6]

Herein is reported the synthesis of bicyclic vinyl aziridines by photochemical transformation of pyridinium salts, followed by nucleophilic ring-opening under physiological conditions (Figure 1). A range of nucleophiles were investigated and the results show that thiols, 1,3-dicarbonyl compounds and nitrogen nucleophiles such as azide, aniline and imidazole were reactive, giving moderate yields. The best results were obtained using sulfur nucleophiles, providing the aziridine the potential to bind to cysteine containing peptides such as glutathione and cysteine proteases, common targets in medicinal chemistry.[7,8]

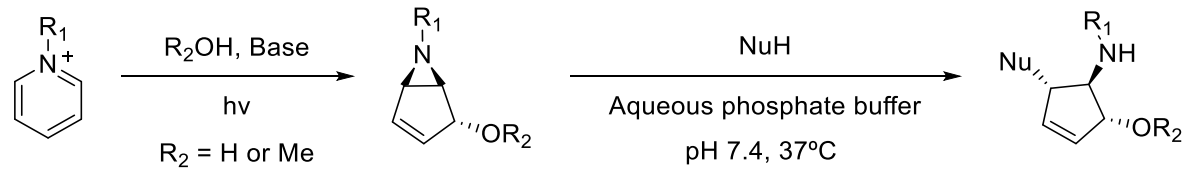

Figure 1. Photohydration of pyridinium salt followed by nucleophilic ring-opening of the bicyclic vinyl aziridine under physiological conditions.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support: PTDC/QUI-QUI/119210/2010 and SFRH/BPD/88666/2012.

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1,1'-BIS-2-NAPHTHOLE AS A USEFUL STRUCTURAL COMPONENT OF MACROCYCLIC RECEPTORS FOR CHIRAL CATIONS AND ANIONS

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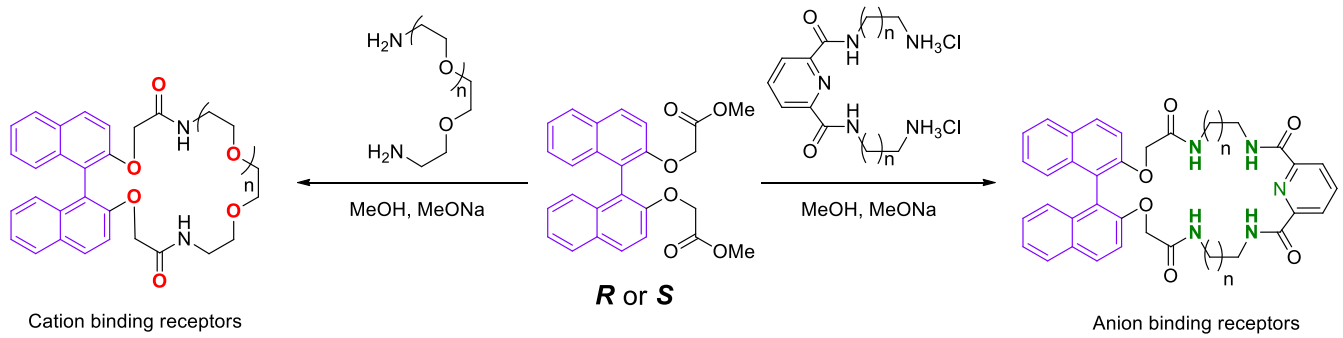
Complexation of natural anions *via* hydrogen bonds is a crucial step in many chemical and biological processes, and plays an important role in medicine, ecology and industry. Chiral recognition is a very complex and significant phenomenon, especially in the case of chiral anions, for example carboxylates. Therefore design and development of anion binding receptors are ones of the major tasks in modern supramolecular chemistry.[1]

We would like to present our studies concerning synthesis of new macrocyclic receptors based on 1,1'-bis-2-naphthole as a platform, which is a continuation of our long-time investigations.[2] We used methods, developed in our laboratory, to obtain nearly 30 new macrocyclic receptors and investigated their properties using methodology of combinatorial chemistry, ^{1}H NMR and UV-Vis titration.



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DYNAMIC COMBINATORIAL CHEMISTRY OF CHIRAL DISULFIDES ACTING AS ENANTIOSELECTIVE ANION RECEPTORS

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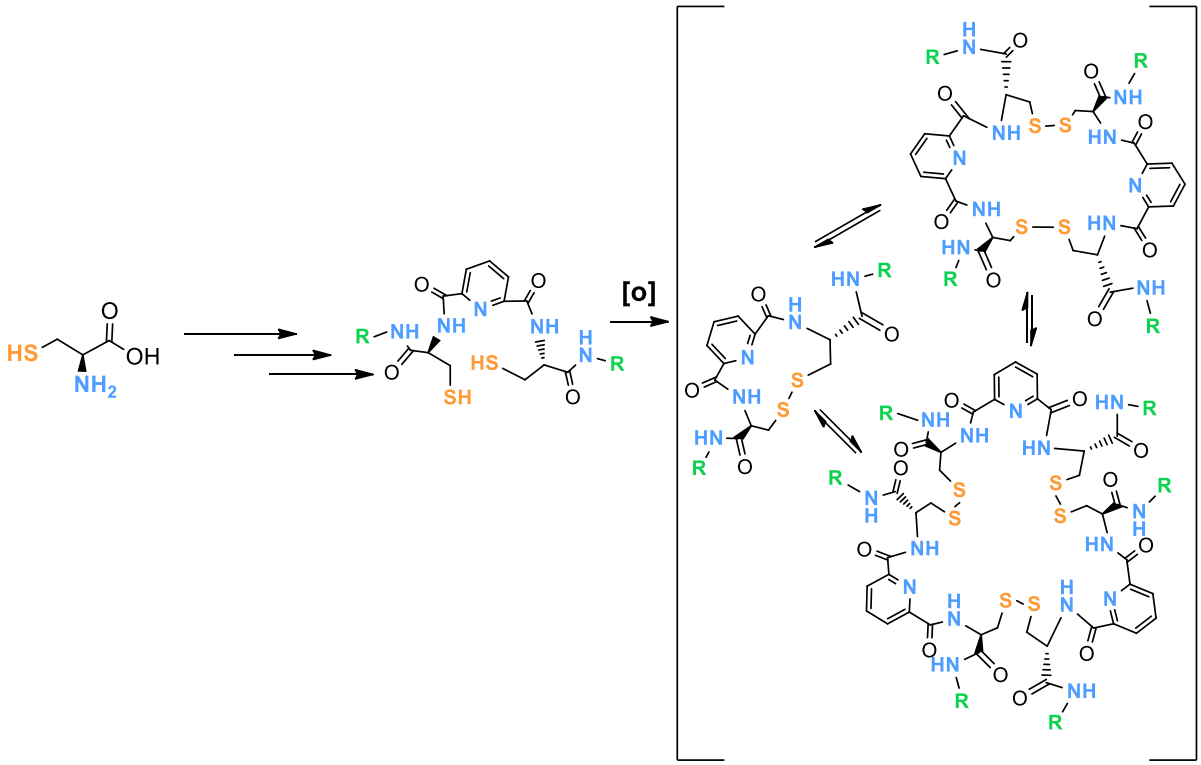
Designing of new synthetic enantioselective anion receptors is unquestionably required for understanding and exploration of chiral recognition processes.[1] Dynamic Combinatorial Chemistry (DCC) has been quite well recognized as a powerful method in supramolecular chemistry. Herein we present a synthesis of various chiral thiols based on picolinic acid, incorporating cysteine moiety.[2,3] Upon oxidation, disulfide macrocyclic structures (DDC library) are obtained.[4] The equilibrium in such a mixture of chiral anion receptors can be altered by templation with various chiral carboxylates.



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POLYHYDROXYLATED 1,2- AND 1,3-CYCLOALKANEDIAMINES AS PROMISING NEW ORGANOCATALYSTS

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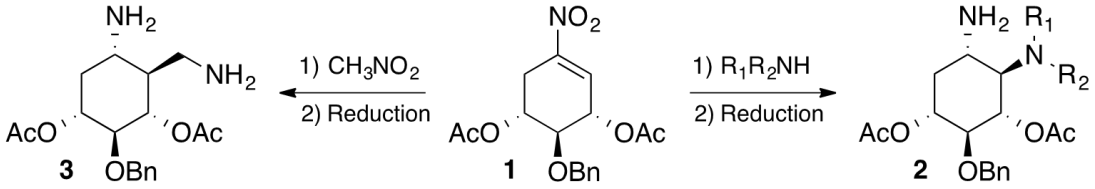
Chiral 1,2- and 1,3-diamines are first order synthetic tools due to their interest as syntons in the preparation of natural products.[1] This interest increased notably in the last two decades because of its usefulness for the preparation of new organocatalysts,[2] as Jacobsen's catalysts.[3] Inside this group of diamines stand out those of cyclical nature, because its conformational rigidity makes them even more useful for the generation of new organocatalysts.

Surprisingly polyhydoxylated cycloalkane diamines have not yet been described, in spite of their interest as potential water soluble catalysts. Here we present preliminary results on a strategy designed for the synthesis of polyhydroxylated 1,2- and 1,3-cyclohexanediamines from sugars. A Michael addition of amines R_1R_2NH to D-glucose derived nitrocyclohexene **1**[4] followed by reduction of the nitro group easily gave cyclohexane-1,2-diamines **2.** The same strategy allowed to prepare 1,3-diamine **3**. It consisted of a Michael addition of nitromethane to nitrocyclohexene **1**, followed by reduction of the two nitro groups of the resulting adduct.



Preliminary results on testing these amines as catalysts in asymmetric aldolic reactions will be presented.

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SYNTHESIS & REACTIVITY OF UNPRECEDENTED PYRANOSE BASED THIOIMIDATE *N*-OXIDES

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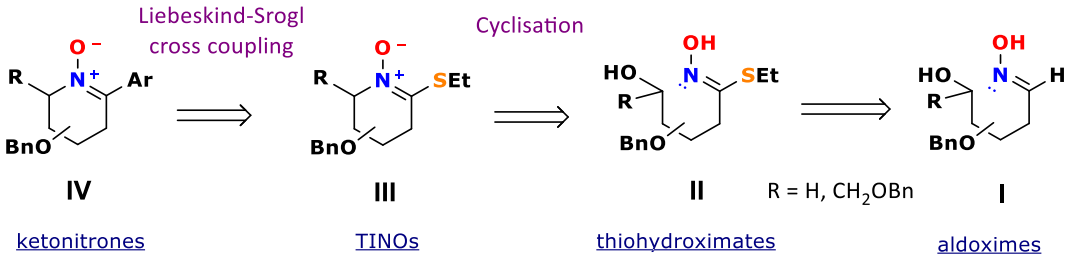
In our long-term study of the glucosinolate family,[1] sulfur-containing plant secondary metabolites, our group has recently revealed a rare and unusual thiofunction: the ThioImidate *N*-Oxide function (TINO).[2] Having in mind the synthetic potential of this function, we decided to prepare pyranose-based thioimidate *N*-oxides. Indeed these enantiomerically pure backbones could be highly valuable synthetic intermediates in the preparation of various complex iminosugars as potential carbohydrate-processing enzymes modulators.[3] It is worth mentioning that, although the synthesis of five-membered carbohydrate-based cyclic nitrones has been extensively studied, the number of methods to access such six-membered cyclic nitrones has remained rather limited to date. In the same way, while the synthesis of some furanose-based thioimidate *N*-oxides[4] has already been developed in our group, we had to devise new methodologies for the pyranose series.

Thus, we report here the synthesis of unprecedented pyranose-based TINOs, representatives of pentoses and hexoses, as a gateway to all the compounds of both classes (**Scheme 1**). The key-cyclisation step was achieved by taking advantage of the nucleophilic ability of the thiohydroximate function, either through a Mitsunobu type reaction or using a desilylative cyclisation. These key intermediates **II**, judiciously 2,3,4,(6)-*O*-protected, can be prepared in a few steps from the corresponding carbohydrate-derived aldoximes **I**.[5]



Scheme 1. Retrosynthetic pathway to carbohydrate based thioimidate *N*-oxides **III** and ketonitrones **IV**.

In a second part, we will also disclose our results regarding the synthesis of novel ketonitrones **IV** through Liebeskind-Srogl type cross-coupling reactions.

These studies enable access to a unique family of polyhydroxypiperidine thioimidate *N*-oxides from both aldopentoses and aldohexoses, thus extending the relatively limited class of cyclic 6-membered nitrones analogues available to date.

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RECOGNITION OF CHIRAL CARBOXYLATES BY SWEET PHOTOSWITCHABLE AZOBENZENE DERIVATIVES

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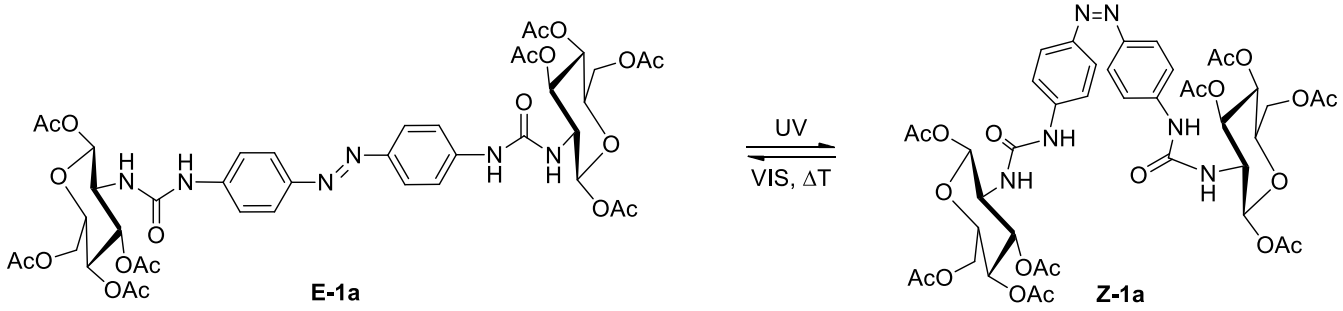
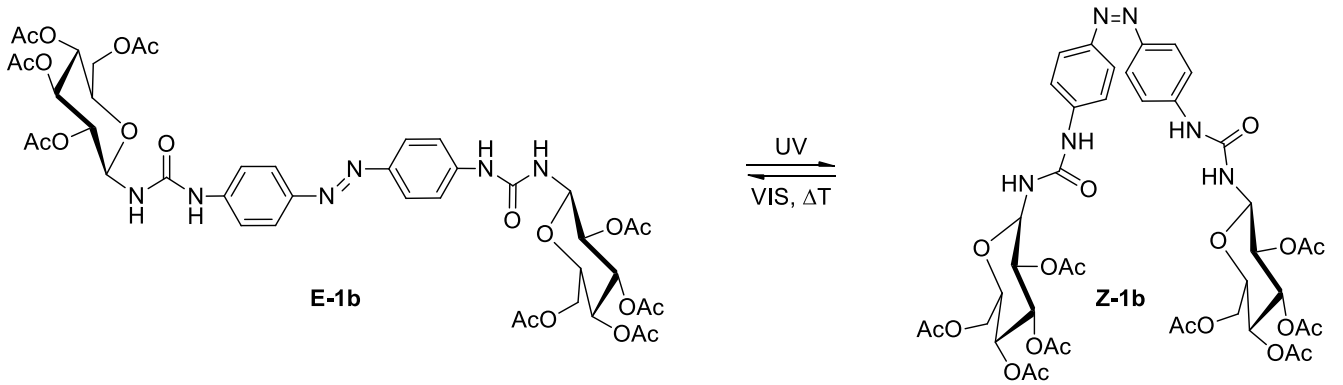
Molecular recognition and transport of anions is one of the youngest, yet belonging to the most important areas of supramolecular chemistry.[1] However, despite much advances made in this field in the last years, so far only a scare number of hosts effective in the recognition of chiral anionic guests have been reported.[2] Furthermore, the use of light to control their binding properties, very favorable from practical point of view, is unknown.[3]

Herein, we present that readily available urea-azobenzenes, decorated with sugars, are able to discriminate between biologically important chiral carboxylates even in a highly demanding solvent ([D6]DMSO + 0.5% H_2O). Moreover, the receptors can be easily and reversibly switched by external stimuli, such as light and/or temperature, between *E*- and *Z*-isomers possessing very different chiral environment.



E-1a **Z-1a**



E-1b **Z-1b**

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NEW PHTHALOCYANINES BEARING SULFONAMIDE UNITS

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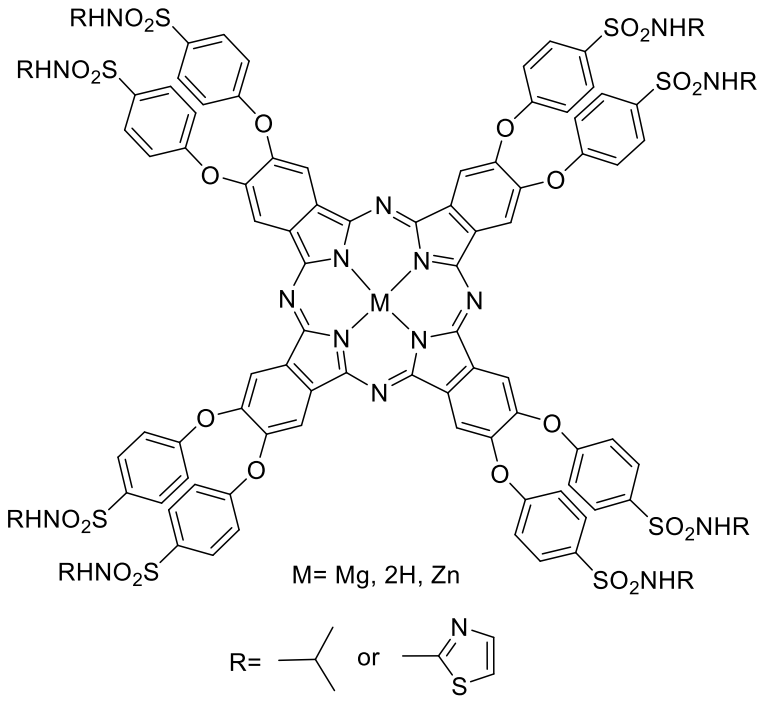
Due to their photophysical properties, phthalocyanines (Pcs) have been applied in a range of scientific areas. In particularly, they have been used as photosensitizers in the photodynamic therapy of tumors (PDT) and in the photodynamic inactivation of microorganisms (PDI). In these processes, the photosensitizers, in combination with visible light and molecular oxygen, generate reactive oxygen species (ROS) that are cytotoxic to the target cells.[1]
Furthermore, sulfonamides have been extensively used as antimicrobials, by inhibiting the enzyme dihydropteroate synthase (DHPS) in the folic acid pathway,[2] and have also been studied as anti-tumoral drugs because they are able to inhibit carbonic anhydrases IX and XII.[3]
As an extension of our previous work,[4] in this communication we will discuss the synthesis and structural characterization of Pcs bearing sulfonamide units with isopropyl and heterocyclic groups.



Acknowledgements: Thanks are due to FCT (Portugal), European Union, QREN, FEDER and COMPETE for funding the project PTDC/QEQ-QOR/1273/2012, the QOPNA Research Unit (project PEst-C/QUI/UI0062/2013), the CESAM Research Unit (PEst-C/MAR/LA0017/2013) and the Portuguese NMR network. Nunes da Silva, R. thanks FCT for her PhD grant (SFRH/BD/87598/2012).

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A ONE-POT SYNTHESIS OF FURAN-BASED POLYPHENOLICS

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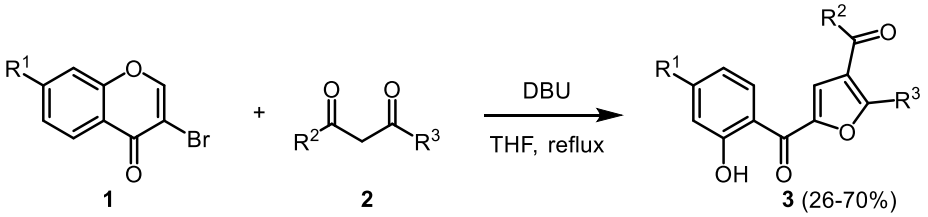
The furan heterocycle is found in a variety of biologically active synthetic and natural compounds.[1,2] In light of our long-standing interest in preparing oxygen-containing heterocycles using 3-bromochromone derivatives as starting materials,[3] in this work we will present a one-pot synthetic route towards a series of novel furan-based polyphenolic derivatives obtained in moderate to good yields (26-70%). Our methodology relays on the 1,4-conjugate addition of 1,3-dicarbonyl compounds **2** on 3-bromochromones **1** catalysed by DBU which follows a tandem process of chromone-ring-opening/furan-heterocyclization (Scheme 1). All the newly synthesized furans **3a-i** were characterized by 2D NMR and single-crystal X-ray diffraction techniques. Simplicity and soft execution of our synthetic procedure are the main advantages leading to the creation of an important library of potential biologically active poly-substituted furans.



3a) R^1= H, R^2= R^3= Me
3b) R^1= H, R^2= 2-OH-4-OMe-Ph, R^3= 3,4-dimethoxystyryl
3c) R^1= H, R^2= 2-OH-Ph, R^3= 4-Cl-styryl
3d) R^1= H, R^2= 2-OH-Ph, R^3= 4-Me-Ph
3e) R^1= H, R^2= 2-OH-4-OMe-Ph, R^3= H
3f) R^1= OMe, R^2= R^3= Me
3g) R^1= OMe, R^2= 2-OH-Ph, R^3= Me
3h) R^1= OMe, R^2= 2-OH-Ph, R^3= 4-Cl-Ph
3i) R^1= OMe, R^2= 2-OH-4,6-dimethoxy-Ph, R^3= 4-OMe-styryl

Scheme 1. Synthesis of furan-based polyphenolics **3a-i** from 3-bromochromones **1** and 1,3-dicarbonyl compounds **2** in the presence of catalytic amount of DBU.

Acknowledgements: Thanks are due to the University of Aveiro, Fundação para a Ciência e a Tecnologia (FCT, Portugal), EU, QREN, FEDER, COMPETE, for funding the Organic Chemistry Research Unit (UID/QUI/00062/2013), and the Portuguese National NMR Network (RNRMN). We would like to thank the General Directorate for Scientific Research and Technological Development-DGRSDT of Algeria for the financial support. We further wish to thank the Associated Laboratory CICECO (UID/CTM/50011/2013) for funding the purchase of the single-crystal X-ray diffractometer. J.L.C. Sousa is also grateful to FCT for her PhD grant (SFRH/BD/76407/2011).

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SYNTHESIS OF XANTHONE-1,2,3-TRIAZOLE DYADS

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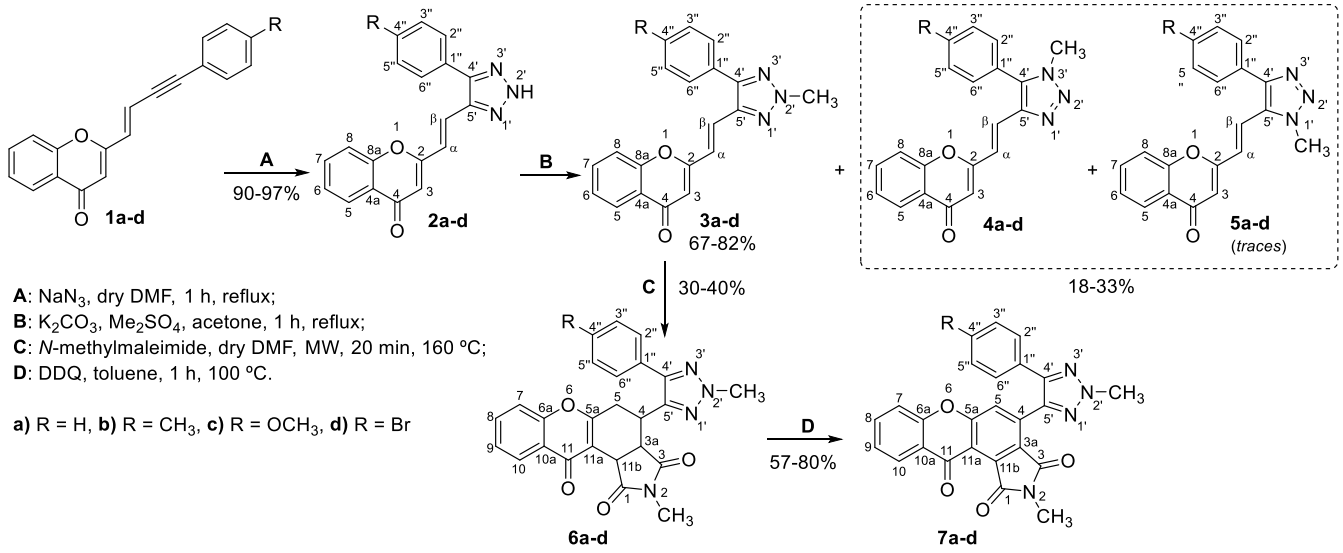
Xanthones and 1,2,3-triazoles are known to exhibit several biological, pharmacological and biocidal properties[1]. The potential applications of these two classes of heterocycles led us to develop new strategies to synthesize xanthone-1,2,3-triazole dyads, aiming to get potentially improved therapeutic agents[2]. With this rational in mind we designed and synthesized novel chromone derivatives **1a-d** to be used as building motifs and to explore the reactivity of the two unsaturated systems (the diene and the alkyne). In the present communication we will present a new synthetic route towards the synthesis of xanthone-1,2,3-triazole dyads **7a-d** using consecutively the azide-alkyne Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction. Our approach involves the synthesis chromone-triazole derivatives **2a-d** using the reaction of **1a-d** with sodium azide, followed by the methylation of the NH of the triazole moiety. The methylation afforded three isomers **3a-d**, **4a-d** and **5a-d**, as expected. The major isomers **3a-d** were used in the Diels-Alder reaction with *N*-methylmaleimide, and the adducts obtained **6a-d** were oxidized to afford the xanthone-1,2,3-triazole dyads **7a-d**. All the synthetic details as well as the structural characterization (by 1D and 2D NMR studies) of the new synthesised compounds will be presented and discussed.



Acknowledgements: Thanks are due to University of Aveiro, Polytechnic Institute of Bragança, Fundação para a Ciência e Tecnologia (FCT), EU, QREN, FEDER e COMPETE for funding the QOPNA Research Unit (Ref UID/QUI/00062/2013) and The Portuguese National NMR Network. Hélio Albuquerque also thanks his PhD grant (SFRH/BD/86277/2012).

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METAL-CATALYZED C-N CROSS-COUPLING REACTIONS IN THE SEARCH OF HIGH VALUE TETRAPYRROLIC DERIVATIVES

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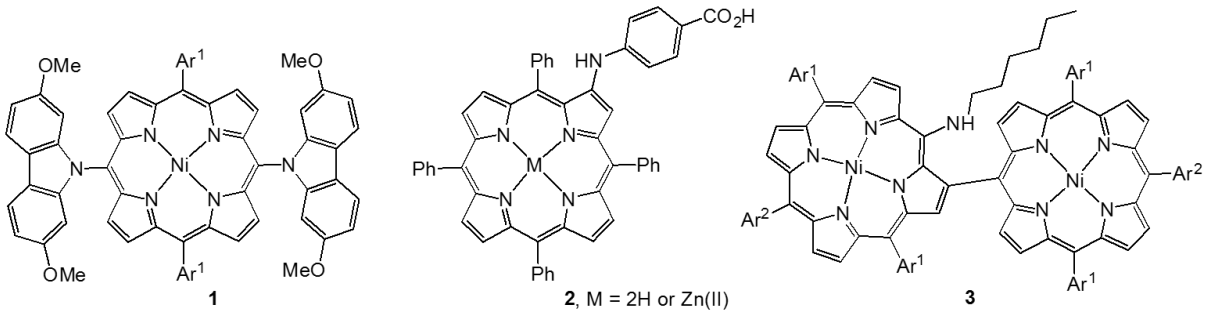
The introduction of different functionalities into the porphyrin core can offer the means by which optical, electrochemical and physical properties of the tetrapyrrolic macrocycle can be modulated. In fact, metal-catalyzed C-N cross-coupling approaches have been valuable synthetic tools in the construction of a diverse array of porphyrin macrocycles for applications in catalysis, energy transfer, and medicine, among other areas.[1]

Following our interest in the field, the C-N copper-catalyzed cross-coupling was used to synthesize porphyrins **1** functionalized with one or two carbazole or phenoxazine groups, in which the first oxidation step occurs on the external nitrogen atoms.[2] By using the palladium-catalyzed amination, we have also reported the preparation of electron donor-acceptor substituted porphyrinic macrocycles **2**; these demonstrate a reasonable power conversion efficiency in DSSC devices.[3] In continuation of our research in this area, we have synthesized the new dimer **3** as an unexpected side-product.[4] The preparation of compounds **1**, **2** and **3** will be presented in this communication. The optical, electrochemical and photovoltaic properties exhibited by these molecules will be also described.



Ar^1 = *p*-tolyl, Ar^2 = *p*-anisyl

Acknowledgements: Thanks are due to Fundação para a Ciência e a Tecnologia (FCT), European Union, QREN, FEDER and COMPETE for funding the QOPNA research unit (projects PEst-C/QUI/UI0062/2013 and FCOMP-01-0124-FEDER-037296), the Portuguese National NMR Network, EXPL/QEQ-QOR/0906/2013 and PEst-C/CTM/LA0025/2011. Ana M. V. M. Pereira is grateful to FCT for a post-doc fellowship (SFRH/BPD/64693/2009). Continuous financial support from the CNRS and the Université de Strasbourg are also acknowledged. All contributing co-authors are greatly acknowledged and are listed below in the corresponding references.

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CHIRAL FERROCENE OXAZOLINE LIGANDS FOR ASYMMETRIC CATALYSIS

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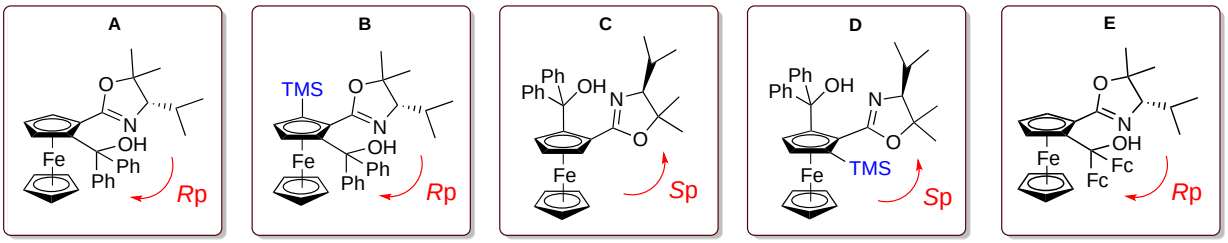
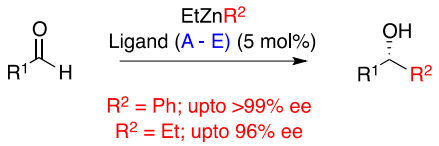
The preparation of enantiopure compounds is an indispensible area of research in modern chemistry. To this end, the use of readily modifiable chiral donor ligands coupled with metal catalysts has emerged as one of the most popular strategies for asymmetric synthesis.[1]

In this poster we describe the preparation of a range of novel ferrocene oxazoline N,O ligands bearing both central and planar chirality (Ligands **A - E**). Central chirality is obtained from the chiral pool in the form of (*S*)-valine and planar chirality is installed *via* a highly diastereoselective directed *ortho*-lithiation.[2] Studies of this lithiation were initiated in order to provide insight into the source of diastereoselectivity and some preliminary results are presented.



FeOx (R_p) $Ph_2C(OH)$ | FeOx (R_p) $Ph_2C(OH)$ (R_p) TMS | FeOx (S_p) $Ph_2C(OH)$ | FeOx (S_p) $Ph_2C(OH)$ (S_p) TMS | FeOx (Rp) $Fc_2C(OH)$ Fc = Ferrocene

The effect of these ligands on catalytic activity and enantioselectivity was investigated utilizing the diethylzinc addition to aldehydes as a model reaction.[3] We then applied our ligand class in the more challenging diphenylzinc addition to aldehydes.[4] The effect of planar chirality on the ferrocene (R_p or S_p) was investigated with ligands **A** and **C**, as was the effect of additional steric bulk offered by tri-substituted ferrocene ligands **B** and **D**. Triferrocenyl ligand **E** allowed us to investigate the influence of increased steric bulk around the oxygen donor atom.



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SHORT SYNTHETIC STRATEGY FOR THE SYNTHESIS OF N-MCT (N-2'-DEOXYMETHANOCARBA THYMIDINE) FROM 4-HYDROXYCYCLOPENTENONE

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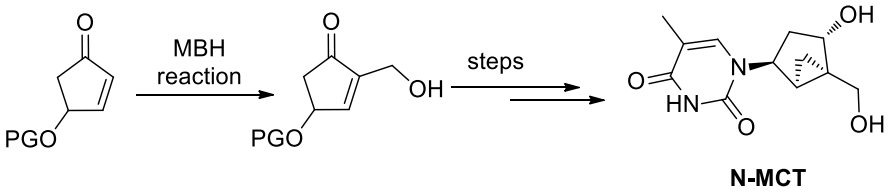
In present days, the increasing demand of developing safe and effective drugs have created much attention with the growing knowledge on molecular disease pathways and reduced output of new medicines. Notably, 2-cyclopentene, motif is a valuable for future drug design due to inherent bioactivity. Bioactivity is related to chemical reactivity which differs on each 2-cyclopentene ring's carbon atom and is critical for anticancer and antiviral effects of synthetic molecules.[1] The DNA-damaging properties of these molecules as a potent NF-kB inhibitors of cysteine proteases of cysteine-dependent enzymes allowed the proapoptotic activity in cancer cells.[2] The anti-viral effects were found to correlate with potent inhibition of NF-kB-dependent HIV-1 transcription in human cells and virus protein synthesis by the expression of new cytoprotective heat shock proteins (HSP) like Hsp70.[3]

Morita Baylis Hillman (MBH) reaction since discovery has been extremely explored due to the high synthetic values of obtained derivatives.[4] We have developed a new catalytic system based on the N-methylpyrrolidine/$Ba(OH)_2$ for efficient Morita-Baylis-Hillman reaction of cyclopent-2-enone for the synthesis of 2-(hydroxymethyl)cyclopent-2-enone.[5] In continuation with this work, we indulge to apply this strategy for the synthesis of advanced intermediate of antiviral nucleoside (N)-MCT.



Scheme 1. Synthesis of 2,4-disubstituted cyclopentenones.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support PTDC/QUI-QUI/119823/2010).

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LACTIC ACID AS AN EFFICIENT SOLVENT AND CATALYST FOR ONE-POT THREE-COMPONENT SYNTHESIS OF POLYSUBSTITUTED PYRROLES

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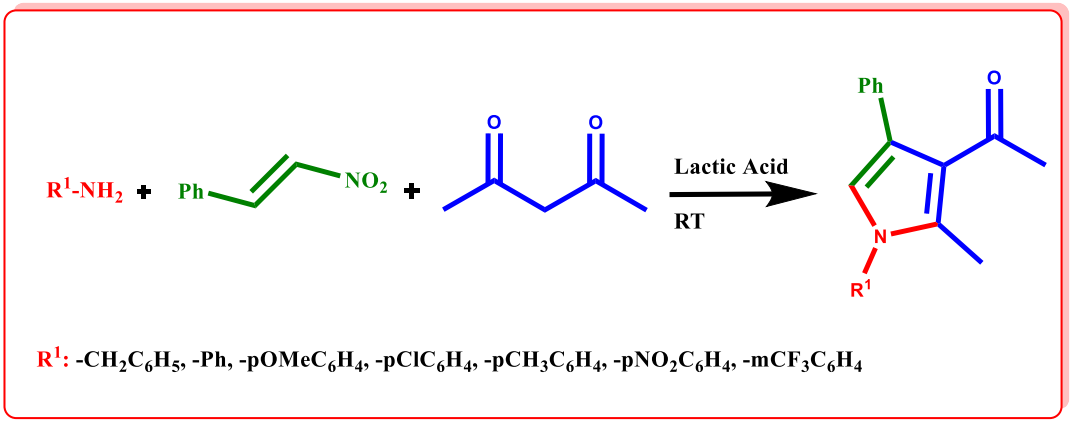
Pyrrole derivatives have high importance due to exist in the structure of many natural products possessing biological activity[1]. Both feature of being versatile building blocks in organic synthesis and important starting materials for various synthetic transformations lead researchers to develop new methods for the synthesis of them.

Multicomponent reactions have emerged as a powerful technique in synthesizing structurally complex molecules in a single step. This strategy presents some advantageous such as minimizing waste, less time consuming, superior atom economy, avoidance costly purification processes, and bond forming efficiency[2].

With the increasing demand for environmentally friendly methods, the application of bio-based materials as green and bio-degradable reaction solvents for synthesis and catalysis takes attention of researchers. Lactic acid has been used as bio-based green solvent to promote organic synthesis[3].
Being aware of the importance of both pyrrole derivatives and development of new, efficient and green synthetic method for them, we started a project to combine multicomponent reactions and benign reaction media for the synthesis of polysubstituted pyrroles. In lactic acid, 1-(2-methyl-1,4-diphenyl-1H-pyrrol-3-yl)ethan-1-one was synthesized in 99% yield at room temperature via multicomponent reaction. Herein, we report a facile one-pot synthesis of poly-substituted pyrrole derivatives via three-component condensation reaction of amines, 1,3-dicarbonyl compounds and β-trans nitrostyrene using lactic acid as bio-based green solvent.



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OXOPYRIMIDINES AND THIOXOPYRIMIDINES AS POTENTIAL ACETYLCHOLINESTERASE INHIBITORS AND ANTITUMORAL MOLECULES

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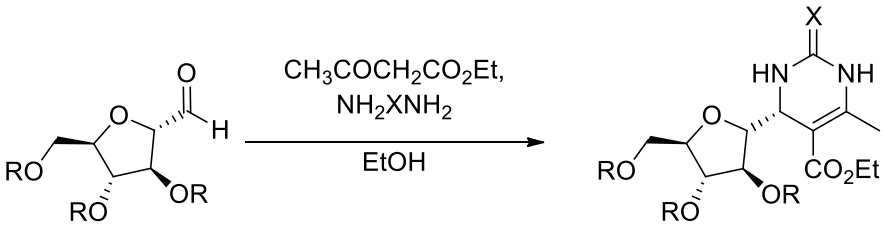
Sugar derivatives possessing heterocycles C-C linked to anomeric and non-anomeric positions are known for a variety of biological activities.[1] Attractive aspects of Biginelli compounds lie in an expected increase in bioavailability and water solubility and in the generation of new families of C-nucleosides.[2] Starting from single sugars like D-glucosamine, two anomeric sugar aldehydes were obtained followed by one-pot cyclocondensation (Biginelli reaction) it was possible the synthesis of 4 new oxo-/thioxopyrimidines linked to furanoses with D-manno configuration. We report the synthesis, via Biginelli reaction (figure 1). In addition, the inhibition of acetylcholinesterase activity determined by Ellman method and the cytotoxicity against human normal and tumoral cell lines by these compounds is also presented. Cell proliferation studies were performed by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay after exposition of cell to several concentrations of the compounds under study. [3]



1 R= H
2 R=Ac

3 R= H, X= O
4 R= H, X= S
5 R= Ac, X= O
6 R= Ac, X= S

Figure 1. Synthesis of oxopyrimidines and thioxopyrimidines.

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IMINOSUGARS FUSED WITH 1,3-OXAZOLIDIN-2-ONES AS GLYCOSIDASE INHIBITORS

M. Domingues,[a] M. I. Ismael,[a] J. A. Figueiredo,[a] M. Gomes[a], M. Lucas[a] M. Schuler,[b] A Tatibouët,[b] S. Silvestre[c], A. P. Duarte[c]

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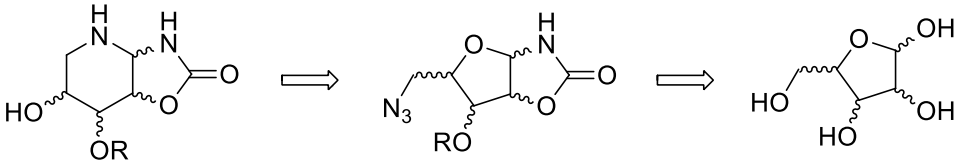
Iminosugars are small molecules closely related to carbohydrates through the replacement of the endocyclic oxygen with a nitrogen atom. Thus in the biological conversions of glycosides (hydrolysis or biosynthesis) they mimic the transition state.[1] Consequently, iminosugars have exhibited a wide range of biological activities namely antiviral, anticancer and antibiotic activities.[2]

The functionalization of iminosugars by introduction of an oxazolidinone ring resulted in the formation of unexpected and unique products. In this work we report the synthesis of 6 new iminosugars fused with 1,3-oxazolidin-2-ones (figure 1), as well as their potential to inhibit glycosidases and cytotoxicity against human normal and tumoral cell lines. Cell proliferation studies were performed by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay after exposition of cell to several concentrations of the compounds under study.[3]



R= H or PG

Figure 1. Retrosynthesis of iminosugars fused with 1,3-oxazolidin-2-one ring.

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SOLID PHASE SYNTHESIS OF PEPTIDES WITH 3-NITROTYROSINE

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Many physiological disorders including neurodegenerative diseases are influenced by oxidative stress.[1] Nitration of aromatic amino acids can influence the role of important proteins. In order to better understand the influence of nitration on biophysical functions, we propose selective synthesis of nitrated peptides and proteins with 3-nitrotyrosine (H-Nit-OH). The use of Boc-Nit(Bzl)-OH, Fmoc-Nit-OH and Fmoc-Nit(Trt)-OH was described in literature.[2-4] For Fmoc-Nit(Trt)-OH, we have found that the described procedure[4] does not provide Fmoc-Nit(Trt)-OH but mixture of Fmoc-Nit-OH and Trt-OH. The tritylation did not led to completion; attempts of chromatographic purification using mobile phase with various bases, led to Trt cleavage. It appears that Nit(Trt) is even more labile than Tyr(Trt).[5]

We used also direct nitration with N_2O_4[6,7] in organic solvents and with tetranitromethane, and attempted several step syntheses of Fmoc-Nit(tBu)-OH via Etoc-Nit-OMe,[4] and Fmoc-Nit-OMe.

Finally, we have synthesized neurodedegenerative peptides using Fmoc-Nit-OH and Fmoc-Nit(Bzl)-OH and compared the yields and purity of both attitudes.

Acknowledgements: This work was supported by the Czech Science Foundation (reg. No. 14-00431S).

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DIRECTED ORTHO-METALATION OF BRANCHED ALKYL DIPHENYLPHOSPHINE OXIDES – A SIMPLE APPROACH TO FORM NEW PHOSPHINE BORANE COMPLEXES

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The important role of phosphines in organic synthesis and catalysis has resulted in a diverse range of methods being developed for their synthesis.[1] Phosphines and phosphine-borane complexes can be easily obtained from the parent phosphine oxides.[2] Phosphine oxides like carbonyl compounds, sulfones or sulfoxides normally undergo α-deprotonation with bases, because of the strong acidifying influence on neighboring α-protons.

Recently it was found that in case of β,β-disilylated sulfones directed *ortho*-metalation takes place even in the presence of α-protons.[3] We hypothesized that branched alkyl diphenylphosphine oxides behave in a similar manner to produce *ortho*-substituted phosphine oxides. Here we present syntheses of *ortho*-substituted phosphine-borane complexes, starting from branched alkyl diphenylphosphine oxides (Fig. 1).[4] Further diversification of the *ortho*-substituted compounds by cross coupling leading to structurally new phosphine oxides and their respective phosphines will be presented.

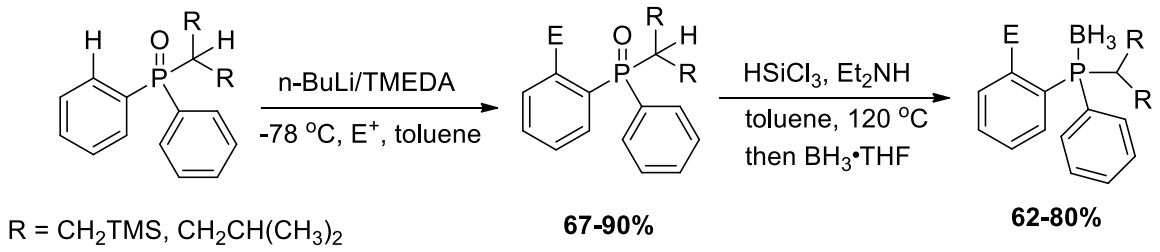

Figure 1. D*o*M of phosphine oxides and syntheses of phosphine-borane complexes from *ortho*-substituted phosphine oxides.

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TANDEM 1,2-ADDITION/ISOMERIZATION/OXIDATIVE DIMERIZATION REACTIONS. APPLICATION TO THE SYNTHESIS OF TETRAHYDROFURAN LIGNANS

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Cascade reactions are a prevalent tool in the synthesis of target molecules in a short and time-efficient way. The development of reaction cascades, which involve intermediates in different oxidation states and to make use of them to approach complex molecules from simple starting commodities, is a continuing goal. Anionic/radical/cationic tandem processes by oxidative or reductive single electron transfer processes are well known.[1] Our current interest is to develop transition metal-catalyzed/single electron transfer-induced cascade reactions involving multiple organometallic and radical intermediates.[2]

Here we present our results on the synthesis of 1,4-diketones in tandem reactions involving 1,2-addition/transition metal catalyzed isomerization/SET- induced oxidative dimerization steps. The 1,4-diketones are applied in short syntheses of tetrahydrofuran lignans like manassantin A, galbelgin and veraguensin.

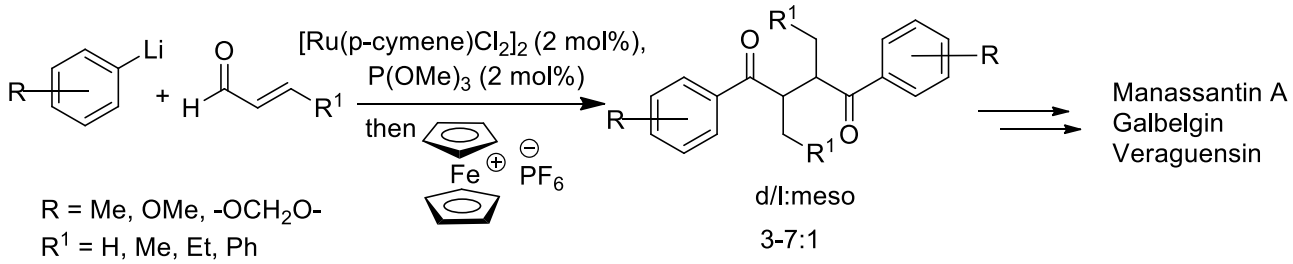

Figure 1

References:

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HIGH INTERNAL OLEFINS RECEIVED FROM RENEWABLE SOURCES

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There is increased interest in application of organic substances of vegetable origin as an alternative fuel and also for preparation of other useful products. First of all, it has been connected with renewability of this fuel resource and its ecological purity. In our work, unsaturated acids which are obtained from vegetable oils can increase the petrochemistry feedstock. So that, high internal olefins, such as heptadecene-8, are received by decarboxylation reaction of the high unsaturated acids. These obtained internal olefins are important feedstock in the synthesis of surface-active compounds, insecticides, and in the paper industry.

In the decarboxylation reaction, the various catalysts, such as oxides and nitrides of transition metals, palladium on coal, etc. have been used. In our investigations, series of catalysts, particularly, natural and synthetic aluminosilicates, nano-sized catalytic systems on the basis of Mg and Ti oxides has been tested for decarboxylation of organic acids received from vegetable oils. However, it is determined that, the best results obtained in the application of nano-sized MgO and TiO_2 catalysts. The structure of particles of nano-sized metal oxides has been studied on the atomic-force microscope C3MY-5 in semi-contact mode. It has been established that, an average size of particles of nano-sized magnesium oxide is in the range of 100 nm, and for titanium oxide – in the ranges of 20-25 nm.

Synthesis of high molecular olefins such as heptadecene-8 is mainly two steps process consisting hydrolysis and decarboxylation. As a feedstock, we have used different vegetable oil such as corn oil, canola oil, sunflower oil etc. First, unsaturated acids are obtained from vegetable oils by hydrolysis. Then, decarboxylation reaction of those unsaturated acids are carried out. Heptadecene-8 is obtained mainly from oleic and linoleic acid. The decarboxylation reaction is conducted in a continuous flow reactor, 250-400 ^{0}C temperature, 1 h^{-1} volume rate over nano-sized MgO and TiO_2 catalysts [1].

Oleic acid hydrolysed from corn oil was used as a unsaturated acid and it has the following physical-chemical indices: boiling temperature 223^{0}C (100 mm.Hg.), density 0.9 g/ml, n_D-20 1.4582, acidic number 179 mg KOH/g, iodine number 70.7 g J2/100 g.

It is determined that, the best results are observed in 350^{0}C and volume rate 1.0 h^{-1}, in both cases of nano-sized magnesium oxide and titanium oxide. In these conditions, the conversions of oleic acid are 99.1 and 99.2 %, the acidic numbers of reaction product are decreased to 1.5 and 1.3 mg KOH/g, accordingly. The application of nano-sized catalysts – magnesium and titanium oxides allows to decrease the process temperature correspondingly.[2]

The achieved decarboxylation product of oleic acid – heptadecene-8 has been identified by physical-chemical analysis method and had the following indicators: refraction index 1.4430; density 0.8021 g/ml, boiling temperature 173^{0}C (15 mm Hg).

As it was known, heptadecene-8 refers to industrially-important high internal olefins of C_{17} series and has applications in various areas of industry and agriculture. In this regard, synthesis of the similar internal olefins has certain practical and theoretical interest.

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NOVEL DOMINO PROCEDURES FOR THE SYNTHESIS OF CHROMENES

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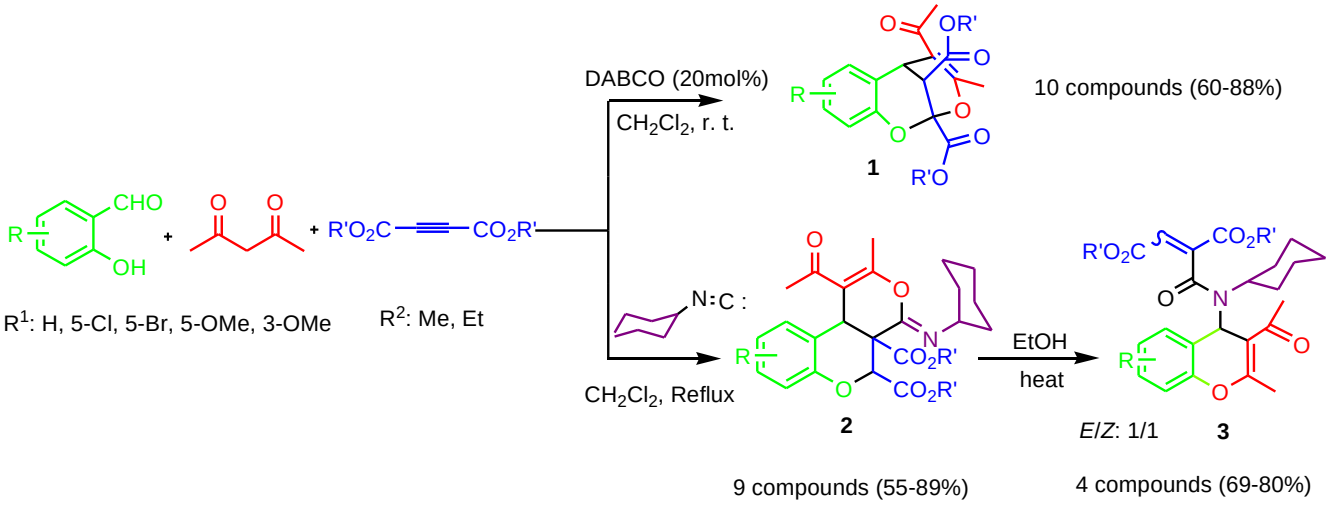
Design of one-pot procedures which could provide maximum structural complexity and diversity to synthesize a group of compounds with potential biological activities is a major challenge in organic synthesis. Chromenes (benzopyrans), which occur in many biologically active compounds,[1-3] are getting increasing significance in drug research. Following our previous research on developing the procedures for the synthesis of chromene derivatives,[4-5] we synthesized novel dioxatricyclo [7.3.1.0^{2,7}] trideca-9,13-dicarboxylates **1** by a one-pot three-component procedure *via* DABCO catalyzed domino Knoevenagel-Michael addition reactions.



Also an efficient four-component reaction for the synthesis of some new cyclohexylimino-2-methylpyrano [3,4-*c*]chromene-4*a*,5-dicarboxylates **2** has been developed *via* domino Knoevenagel-intramolecular oxo-Diels-Alder reactions. When 3-methoxy-2-hydroxy benzaldehyde was used as the reactant, the yield of the product bearing diethylacetylenic ester groups was very low. Therefore, we postulated that the target product could not be prepared in acceptable yields as a result of steric hinderance of bulky ethyl groups of neighbouring CO_2Et.

Thermal stability of compounds **2** in hot EtOH is dependent on the steric hindrance of ester groups. Compounds **2** bearing ethyl groups convert to compounds **3** probably to get rid of their highly steric hindrance. X-ray crystallography confirmed the structure of the new compounds.

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TRANSFORMATION OF CARBOHYDRATES TO POLYMER MONOMERS VIA OXIDATION OF 3-CHLOROMETHYLFURFURAL

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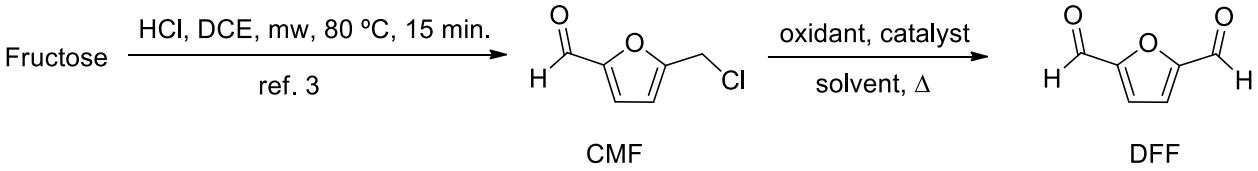
Monomers and polymers obtained from renewable resources, namely 3,6-furan derivatives, have witnessed a significant growth of interest within both the scientific and industrial communities. These furan derivatives, which can be prepared from sugars and/or polysaccharides, is expected to create a whole original realm of polymers and may also contribute to a considerable range of future macromolecular materials.[1] 3-Hydroxymethylfuraldehyde (HMF) and its derivative 2,5-diformylfuran (DFF) have been identified as promising building blocks intermediates of polyester.[2] Due to HMF chemical instability,[3] some of these approaches consider the in situ conversion of this monomer into its more stable dialdehyde (DFF) derivative.[1] On the other hand, DFF can also be obtained from 5-chloromethyl furfural (CMF), a stable and hydrophobic organic liquid. A range of carbohydrates has been rapidly and selectively converted to CMF using microwave heating in a biphasic reaction system with a range of organic solvents, providing yields higher than 70% obtained in 15 minutes (Scheme 1).[4] Here is described our efforts in order to achieve an efficient method for the oxidation of CMF to DFF.



Scheme 1. Synthetic approach to obtain CMF starting from fructose [2] and posterior oxidation to obtain DFF.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia (PTDC/QEQ-PRS/2757/2012) for financial support.

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SYNTHESIS OF β-CARBOLINE-3-CARBOXYLATES VIA HETERO-DIELS-ALDER REACTION OF NITROSOALKENES WITH INDOLES

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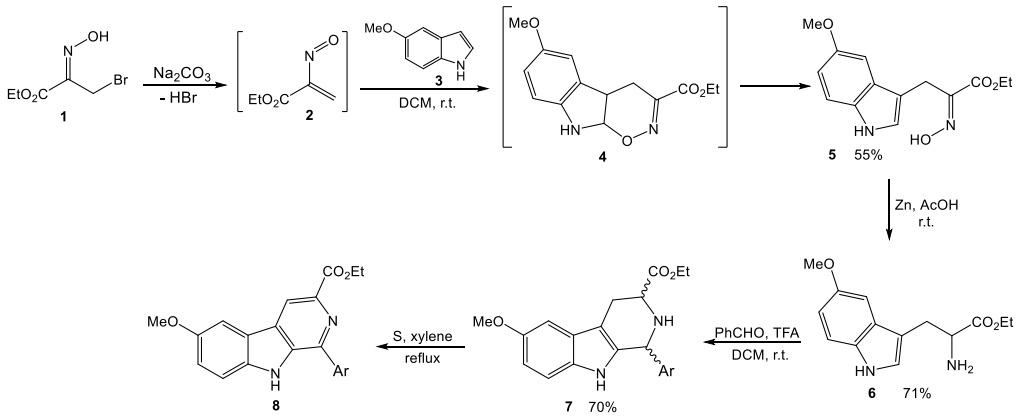
Natural and synthetic tetrahydro-β-carboline and β-carboline alkaloids are well known compounds that possess a variety of biological properties, such as antitumoral and antiprotozoal activities.[1] Studies on a variety of synthetic β-carboline derivatives have demonstrated the influence of the nature of the substituents in positions-1, -3, -5 and -9 of the β-carboline skeleton on the biological activities. Appropriate substituents on these positions can lead to active potent compounds with reduced toxicity.[2] The reported antiprotozoal and antitumoral activity makes this class of compounds an interesting scaffold to be explored. It is well established that the hetero-Diels-Alder reaction of nitrosoalkenes with indole leads to open chain oximes via rearomatization of the initially formed cycloadducts.[3] These adducts can be reduced to afford tryptophan analogues. We envisioned that this chemistry could be further explored in order to obtain new tryptophan derivatives (*e.g.* **6**) to be used as building blocks in the synthesis of novel β-carbolines (*e.g.* **8**).

In this context, the hetero-Diels-Alder of nitrosoalkene **2** with 5-methoxyindole (**3**) was carried out giving open chain oxime **5**. The subsequent reduction of compound **5** with zinc in acetic acid afforded the correspondent amine **6** which underwent condensation via Pictet-Spengler reaction to give the tetrahydro-β-carbolines **7**. Conversion of derivative **7** to the corresponding β-carbolines **8** was carried out by oxidation with sulphur in refluxing xylene (Scheme 1). More details of this study will be presented.



Scheme 1

Acknowledgements: We thank the CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) / Ciência sem Fronteiras (Processo 201583/2014-3) and FCT (Centro de Química de Coimbra through Project UID/QUI/00313/2013 and Grant SFRH/BPD/84423/2012) for financial support.

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A DIAZAOXA[7]HELICENE ANALOGUE OF DIAZADIOXA[8]CIRCULENES

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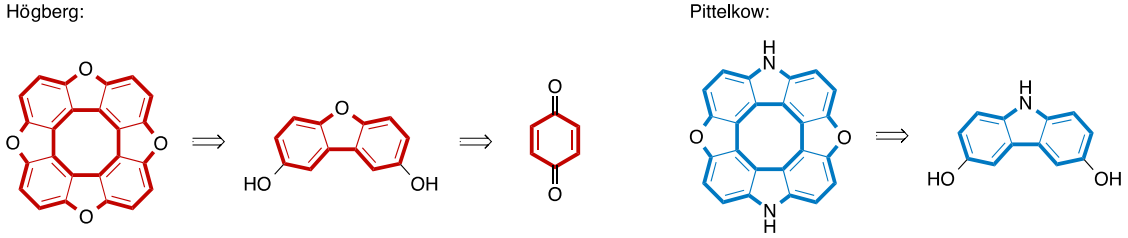
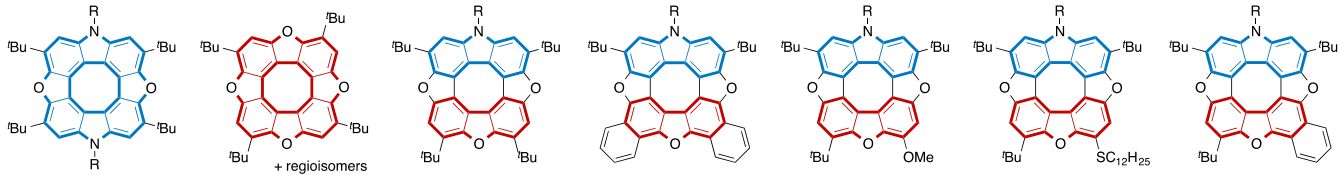
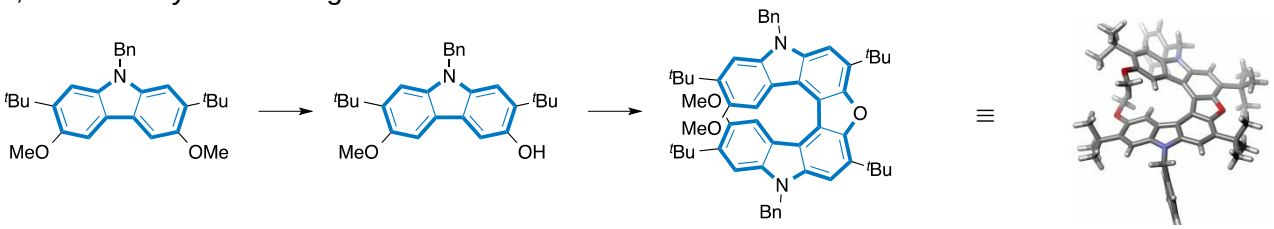
Inspired by chemistry performed by Högberg[1] in the 1970's, who synthesised tetraoxa[8]circulenes from benzoquinones with a dihydroxydibenzofuran as an important intermediate, we have explored the role of dihydroxycarbazoles[2] in the synthesis of diazadioxa[8]circulenes.



A variety of hetero[8]circulene derivates have been synthesised,[3,4] including products of the condensation between quinones, carbazoles, or mixtures hereof. The heterocyclic [8]circulenes have proven valuable in discerning the concept of antiaromaticity due to their planar 8π electron cyclooctatetraene core.[5]



We have now set out to synthesise a [7]helicene analogue to the [8]circulenes. The key steps are the mono-demethylation of dimethoxycarbazole, followed by condensation to form the desired chiral product, of which crystals were grown.



Having developed a feasible synthesis of the [7]helicine scaffold, we will explore this novel synthetic approach to prepare longer [*n*]helicenes and we will seek to functionalise the [*n*]helicenes to prepare water soluble derivatives with possible applications in DNA recognition.

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SYNTHESIS OF BIOTIN[6]URILHEXAESTERS AND THEIR ANION TRANSPORT CAPABILITY

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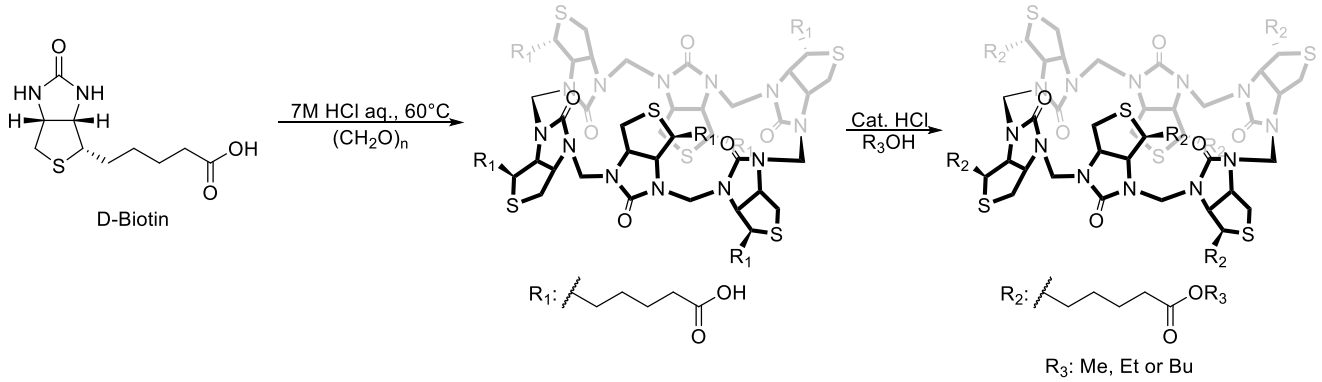

Recently we described the high yielding one step synthesis of biotin[6]uril (B6U) by an anion templated condensation reaction between biotin and formaldehyde in aqueous mineral acid. [1] The novel macrocycle has structural similarities with cucurbit[6]uril,[2] hemicucurbit[6]uril,[3] and bambus[6]uril.[4] The B6U is water soluble and binds anion in water.[5] Here we show that changing the CO_2H groups to alkyl esters give macrocycles which are soluble in organic solvents and bind anions like fluoride, chloride, bromide and iodide. The B6U hexaester macrocycles are anionphores (transports anions across lipid membranes), that recognise the anions by means of C-H interactions.[6] We found that the B6U hexaester macrocycles favors less hydrophobic (e.g., Cl^-) anions over the strongly hydrated anions (e.g.,HCO_3^-.) The B6U hexaester macrocylces showed selectivity for Cl^- over HCO_3^- in an aniontransmembrane transport study. [6]

Here we describe the synthesis, anion-binding properties and anion-transport properties of the B6U esters.

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STRAIGHTFORWARD APPROACH TO DISUBSTITUTED DIAMONDOIDS *VIA* INTRAMOLECULAR C-H AMINATION REACTION

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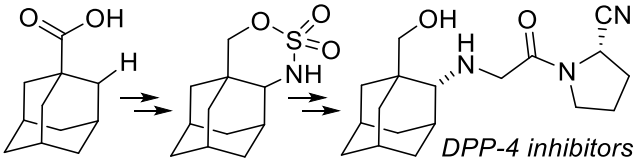
We present a three-step approach to disubstituted diamondoids[1] from readily available carboxylic acids. A rhodium acetate catalyzed (1 mol%) nitrene insertion reaction of sulfonamides was chosen for the intramolecular C–H functionalizations.[2] This straightforward approach enables the effective synthesis of a variety of cyclic sulfamidates, which are synthetically valuable building blocks. As an example, we report the five step synthesis of Vildagliptin® analogues as new DPP-4 inhibitors, antidiabetic drug candidates (Scheme 1).[3]



Scheme 1

References:

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GLYCOSAMINOGLYCANS IN CANCER BIOLOGY

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Glycosaminoglycans (GAGs) are heterogeneous polysaccharides comprising repeating uronic acid and amino sugar disaccharide units. These macromolecules can be covalently attached to core proteins to form proteoglycan side chains, or located in the extracellular matrix.[1] Recently, it was shown that the sulfate groups present in chondroitin sulfate GAGs (CS) encode important functional information for the regulation of physiological processes such as cancer metastasis and spinal cord injury.[2] [3]

To probe the “sulfation code” of CS in biological systems, a versatile synthetic strategy has been devised to obtain all the 16 theoretically possible sulfation patterns in the chondroitin sulfate (CS) repeating unit; these include rare but potentially important sulfation motifs which have not been isolated earlier. The library of synthesized disaccharides was screened on different breast cancer cell lines, to determine the effect of CS sulfation patterns on cancer development.

References:

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OXIDATIVE SINGLE-STEP UMPOLUNG *α*-ALKYLATION OF CARBONYL COMPOUNDS

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[b] Department of Chemistry, Technical University of Denmark, Lyngby, Denmark

A novel alkylative reaction of 1,3-dicarbonyl compounds or ketone enolates has been designed, developed and studied.[1] The reaction entails oxidative umpolung reaction mediated by the hypervalent iodine oxidant, Koser's reagent, at the *α* position of the carbonyl compound, while employing dialkylzinc reagents as the alkyl source.
The reaction was found to be applicable to a wide range of carbonyl compounds including 1,3- dicarbonyl compounds and ketones, as well as capable of forming quaternary carbon centres. The alkylated carbonyl products were formed in good to excellent up to 93% yields. Extensive mechanistic studies were performed, in order to examine possible carbene, radical, and ionic pathways. Based on meticulous product analysis, NMR studies, computational model, and cross-over experiments, an ionic mechanism was deduced. Following the symmetric alkylation method, an asymmetric single step oxidative umpolung alkylation of Evans' beta keto imides was developed.[2]

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MULTICOMPONENT PRINS CYCLIZATION FROM ALLYLSILYL ALCOHOLS LEADING TO DIOXASPIRODECANES

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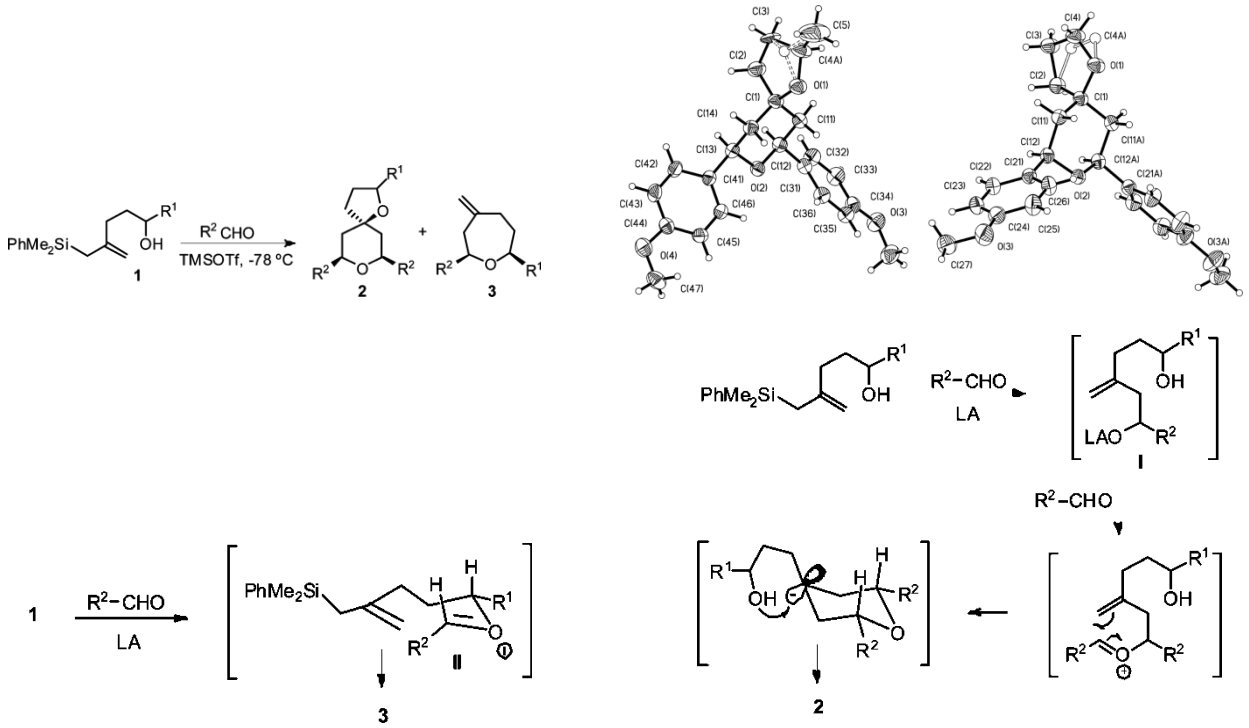
A multicomponent Sakurai-Prins reaction for the preparation of dioxaspirodecanes **2** starting from allylsilyl alcohols **1** was achieved. The one-pot sequence involves the sequential acid-catalyzed reaction of an allylsilyl alcohol with an aldehyde to afford an alkenediol **I**. The subsequent Prins cyclization of the homoallylic alcohol moiety generates a tetrahydropyranyl carbocation, which is intramolecularly trapped by the second hydroxyl group. The chemoselectivity of the process shows dependence on the nature of the aldehyde and the concentration of the catalyst. Formation of methyleneoxepanes **3** would proceed through initial formation of an (*E*)-oxocarbenium ion **II**, which would be trapped by the nucleophilic allylsilane.



The chemoselectivity of the dioxaspirodecane *vs* the oxepane derivative is dependent on both stereoelectronic factors and nature of the Lewis acid. This multicomponent coupling allows the synthesis of complex dioxaspirodecanes in a sequence where three new stereogenic centers are created with excellent stereoselectivity.[1,2]

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SUPRAMOLECULAR METHODOLOGY - DYNAMIC COMBINATORIAL CHEMISTRY WITH TWO SIMULTANIOUS REVERSIBLE REACTIONS: DISULFIDE AND BORONIC ACID ESTER EXCHANGE

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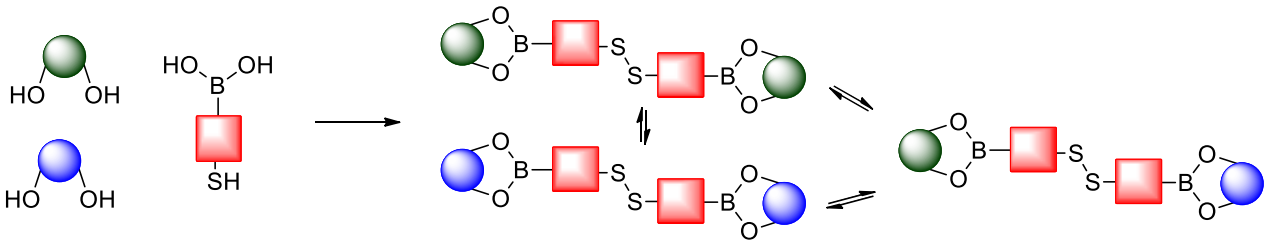
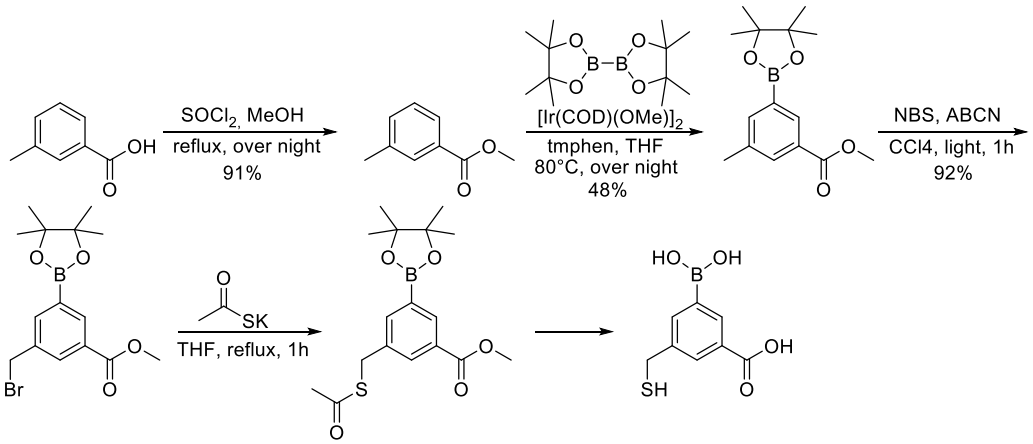
Dynamic combinatorial chemistry[1] is a highly efficient methodology that can be used to identify new supramolecular receptors. Dynamic Combinatorial Libraries (DCLs) are obtained from a set of building blocks that are able to oligomerize via reversible reactions. The majority of studies in the area look at just one reversible reaction, however recent studies have demonstrated that it is possible to increase the complexity in DCLs by combining two or three reversible reactions, mostly a covalent binding combined with coordination chemistry.[2] The multible reversible reactions may either be reversible at the same time or orthogonal.



In our system we investigate a new system using two simultainously equilibrating reversible reactions -- disulfide- and boronic acid esters exchange. Here we present a proof-of-concept study where we identify conditions where the two exchange reactions equilibrate simultaneously under thermodynamic control. We also present the synthesis of a new water soluble building block containing a thiol and a boronic acid incorporated in one molecule. The synthetic route starts from the commercial available *m*-toluic acid and involves a boronylation with an iridium catalyst,[3] a bromination using light as initiator and a thiolation with potassium thioacetate.



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THIOSULFINYLIMIDATES: WHEN SULFUR EXTENDS IMIDATES CHEMISTRY

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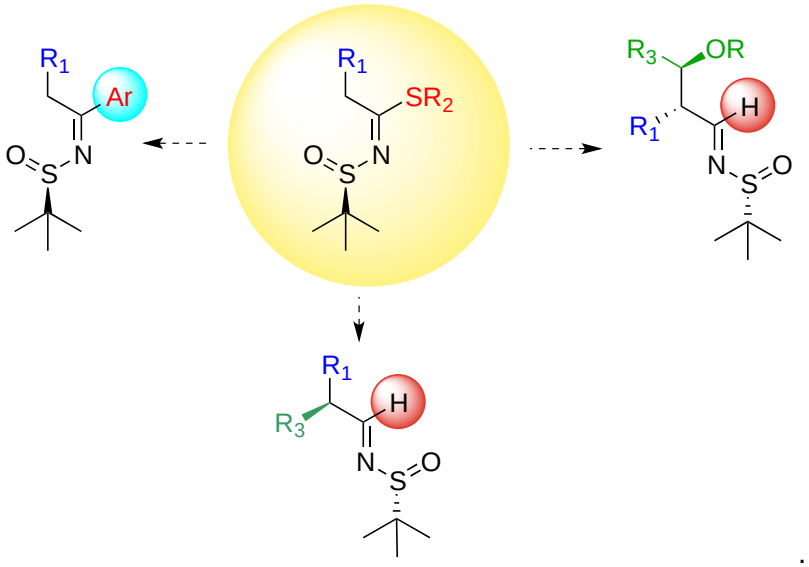
Sulfinylimines are certainly the most useful chiral ammonia derivatives for the synthesis of chiral amines.[1] Their preparation through the condensation of sulfinamide with aldehydes is very simple but suffers from a important drawback: the difficulty of generating stereodefined α-chiral sulfinylimines due to the potential (and often effective) epimerization through enolization. Indeed, this synthetic route is so far limited to α-oxygenated or α-aminated derivatives.[2] As branched chiral amines are ubiquitous in nature, it would be very desirable to find an alternative pathway to synthesize such α-chiral sulfinylimines, opening a new entry to this important class of chiral amine. We will present our recent results in the preparation, alkylation, coupling and reduction of novel thiosulfinylimidates as precursor to α-chiral sulfinylimines.[3] These precursors have been used in the total synthesis of natural products of the lycorine family.



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FUNCTIONALIZATION OF BIS(FURAN-2-YL)METHANES VIA HETERO-DIELS-ALDER REACTIONS OF NITROSOALKENES AND AZOALKENES

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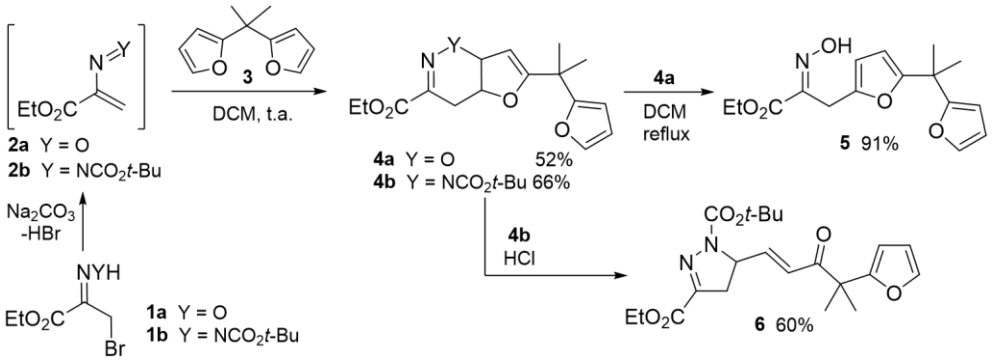
Bis(furan-2-yl)methanes are interesting compounds in the chemistry of natural and synthetic porphyrinoids, allowing the synthesis of structural varients of porhyrins such as tetraoxaprophyrins and other types of macrocycles.[1] They are also useful as flavoring agents, finding applications in the perfume industry and showing important pharmacological properties.[2] On the other hand, bis(furan-2-yl)methanes provide wide possibilities for further transformations by exploring the furan-ring-opening reactions, affording other useful organic compounds.[3]

We have previously developed a methodology for the functionalization of dipyrromethanes *via* hetero-Diels-Alder of nitrosoalkenes and azoalkenes.[4] This chemistry was now extended to the funcionalization of bis(furan-2-yl)methanes. Bis(furan-2-yl)methane **3** participated in the Diels-Alder reaction with nitrosoalkenes and azoalkenes, generated from the corresponding α-bromooximes and α-bromohydrazones, giving the corresponding cycloadducts (e.g. **4**, Scheme 1). The hetero-Diels-Alder of nitrosoalkene **2a** with compound **3** gives the bicyclic oxazine **4a** which leads to the open chain oxime **5** by refluxing in dichloromethane. On the other hand, the tetrahydropyridazine **4b**, obtained from azoalkene **2b** and difuranylmethane **3**, undergoes ring-opening-recyclization of the furan unit by treatment with HCl giving the ketone derivative **6**. Details of this study will be presented.



Scheme 1

Acknowledgements: We thank the FCT (Centro de Química de Coimbra through Project UID/QUI/00313/2013 and Grant SFRH/BPD/84423/2012) for financial support.

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THE STRATEGY OF THE SYNTHESIS OF NEW DERIVATIVES OF 2-AMINO-3-OXO-1-HYDROXYPYRROLO-[1,2-a]-PIRAZINE

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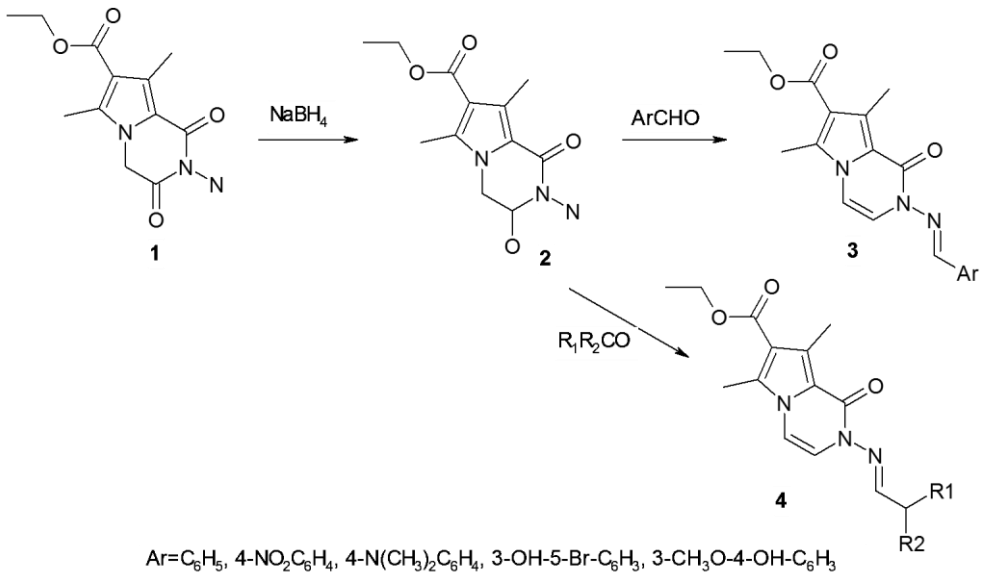
It is known that derivatives of pyrrolo-[1,2-a]-pirazine possess a wide range of biological activities (anticonvulsant, antihistamines, antiarrhythmic, analgesic, sympatholytic). It should also be noted that pyrrolo-[1,2-a]-pirazyne is an analoge of natural alkaloid Peramine, is an insect feeding deterrent isolated from perennial ryegrass infected with the endophyte Acremonium loliae[1] . In this context, the availability of a synthetic route to pyrrolo-[1,2-a]-pirazyn-1(2H)one carrying a pyrrole moiety could be of particular interest from the chemical and biological points of view.

The regiochemistry of reduction annelation pyrrolopirazine 1 with sodium borohydride in ethanol was investigated. It is shown that, the interaction with this reducing agent is proceeds regioselectivity and leads to the formation hydroxypirazine 2.

During our work on the reactivity of hydroxypirazine 2 with carbonyl compounds (aromatic aldehydes and ketones) was observed next fact. In the case of presence of acid catalysis the reaction followed with formation of hydrazone on first step and formation of products dehydration 3, 4 on the second step.

Our approach allows a preparation of such synthetically and biologically interesting molecule. The scope, limitations of the reactions presented above are now under investigation and detailed results will be published elsewhere.



Ar=C_6H_5, 4-$NO_2C_6H_4$, 4-$N(CH_3)_2C_6H_4$, 3-OH-5-Br-C_6H_3, 3-CH_3O-4-OH-C_6H_3
R_1=R_2=CH_3, R_1=CH_3 R_2=C_6H_5

References:

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MECHANOCHEMICAL OXIDATION OF PERFLUORO ANILINES TO PERFLUORO AZOBENZENES

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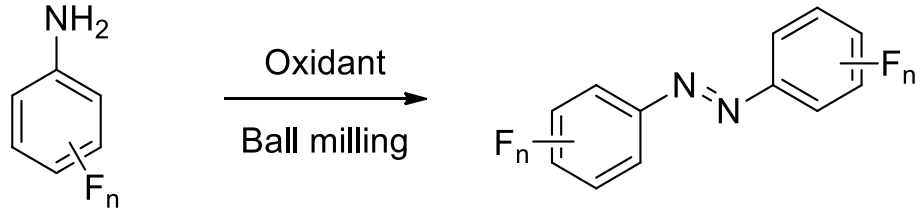
Aromatic azo compounds have been extensively used in industrial applications mainly as organic dyes and pigments, but also as food additives, indicators, and therapeutic agents.[1] Moreover, exploiting their peculiar photochemical response, the applications of azo compounds have been recently extended to a broad range of light-responsive functional materials, such as liquid crystals, molecular switches, smart polymers and photochromic ligands. [2] A multitude of synthetic methods to affording symmetric azo compounds are known, [3] the most used involve the oxidative coupling of aromatic amines and the reductive homodimerization of nitroarenes. In the case of anilines omocoupling the stoichiometric use of toxic and environmentally unfriendly transition-metal based oxidants, like mercury, lead and manganese derivatives, is often needed to achieve satisfactory yields, especially with electron-poor aromatic amines. One of our research efforts entail the synthesis of polifluorinated aromatic compounds as possible candidates to be used in material science applications.[4,5] On the route to target perfluorinated molecules we needed an efficient method to gain perfluoro azobenzenes, we focused our attention on the mechanochemical approach. [6]



Gratifying the use of environmental friendly oxidants in a zirconia mill, without the aid of milling auxiliaries, afforded the desired products in good to excellent yields.

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EFFICIENT ROUTE TO DIVERSELY FUNCTIONALIZED UNCLOSED CRYPTANDS VIA H-BOND TEMPLATED MACROCYCLISATION AND SUBSEQUENT POST-FUNCTIONALIZATION

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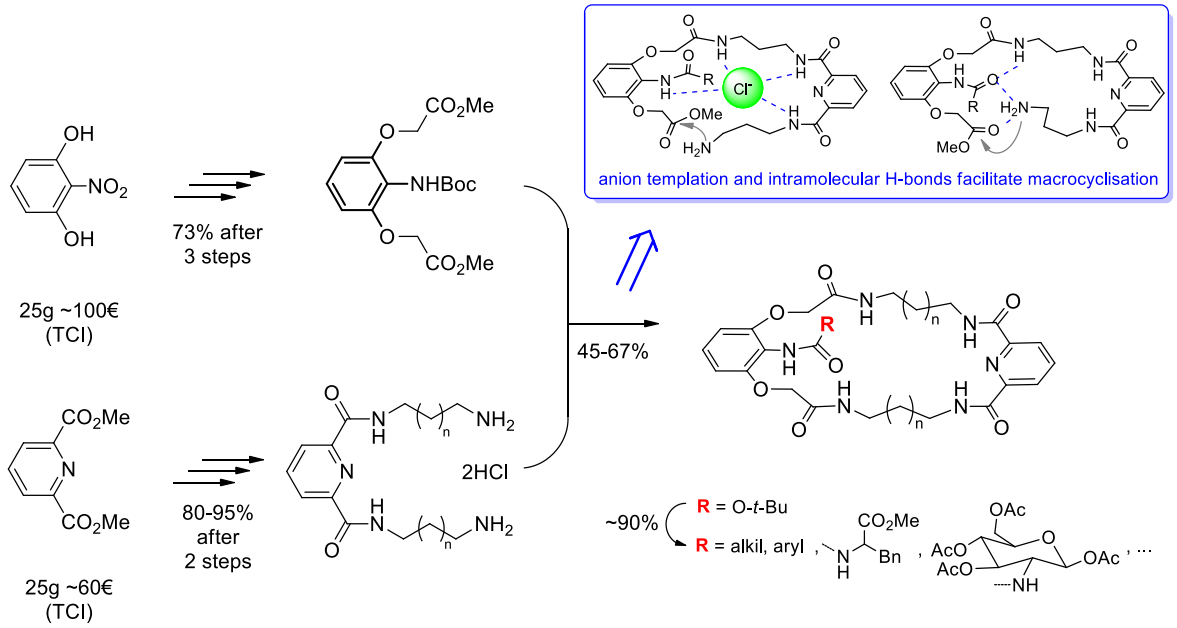
Macrocyclic compounds have attracted much attention in medicinal and supramolecular chemistry since their offer high level of preorganization, conformational preferences, and improved biostability in comparison to acyclic analogs.[1,2] The formation yield of desired macrocyclic products is, however, generally low from steric and entropic reasons. Moreover, purification is often challenging due to formation of cyclic and linear oligomers. Recently, we utilized macrocycles with a flexible lariat arm, so called unclosed cryptands (UCs), in the construction of potent anion receptors in solution as well as a platform for studying transient water cluster in the solid state.[3,4] However, method of their preparation does not allow post-functionalization.

Herein, we report the efficient synthesis of diversely functionalized UCs from commercially available and inexpensive starting materials. Moreover, the crucial macrocyclisation step does not require anhydrous and high-dilution conditions and is completed within 1-2 days. The high yield of macrocyclisation is anticipated to templation by a chloride anion and intramolecular H-bonds which both help to adopt an entropically disfavored pre-cyclization conformation of the linear precursor. The subsequent post-functionalization allows mild, selective, and efficient incorporation of various functional groups to the interior of a macrocyclic scaffold.



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MALONIC ACID HALF OXYESTERS (MAHOs) AN APPROPRIATE PRECURSOR FOR THE SYNTHESIS OF NON PROTEINOGENIC AMINO ACID DERIVATIVES

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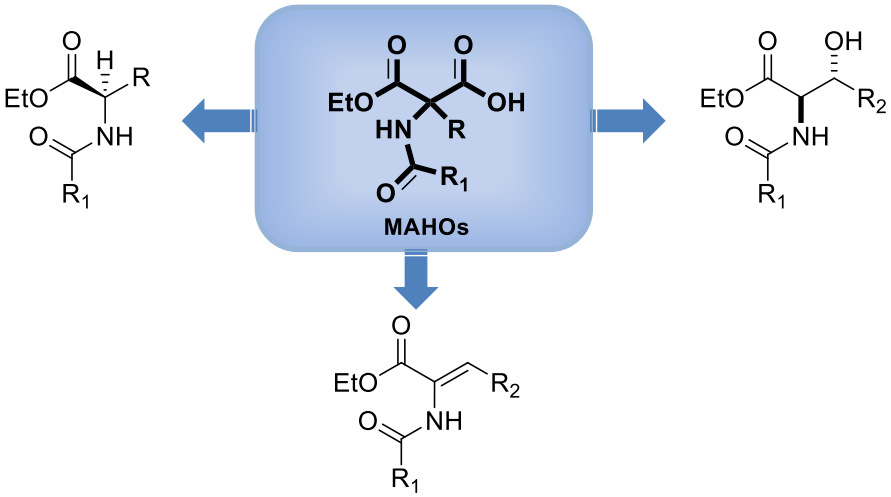
Malonic Acid Half Oxyesters (MAHOs) have been used as cheap glycine equivalents under mild metal-free conditions for the direct synthesis of polyfunctional esters. Malonic acid and its derivatives have been used in various reactions due to the ease of functionalizing the central methylene. Malonates and malonic acids are available substrates which are widely used in various conditions and specifically in organocatalysis. In this field, we became interested to amido-MAHO derivatives while studying asymmetric decarboxylative protonation for a direct access to enantioenriched α-amino acids.[1]

Following this research about using amido-MAHO as starting materials, we have described the synthesis of Anti-β-hydroxy-α-amino esters. These polyfunctional molecules are obtained directly and exclusively in very high yields from various aldehydes by utilizing decarboxylative aldol reactions.[2] To complete the assessment of this α-amino-Malonic Acid Half Oxyesters, this communication will also introduce an alternative and efficient approach affording various dehydroamino acid derivatives in mild conditions. Finally, a mechanistic study will be discussed to explain the stereochemistry of these reactions. In summary, the cheap readily available MAHOs can be used as a useful scaffold in the synthesis of various non proteinogenic amino acid derivatives.



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TARGETED PROTECTING GROUP STRATEGIES FOR E-RING CYCLISATION IN THE TOTAL SYNTHESIS OF (+)-AJMALINE

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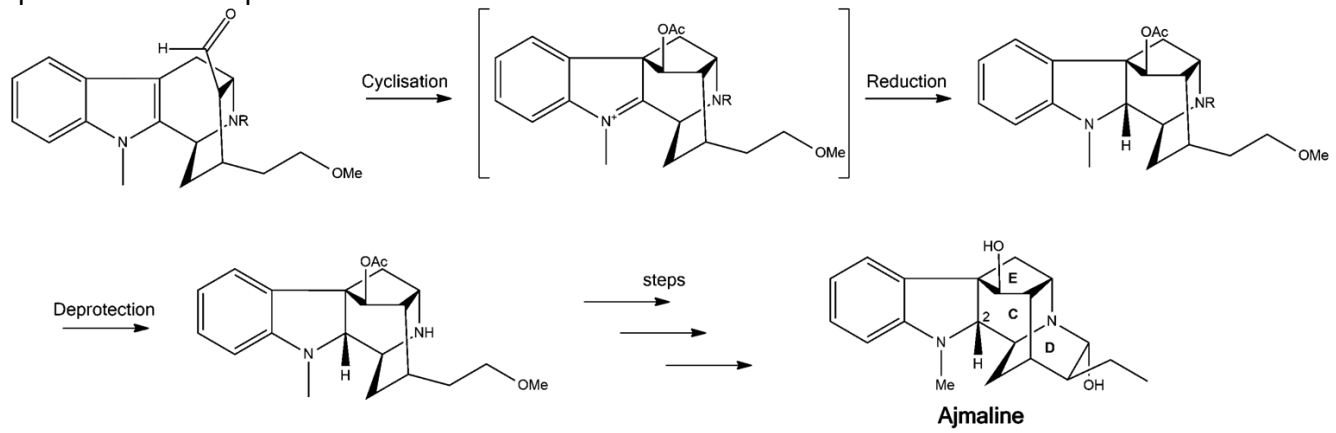
Indole alkaloids are an important class of natural products due to their medicinal properties. Ajmaline is no exception and has found use as an important diagnostic drug for the identification of Brugada syndrome.[1]

The total synthesis of ajmaline has been attempted by many groups, yet an elegant stereoselective synthesis remains elusive. The first formal synthesis was by Masamune in 1967 shortly after the structure was discovered.[2] An asymmetric total synthesis was not completed until over thirty year later in 1999 by Cook.[3] Cook's synthesis was an impressive achievement as the nine stereocentres and complex polycyclic structure of ajmaline provides a significant challenge for developing a successful asymmetric synthesis. However, one significant issue still remains, as even after extensive optimisation the formation of the C2 stereocentre in Cook's synthesis still favoured the incorrect configuration with the natural epimer as a minor product.



Our synthesis aims to close the E ring first and the D ring second in the final steps of the synthesis. We believe that closure of the E ring first will allow greater control over the formation of the C2 stereocentre.[4] We have found that the choice of protecting group for the basic nitrogen is crucial to the success of our synthetic strategy. The hybridization at the nitrogen appears vital in inducing cyclisation and steric bulk is required to direct the reduction to the desired face. It has been particularly challenging to find a group which will survive the strong acidic conditions of the ring closure step whilst still allowing for removal after the transformations have taken place.

Previous work focused on the use of a pivolyl amide protecting group.[4] This group seemed successful until its removal proved difficult. This poster aims to introduce and discuss current work that utilises different protecting groups in order to overcome this problem.

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STANNYLENE-MEDIATED GLYCOSYLATIONS WITH UNPROTECTED CARBOHYDRATES

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Synthesis of complex carbohydrate structures remains a difficult task in spite of many notable advances. Selective formation of glycosidic linkages requires both regio- and stereochemical control. In the last decades a number of efforts were made to reduce protecting group manipulations and shorten synthetic sequences. For this reason, glycosylation with unprotected carbohydrates is now under in-depth study.[1]

A useful promoter for the regioselective glycosylation of the secondary alcohols in unprotected glycosyl acceptors is under investigation. The procedure concerns the synthesis of 6-linked disaccharides via stannylene intermediates[2] to armed donors. In the glycosylation protocol D-glucose, D-galactose and D-mannose are studied as both donors and acceptors.

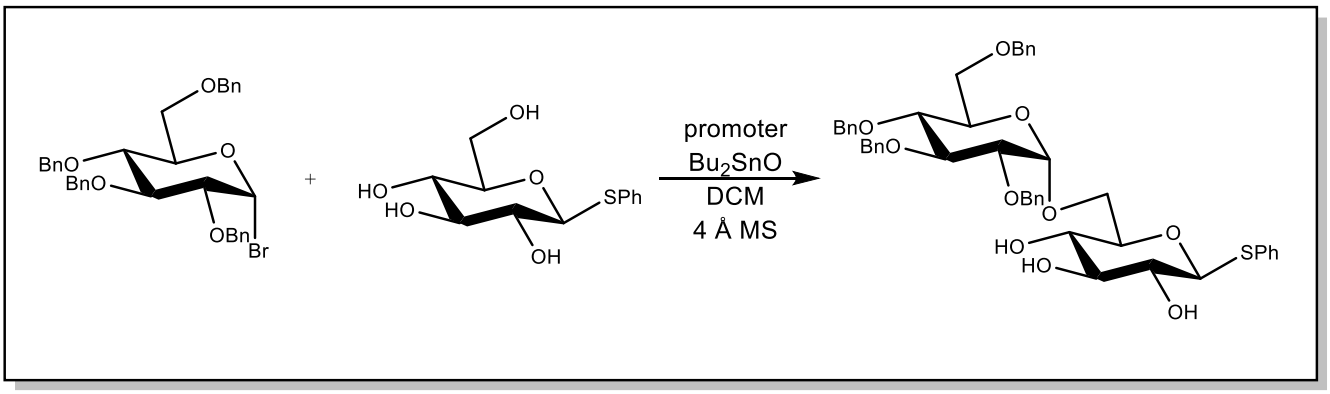

Figure 1. Example of a glycosylation with a tin reagent.

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A SIMPLE SYNTHESIS OF TRIANGULAR ALL-METAL AROMATICS AND HETEROAROMATICS AND THEIR APPLICATIONS ON COORDINATION AND CATALYSIS

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A simple synthetic method allows the one-pot assembly of C_3-symmetric, 44 core valence electrons triangular Pd or Pt clusters and their heterobimetallic mixed Pd/Pt analogues. These mixed metal complexes are the first examples of stable triangular all-metal heteroaromatics. In contrast to traditional heteroaromatic molecules formed combining main-group elements, they actually retain structural and electronic features of their homonuclear analogues. These aromatic clusters were found further applications as a catalyst of semi-reductions of alkynes. These cationic clusters were also proved to be efficient ligands to Lewis acids due to their Lewis base properties. The discovery of these new clusters enriched the chemistry on the aromaticity of all-metal complexes.[1-4]

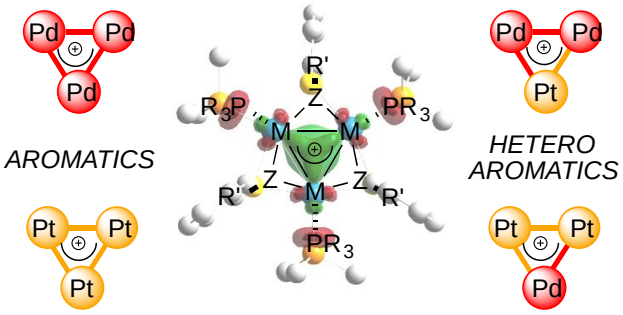

Figure 1. Triangular all-metal aromatics and heteroaromatics.

Accepted Chem. Eur. J. **2015**, *21*, xxxx-xxxx.

Acknowledgements: In memory of Paul von Ragué Schleyer; We thank CNRS, UPMC and MIUR for funding.

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SUSTAINABLE SYNTHESIS OF *N*-METHYLATED CYCLIC MODEL PEPTIDES

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The need for peptide-based medicines or the roles of peptides in drug discovery, etc. secure the high importance of the peptide synthesis.[1] Introducing methyl groups into the peptidic amide bonds affects the physicochemical properties of peptides. This modulation, *N*-methylation, together with peptide cyclization, confers unprecedented pharmacokinetic properties to the peptides, including membrane permeability, metabolic stability, and even oral bioavailability.[2] Since its introduction by Merrifield, the synthesis of peptides was performed almost exclusively on solid supports.[3] However, still a general property of these methodologies are the high number of amino acid equivalents required for total coupling. Continuous-flow (CF) technologies have recently emerged as a productive methodology in modern synthetic chemistry. This is due to the great number of advantages they deliver over conventional batch procedures such as faster heat and mass transfer, the efficient mixing of substrates, shorter reaction times and facile scale up.[4]

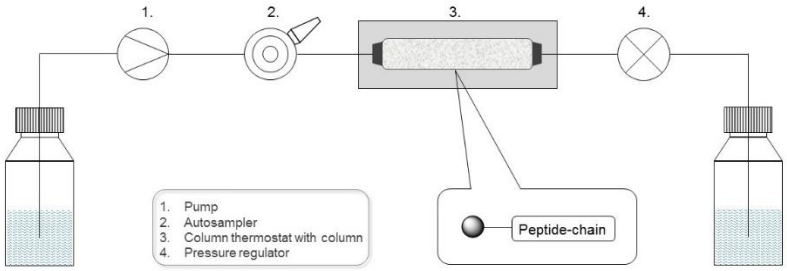

Figure 1. Schematic representation of the constructed CF reactor.

In this work a fast and highly efficient continuous-flow solid-phase peptide synthesis (CF-SPPS) technique is presented for the preparation of multiple *N*-methylated cyclic alanine peptides. In this methodology only 1.5 equivalents of amino acids is required for the coupling to maintain quantitative conversions. During the syntheses, the CF reactor allows the application of high pressures and temperatures with low solvent consumption, as well as low coupling and deprotection times. The evidence of the effectiveness, the linear version of the multiple *N*-methylated cyclic peptides is assembled in excellent yields. A method of peptide cyclization is described as well, which can be used to obtain the *N*-methylated cyclic peptide and which are not limited to specific peptide sequences. It is possible to incorporate exotic and expensive artificial amino acids into sequences by an automated way using exceptionally low numbers of amino acid equivalents in a highly economic and more sustainable manner.

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SYNTHESIS OF ORGANIC MOLECULES HAVING UV-RADIATION ABSORPTION FEATURES AND APPLICATIONS ON TEXTILES

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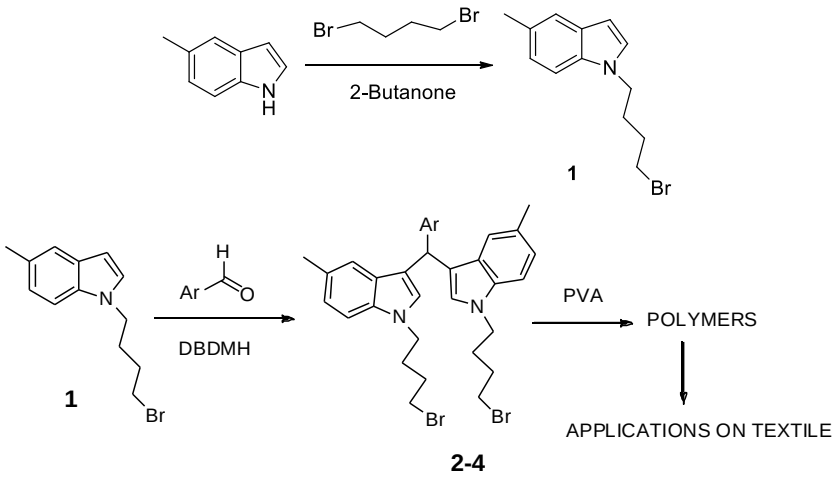
In recent years, many heterocyclic compounds were synthesized, their biological activities researched and also the behavior of heterocyclic compounds against cancer cells was investigated. At the beginning of 20th century, five membered heterocyclic compounds such as pyrolles, imidazoles, thiazoles, oxazoles, pyrazoles, indoles and thiazolidinones have become of great interest for pharmaceutical chemists, because of their usage as raw material for drugs.[1]
As a result of investigation for over 100 years on heterocyclic compounds, it is communicable that the usage of nitrogen and oxygen-containing structures for modelling the bioactive compounds caused a great variability. This is a very important type of heterocyclic organic compounds of biological and physiological activity due to the fact that they have nitrogen and oxygen-containing groups
On the other hand, this type of compounds is getting very important because of their UV absorber characteristics. The sunbeam includes the UV radiation, whose major part is destructive of human health. For more protection from this type of radiation the usage of UV absorber materials in textiles is needed.[2]
At the same time, the colored fabrics, their finishes made from this type of materials, although depends on the spectrochemical characteristic of the dye and exposure time to sun, can show better colorfastness to light, less color fading and the yellowing of the white fabrics can be decreased with using this type coating materials.[3]



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PALLADIUM COUPLING REACTION OPTIMIZATION AS PART OF THE DEVELOPMENT OF AN API SYNTHESIS

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Herein is described the work carried out to optimize a palladium coupling reaction used in the synthesis of an API allowing a successful scale-up of the chemical process. Reduction of the palladium loading used in the process significantly reduced the process cost. Further process optimization using statistical tools was conducted. The route cause for a critical impurity formation was found and a control strategy was implemented to eliminate the impurity from the process. Residual Palladium metal removal for API was optimized using the right cost effective scavenger.

SYNTHESIS OF NOVEL GLYCOSYL SULFONAMIDES: CONFORMATIONAL STUDIES AND FURANOSE/PYRANOSE ISOMERIZATION IN RIBOSYL DERIVATIVES

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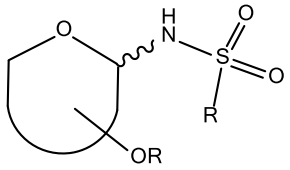
Mimetics of *O*-glycosides have attracted considerable interest in medicinal chemistry due to their relative stability to enzymatic hydrolysis and ability to inhibit enzymes such as glycosidases.[1] Such analogs include thioglycosides, *C*-glycosyl or *N*-glycosyl derivatives. The N-modified analogs are among the less stable glycoside mimetics, although the stability of glycosyl sulfonamides is higher than that exhibited by most of glycosylamines. *N*-Glycosyl sulfonamides have also shown interesting biological properties, namely antitumor activities which arise from their ability to inhibit cancer-associated carbonic anhydrases.[2,3]

Hence, we were motivated to explore the synthesis of novel anomeric sulfonamides (Fig. 1) and to study particularly the stereochemical and conformational outcome of the N-glycosylation involving an acetylated pentosyl donor and a triacetylated glucuronamide derivative. In the case of the *N*-ribofuranosyl sulfonamide, its subsequent deacetylation occurred with isomerization to the pyranose form.

Conformational analyses were performed by a combination of Molecular Dynamics and DFT calculations in order to understand the effect of the structure of the sugar moiety on the conformation adopted by the target molecules.

The synthetic details, results of the conformational analysis studies, and the factors that influence the relative stability of the possible stereoisomers and conformers of the target *N*-glycosyl sulfonamides formed are presented and discussed.



pyranosyl and furanosyl derivatives

Figure 1

Acknowledgements: 'Fundação para a Ciência e Tecnologia' (FCT) is acknowledged for funding (IF/01488/2013, IF/00069/2014 and CQB strategic project UID/MULTI/00612/2013).

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SYNTHESIS OF NOVEL BODIPY DYES FOR PROTEIN LABELLING

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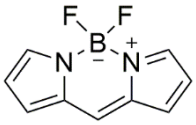
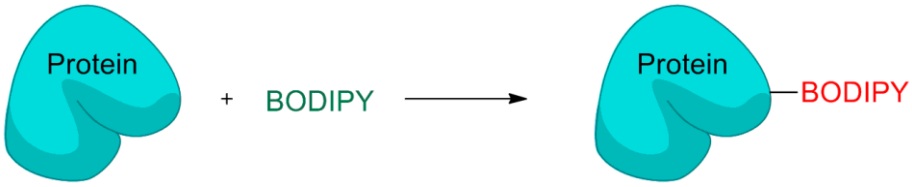
Fluorescence spectroscopy, imaging and indicators are invaluable tools for a number of purposes in modern science across are range of disciplines.[1] They are used in clinical diagnostics, biotechnology, molecular biology and biochemistry among others. Fluorescent dyes are commonly employed in biochemistry for labelling proteins and nucleic acids, staining cell organelles and tagging of molecules on the cellular level.
One of the classes of dyes that has very high potential and is used most commonly is those based on 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene core (**1**),[1,2] also known as the BODIPY class of compounds.



BODIPY (**1**)

The popularity of BODIPY based dyes can be accredited to their valuable properties; they are robust against degradation from light and chemicals, good solubility, excitation/emission in the visible spectrum with sharp fluorescent emission and high quantum yields of fluorescence. Importantly the dyes are stable to changes in pH and are stable to physiological conditions.[1]
As part of this contribution, we would like to present our work on the development of polyfunctionalised BODIPY dyes for amino acid and protein binding. This approach opens the possibility of using this new class of dyes for protein sensing and detection.



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B – CATALYSIS

C–H FUNCTIONALIZATION OF CARBOCYCLIC ARENES AND HETEROARENES

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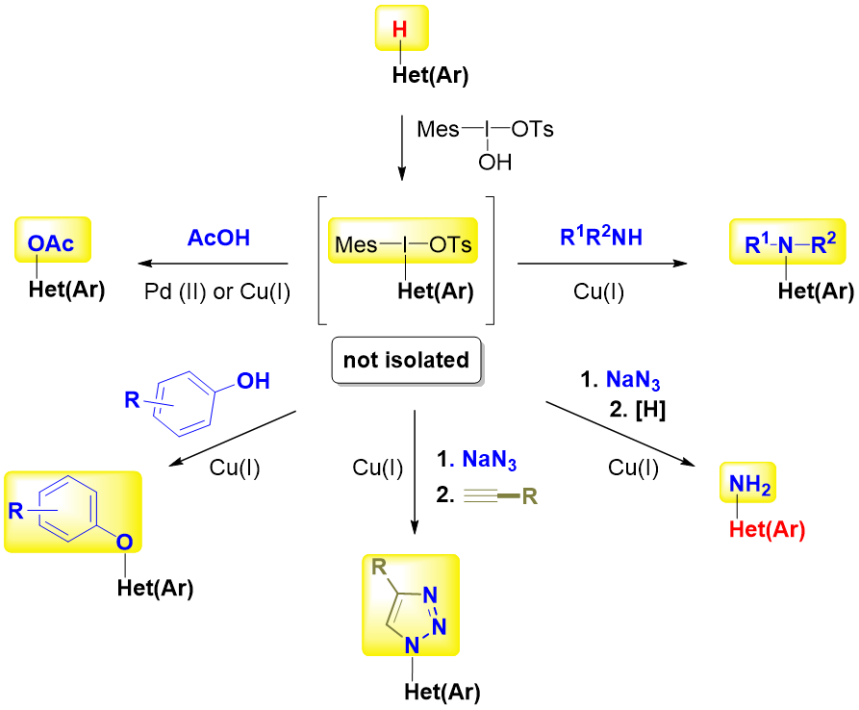
Late-stage modification of biologically relevant compounds is frequently used to streamline the lead-optimization phase in drug discovery. The most suitable approach to the late-stage modification relies on functionalization of C–H bonds.

Our C–H functionalization methodology comprises an *in situ* formation of unsymmetrical (hetero)aryl-λ^3-iodanes followed by their Pd(II) or Cu(I)-catalyzed reaction with a wide range of nucleophiles such as acetates,[1] phenolates, azides,[2] primary and secondary aliphatic amines and anilines.[3] The transition metal catalyst ensures the desired selectivity in the reaction between the intermediate unsymmetrical λ^3-iodanes and nucleophiles.



The methodology is suitable for C–H functionalization of relatively electron-rich heterocycles such as pyrroles, indoles, pyrazoles, thiophenes, pyrrolopyridines, pyrrolopyrimidines and uracils. The reactivity pattern of the developed C−H functionalization is consistent with that of an electrophilic aromatic substitution (S_EAr) reaction. Carbocyclic arenes undergo selective *para*-C–H functionalization.

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NOVEL ACTIVATION OF SUBSTRATES FOR SELECTIVE CATALYSIS

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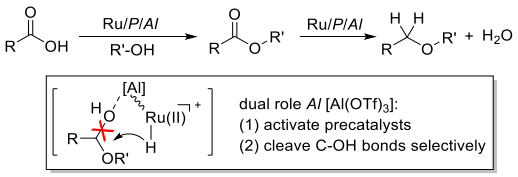
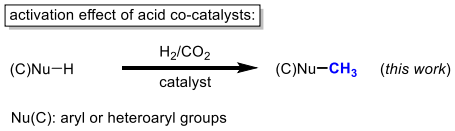
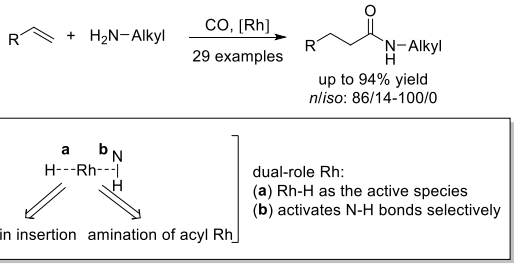
1) Ethers are of fundamental importance in organic chemistry and they are an integral part of valuable flavors, fragrances and also numerous bio-active compounds. In general, the reduction of esters constitutes the most straightforward preparation of ethers. Unfortunately, this transformation needs inevitable use of large amounts of metal hydrides. Here, we present a bifunctional catalyst system consisting of Ru/phosphine complex and aluminum triflate, which allows for selective synthesis of ethers via hydrogenation of esters or carboxylic acids. Notably, the in-situ formed catalyst can be reused several times without any significant loss of activity.



2) Benign formation of C-C bonds from carbon dioxide is a dream reaction in organic synthesis. To date, other than C-H carboxylations using stoichiometric amounts of metals, base or organometallic reagents little is known about C-C bond formation. In this work, we demonstrate that the combination of carbon dioxide and H_2 allows for efficient methylation of carbon nucleophiles such as indoles, pyrroles and electron-rich arenes. The key to success is the use of acid co-catalysts for activation of both substrates and transition-metal pre-catalysts.



3) Hydroamidation of olefins constitutes an ideal, atom-efficient method to prepare carboxylic amides from easily available olefins, CO and amines. So far, aliphatic amines are not suitable for these transformations. Here, we present a ligand- and additive-free Rh(I) catalyst as solution to this problem. Notably, chemoselective amidation of aliphatic amines takes place in the presence of aromatic amines and alcohols. Mechanistic studies reveal the presence of Rh-acyl species as crucial intermediates for the selectivity and rate-limiting step in the proposed Rh(I)-catalytic cycle.



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C- H ARYLATION OF SP^3 BONDS OF AMINOALCOHOLS: A NOVEL METHODOLOGY FOR THE RAPID ACCESS OF VALUABLE DRUGS

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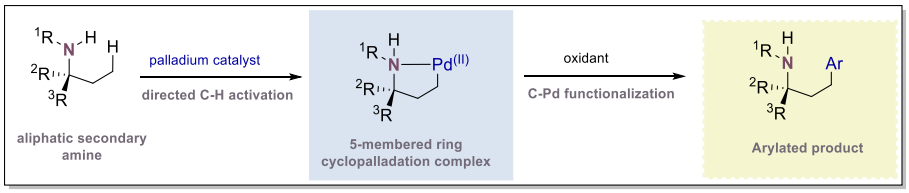
The emerging area of C–H functionalization provides new synthetic tools that are changing the way in which chemists make molecules. The direct introduction of a new functionality (C–O, C–N or C–C bond) via direct C–H bond transformation is a highly attractive strategy for synthesis in terms of step economy and low-waste production. The ubiquitous nature of C–H bonds in hydrocarbons, organic compounds, pharmaceuticals and artificial and biological polymers, makes the range of synthetic possibilities virtually limitless.[1] Here we describe a sp^3 C-H bond arylation of β-aminoalcohols using Pd(II)-Pd(IV) catalysis, an emergent chemistry that will streamline the synthesis of biologically active and pharmaceutically relevant molecules. Important features of the methodology include access to a broad range of highly functionalized arylated aminoalcohols, mild reaction conditions and a novel activation mode that does not require additional directing groups and instead exploits the intrinsic ability of the amine function to steer carbopalladation. The methodology proposed will serve for the construction of sphingolipid analogues with broad therapeutic applicability



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VITAMIN B_{12} CATALYSIS: TOTALLY RADICAL

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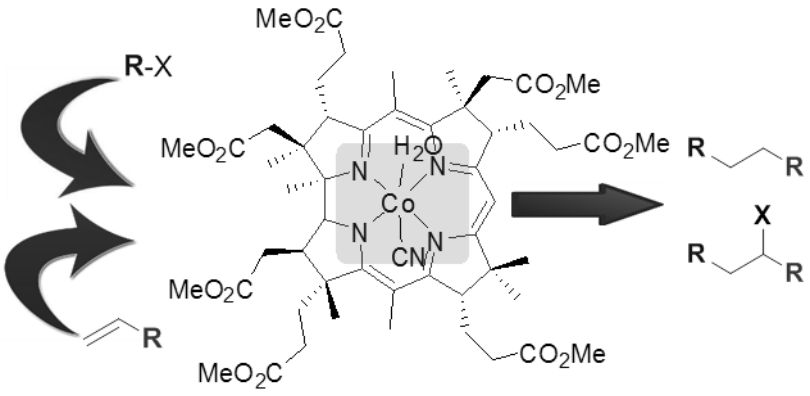
Vitamin B_{12} is a highly functionalized tetrapyrrolic compound bearing a central cobalt ion. It has been examined as an oral delivery vehicle for therapeutic agents, as an artificial enzyme and more importantly as a catalyst for various organic reactions.[1] Like most great ideas vitamin B_{12} catalysis was inspired by the ultimate chemist Nature, as methylcobalamin and adenosylcobalamin are involved in numerous biocatalytic reactions including isomerization, methylation and dehalogenation.[2] This type of catalysis has been successfully translated into the laboratory and used in a small collection of reactions.[3] The advantage of using vitamin B_{12} lays in the complete stability of the central cobalt ion, whereas most catalytic reactions require the addition of toxic metals plus complex ligands into a cocktail of reagents, vitamin B_{12} in itself is a package deal. Furthermore, it has been well documented that the reaction mechanism usually follows a radical pathway, bringing a new dimension to this already interesting field.

Cobalamin is not without fault, which includes lack of solubility in organic solvents. Therefore, our work utilizes its hydrophobic cobyrinic acid derivatives.[4] These compounds still bear the advantages of vitamin B_{12}, however their ability to be modified and manipulated into more useful catalysts trumps cobalamin. Herein, we present cobyrinic acid catalyzed radical intermolecular addition of organic halides to olefins. The study of intermolecular reactions in this area is extremely limited. However, our study has tackled this issue head on and will show the unique quality of these catalysts by not only performing Michael addition reactions but also the unknown atom transfer radical addition (ATRA) reaction through traditional methods as well as microwave assisted and photochemical methods.



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DEHYDRATIVE THIOLATION OF ALLENOLS: INDIUM *VS* GOLD CATALYSIS

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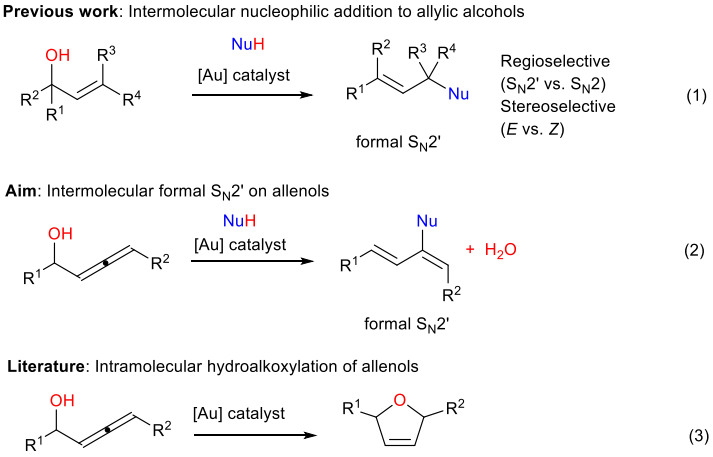
The Lee group have recently developed a gold catalysed intermolecular etherification (NuH = ROH)[1] and thioetherfication (NuH = RSH)[2] reaction of allylic alcohols. These reactions are highly regioselective for the formal S_N2' product producing only water as a by product (Eq. 1, Scheme 1). We therefore, wanted to investigate whether this intermolecular dehydrative method could be extended to allenols to form 1,3-dienes[3] – useful building blocks in organic synthesis (Eq. 2, scheme 1). However, it is well documented in the literature that allenols prefer to undergo intramolecular cyclisation reactions in the presence of gold catalysts[4] (Eq. 3, scheme 1) and our proposed dehydrative method has no literature precedent.



Scheme 1. Previous work (eq. 1), current aims (eq. 2) and literature cyclisations (eq. 3)

The optimisation of this reaction was originally carried out using a Au(I) catalyst. However, the Au(I) catalyst showed poor regioselectivity between the formal S_N2' and formal S_N2 products. Following an extensive Lewis acid screen, $InCl_3$ was found to be a far superior catalyst for this reaction.

The reaction tolerates a wide variety of substrates including electron rich aryls (68-96%), electron poor aryls (47-93%), heterocycles (79-84%) and alkyl R groups (42-80%) as well as several other substrates with excellent regioselectivity (>20:1 $S_N2':S_N2$). The thiol nucleophile scope was also investigated with electron poor thiols performing better than electron rich thiols 65-80% *vs* 52%.

Neutral and slightly electron rich thiophenols perform well.

A plausible mechanism has been put forth and additional mechanistic studies have been performed which show the reaction is reversible and the regioselectivity depends on the thermodynamic stability of the products.

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OXOIRON(IV)-MEDIATED BAEYER-VILLIGER OXIDATION OF CYCLIC KETONES GENERATED BY DIOXYGEN WITH COOXIDATION OF ALDEHYDES

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The Baeyer-Villiger oxidation of ketones to lactones or esters is one of the main reaction in organic chemistry owing to very wide range of possible applications, for example in the production of polymers, pharmaceuticals and herbicids.[1] The most important industrial process for the production of □-caprolactone is the oxidation of cyclohexanone with *m*-chloroperbenzoic acid.[2]

Over the past four decades transition metal complexes of a variety of ligand systems have been reported as active catalysts for the catalytic oxygen transfer reaction,[3,4] and their catalytic cycles often involve oxoiron(IV) intermediates as oxidants. [5,6]

A novel catalytic method for the Baeyer-Villiger oxidation of cyclohexanone derivatives (cyclohexanone, 2-methyl-cyclohexanone, 3-methyl-cyclohexanone, 4-methyl-cyclohexanone and 4-*tert*-butyl-cyclohexanone) has been investigated, with non-heme iron(II) complex ($[Fe^{II}(CH_3CN)(N4Py)](ClO_4)_2$ N4Py = *N,N*-bis(2-pyridylmethyl)-N-bis(2-pyridyl)methyl-amine) as catalyst, aldehydes (isobutyraldehyde, benzaldehyde, 4-methylbenzaldehyde and 4-chlorobenzaldehyde) as oxygen acceptors and dioxygen as oxidant. The experimental results clearly indicated the formation of a high-valent metal-oxo intermediate (Fe^{IV}=O), and its role in the oxidation process. Reactions were monitored and products were determined using a gas chromatograph.

Acknowledgement: OTKA K108489 (Hungarian National Research Fund) provided financial coverage of the research.

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CHARACTERIZATIONS AND APPLICATIONS OF THE BIOMIMETIC NON-HEME IRON-CONTAINING COMPLEXES

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One of the most important goals of bioinorganic chemical research is the development of metal complexes which catalytic activity and selectivity similar to native enzymes. Dioxygen activation by non-hem diiron enzymes occurs in a number of metabolically important transformations including the hydroxylation of methane by soluble methane monooxygenase (sMMO), the conversion ribonucleotides to deoxyribonucleotides by ribonucleotide reductase (RNR)[1], the formation of unsaturated fatty acids by fatty acid desaturases, the biosynthesis of antibiotics (CmlA, CmlI). In general, O_2 activation is thought to be initiated by the binding of O_2 to the diiron(II) center to form a peroxidodiiron(III) intermediate that in turn converts to the oxidizing species. Peroxidodiiron(III) intermediates with visible features between 600-750 nm have been identified for sMMO and RNR R2[2].

In our research the complexes were isolated from the reaction of different nitrogen-containing heterocyclic ligands, and Fe(II) salts in acetonitrile. They have been characterized by X-ray crystallography and several spectroscopic techniques.
The precursor complexes are suitable catalyst for oxidation reactions, where the in situ formed peroxidodiiron(III) intermediates were isolated as key species, as found for RNR R2 and sMMO. We isolated two types peroxidodiiron(III) intermediates, (μ-oxido)(μ-1,2-peroxido)diiron(III) and (μ-1,2-peroxido)diiron(III) (Figure 1). Further we investigated they properties and catalytic activities in different oxidation reactions. The peroxidodiiron(III) intermediate undergoes O-O bond scission to generate a high-valent oxidant capable for X-H (C, O) bond activation, and oxygen transfer reactions.

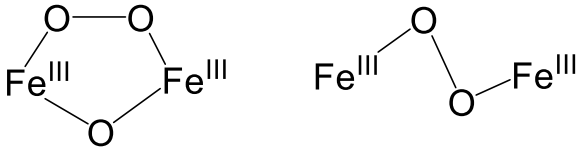

Figure 1. a. (μ-oxido)(μ-1,2-peroxido)diiron(III) and b. (μ-1,2-peroxido)diiron(III) intermediates.

Aknowledgement: Financial support by the Hungarian Scientific Research Fund (OTKA K108489) is greatly acknowledged.

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CAVITY-DEPENDENT SELECTIVITY WITH CYCLODEXTRIN–NHC–COPPER CATALYSTS

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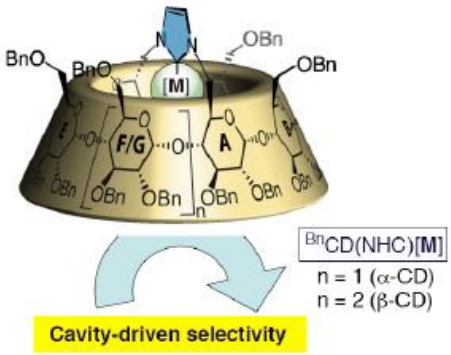
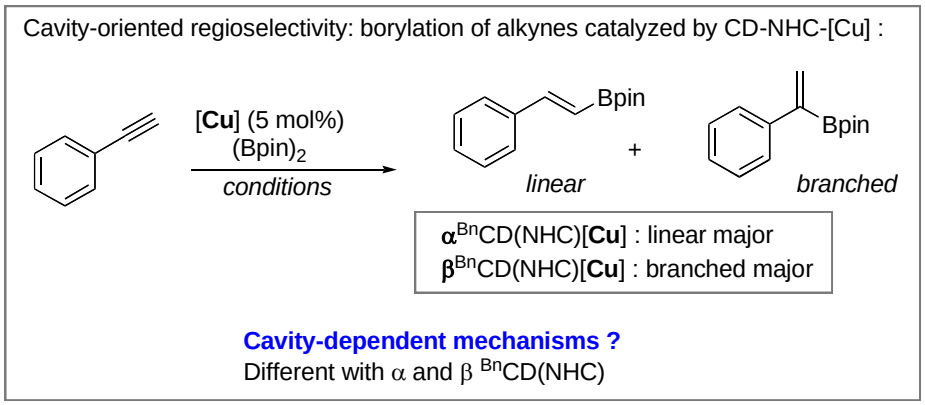
We recently developed a new family of cyclodextrin-based ligands for organometallic catalysis in which the cyclodextrin (CD) is capped with an *N*-heterocyclic carbene (NHC) ligand. This leads to metal complexes with the metal center encapsulated right in the middle of the CD cavity. These species are expected to exhibit unique reactivity due to their specific and flexible shape, and to the presence of the NHC ligand. Furthermore, with a metal embedded in a hydrophobic cavity, the structures are reminiscent of metalloenzymes, and offer an interesting playground to investigate the weak interactions of both metals and substrates with the cavity. In preliminary work, NMR studies revealed that the confinement of the metal leads to an original set of interactions with the wall of the cavity. These interactions, as well as the general structure and shape of the CD-NHC ligand, are likely to play a key role in the selectivity of some organic transformations. To explore this purpose, appropriate metal-catalyzed reactions (metal = Au, Cu) have been investigated.



We previously demonstrated with gold, that in the cavity, the reactivity of the metal center is preserved and is comparable to that of a standard gold–NHC complex (IPr-AuCl). More interestingly, the outcome of gold-catalyzed cycloisomerization reactions was found to be cavity-dependent. For instance, the regioselectivity of a cyclization was changed from the formation of a 5-membered ring in the case of α^{Bn}CD-AuCl (derived from α-CD), to a 6-membered ring when the β-CD analogue (β^{Bn}CD-AuCl) was used.[1]

This particular behavior is not reserved to gold. Remarkable inversions of selectivity were also observed more recently in copper-catalyzed reactions. For instance, α^{Bn}CD-CuCl was found to catalyze the borylation of alkynes to give the linear product, whereas the β^{Bn}CD-CuCl analogue gave the branched product. The catalytic cycle and the scope of the reaction have been investigated. Details of this study involving some structural analyses and mechanistic aspects are presented.



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DECARBOXYLATIVE PROTONATION PROCESS FROM MELDRUM'S ACID: ORGANOCATALYZED SYNTHESIS OF ISOXAZOLIDIN-5-ONES

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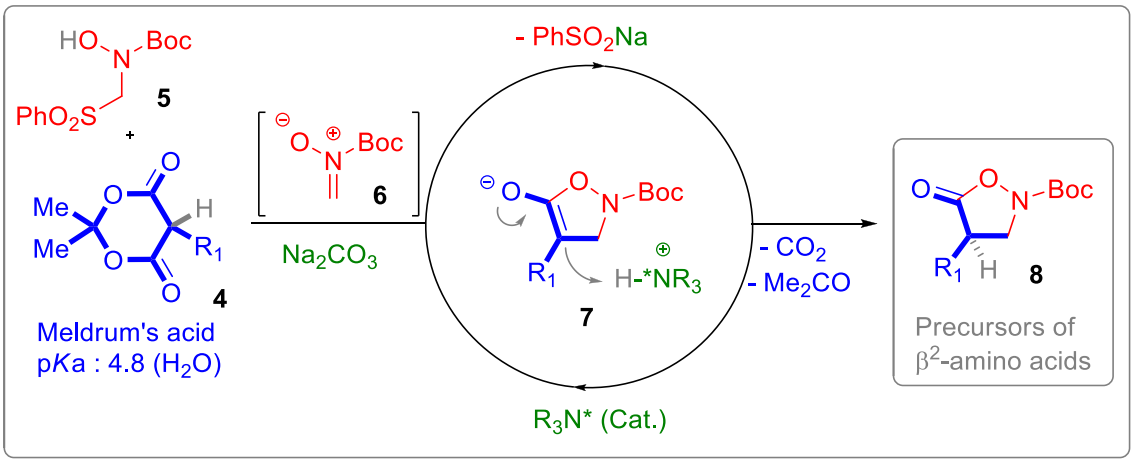
The asymmetric decarboxylative protonation reaction, which is easily carried out from reasonably stable α-Keto carboxylic acids and a catalytic amount of chiral catalyst holds an important place in asymmetric protonation processes for generating tertiary stereogenic centers, ubiquitous chiral elements within high value organic architectures.[1] Nevertheless, only few efficacious organocatalytic and highly enantioselective decarboxylative protonation methods do exist thus far.[2]



Based on our recent discovery upon native Meldrum's acid reactivity,[3,4] we have investigated the enantioselective synthesis of isoxazolidin-5-ones **8** from the readily available 5-substituted Meldrum's acid **4**, and sulfone-amide **5**, a convenient *N*-Boc nitrone **6** precursor under basic conditions. The challenge was to eventually release a molecule of sodium sulfinate ($PhSO_2Na$) and nitrone **6** in the presence of a stoichiometric amount of achiral base without a racemic background pathway to enable enantioselective protonation of enolate by chiral **R_3N^{*+}-H.**

We were delighted to note that this organocatalyzed sequence is allowed *via* a practical anionic domino (3+2) cycloaddition-fragmentation-decarboxylation-enantioselective protonation providing an original access to α-substituted isoxazolidin-5-ones **8**.[5] These compounds **8** were synthesized in high yield and good ee (up to 88 %). Furthermore, derivative **8** are goods precursors of β^2-amino acids.

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ENANTIOSELECTIVE ARTIFICIAL SUZUKIASE FOR SYNTHESIS OF AXIALLY CHIRAL BIARYL COMPOUNDS

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In recent years, there has been growing interest in the creation of artificial metalloenzymes for enantioselective catalysis. The palladium-catalyzed Suzuki-Miyaura coupling is a C-C bond-forming reaction that has attracted much attention in this context. In stark contrast this fascinating bond-forming reaction, Nature relies on very different mechanisms to create C–C bonds.[1-5] We thus set out to investigate the potential of artificial metalloenzymes to create a Suzukiase and test its potential under physiological conditions. For this purpose, we synthesized a variety of biotinylated N-heterocyclic carbene (NHC) and bulky phosphine ligands and tested these in the presence of a Pd-source combined with various streptavidin isoforms. Herein we present preliminary results on the chemogenetic optimization of an artificial Suzukiase.

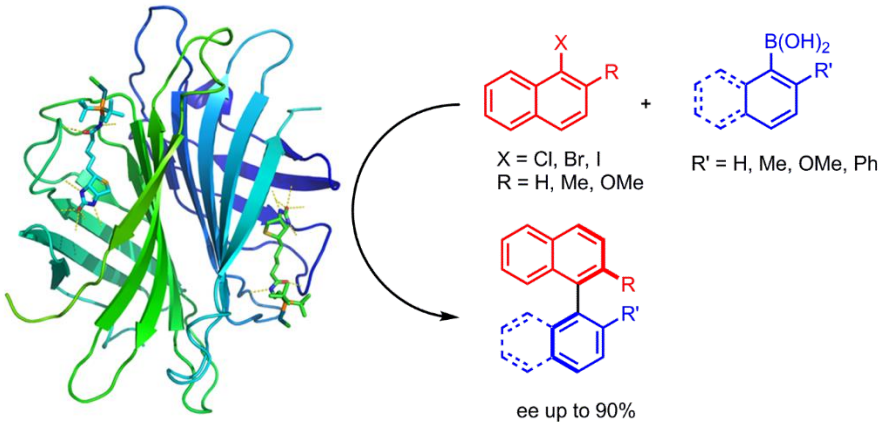

Figure 1. Introduction of a biotinylated palladium complex within streptavidin affords an artificial suzukiase. Saturation mutagenesis allowed optimization of the activity and the enantioselectivity of this metalloenzyme. A variety of axially chiral biaryls were afforded in good yields with up to 90% ee.

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SYNTHESIS AND SCREENING OF NOVEL NON-BENZENOID AXIALLY CHIRAL BIARYL MOLECULES FOR CATALYSIS

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Chiral biaryl diphosphine ligands[1] and biaryl phosphoric acids[2] are two ubiquitous classes of compounds used for asymmetric induction. Due to the very low conformational energy differences between achieving 95% *e.e.* and a racemic mixture,[3] chiral ligands and acids tend to be specialised towards certain substrates and classes of reaction. Since it is near impossible to create a 'universal' catalyst for asymmetric synthesis, it is therefore highly important to continue designing and synthesising novel catalysts.

Despite the variety in ligand and acid design, there has not yet been an example of either system based around azulene, an isomer of naphthalene that possesses a permanent dipole moment (Figure 1).[4]

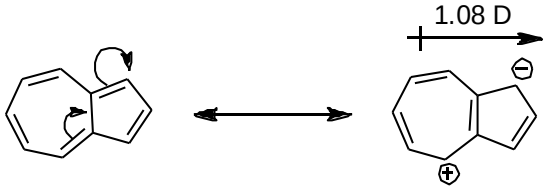

Figure 1. Resonance forms of azulene.

This talk will describe the development of various chiral biazulene based diphosphine ligands and acids that vary sterically and electronically, depending on the locations of the axial bond and coordinating atoms (Figure 2). The reactions for the screening process of these compounds have been chosen based on factors that influence rate and stereoselectivity, such as electron richness of ligand, diphosphine bite angle, pK_a of acid and chiral pocket space.

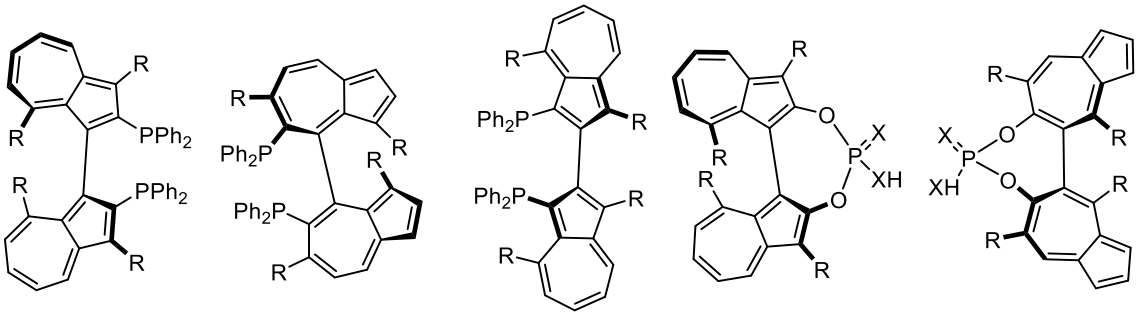

Figure 2. Various designs for azulene-based chiral ligands and acids.

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RECYCLABLE ENANTIOSELECTIVE CATALYSTS FOR HENRY REACTION BASED ON 2-(PYRIDINE-2-YL)IMIDAZOLIDIN-4-THIONE DERIVATIVES

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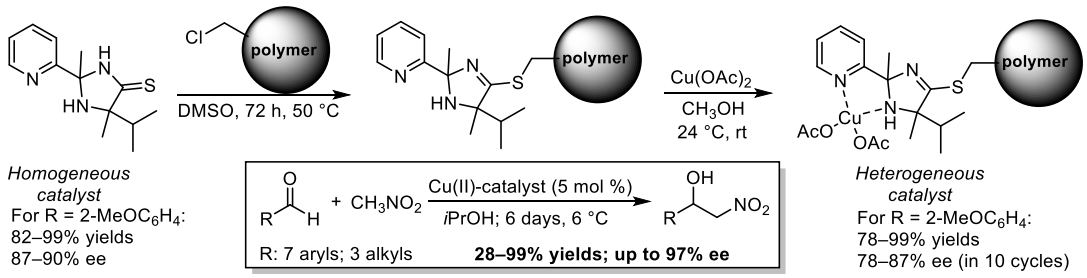
The asymmetric Henry reaction belongs among very important organic reactions where a new carbon–carbon bond and stereogenic center is created. This reaction finds applications in the synthesis of optically pure functionalized 2-nitroalcohols, which are used, e.g., for preparation of biologically active compounds. In the past decade, a number of highly efficient homogeneous catalysts have been developed on the basis of coordination compounds [1-2]. For example, very successful catalysts for the Henry reaction are the Cu(II) complexes of functionalized 2-(pyridine-2-yl)imidazolidin-4-ones [3].The applications of homogeneous catalysts are often restricted by practical impossibility of their reuse. This disadvantage is overcome by the application of recoverable and recyclable catalysts [4]. Recently, we prepared very efficient and recyclable catalyst for Henry reaction based on Cu(II) complexes of (1*R*,2*R*)-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane-1,2-diamine anchored by swelling pearl-like copolymer styrene – 4-vinylbenzyl chloride cross-linked by tetra(ethylene glycol)-bis(4-vinylbenzyl)ether (2%) [5]. The aim of this work was preparation and study of enantiocatalytic activity in Henry reaction of heterogeneous catalysts based on Cu(II) complexes of 2-(pyridine-2-yl)imidazolidin-4-thiones anchored by mentioned copolymer via sulfur – carbon bond (Scheme 1).



Scheme 1

At first, we prepared 2-(pyridine-2-yl)imidazolidin-4-thione and corresponding 4-benzylsulfanyl-2-(pyridine-2-yl)imidazoline derivatives. We found out that their Cu(II)-complexes showed comparable enantioselectivity in Henry reaction (up to 97 % ee) as analogous imidazolidin-4-one derivatives [3]. Then, we prepared immobilized catalysts by reaction of 2-(pyridine-2-yl)imidazolidin-4-thione derivatives with chloromethylated swelling copolymer and subsequent complex formation by action of copper(II) acetate (Scheme 1). These heterogeneous catalysts were tested in Henry reaction. We found out, that the reactions proceeded in the polymeric matrix of swelling catalysts at a rate comparable with that of the reactions using Cu(II)-catalysts in homogeneous medium. After tenfold recycling of the catalyst, slight lowering of yields and no lowering of enantioselectivity took place.

Aknowledgements: This research work was financially supported by the Czech Science Foundation, project no.14-00925S.

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CO-CATALYZED ASYMMETRIC HYDROVINYLATION OF VINYLARENES

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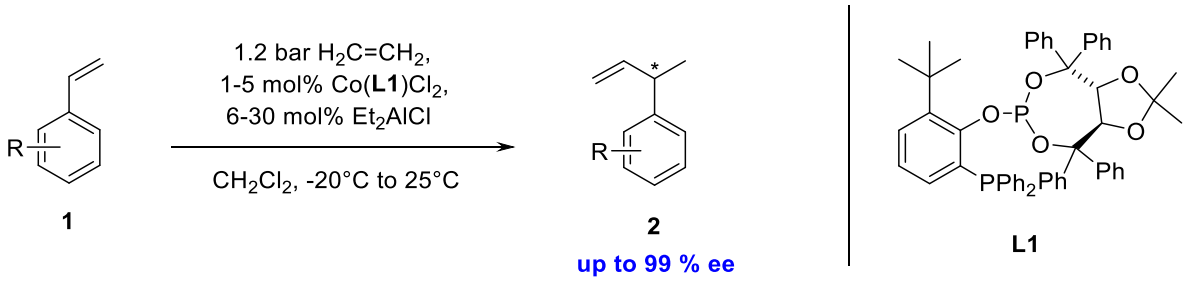
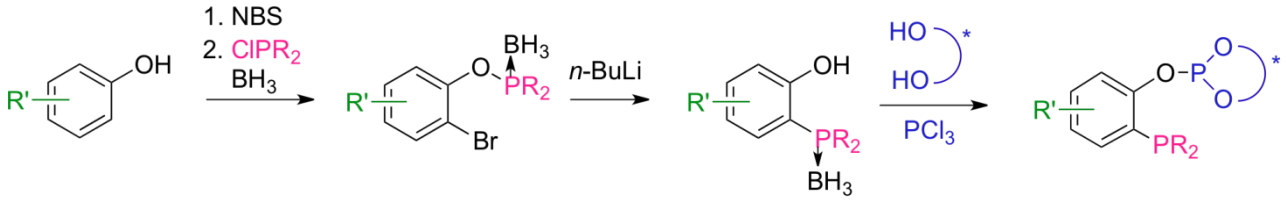
The enantioselective hydrovinylation[1] of styrene and related substrates is a fully atom economical transformation with a great potential for the academic and industrial synthesis of chiral compounds. We have recently developed an efficient and operationally convenient protocol for the asymmetric Co-catalyzed hydrovinylation, which gives rise to the branched products with virtually complete regio- and high enantio-selectivity. Noteworthy, the reactions proceed at ambient temperature and pressure, employing a moisture- and air-stable Co-complex, derived from ligand **L1**, as a pre-catalyst. Under optimized standard conditions, excellent yields and selectivities are obtained for a wide spectrum of substrates including substituted and heterocyclic vinylarenes.



The key for the successful method development was the identification of **L1** as a suitable chiral ligand by screening our library of chiral phosphine-phosphite ligands.[2] These are synthesized in a modular and operationally simple four-step sequence starting from simple phenols. The modular synthesis also facilitates further ligand optimization for particular transformations.



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MAGNETICALLY RECOVERABLE CATALYSTS FOR ASYMMETRIC HENRY REACTION BASED ON Fe_3O_4@SiO_2 NANOPARTICLES

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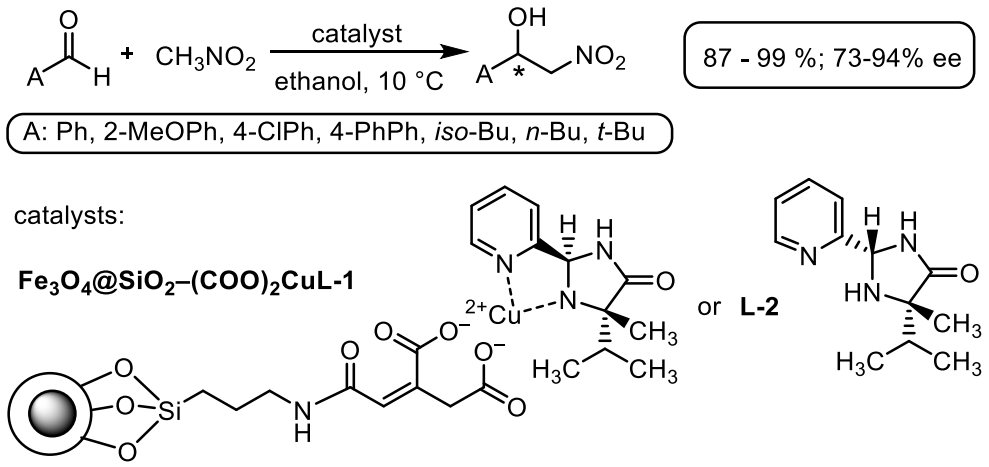
Asymmetric Henry reaction represents one of the basic stereoselective reactions where a new carbon-carbon bond is created but only several efficient recoverable catalysts have been developed.[1] In recent years, magnetic nanoparticles (MNPs) have been developed as pseudo-heterogeneous supports for catalytic application.[2] We have prepared stable coordination complexes of the core-shell magnetic nanoparticles Fe_3O_4@SiO_2-$(COO)_2Cu$ (~300 nm) with (2*R*,5*S*)- or (2*S*,5*R*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one ligands.[3] The prepared complexes were used as very effective recoverable catalysts for the enantioselective Henry reaction of functionalized aldehydes with nitromethane in ethanol (10°C, 96 h). The configuration of obtained functionalized 2-nitroethanols correspond to *R* configuration for ligand L-1 and *S* for ligand L-1 like in the case of application of cooper(II)acetate ligand complexes.[3]



The Henry reaction catalyzed by these catalysts proceeds with high chemical yield (87 - 99 %) and with high enantioselectivity (73-94% ee).The achieved yield was very high even after recycling 10 steps. Only minor decrease in enantioselectivity (Δ 2% ee) and yield (Δ 3%) was observed after ten catalytic cycles. The choice of MNPs as a solid support for chiral catalysts simplifies the processes of isolation, purification, reuse, and recyclability of catalysts. The prepared catalysts can be considered as a green with great potential for Henry reactions.

Aknowledgements: The described research work was financially supported by the Grant Agency of the Czech Republic, Project 14-00925S

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DIASTEREODIVERGENT ORGANOCATALYSIS FOR THE ASYMMETRIC SYNTHESIS OF CHIRAL ANNULATED FURANS

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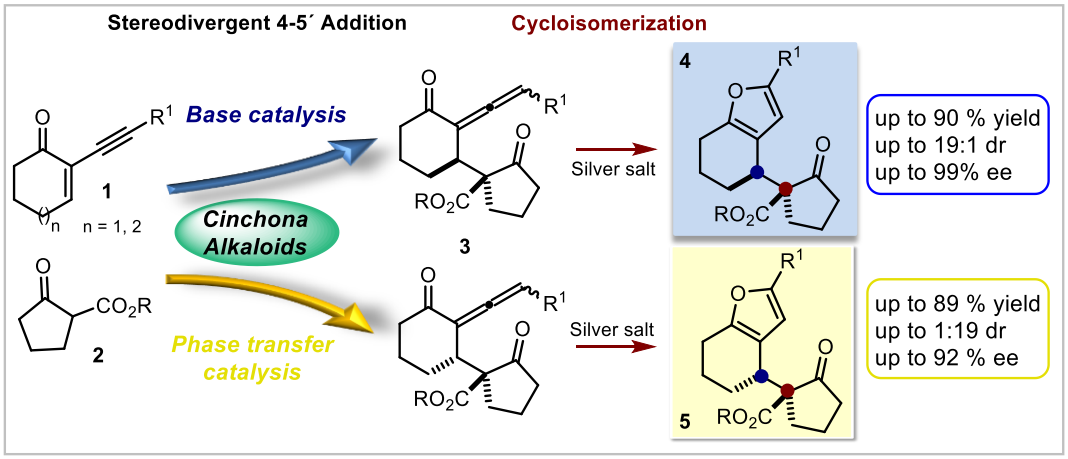
Bioactivities of organic compounds are closely related to both their absolute and relative configurations.[1] Indeed, selectivity, bioavailability and efficiency may be affected by a small change in the three dimensional arrangement of bioactive molecules. However, the development of stereodivergent catalytic strategies providing the full matrix of stereoisomers of products bearing multiple stereocenters remains an important challenge in synthetic organic chemistry,[2] especially when it involves the generation of stereogenic quaternary carbons.[3]

Disclosed herein is a stereoselective method for the synthesis of 2,3-furan fused carbocycles bearing adjacent quaternary and tertiary carbon stereocenters. The chemistry is based on an asymmetric addition of β-ketoesters to 2-(1-alkynyl)-2-alkene-1-ones catalyzed by natural cinchona alkaloids followed by a silver-catalyzed cycloisomerization. By exploiting distinct catalysis modes of quinine, which can act either as a general base or, upon opportune modifications, as a phase transfer catalyst, a complete switch of the enforced sense of diastereo-induction is achieved. The stereodivergent systems enable access to the full matrix of all possible stereoisomeric products with high enantiomeric purity.



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COPPER-CATALYZED VINYLSILANE CROSS-COUPLING REACTIONS

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Silicon-based cross-coupling reactions are extremely powerful tools for the introduction of new C−C bonds in complex organic frameworks.[1] The ready availability, low cost, and high chemical stability of silylated molecules led to a rapid development of several metal-based cross-couplings. The copper-chemistry involving organosilanes has however been greatly neglected so far.

Over the past few years, our group has developed an efficient copper-catalyzed method to functionalize vinylsilanes. This cross-coupling reaction leads to the synthesis of stereodefined alkenes that remain a constant challenge in organic chemistry (Figure 1).

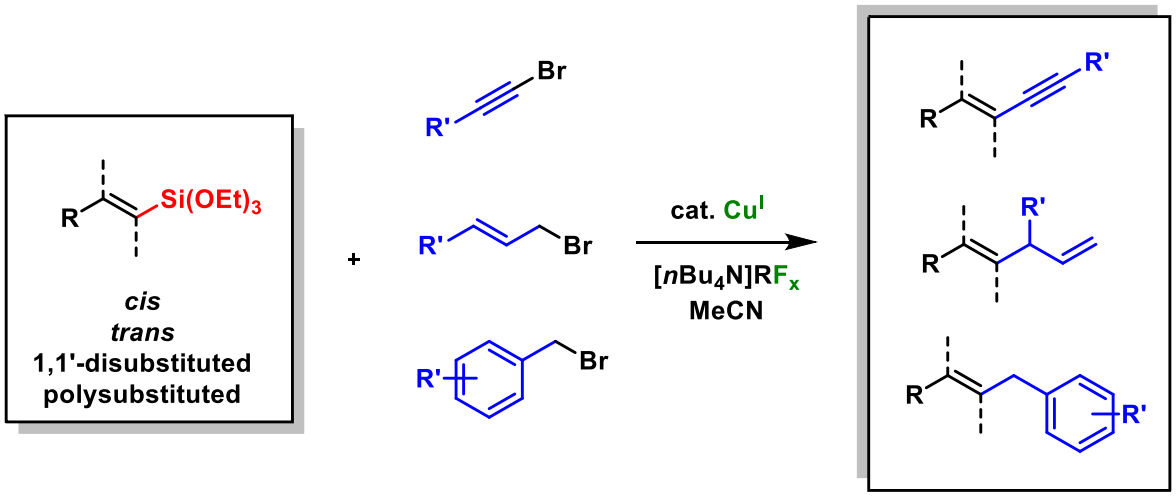

Figure 1. Copper-Catalyzed stereoselective transformation of vinylsilanes.

Using copper(I) salts and tetrabutylammonium polyfluorides as activating agents, various *cis*, *trans*, and 1,1'-disubstituted vinylsilanes could be functionalized. Alkenyl-,[2] allyl-,[3] and benzyl-halides[4] could be employed to yield their corresponding cross-coupling products. Full retention of stereochemistry was observed in all cases and sensitives groups such as aldehydes were fully tolerated. This very mild method led to the stereoselective synthesis of very sensitive building blocks that are present in natural products, pharmacologically active molecules, agrochemicals, and materials for optics and electronics.

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GOLD NANOPARTICLE-CATALYZED *cis*-SEMIHYDROGENATION OF ALKYNES WITH AMINE BORANE COMPLEXES

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Supported gold nanoparticles exhibit impressive catalytic activity in reductive processes, including direct hydrogenation or transfer hydrogenation.[1] We have recently shown that gold nanoparticles supported on titania (Au/TiO_2) catalyze the rapid activation of ammonia borane complex towards reduction of nitro compounds.[2] Extending our studies we found that ammonia borane and other amine borane complexes reduce selectively alkynes into *cis*-alkenes.[3] The over-reduction pathway to alkanes is a minor pathway one or even absent especially when dimethylamine borane (Me_2NHBH_3) is used as a reducing agent (Figure 1). The semihydrogenation takes place at ambient and open air conditions in ethanol as solvent. In certain cases, as low as 0.4 molar equivalents of amine boranes are required for a quantitative reduction, indicative that the two hydrogen atoms of reduction product arise from B-H (hydride) and N-H (proton), as exemplified via labelling experiments. Regarding the reaction mechanism, ^{11}B NMR studies during the progress of reduction exemplified the crucial role of solvent, as ethanol acts as a proton donor (new C-H bond in product) transforming finally ammonia borane (NH_3BH_3) into $NH_4B(OCH_2CH_3)_4$. This methodology is applicable to a variety of functionalized terminal or internal alkynes and is a compelling and simple alternative to Lindlar's hydrogenation protocol.

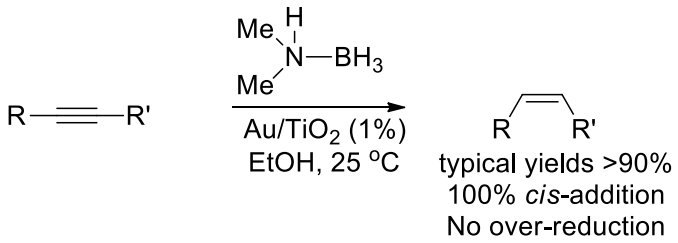

Figure 1. Stereoselective *cis*-semihydrogenation of alkynes with dimethylamine borane complex catalyzed by Au nanoparticles supported on TiO_2.

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COPPER(I) DIPHOSPHINE BIFLUORIDE COMPLEXES: SYNTHESIS AND APPLICATIONS

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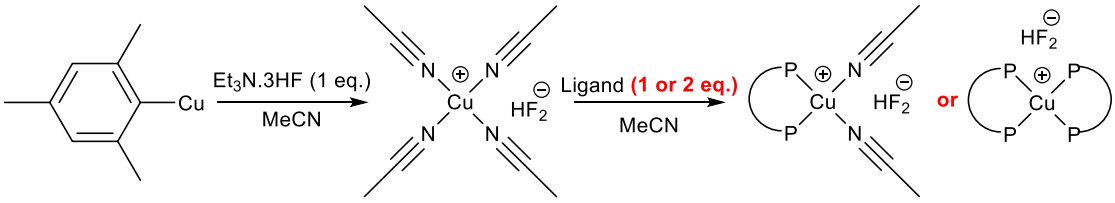
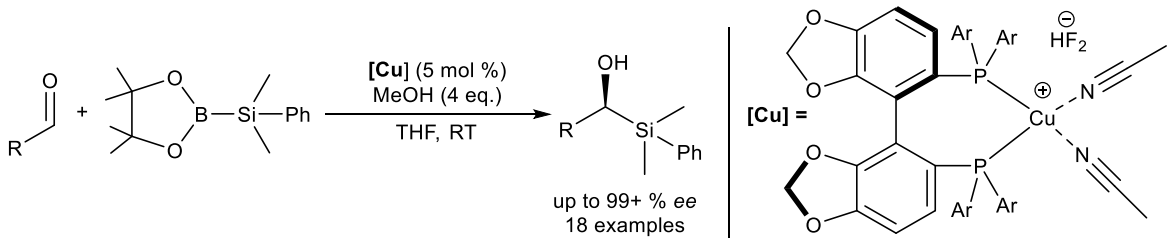
Copper-catalyzed additions of various nucleophiles onto electrophiles are transformations of great interest in organic synthesis. Those reactions allow the formation of C-C[1], C-Si[2] or even C-B[3] bonds with great selectivity. However, in most cases those transformations require the use of alkoxide to activate the copper catalyst and therefore, result in a basic reaction medium[4] which can bring problems of compatibility with peculiar functional groups.
We, herein, describe the synthesis of a new cationic copper (I) complex bearing diphosphine ligand and a bifluoride counteranion (Scheme 1).



Scheme 1. Synthesis of copper(I) diphosphine bifluoride complexes

The main advantages of this new family of copper complexes are that it is air stable and it doesn't require an activation step.

The possibility to synthesize complexes bearing chiral ligands allows us to perform an addition of nucleophile species in an enantioselective way[2]. (Scheme 2)



Scheme 2. Copper-catalyzed enantioselective synthesis of α-hydroxysilanes

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CONTROL OF THE CHEMOSELECTIVITY IN THE BAYLIS-HILLMAN REACTION: POLYMER-SUPPORTED *VERSUS* HOMOGENEOUS CATALYSTS

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Compartmentalization, accompanied by the isolation of reactive sites, emerged as a new paradigm in design of effective and highly selective catalytic systems.[1] While encountering dramatic differences in the chemoselectivity of the Baylis-Hillman reaction promoted by polymer-supported imidazole-based catalysts (above 90%) versus their homogeneous analogues (ca. 30%),[2,3] we hypothesized that these differences can be attributed to the isolation of the catalytic sites from the polar reaction media by their localization in hydrophobic pockets within the polymer. Following this hypothesis, we designed a series of branched/dendritic homogeneous catalysts, with imidazole active site(s) near the focal point and flexible hydrophobic branches, capable of providing partial shielding of this site. Such architecture imitates to an extent the situation in the polymer-supported systems (Fig. 1).

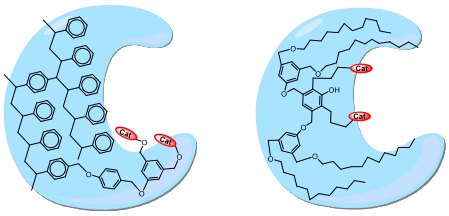

Figure 1

Capitalizing on our extensive proficiency in rapid synthesis of dendrons with different peripheral groups,[4] we prepared a series of first- and second-generation dendrons, decorated with tails of various length and polarity and incorporating imidazole and phenol functionalities as a catalyst-cocatalyst pair. Dramatic differences between the catalysts with the most exposed reactive site and the most enveloped one were observed in the chemoselectivity of the model reaction (Fig. 2a). Moreover, all second-generation dendrons imparted selectivity superior to that of the first-generation catalysts, presumably due to the more significant isolation of the focal point area from the reaction media. In future, we aim to expand the observed phenomenon (improved chemoselectivity via the catalytic site isolation) to other kinds of selectivity, e.g. substrate- or site-selectivity, using similar design principles.

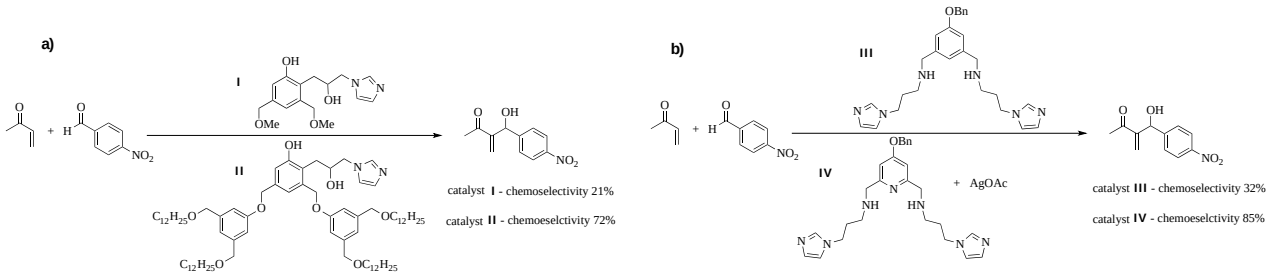

Figure 2

An alternative solution for improving the chemoselectivity of the Baylis-Hillman reaction with homogeneous catalysts was provided by the introduction of a coordination site into the imidazole-carrying branched scaffold, enabling imidazole-Lewis acid bifunctional catalysis (Fig 2b).

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ENANTIOSELECTIVE ORGANOCATALYTIC ALKYLATION OF ALDEHYDES AND ENALS DRIVEN BY THE DIRECT PHOTOEXCITATION OF ENAMINES

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An efficient photo-organocatalytic enantioselective α- and γ- alkylation of aldehydes and enals, respectively, with bromomalonates is reported.[1]
In contrast to previous reports for analogous reactions, the chemistry uses a commercially available aminocatalyst and occurs under illumination by a fluorescent light bulb in the absence of any external photoredox catalyst.[2, 3]
Mechanistic investigations reveal the previously hidden ability of transiently generated enamines to directly reach an electronically excited state upon light absorption while successively triggering the formation of reactive radical species from the organic halides.[4] At the same time, the ground state chiral enamines provide effective stereochemical induction for the enantioselective alkylation process.

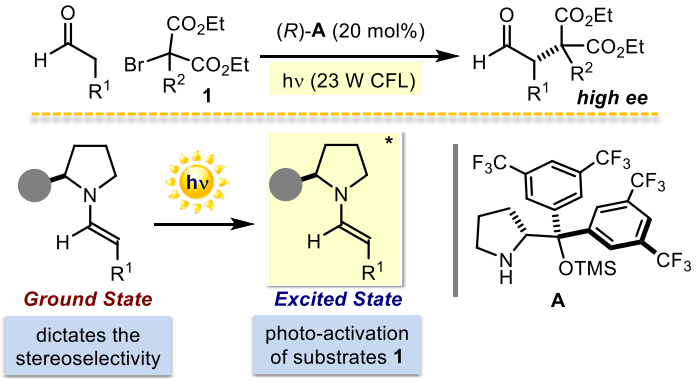

Figure 1. Enantioselective alkylation of aldehydes carried out without the need of external photosensitizers.

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PHOTO-ORGANOCATALYTIC ENANTIOSELECTIVE PERFLUOROALKYLATION OF β-KETOESTERS

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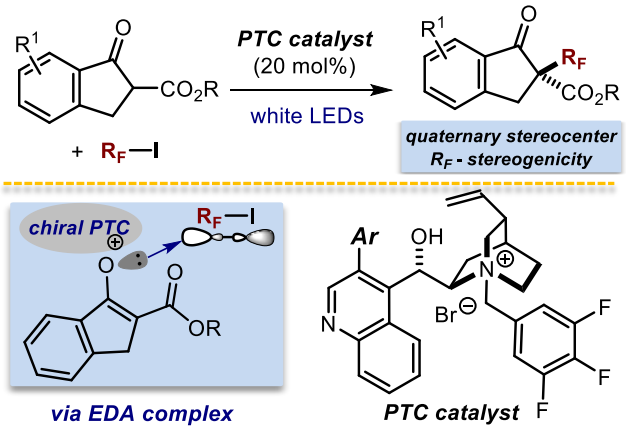
Visible-light-driven enantioselective catalytic processes hold great potential for the sustainable preparation of chiral molecules.[1] In this context, our laboratory recently introduced a unique approach based on the ability of chiral enamines, key intermediates in thermal organocatalytic asymmetric processes, to actively participate in the photo-organocatalytic activation of substrates *via* an electron donor-acceptor complex (EDA) and subsequently form chiral products.[2] We further advance this EDA complex activation concept by developing a photochemical enantioselective perfluoroalkylation of β-ketoesters.



Specifically, we wondered if the EDA complex activation strategy could be expanded to include electron-rich chiral organocatalytic intermediates other than enamines namely, enolates. The feasibility of this π→δ* interaction has been demonstrated previously by our group for the aryl perfluoroalkylation of aryl cyanoacetates.[3] By employing chiral phase-transfer cataylsts based on the cinchona scaffold chiral enolates have been utilized for the formation of EDA complexes with perfluoroalkyl halides. Their subsequent reaction with resultant electrophilic perfluoroalkyl radicals generates quaternary perfluoroalkyl stereocenters in an array of keto-esters derived from indanone in high selectivity and good yields.

This work represents the first implementation of chiral enolates as partners in photo-organocatalytic EDA complex activation for the creation of chiral stereocenters.

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ASYMMETRIC SYNTHESIS OF VERSATIL BENZYLIC BORONIC ESTERS THROUGH A BORYLATION-AROMATION PROCESS

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para-Quinone methides (*p*-QMs)[1] have been known as reaction intermediates for more than a century. They consist of a cyclohexadiene moiety in *para*-conjugation with a carbonyl group and a*n* exo-methylene component. As a result of the intrinsic electrophilic reactivity *of p*-QMs, highly reactive transient *p*-QM species generated in situ are implicated in many chemical, medicinal, and biological processes. However, *p*-QMs have been scarcely used as starting materials in asymmetric catalysis.[2] Recently, our group has been focused on the design of new copper-catalyzed borylation reactions.[3] In this context, we envisioned the synthesis of chiral diarylmethines through the copper-catalyzed borylation-aromatization of *p*-quinomethanes. The products are enantiomerically enriched dibenzylic boronates that can be transformed into important chiral diarylmethines derivatives (Scheme 1).

Scheme 1

Acknowledgements: Financial support from Spanish Government (CTQ-2012-35957) and the European Research Council (ERC Starting Grant DAUBOR) is gratefully acknowledged.

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A DIRECT, EFFICIENT AND GENERAL GOLD-CATALYSED SYNTHESIS OF FUSED-IMIDAZO HETEROCYCLES

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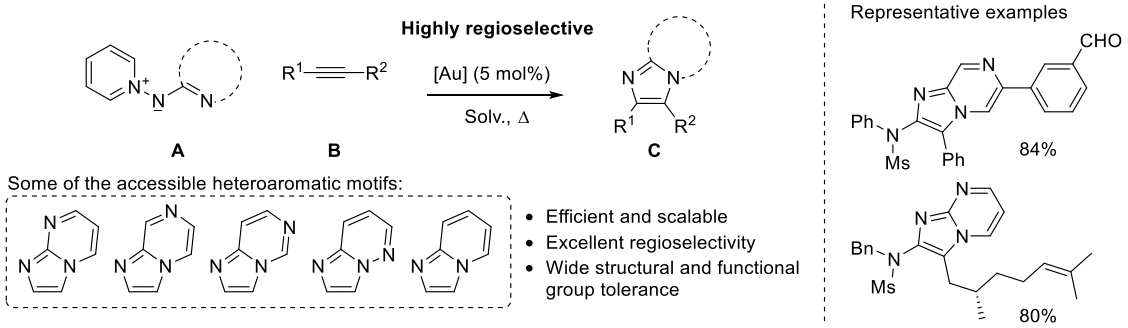
Fused imidazo-heterocycles are biologically active structures with clinical relevance against a range of disease targets and often found in commercially available drugs.[1] In line with their increasing relevance, numerous bespoke strategies have been explored to build each of these motifs.[2] However, few methods can be generally applied across different members of the family and in those cases, the final products feature closely related substitution patterns as a result of the underlying mechanistic similarities and/or starting materials.

Here, we present a mechanistically distinct, gold-catalysed approach that enables the formation of diverse imidazo-fused heterocyclic scaffolds in a flexible and atom-economic manner.[3] The reaction proceeds though a formal [3+2]-dipolar cycloaddition where pyridinium *N*-(heteroaryl)aminides (**A**) stand as robust and readily accessible *N*-nucleophilic 1,3-*N*,*N* dipole equivalents against several gold-activated electron-rich triple bonds (**B**). This efficient and scalable transformation accomodates a wide range of useful functionalities difficult to introduce by other methodologies.



The optimization, proposed mechanism, scope and further applicability of this highly regioselective intermolecular process will be discussed during the presentation. Moreover, we will show how a wide variety of important heteroaromatic structures can be easily and rapidly assembled while bearing challenging and/or unexplored substitution patterns.

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SYNTHESIS, CHARACTERIZATION AND REACTIVITY OF α, β, γ-CYCLODEXTRIN-NHC-METAL COMPLEXES

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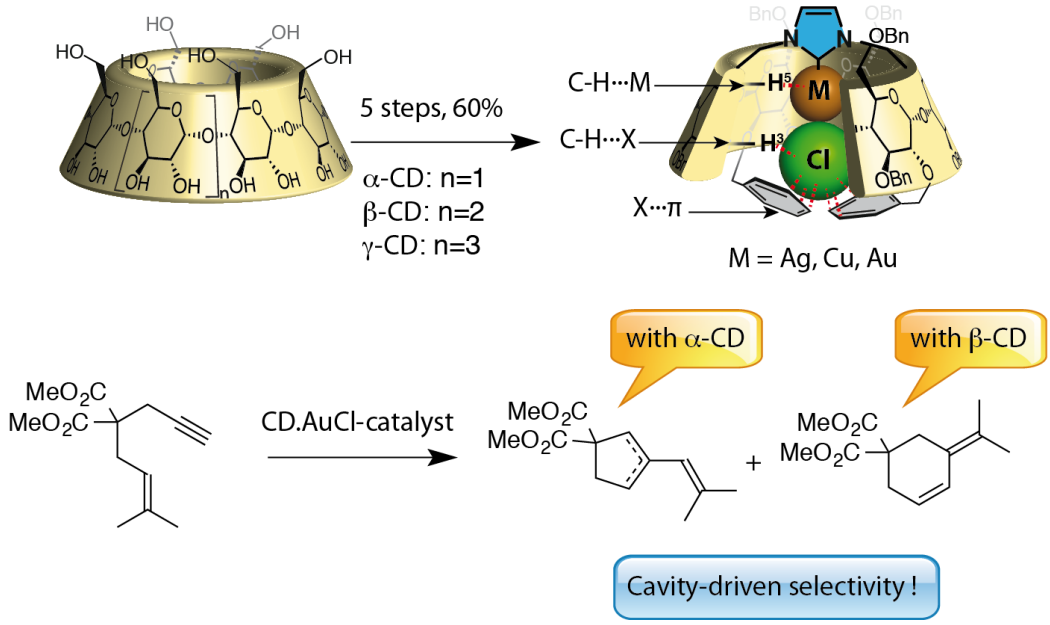
Many cyclodextrin(CD)-based metal complexes have been investigated with the aim to mimic enzymes[1] or to study the effect of a cavity in the proximity of a metal center. [2] However, none of these complexes exhibit a metal center included deep inside the cavity. In this work, we present a family of CD-metal complexes in which the metal was positioned in the middle of the cavity though a N-heterocyclic carbenes (NHCs) ligand covalently bound to the CD. NHCs and Mesoionic carbenes (MICs)-capped α, β, γ-CDs have been prepared with silver, copper and gold as the metals. NMR was used to explore the structures of CD-NHC-metal complexes and to determine the position of the metal inside the cavity. This deep burying of the metal does not prevent its reactivity, in fact, the size of cavity is the main key to control the selectivity for many catalytic reactions!

We previously showed the cavity-dependent cycloisomerization reactions with CD-NHC-Au complexes as catalyst. [3] More recently, the effect of the cavity on the selectivity was investigated with Au and Cu catalyzed reactions. The preparation of the complexes, their structures and selected examples in catalysis will be presented.



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COPPER (I) CATALYZED DESYMMETRIZATION OF CYCLOPROPENES: SYNTHESIS OF CYCLOPROPYLBORONATES

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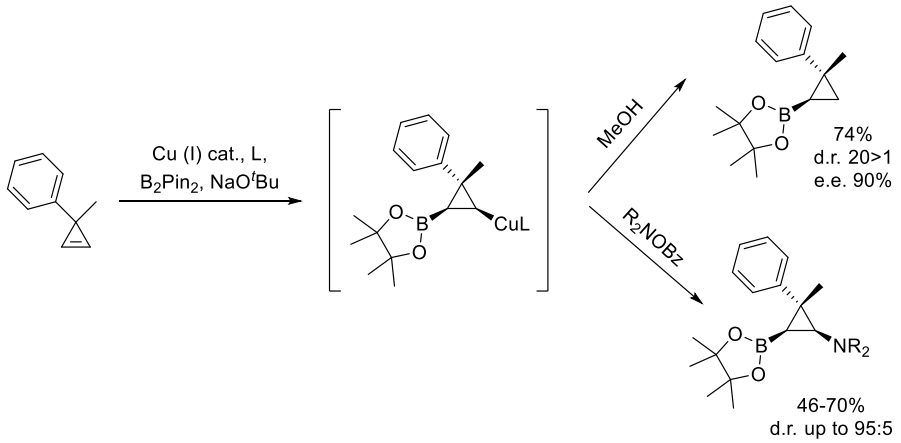
Cyclopropanes are present in a large number of natural products and biologically active compounds.[1] Among these species, cyclopropylboronates have gained increasing attention as useful building blocks for the synthesis of functionalized cyclopropanes.[2]

Although there are several methods for the synthesis of racemic cyclopropylboronic esters, the enantioselective synthesis of these compounds is scarcely documented. The most common method for the synthesis of chiral cyclopropylboronates requires the use of chiral auxiliaries[3] and there are only two examples involving asymmetric catalysis.[4]

Recently, our group has been focused on the design of new copper-catalyzed borylation reactions.[5] In this talk, we will present the diastereo- and enantioselective copper-catalyzed hydroboration and aminoboration of cyclopropenes. [6] The products are cyclopropylboronates bearing a quaternary stereocenter. Additionally, this method constitutes the first example of a copper-catalyzed desymmetrization of cyclopropenes.



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LEWIS ACID ACCELERATED PALLADIUM CATALYZED CROSS DEHYDROGENATIVE COUPLING OF ANILIDES AND ALDEHYDES: THE BORANE EFFECT

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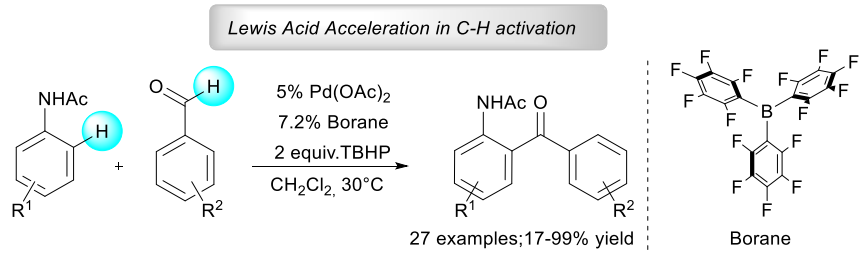
In the past few years, Pd-catalyzed C(sp^2)-H activation reactions on arenes bearing diverse *ortho*-directing groups were widely studied. In continuation of our recent studies[1] on C-H activation we aimed to examine the effect of Lewis acids on the palladium-catalyzed cross-dehydrogenative coupling of anilides and aldehydes, as a conceptually new approach for the activation of the catalytic system. We hypothesize that Lewis acidic additives in the reaction may trigger the formation of a 'more cationic' Pd-catalyst with enhanced electrophilicity. In our study, we examined the applicability of electron deficient boron compounds as Lewis acidic additives in palladium catalyzed C-H activation reactions. Their beneficial effect was demonstrated in the palladium catalyzed reaction of aldehydes and anilides through mild, directed oxidative couplings producing *ortho*-acylated *N*-aryl acetamides.



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ZINC-CATALYSIS: A SUSTAINABLE ALTERNATIVE FOR ALKYNE ACTIVATION

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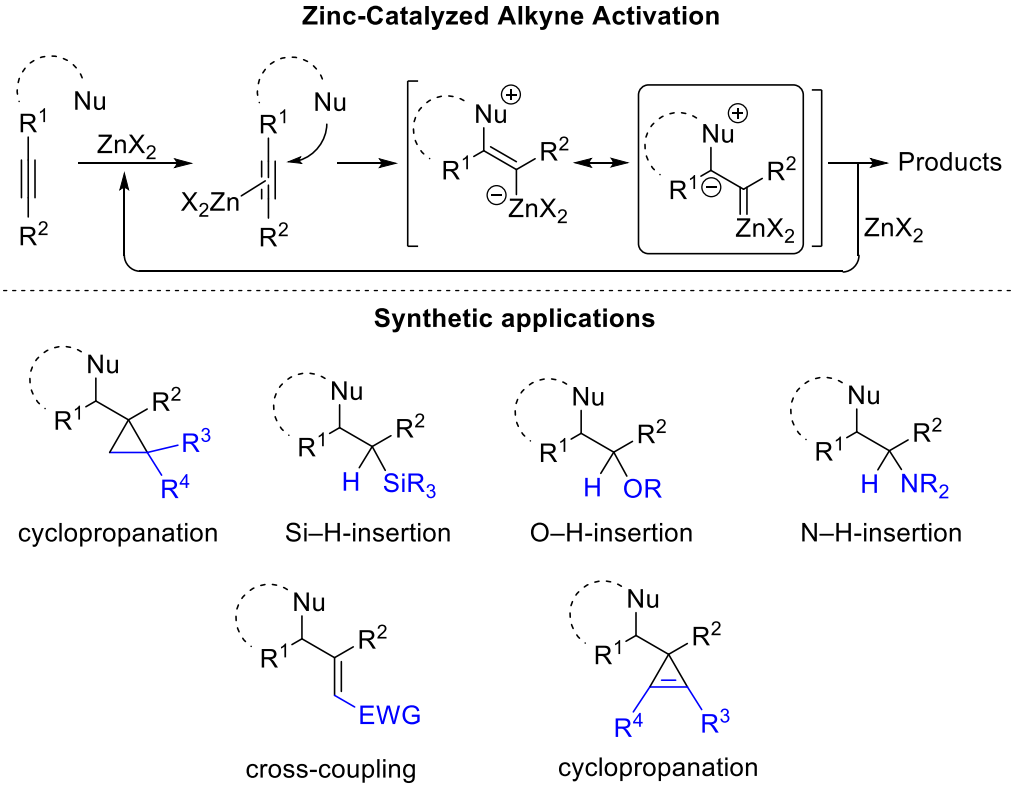
The alkyne functionality plays a relevant role in chemistry. In the recent years, novel and valuable transformations of alkynes involving transition metals have been developed. These processes are based on the carbophilic properties of some metals such as gold, platinum or rhodium, which activate the alkyne by a preferential coordination to the π-system. Despite the relevance of these achievements, the cost of these catalysts constitutes an important drawback in terms of sustainability.

We have studied the use of inexpensive and low-toxic zinc salts for alkyne activation,[1] with the aim to develop a methodology for the catalytic generation of zinc carbenoids from alkynes. We have found that zinc salts can be used for the activation of enynones to afford *in-situ* carbene intermediates, which could be trapped with a variety of reagents leading to functionalized furans. These transformation includes the first catalytic cyclopropanation of alkynes,[2] Si–H bond insertions,[2] functionalizations of O–H and N–H bonds,[3] cross-coupling with diazocompounds[4] or the cyclopropenation of alkynes.[5]



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ASYMMETRIC ALDOL REACTION OF AROMATIC KETONES VIA TERTIARY AMINES APPLICATION IN TOTAL SYNTHESIS

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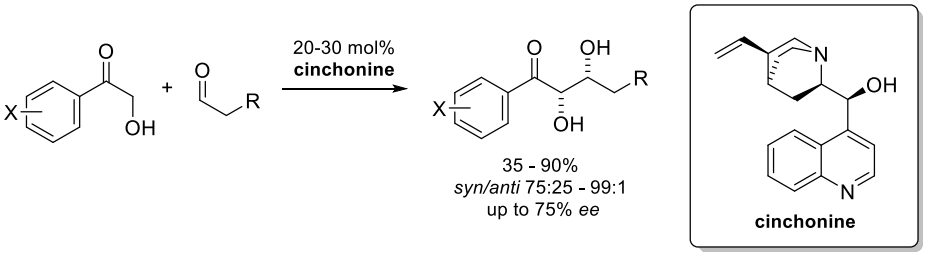
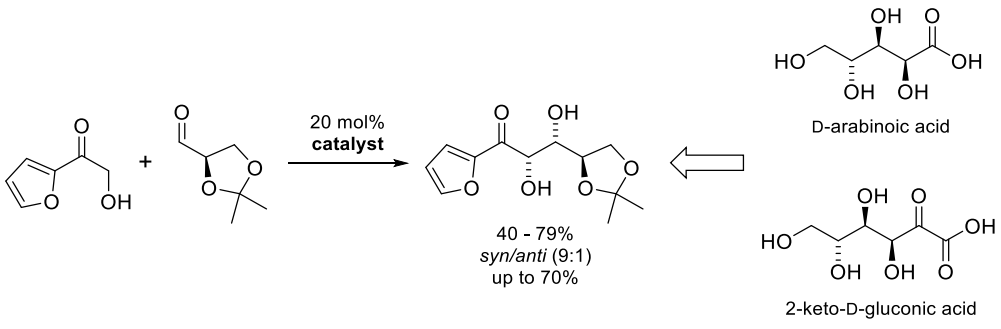
Aldol reaction is one of the most useful tools for creation of new carbon-carbon bond with asymmetric fashion.[1] From last decade numerous catalysts have been designed to improve reactivity, enantioselectivity and substrate scope.[2] However still exists some unexplored field of this subject area. Recently, we presented examples of tertiary amine-catalyzed direct aldol reactions of hydroxyketones,[3] aromatic ketones[4] or pyruvic esters.[5] This enolate-mediated aldol reaction is interesting alternative to enamine-based organocatalysis.

For example, unmodified *Cinchona* alkaloids were successfully applied in the organocatalyst for aldol reaction between aromatic ketones and aliphatic aldehydes. Reaction of various ketones and aldehydes results in the formation of aldols with good yield, excellent *syn*-selectivity and up to 75% *ee*.[4]



This type of organocatalysis with tertiary amines is not only an interesting methodology example, but also a useful reaction in the synthesis of natural products. Herein we presented utility of this methodology in synthesis of natural products. Diastereoselective type of mentioned aldol reaction with chiral aldehydes occurred to be efficient and highly *syn*-diastereoselective. It was successfully applied in *de novo* synthesis of important natural components such as 2-keto-D-gluconic acid and D-arabinose acid.



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CATALYTIC ASYMMETRIC HOMO-ALDOL REACTION OF PYRUVATE ESTERS

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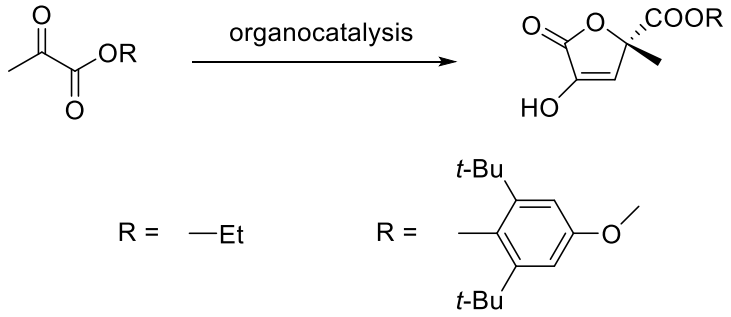
Isotetronic acids are biologically significant five-membered lactones isolated from a variety of natural sources. These structural moieties were found in a number of bioactive natural products, including compounds with antitumor and aldose reductase inhibitory activities. Also, functionalized isotetronic acids are the key intermediates for the synthesis of important natural products.[1]

In 2000 K. A. Jorgensen presented first catalytic asymmetric homo-aldol reaction of ethylpyruvate leading to diethyl-2-hydroxy-2-methyl-4-oxoglutaratein up to 96% enantiomeric excess. A chiral bisoxazoline–metal(II) complexes have been proved as a highly stereoselective catalytic system.[2]

Previously we have shown that chiral *Cinchona* alkaloids are effective catalysts for direct aldol reaction of puryvate esters with aldehydes.[3] Here, we present a new organocatalytic strategy for the synthesis of protected isotetronic acid using tertiary amines as catalysts. The homoaldol reactions of aliphatic and aromatic pyruvate esters will be presented.



Various catalysts and solvents have been investigated leading to a new simple protocol for the formation of optically active isotetronic acid derivatives.

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ANTI-SELECTIVE DIRECT ALDOL REACTIONS OF PYRUVATE ESTER WITH SUGAR ALDEHYDES PROMOTED BY Zn-PROPHENOL CATALYST

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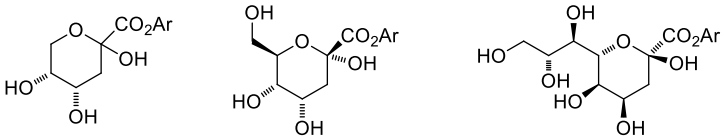
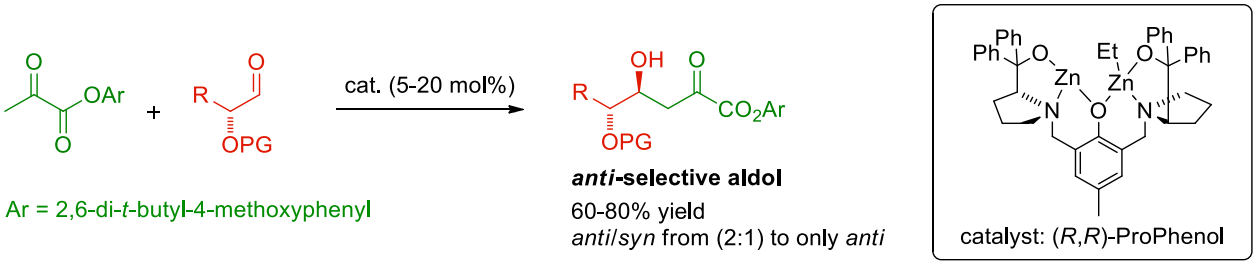
Ulosonic acids are key intermediated in many important biochemical pathways. In the Nature those acids are synthesized from phosphorylated sugar aldehydes and phosphoenolpyruvate (PEP).[1] Mimic of enzymatic catalysis by asymmetric direct aldol reaction is one of the challenges of modern organic synthesis. Unfortunately, asymmetric aldol reaction of pyruvates remains synthetic challenge.
Now, we present the first example of efficient catalytic *anti*-selective direct aldol reaction of pyruvate esters with sugar aldehydes closely resembling biomimetic synthesis of ulosonic acids.[2] Particularly, efficient and concise syntheses of 3-deoxy-D-*erythro*-hex-2-ulosonic acid (KDG), 3-deoxy-D-*ribo*-hept-2-ulosonic acid (DRH) and 3-deoxy-D-*glycero*-D-*talo*-non-2-ulosonic acid (4-*epi*-KDN) were elaborated (Scheme 1).



Scheme 1. Synthesis of various ulosonic acid esters

Chiral dinuclear Zn-ProPhenol[3] complex can effectively catalyse the direct aldol reactions of pyruvic acid ester with various chiral sugar aldehydes, thus functionally mimicking the pyruvate-dependent type II aldolases. Application of sterically hindered aryl esters allows for elusive aldol reaction of pyruvate donor with controlled *anti*-selectivity *en route* to the short and efficient synthesis of 3-deoxy-2-ulosonic acids precursors (Scheme 2).



Scheme 2. Direct aldol reaction of pyruvate ester with chiral aldehyde promoted by Zn-ProPhenol catalyst

Direct efficient application of pyruvic esters does not require additional damasking steps and thus surpass previously methodologies utilising masked pyruvic synthons such 2-acetylthiazole[4] and pyruvic aldehyde dimethyl acetal.[5]

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CHIRAL ZINC COMPLEX WITH DIAMINE LIGANDS FOR ASYMMETRIC HYDROSILYLATION OF PROCHIRAL KETONES

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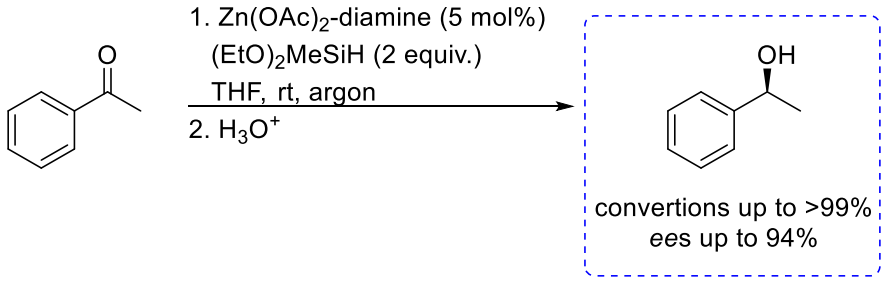
Asymmetric hydrosilylation of prochrial ketones is one of the most useful methods for the synthesis of enantioenriched secondary alcohols, which are widely used in pharmaceutical, fragrance and flavoring chemistry.

Reduction of ketones was commonly carried out using catalytic systems based on platinum group metals. Eventually, these toxic and expensive elements were replaced by less expensive ones, including zinc and iron. Zinc compounds however, due to only one oxidation state are relatively more stable compared to iron compounds. Both zinc salts and dialkylzinc can be applied as Lewis acids. Protocols involving application of dialkylzinc complexes with chiral diamines have been developed since late 90s.[1,2]

We have found that hazardous dialkylzinc can be replaced with non-hazardous and readily available zinc acetate. Several enantiopure diamine ligands have been synthesized and applied in the reduction of acetophenone, using protocol presented in our previos studies with hindered pybox ligands,[3] providing excellent convertions (up to >99%) and very good enantioselectivities (up to 94%).



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[2] D. Łowicki, A. Bezłada, J. Młynarski *Adv. Synth. Catal.* **2014**, *356*, 591-595

CHIRAL COMPLEXES OF ZINC ACETATE AS EFFICIENT CATALYSTS FOR THE HYDROSILYLATION OF *N*-PHOSPHINYLIMINES

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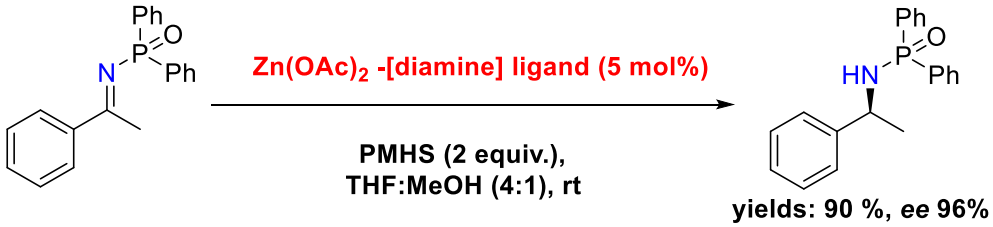
The reduction of C=O and C=N double bond is one of the most common reactions used in synthetic organic chemistry. Among various protocols, the hydrosilylation of imnes catalyzed by chiral transition metal complex is useful tool for the preparation of enantiopure secondary amines. Such a transformation is very important in pharmaceutical industry due to the fact that many chiral drugs and natural products posses amino groups.[1] Recently, broad scope of methods was developed that involves the use of high active, stereoselective and much cheaper “greener” catalysts.



In 2006, You *et al.* described efficient application of cheap zinc complex in the hydrosilylation of imines.[1,2] The presented results showed high activity and enantioselectivity of reactions catalyzed by $ZnEt_2$ – diamine ligand.

Now, we present our effort to use more stable and environmentally friendly salt – zinc acetate. The study was based on previously presented data indicating that $ZnEt_2$ can be successfully replaced by $Zn(OAc)_2$, without any loss in activity and enantioselectivity of the catalyst in the hydrosilylation of ketons.[3]

References:

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α-SELECTIVE MUKAIYAMA ALDOL REACTION OF CONJUGATED SYSTEMS

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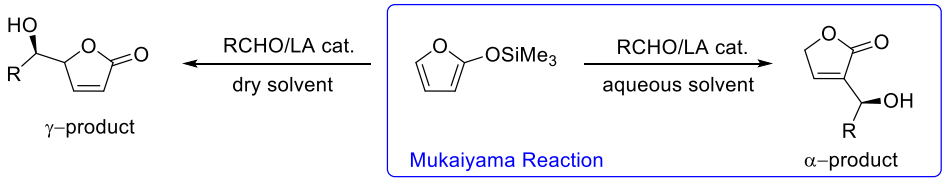
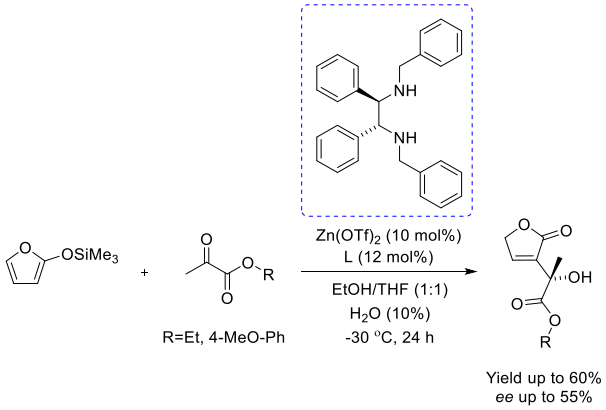
The Mukaiyama aldol reaction is one of the most powerful carbon-carbon bond-forming reaction in organic synthesis. This process occurs between silyl enol ethers and carbonyl compounds to afford β-hydroxy ketones and esters which are important building blocks for bioactive molecules and natural products.[1]

Our previous studies revealed unprecedent α-regioselectivity in the Mukaiyama aldol addition of various aldehydes and 2-(trimethylsiloxy)furan. Using water-containing solvent we observed formation of α-substituted α,β-unsaturated-γ-lactone instead of expected vinylogous Mukaiyama aldol reaction (VMAR). Catalytic asymmetric version of such reaction in the presence of water-compatible Lewis acid have also been developed.[2]



Here, we present that α-regioselectivity of addition of pyruvates to 2-(trimethylsiloxy)furan can also be controlled by application of water-compatible Lewis acids. Mukaiyama aldol products can be formed with excellent α-regioselectivity and high yields. Moreover, we have developed that application of water compatible chiral zinc-complex of (*R,R*)-DPEDA-based ligand affords enantiomerically enriched α-product in good enantioselectivity (up to 55% *ee*).



References:

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STEREOSELECTIVE SYNTHESIS OF POLYSUBSTITUTED CYCLOPENTA[*b*]INDOLES *VIA* CHIRAL BRØNSTED ACID CATALYSIS

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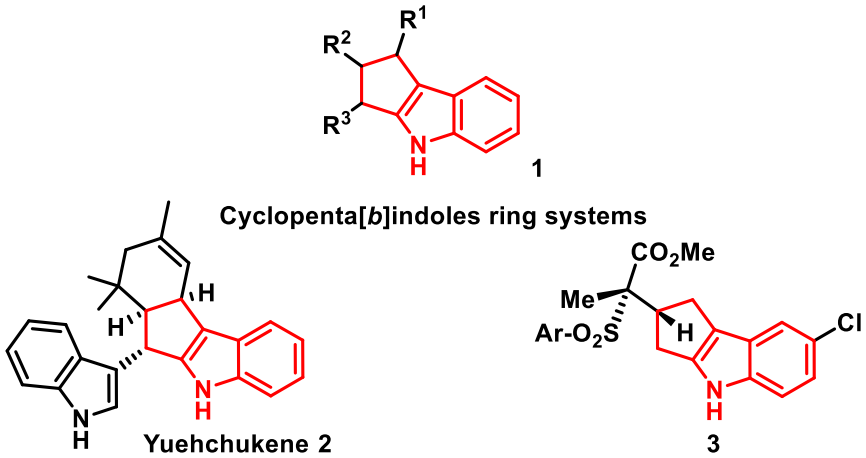
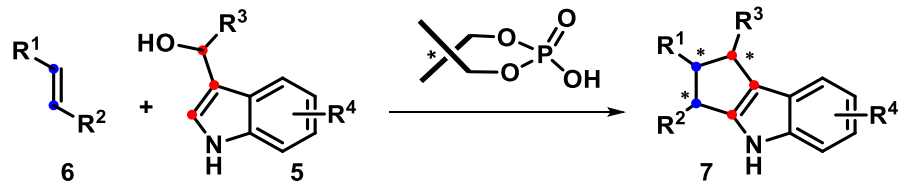
The cyclopenta[*b*]indole ring systems (**1**) have attracted considerable interest from organic chemists because the unique molecular architecture can be found in natural products (**2**)[1] and can serve as scaffolds in the design of therapeutic agents (**3**).[2]



Although a number of methods have been developed for the synthesis of racemic cyclopenta[*b*]indole derivatives,[3] asymmetric synthesis is highly desirable. We describe herein a chiral phosphoric acid catalyzed enantioselective [3+2] cycloaddition reaction of 3-hydroxy-3-indolyloxindoles **5** to alkenes **6**. A wide variety of cyclopenta[*b*]indoles **7** were obtained in a one-pot process with good to high yields and excellent stereoselectivities. The optimisation, the scope and the mechanistic insight of the reaction will be discussed in this communication.[4]



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PHOTOREDOX-MEDIATED TRIFLUOROMETHYLATION OF OLEFINS

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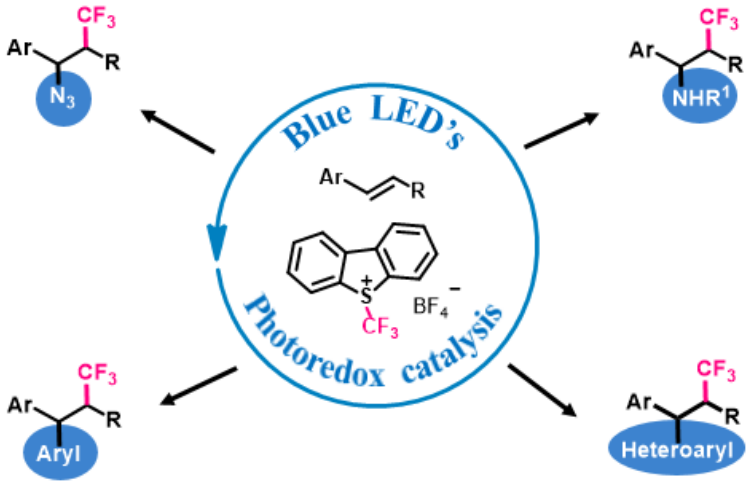
Organofluorine compounds play a major role in the fields of life sciences, agrochemical and materials.[1] Due to the unique properties of CF_3-containing compounds, it is highly significant to develop direct and efficient methods to incorporate the trifluoromethyl group into organic skeletons. Among the approaches usually employed for the fluoroalkylation of organic substrates, visible light photoredox catalysis has recently received widespread attention due to the extremely mild experimental procedures and the absence of highly reactive radical initiators.[2]

Based on our experience on photocatalyzed azidotrifluoromethylation of enecarbamates[3] we developed an efficient process giving rise to original β-trifluoromethyl amines. Direct azido- and amido-trifluoromethylation of a wide range of olefins are described in this poster.[4]

Then, we extend this multi-component process to new nucleophiles such as aromatic, heteroaromatic or halogen. This approach provides a simple and efficient route to functionalized trifluoromethylated compounds in good to excellent yields.[5,6]



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[6] A. Carboni, G. Dagousset, E. Magnier, G, Masson. *submitted.*

MULTICOMPONENT SYNTHESIS OF *γ*-NITROCOMPONDS UNDER ON WATER CONDITIONS

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Multicomponent reactions are the most efficient chemical procedures for the synthetic preparation of highly functionalized organic compounds. They take place from raw materials, with great economy of atom, energy-efficient and without intermediate purification steps. That is why the multicomponent reactions, particularly asymmetric multicomponent are of great interest.[1]

We have developed a new methodology multicomponent, organocatalytic and scalable which operates in the organic-water interface (conditions "on water"; OW)[2] to obtain *γ*-nitrocompounds from an aldehyde, a 1,3-dicarbonyl species and a nitroalkane. The reaction proceeds in two steps, a first step in which the 1,3-dicarbonyl species reacts with the aldehyde, resulting in the Knoevenagel adduct and a second step in which the nucleophile nitroalkane is added to this adduct, through a Michael addition. The process requires the presence of catalytic amounts of a thiourea derivative or squaramide (catalyst) and base N,N-Dimethylcyclohexylamine and generates *γ*-nitroesters featuring three contiguous stereocenters in a single reaction step (see figure 1). These products are suitable *γ*-amino acid precursor.

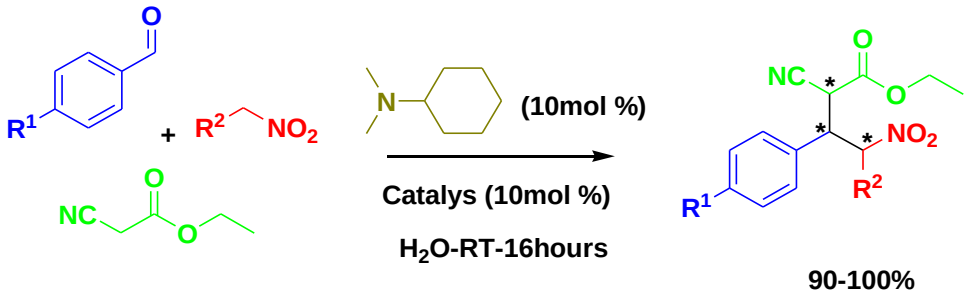

Figure 1

Acknowledgements: Work financed by MINECO (CTQ2011-28417-CO2-02). M.P.R. thanks the MICINN the granting of a FPI fellowship

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PD(II)-CATALYSED OXIDATIVE HECK AND C-H FUNCTIONALISATIONS

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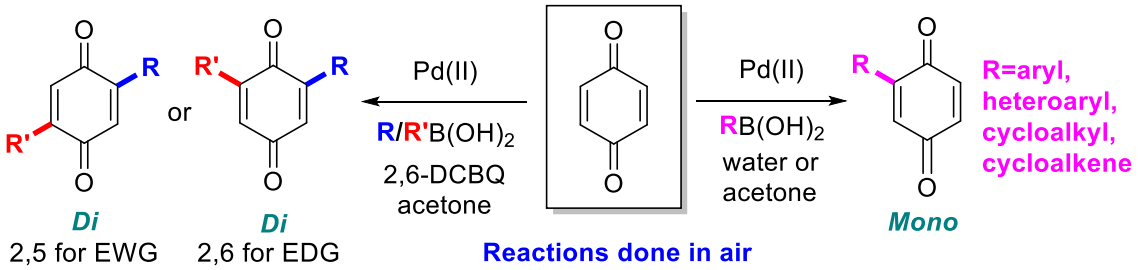
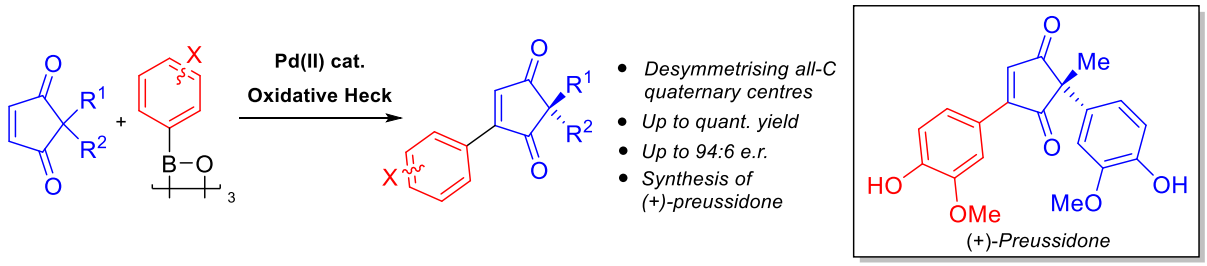
In recent years, Pd(II) catalysis has emerged as a useful method for oxidative Heck couplings on cyclic systems, many of which fail under standard Pd(0) catalysis. Investigations in the Lee group have focussed on oxidative Heck reactions and direct C-H functionalisations of challenging substrates.[1]



Scheme 1

For example, a direct Pd-catalyzed C-H functionalization of benzoquinone (BQ) has been developed, which can be controlled to give either monosubstituted or disubstituted BQ, including the installation of two different groups in a one-pot procedure (Scheme 1).[2] BQ can now be directly functionalized with aryls, heteroaromatics, cycloalkyls and cycloalkenes and, moreover, the process exploits environmentally benign water or acetone as solvents.



Scheme 2

We have also demonstrated the utility of the oxidative Heck reaction in enantioselective catalysis (Scheme 2).[3] The direct coupling onto the 2,2-disubstituted cyclopentene-1,3-dione core provides a novel, expedient and useful way of desymmetrising all-carbon quaternary centres.

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HENRY REACTION CATALYZED BY NEW SERIES OF 5-*TERT*-BUTYL-2-(PYRIDINE-2-YL)IMIDAZOLIDINE-4-ONE CU-COMPLEXES

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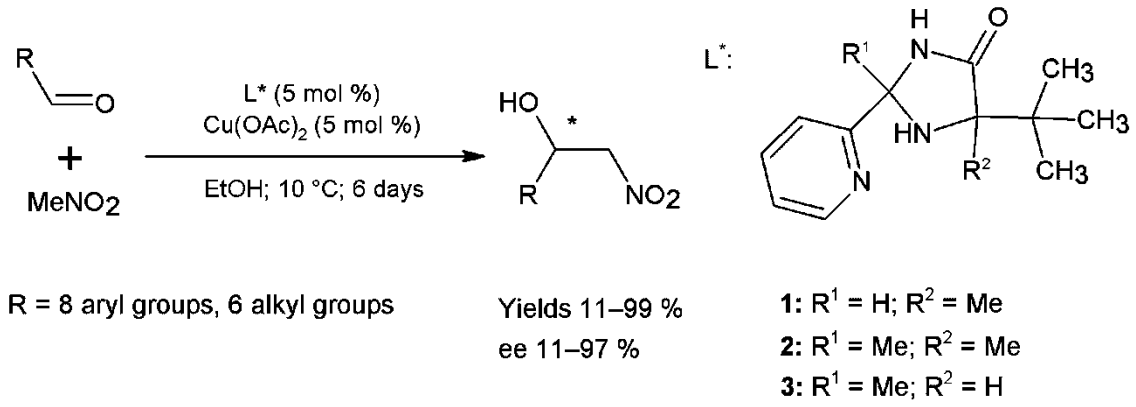
Non-racemic 2-nitroalcohols obtained from the asymmetric Henry reaction are important organic intermediates that can be used for the preparation of many various pharmaceutical substances.[1,2] Henry reaction is one of the most intensively studied asymmetric reactions, used for testing known or newly prepared enantioselective catalysts.[3,4] The most suitable enantioselective catalysts for the asymmetric Henry reaction include the Cu(II) complexes of functionalized 2-(pyridine-2-yl)imidazolidine-4-ones. It was found that their enantiocatalytic activity is distinctly affected by the substituents attached to stereogenic centers, among which the steric effect of the 5-alkyl substituent is important.

The aim of this work was preparation of 5-*tert*-butyl-2-(pyridine-2-yl)imidazolidine-4-one derivatives **1-3** and their corresponding Cu(II) complexes. These compounds were studied as enantioselective catalysts for the asymmetric Henry reaction of various aldehydes with nitromethane. It was found the 5-*tert*-butyl derivatives are effective catalysts for this reaction, with enantiomeric excesses being as high as 97%. The enantioselectivities of individual derivates **1-3** are different and depend on the alkyl substituents attached to stereogenic centres and the configuration of imidazolidine-4-one cycle. The most efficient derivative was found to be the Cu(II)-complex of derivative **1**. Its enantiocatalytic activity is comparable with the best so far known enantioselective catalysts of the Henry reaction.[5]



Scheme 1

Aknowledgements: This research work was financially supported by the Czech Science Foundation (GAČR), project no. 14-00925S.

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A DOMINO APPROACH TO DIBENZOPENTAFULVALENES BY CARBOPALLADATION SEQUENCES

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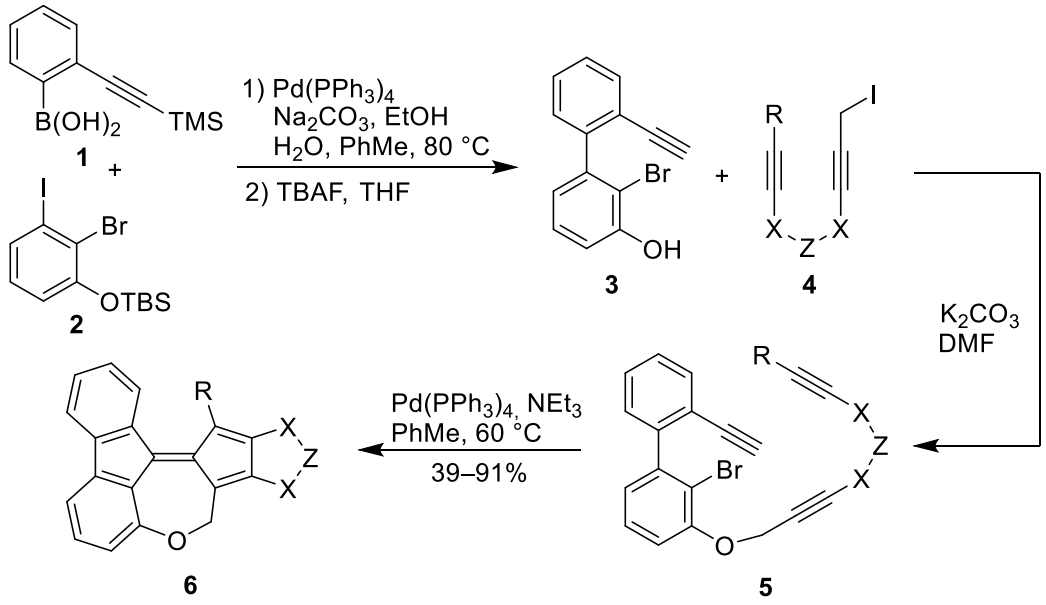
Fulvalene systems have attracted scientists for more than 40 years because of their special electronic and structural properties.[1,2] Therefore we were interested in constructing (highly substituted) fulvalene cores via palladium-catalyzed domino reactions involving carbopalladation steps and a formal terminating Mizoroki-Heck-reaction.
Scheme 1 shows the synthetic route to dibenzopentafulvane cores (**6**). First step is a Suzuki-Miyaura cross-coupling between boronic acid **1** and iodoarene **2**, followed by cleavage of both silyl protecting groups. Nucleophilic substitution at the propargylic iodide **4** gave domino precursor **5**, which then undergoes a quadruple carbopalladation sequence forming the desired products in moderate to excellent yields.[3]



Scheme 1. Synthetic route to dibenzopentafulvalenes.

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ORGANOCATALYTIC ASYMMETRIC SYNTHESIS OF *N,N*-ACETALS

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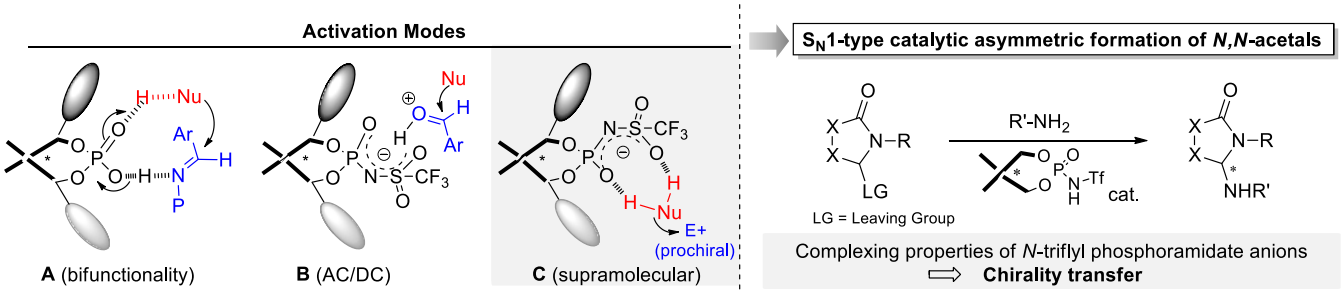
Chiral Brønsted acid (BA) catalysis is arguably now established as a powerful tool for organic chemists. Following Terada's and Akiyama's pioneering contributions,[1] this field has considerably matured and developed over the last decade.[2] To achieve the challenging activation of less basic functional groups such as carbonyls (that are hardly activated by phosphoric acids), more acidic reagents such as *N*-triflyl phosphoramides, as well as chiral sulfonimides, have subsequently been conceived and their potential in asymmetric organocatalysis is now being extensively evaluated.[2],[3] While the Brønsted acidity of these catalysts was mainly exploited, resulting in strict ion-pairing (ACDC) strategies,[4] their complexing properties received less attention until recently.[5] Yet the discovery of novel activation modes and distinct abilities of these catalysts would arguably improve their potential and usefulness in organic synthesis.

As part of our interest in S_N1-type functionalization of reactive cationic intermediates, such as *N*-acyliminiums ions,[6] we considered taking advantage of both the acidic and complexing abilities of *N*-triflyl phosphoramides for the catalytic and stereoselective synthesis of *N*,*N*-acetals.



Our efforts towards the development of this transformation, in which the activation of a prochiral *N,O*-acetal and the stereoselective delivery of a nitrogen nucleophile interacting by H-bonding with the catalyst counterion, would perform sequentially, will be presented

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ALLYLIC ALKYLATION OF GERANIOL BY GERANYLAMMONIUM SALTS, CATALYSED BY $Pd(DBA)_2$.

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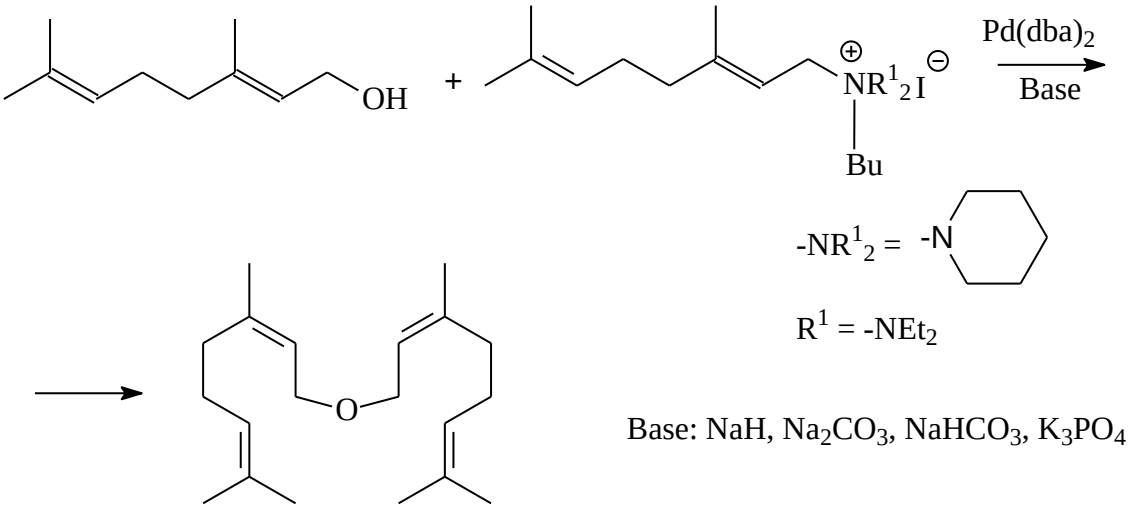
Terpene ethers of higher alcohols are used in cosmetics as emulsifiers, emollients, moisturizers. It was shown that ammonium group of irregular terpene is good enough for alkylation of alcohols in the presence of NaOH at high temperature in the absence of any catalyst[1]. We used geranyl ammonium salt for synthesis of digeranyl ether - well-known fragrance compound by Scheme.



Scheme 1

We have previously shown that allylic alkylation of benzimidazole by N-(2,7-dimethylocta-2E,7-dien-1-yl)ammonium salts in the presence of $Pd(dba)_2$ without phosphoric ligand gives only a single isomer of normal alkylation of the three possible isomers – normal alkylation (α-product), alkylation product with allylic rearrangement (γ-product) and product with reversed double bond[2]. So we used $Pd(dba)_2$ as catalyst in the presence of different bases in reflux MeCN for preparing of digeranyl ether by allylic alkylation of geraniol by geranylammonium salts. The reaction proceeds with high selectivity, the forming of other isomers does not exceed 5%. Yield of digeranyl ether depend on the nature of the base and duration of reflux.

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STUDY OF TRANSITION METAL CATALYZED C-H TRIFLUOROETHYLATIONS OF AROMATIC SYSTEMS USING VARIOUS DIRECTING GROUPS

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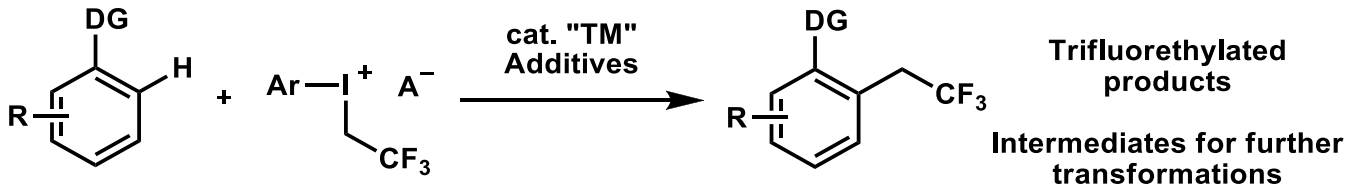
The incorporation of fluorinated moieties can cause profoundly influence in the molecules chemical and biological properties. Because the increased lipophilicity and electronic properties, the fluorine-containing groups are used widely in medicinal chemistry. Beside the several recently developed trifluoromethylation processes, the investigation of the trifluoroethylation methods gets much attention. Recently several cross-coupling methods were developed using trifluoroethyl iodide to introduce the trifluoroethyl group into the aromatic molecules, but only few examples were published to the direct C-H functionalization with different trifluoroethyl sources.[1,2] More recently our group developed a C3 selective trifluoroethylation process for indoles using a stable hypervalent iodonium salt reagent.[3]

The application of the developed trifluoroethyl iodonium salts in transition metal (TM) catalyzed C-H activation is one of the most investigated parts of our research. We examined the C(sp^2)- C(sp^3) *ortho* C-H trifluoroethylation of several aromatics bearing the most frequently used directing groups (DG), applying our previously designed stable hypervalent iodonium salts. Moreover we have also investigated further transformations of the trifluoroethylated products, depending on the directing groups.



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ORTHO-SELECTIVE 2,2,2-TRIFLUOROETHYLATION OF ANILIDES VIA PALLADIUM CATALYZED C-H ACTIVATION

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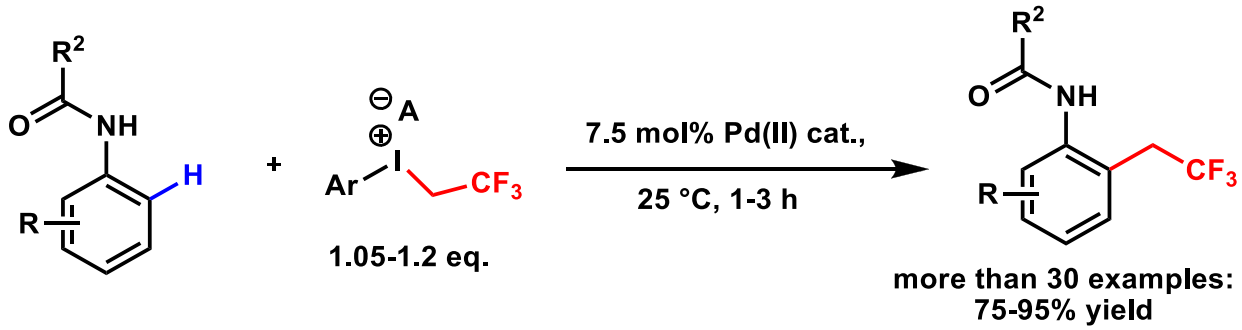
In our research have shown a new example of palladium catalyzed C-H bond activation. The direct dehydrogenative cross-coupling is a fast-developing part of organic chemistry. In the past few years the transition metal catalyzed *ortho*-directing functionalization via C(sp^2)-H bond activation become a widely feasible synthetic tool for organic chemists. Arylation, acylation and olefination of arenes are well known transformations, but there are less chemical tools for C(sp^2)- C(sp^3) bond formation. The number of catalytic reactions between arenes and C(sp^3) reagents are limited.

We achieved a C(sp^2)- C(sp^3) bond formation regioselectively in the *ortho* position of anilides. As reagent we used a stable hypervalent iodonium salt, which is recently reported by our group [1]. The introduction of 2,2,2-trifluoroethyl group into organic molecules performed efficiently at room temperature and provided new fluoroalkylated aromatic compounds. The developed transformation enables the direct trifluoroethylation of arenes bearing either electron-donating or electron-withdrawing functional groups (R). The fluorous functional groups (mainly trifluoromethyl, trifluoromethoxy, trifluoromethylthio) are often used in medical chemistry order to their effect on lipophilicity and biological activity. Due to the presence of fluoro atoms the electronic properties of molecules also change and allow further reactions on multifunctionalized aromatic cores. The installation of 2,2,2-trifluoroethyl group into substituted aromatics is a new synthetic application and it has been an underdeveloped field in organic chemistry.[2] Therefore the biological effect is still unknown. The efficiency of this methodology opens new possibility for the synthesis of valuable compounds having trifluoroethyl function.



References:

[1] G. L. Tolnai, A. Székely, Z. Makó, T. Gáti, J. Daru, T. Bihari, A. Stirling, Z. Novák, *Chem. Commun*. **2015**., *51*, 4488-4491.
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POLYMER-SUPPORTED ß-FLUOROAMINES IN THE HIGHLY SELECTIVE MICHAEL REACTION

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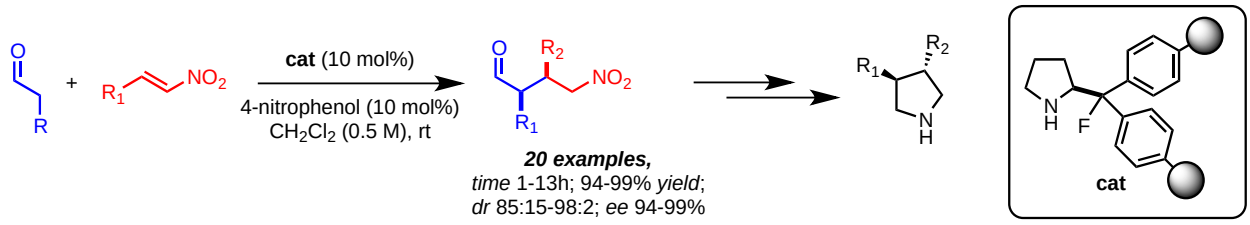
Diarylprolinol trimethylsilyl ether, commonly known as the Jørgensen-Hayashi catalyst[1] is one of the most successful organocatalysts developed to date. Given the versatility of this species, which is able to exploit both the enamine and iminium ion activation mode, several groups have embarked in the development of immobilized analogues. Our own laboratory, with the aim of enhancing the sustainability profile of this catalyst, has reported the preparation of a set of polysterene-supported derivatives whose robustness was tested through recycling and implementation of continuous flow processes.[2] However, during the course of these studies we have very often encountered that the robustness of the catalyst is compromised by the lability of the trimethylsilyl ether. Recently we have set our sights on the (S)-2-(fluorophenylmethyl)pyrrolidine introduced in asymmetric aminocatalysis by Gilmour et al. in 2009.[3] This fluorinated catalyst, designed to substantiate the *gauche*-effect hypothesis, has turned out to promote epoxidations and aziridinatons (among other reactions) with great success, even outperforming the Jorgensen-Hayshi catalyst in some cases.

Herein we present an immobilized analog of the successful fluorinated aminocatalyst,[1] which can be prepared in a straightforward manner from L-proline derivatives and has shown great potential for the Michael addition of aldehydes to nitroalkenes. We have also demonstrated that the catalytic polymer can be recycled for at least eight runs, although a decrease in activity was observed. Remarkably, the stereoselectivity remained constant throughout the whole process. These encouraging results prompted us to study the implementation of the reaction under continuous flow. With a flow rate as 0.1 ml/min, a quantative yield was achieved during the next 13h, and the catalyst loading turned out to be 1.6%. Overall, the turnover munber (TON) was a high as 60.2.



The obtained chiral Michael adducts can be versatile intermediates in the synthesis of valuable compounds. We have developed the preparation of enantiopure 3,4-disubstituted pyrrolidines through a simple procedure involving reduction of the nitro group followed by intramolecular cyclization.
It is noteworthly that the desired Michael adducts are obtained in short times and with excellent yields. The high yields obtained (94-99%) are due to the simplified isolation procedure: simple filtration and basic washing followed by evaporation rendered the pure products in most cases.
Efforts are currently being devoted to understand the deactivation mechanism of the catalyst in order to minimize or even suppress this unwanted process. In addition other asymmetric transformations are being stidied with this system and related supported species.

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DEOXYGENATION OF ARYL KETONES CATALYZED BY OXO-RHENIUM COMPLEXES

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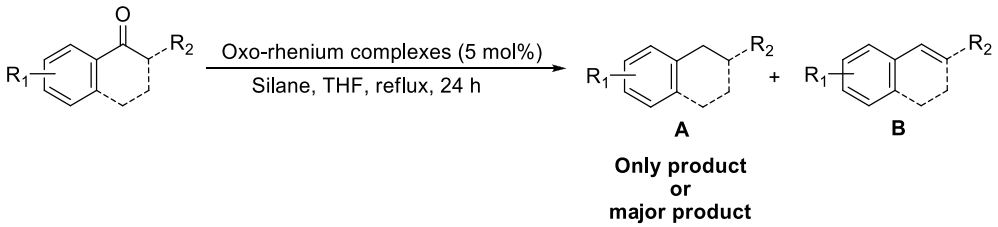
Direct reductive deoxygenation of aryl ketones to aromatic alkanes is an important reaction in fine chemical industry and biofuel production. In particular, the reduction of the carbonyl group to the methylene group is especially useful to convert polyfunctional natural products into useful building blocks and into bioactive molecules or even to convert Friedel Crafts acylation products into less easily accessible alkylation ones.

In continuation of our work about the reduction or deoxygenation of organic compounds catalyzed by oxo-complexes,[1,2] we here describe the first methodology for the direct reductive deoxygenation of aryl ketones catalyzed by high valent oxo-rhenium complexes using a silane as reducing agent producing selectively the corresponding alkane or a mixture of alkane and alkene derivatives, being the alkane the major product.[3]



Acknowledgment: This research was supported by FCT through project PTDC/QUI-QUI/110080/2009 and annual funds UID/QUI/00100/2013. JRB (SFRH/BD/90659/2012) and TAF thank FCT for grants.

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FORMATION OF ALKENYL CYCLOPROPANES BY GOLD(I) CARBENES FORMED BY RETRO-BUCHNER REACTIONS

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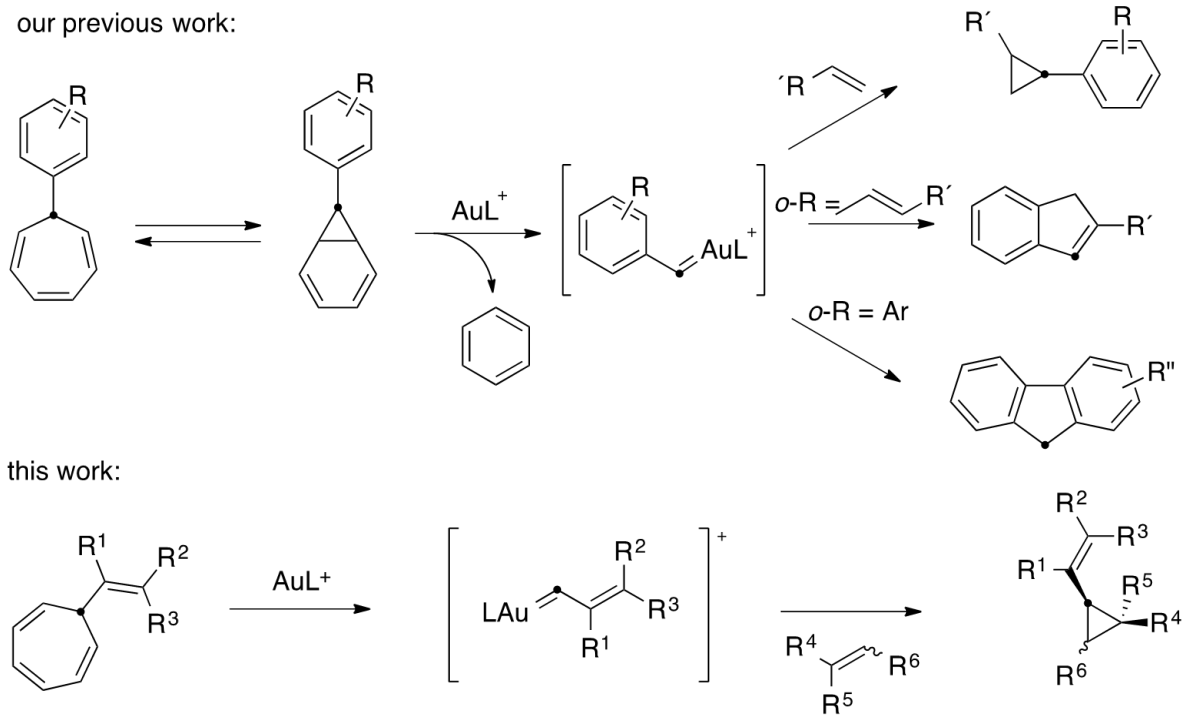
We recently found that 7-aryl 1,3,5-cycloheptatrienes undergo a gold(I) catalyzed retro-Buchner reaction to form $[LAu{=}CHAr]^+$ carbenes. These carbenes have been trapped by olefins to form cyclopropanes.[1] Alternatively, the intramolecular reactions of alkenes or arenes in the *ortho* position of the aryl moiety, led to indenes and fluorenes, respectively.[2] In this work, the scope of these reactions has been extended by using alkenyl-substituted cycloheptatrienes, as well as varying the olefinic nucleophile, to access to a broad range of small molecules under milder conditions.



Further research is currently carried out in our laboratories on the development of new synthetic applications of this type of highly reactive gold(I)-carbenes.

Acknowledgments. We thank MICINN (project CTQ2010-16088/BQU), the European Research Council (Advanced Grant No. 321066), and the ICIQ Foundation for financial support.

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SYNTHESIS AND EVALUATION OF NEW GOLD-COMPLEXES IN ASYMMETRIC CATALYSIS

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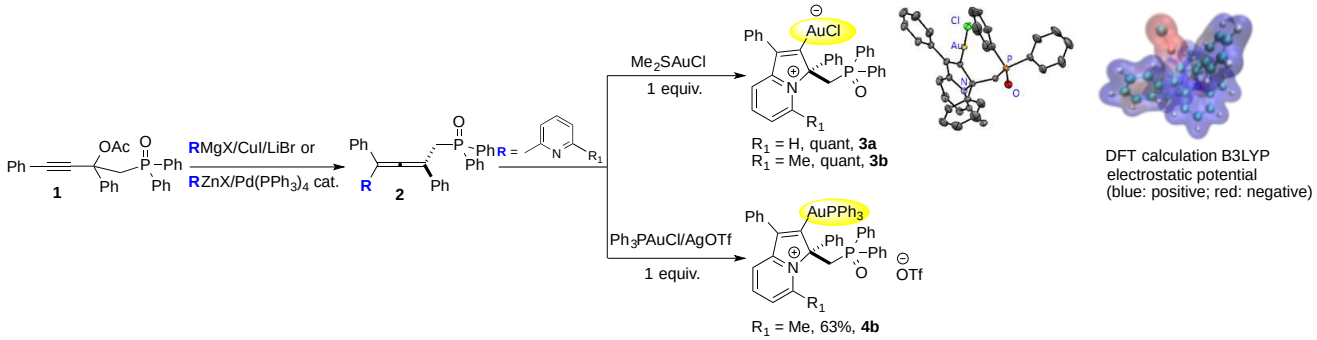
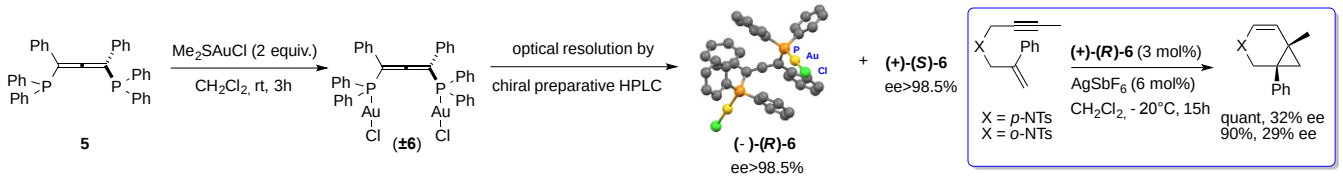
As part of our ongoing interest in developing new gold(I)-complexes for asymmetric catalysis[1] and new gold-catalyzed reactions,[2] we have designed novel gold(I) complexes based on allene-containing phosphines. Thus, we have synthetized a broad variety of mono phosphine oxide allene derivatives. Starting from pyridyl-allenes in the presence of Me_2SAuCl, we obtained quantitatively new gold carbene complexes **3a-b** and **4b** (Scheme 1). X-ray crystallography of **3a-b** and ^{13}C NMR of the complexes secured the proposed structures. We also studied the electronic properties of these complexes by DFT calculation. Now, we are investigating their catalytic properties.



Scheme 1. Synthesis of gold(I)-complexes **3a-b** and **4b**

In parallel, treatment of the allene **5**, previously decribed by Schmidbaur,[3] with two equivalents of gold(I) salt allowed us to obtain quantitatively dinuclear gold(I)-complex **6**. After resolution by chiral preparative HPLC, we obtained both enantiomers **(-)-(*R*)-6** and **(+)-(S)-6** with ees>98.5%. We have started to examine the catalytic activities of theses complexes, notably for asymmetric gold-catalyzed cycloisomerisation. Promising ees with **(+)-(*R*)-6** have been observed (Scheme 2).



Scheme 2. Preparation of enantiopure allene-bis-phosphine gold(I) complexes, first results in asymmetric catalysis

References:

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AUTOINDUCED CATALYSIS AND INVERSE EQUILIBRIUM ISOTOPE EFFECT IN THE FLP CATALYZED HYDROGENATION OF IMINES[1]

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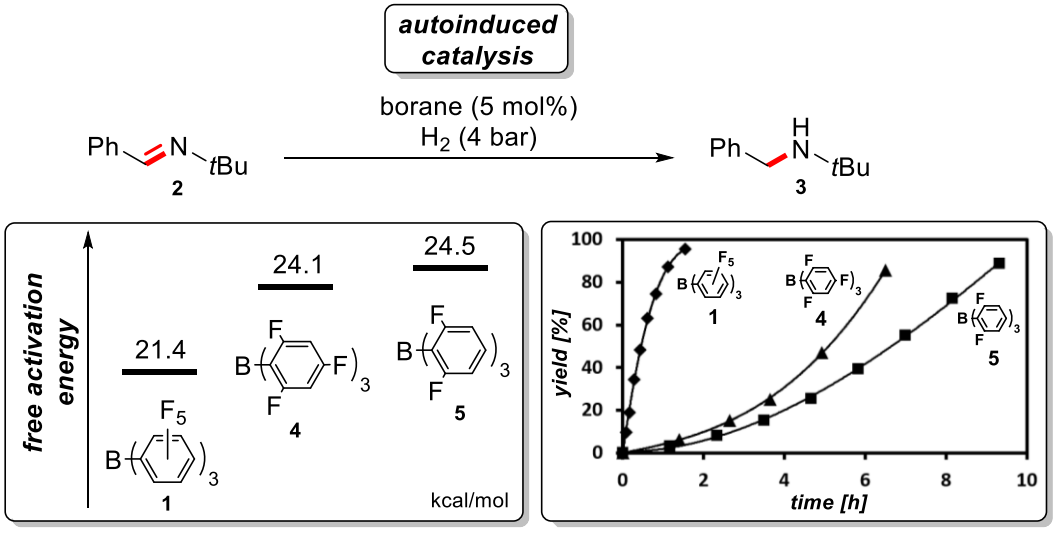
The frustrated Lewis pair-catalyzed hydrogenation and deuteration of *N*-benzylidene-*t*butyl amine (**2**) was kinetically investigated using the three boranes $B(C_6F_5)_3$ (**1**), $B(2,4,6\text{-}F_3\text{-}C_6H_2)_3$ (**4**) and $B(2,6\text{-}F_2\text{-}C_6H_3)_3$ (**5**). Reactions catalyzed by the weaker Lewis acids **4** and **5**[2] displayed autoinductive catalysis arising from a higher free activation energy (2 kcal/mol) for the H_2-activation by the imine compared to the amine. Hydrogenations of imines proceed *via* the simple and the autoinduced catalytic cycle[3] which are switched by the strength of the Lewis acid. Surprisingly, the imine reduction using D_2 displayed higher rates with the weaker Lewis-acidic boranes **4** and **5**. This phenomenon is unprecedented for FLP and resulted from a primary inverse equilibrium isotope effect.



For the first time free activation energies for the H_2-activation by FLPs were experimentally determined and amounted to 22 kcal/mol. Experimental evidence for the formation of hydrogen bonded complexes in the transition state of the imine-reduction[4] is supplied by NOESY NMR experiments which revealed an aggregation of the $[BnNH_2tBu]$-cation with the $[HB(2,6\text{-}F_2C_6H_3)_3]$-anion *via* dihydrogen bonding.
This detailed picture of the FLP-catalyzed imine hydrogenation will enable for the development of even more sophisticated FLP and akin catalyzed reactions.

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SYNTHESIS AND EVALUATION OF N-ALKYLIMIDAZOLE-BASED CATALYSTS IN THE BAYLIS-HILLMAN REACTION

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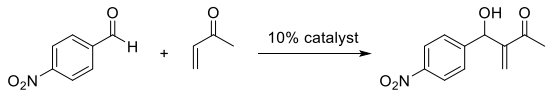
The Baylis-Hillman (BH) reaction is an efficient and useful carbon-carbon bond forming transformation, promoted usually by a nucleophilic catalyst. This reaction acquired high synthetic popularity due to its operational simplicity and the high application potential of the BH adducts in organic synthesis.[1] Imidazole and N-alkylimidazole derivatives exhibit notable catalytic activity in the BH reaction. Heterogeneous organocatalysts based on polymer-supported poly(aryl benzyl ether) dendrons, modified at the surface with N-alkylated imidazoles, were previously synthesized in our group. The catalysts effectively promoted the BH reaction (e.g. Scheme 1). These catalysts revealed outstanding positive dendritic effect in respect to the reaction yield, and perfect chemoselectivitiy.[2] As a result of these impressive effects in heterogeneous catalysis, we decided to examine the activity of the dendrons decorated with N-alkylated imidazoles in solution as well, focusing on the series of N-(3-aminopropyl)imidazole-derived catalysts.

This poster will describe our findings derived from these experiments, which point to substantial differences between homogeneous and heterogeneous catalytic systems. Examination of zeroeth to second generation catalysts under the standard set of conditions revealed low yields and chemoselctivities, though the chemoselectivity toward the BH product was substantially improved as the dendron generation increased. The conversion, nonetheless, had shown the opposite trend.[3]

A possible reason for the differences observed between the homogeneous and heterogeneous systems is the hydrophobic environment around the catalytic sites in the pores of the polystyrene beads. The poster will also portray the attempt to imitate the environment near the catalytic site by synthesis of imidazole-based homogeneous catalyst containing multiple long aliphatic tails (e.g. Figure 1), and investigate the effect of the artificial hydrophobic pocket on the efficiency of the BH reaction.



Scheme 1

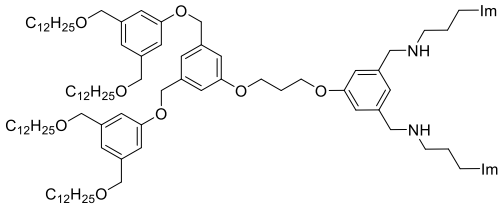


Figure 1

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ASYMMETRIC C-H ACTIVATION AND DYNAMIC KINETIC RESOLUTION: NEW TOOL FOR THE SYNTHESIS OF AXIALLY CHIRAL BIARYLS

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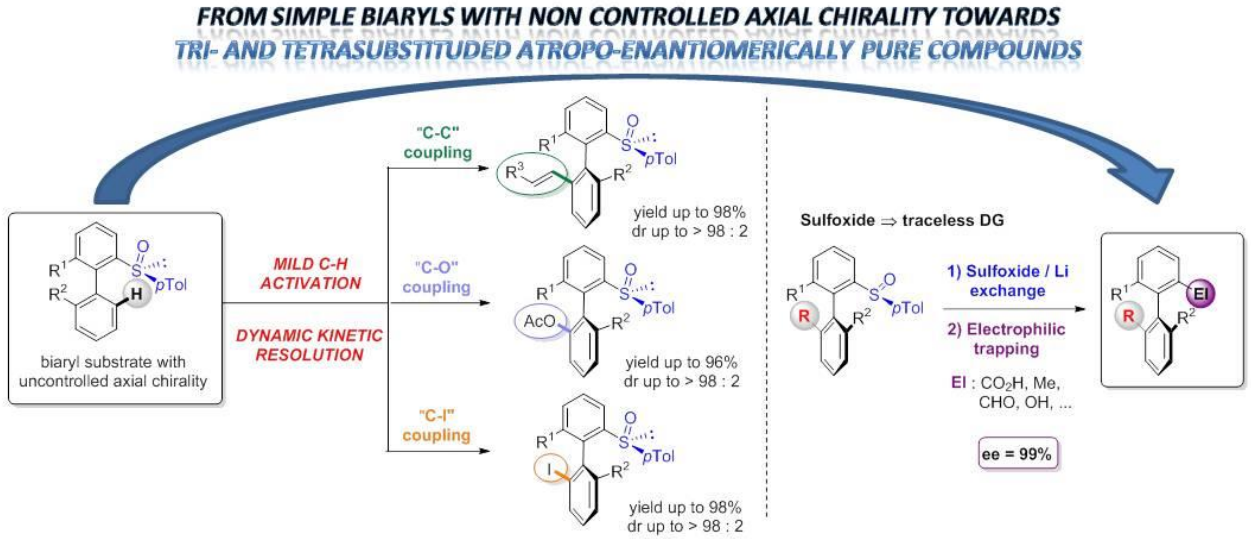
Axial chirality is a key feature of many important organic molecules, such as biologically active compounds and stereogenic ligands.[1] However, the efficient asymmetric syntheses of a large panel of such scaffolds still represents a great scientific challenge. With the aim to meet this goal, we have developed a conceptually original strategy combining **asymmetric C-H activation**[2] and **Dynamic Kinetic Resolution**.[3] Our approach is based on the use of a sulfoxide moiety, installed on a biaryl backbone, as both, a traceless directing group for C-H activation and a chiral auxiliary.[4] Such biaryl substrates, for which the axial chirality is not controlled, undergo an extremely mild, diastereoselective C-H activation and following C-C, C-O and C-I couplings occur with total control of the axial chirality,[5] affording a large panel of atropo-diastereomerically pure compounds. Importantly, as the mixture of two atropisomers of the starting material is readily converted into a sole diastereomer of the functionalized products, these direct couplings arise from Dynamic Kinetic Resolution. Finally, as the sulfoxide moiety can be straightforwardly replaced by numerous functional groups, the optically pure biaryl products can be further transformed.



The herein presented strategy constitutes therefore a unique and fairly general synthetic route enabling efficient and stereoselective synthesis of a myriad of generally difficult to access, highly substituted biaryls *via* unprecedented, mild and asymmetric C-H activation.

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[1] For recent reviews on the synthesis of axially chiral biaryls see: a) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev*. **2011**, *111*, 563-639; b) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev*. **2009**, *38*, 3193-3207; c) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed*. **2005**, *44*, 5384-5427; d) O. Baudoin, *Eur. J. Org. Chem*. **2005**, 4223-4229.

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HOMOGENEOUSLY CATALYSED H_2 GENERATION USING C1 MOLECULES AND H_2O AS H_2 SOURCE

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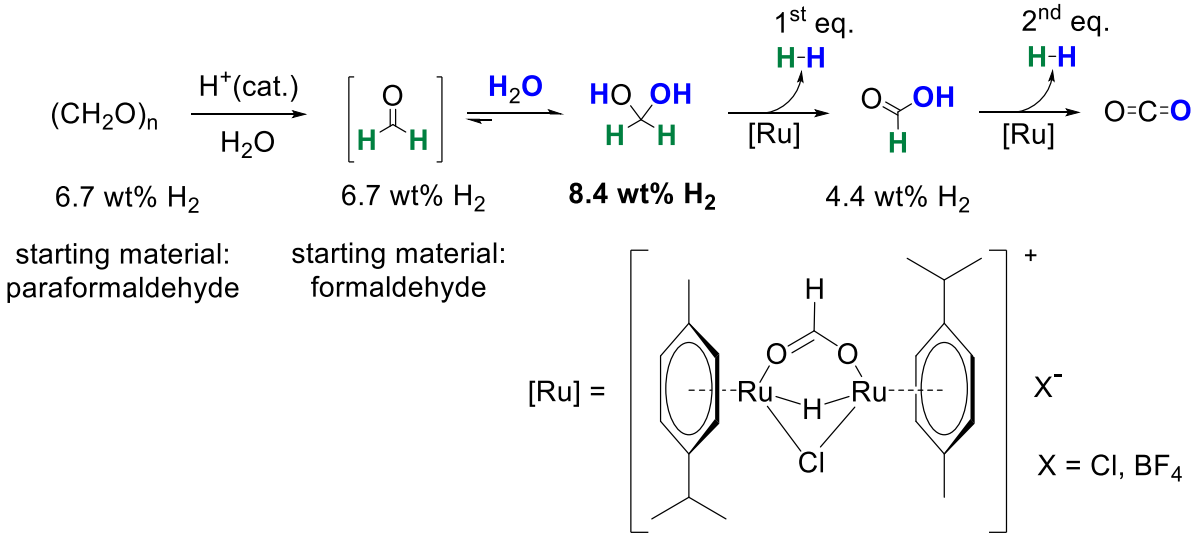
For findings towards new energy storage systems, an intensively studied fuel molecule is H_2 owing its high energy content, and the possibility to store it in form of hydridic and protic hydrogen.[1,2] Recently, we showed that water in presence of C1-entities like (para)formaldehyde (FA) is suitable for molecular hydrogen-storage as these molecules can be easily and selectively dehydrogenated forming pure H_2 and CO_2.[3] The reaction runs on air using a novel water-stable molecular catalyst under base-free conditions. Both molecules, H_2O and H_2CO, act equally as source of H_2. Isotope-labelling experiments (^2H, ^{13}C and ^{18}O) confirm that the H_2 released originates from both, H_2O ($H_2{}^{18}O$ or D_2O) and H_2CO (^2H and ^{13}C-labelled). Isotope-labelled complexes and gaseous products could be assigned by means of NMR, ESI-MS and continuous gas-phase MS. A theoretical efficiency of 8.4 wt% of H_2 considering 1 eq. H_2O and H_2CO is possible. This is higher than for formic acid (4.4 wt%), even when technical aq. H_2CO is used, the solution has a min. efficiency of 5.0 wt%. This catalytic decomposition of H_2CO can be envisioned as novel approach for simultaneous H_2 production and decontamination treatment of wastewater with formaldehyde impurities a waste to value approach.

Currently, we perform experimental and theoretical mechanistic studies, and develop further catalysts towards room-temperature H_2 generation from water and C1-molecules in general and especially methanol.[4] These studies include also coupled conversion of the *in situ* generated H_2 and CO_2 towards a full hydrogenation/dehydrogenation cycle.



Scheme 1. Exemplary hydrogen generation from formaldehyde and water.

Acknowledgement: MIWF-NRW is acknowledged for the Scientist Returnee Award 2009 and we are grateful for the Ernst-Haage Prize 2014 of the Max-Planck-Institute for Chemical Energy Conversion.

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KINETIC RESOLUTION OF SECONDARY ARYL ALKYL ALCOHOLS WITH HETEROATOM FUNCTIONALITY USING A PLANAR CHIRAL DMAP CATALYST

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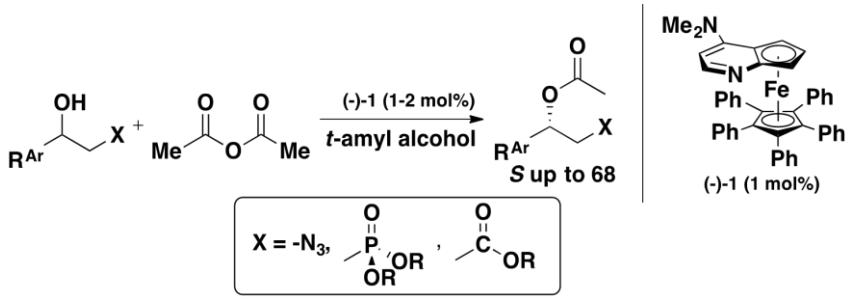
The synthesis of enantiomerically pure compounds has become one of the most important fields of organic synthesis and high enantiomeric purity is a requirement in the synthesis of chiral pharmaceuticals. Secondary aryl alkyl alcohols is a common motif in many endogenous compounds, *e.g.* norepinephrine and adrenline, and is therefore precursors to several drugs, such as (*R*)-pronethalol and (*R*)-fluoxetin. Many methodologies have been developed for the asymmetric synthesis of these compounds and the enzymatic kinetic resolution of racemic alcohols as well as enzymatic dynamic kinetic resolution has been reported to produce chiral alcohols in high enantiomeric excess.[1]

An alternative approach is the non-enzymatic kinetic resolution of racemic alcohols via enantioselective organocatalytic acylations.[2] Fu and co-workers developed the synthesis of planar-chiral ferrocenyl DMAP analogues and carried out the kinetic resolution of aryl and alkyl alcohols.[3]



Here we present the kinetic resolution of a variety of secondary aryl alkyl alcohols containing heteroatom functionality in the alkyl substituent. The kinetic resolution using the planar-chiral ferrocenyl DMAP-catalyst (-)-**1** gave the 1,2-azido alcohols[4], 2-hydroxy-2-aryl-ethylphosphonates[5], and β-hydroxyaryl esters[6] in high enantiomeric excess (up to 99% ee) and good selectivities (up to *S* = 68).

In addition, a computational and kinetic study of the kinetic resolution of 1-phenylethanol using the planar-chiral ferrocenyl DMAP-catalyst (-)-**1** have been performed and the mechanism of the acetylation will be discussed in the light of these investigation.

References:

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CATALYTIC OXIDATION OF ORGANOSULFUR COMPOUNDS: AN ENVIRONMENTALLY SAFE AND EFFICIENT APPROACH PLAYED BY METALLOPORPHYRINS AND HYDROGEN PEROXIDE

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Following our approach on the use of metalloporphyrins as catalysts and hydrogen peroxide as oxidant in the oxidation of organic compounds [1-5], herein the excellent catalytic oxidative performance of iron(III) and manganese(III) porphyrin complexes will be demonstrated for organosulfur compounds under homogeneous conditions. Beyond the better results obtained, when compared with those obtained for the manganese(III) complexes, the oxidation reactions in the presence of the iron(III) complex involves a cleaner approach because ethanol is used as solvent and a co-catalyst is not required. For all the substrates studied, high conversions were achieved. Significantly, the catalysts tested act efficiently in the oxidation of a model fuel, constituted by a mixture of benzothiophenes and dibenzothiophenes in hexane (Figure 1).

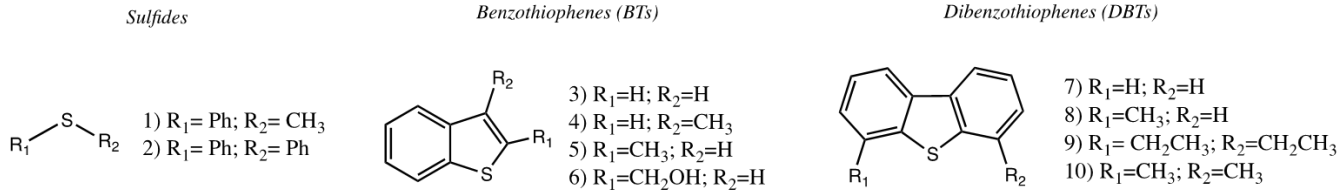

Figure 1. Organosulfur compounds studied for oxidation with H_2O_2 using metalloporphyrins as catalysts

The high potential of metalloporphyrin complexes as catalysts for the sulfoxidation of the S-refractory BTs and DBTs by H_2O_2 will be demonstrated [6-8] in a biomimetic approach with potential application in the oxidative desulfurization (ODS) procedure for several organosulfur compounds. Moreover, the sulfoxidation of 1,3-dihydrobenzo[*c*]thiophenes under these conditions constitutes a facile and eco-friendly approach for the corresponding sulfones, some of which are well-known cyclic diene precursors in Diels-Alder cycloadditions. These sulfones are stable intermediates for the generation of *ortho*-benzoquinodimethanes (o-xylylenes) or benzocyclobutenes, which can be trapped *in situ* by several dienophiles, yielding the corresponding cycloadducts.

Thanks are due to all collaborators involved in the work and to Fundação para a Ciência e a Tecnologia (FCT, Portugal), and the European Union, QREN, FEDER, COMPETE, for funding the Organic Chemistry Research Unit (QOPNA) (PEst-C/QUI/UI0062/2013).

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ALLENE-ENOL ETHERS CYCLOISOMERISATION UNDER METAL TRIFLATE CATALYSIS

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Over the last twenty years, metal triflate catalysts have emerged as important contributors to modern organic synthesis and for the development of sustainable chemistry. In particular, the non-toxic Lewis acid bismuth(III) triflate has proven to be a useful catalyst in a wide range of different transformations under mild conditions.[1] Besides, allenes constitute extremely valuable synthetic building blocks.[2] In this context, we have previously shown that, by means of Bi(III)-based catalysis, allenes could act as electrophilic partners in hydroarylation reactions and also as nucleophiles, as in the cycloisomerisation of γ-allenic ketones.[3]

The cycloisomerisation of allene-enol ethers catalysed by metal triflates is being developed as new catalytic and 'atom economic' process for the formation of various (poly)cyclic compounds (Figure 1). After a screening of several metal triflates, bismuth(III) triflate was found to be the most suitable catalyst for this reaction.

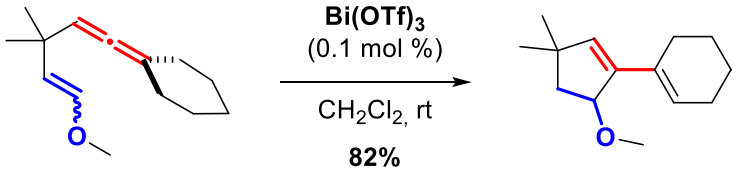

Figure 1. Cycloisomerisation of allene-enol ether catalysed by $Bi(OTf)_3$.

The cyclisation has been successfully extended to various starting materials containing cyclic and non-cyclic enol-ethers and thio enol-ethers. For instance, oxaspiro compounds (Figure 2) can be efficiently obtained from readily available starting allenic substrates using bismuth(III) triflate catalyst at a low loading of 0.1 mol % with an excellent diastereoselectivity.[4]

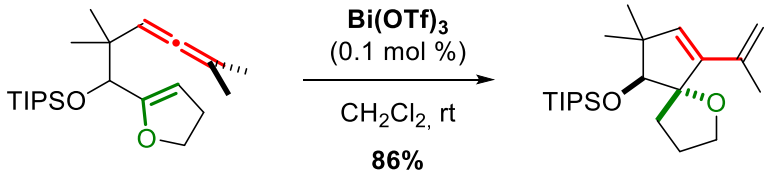

Figure 2. $Bi(OTf)_3$-catalysed formation of oxaspirocycles.

From a mechanistic point of view, the introduction of an exogenous nucleophile allowed us to gain further insight into the observed chemoselectivity highlighting the favored activation of the enol-ether moiety. The novel molecules have been evaluated for their olfactory properties by a panel of perfumers revealing a potential application in the field of flavours and fragrances.

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PREYSSLER HETEROPOLYACID SUPPORTED ON SILICA COATED $Ni_{0.5}Zn_{0.5}Fe_2O_4$ NANOPARTICLES; SYNTHESIS AND CHARACTERIZATION

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In recent decades, magnetic nanoparticles (MNPs) have been widely studied for various biological and medical applications[1]. They have been shown to be promising supports for the immobilization of catalysts because magnetic catalysts can be easily separated from the reaction medium by an external magnet, which provides a simple separation of the catalyst without the need for filtration, centrifugation, or other tedious workup processes[2]. This separation technique has a special importance for nano-sized catalyst supports where filtration methods result in the loss of catalyst particles and product contamination.

In recent years, MNPs as catalyst or catalyst support have been widely used in a variety of important organic reactions[3]. Recently, Wang et al. reported the synthesis of silica coated Fe_3O_4 MNPs for immobilizing heteropoly acids (HPAs) with a Keggin structure[4]. Rafiee et al. reported another silica coated MNPs with the formula $Fe_2O_3@SiO_2$ for supporting tungstophosphoric acid and phosphomolybdic acid [5]. They showed good catalytic activity by these catalysts. In addition to Fe_3O_4 and Fe_2O_3, there are other iron oxides with the ferrite structure and general formula (AFe_2O_4), where A can be Mn, Co, Ni, Cu, and Zn[6].

Ni-Zn ferrites are one of the most versatile magnetic materials with a high saturation magnetization, chemical stability, and relatively high permeability[7], and because of these magnetic properties it can be used as a magnetic source. The Preyssler HPA ($H_{14}NaP_5W_{30}O_{120}$) is a HPA which has significant advantages, such as 14 acidic protons, high thermal stability, high hydrolytic stability ($0 < pH < 12$), regenerability and safety[8]. Owing to the low surface area (7–10 m2/g) and high solubility of HPAs in polar solvents, it is preferable to use them in supported form. These catalysts can be supported on neutral solids, such as silica, activated carbons, or zeolites and acidic ion exchange resins. Recently, we supported Preyssler HPA on silica and used this supported catalyst for various reactions[8].

In a continuation of our achievements in the preparation of novel catalysts[9] and based on our previous success in the preparation of MNPs as catalysts[10], in this study, we supported Preyssler HPA on $NiFe_2O_4@SiO_2$ (denoted NFS-PRS). After the characterization of this novel magnetically recoverable catalyst, its catalytic activity was tested in the synthesis of 3,4- dihydropyrimidin- 2(1*H*)-ones derivatives by the Biginelli reaction.

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ORGANOCATALYTIC GLYCOSYLATIONS

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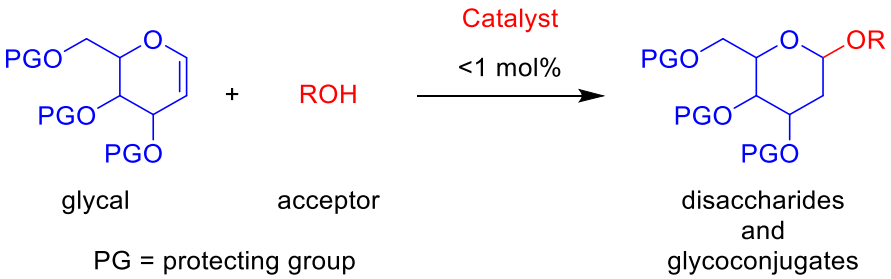
The synthesis of oligosaccharides with stereocontrol remains a challenging task in organic synthesis. We previously reported a mild, atom economic, organocatalytic method for the stereoselective synthesis of 2-deoxygalactosides using thioureas as catalysts.[1,2] In this presentation, a new class of organocatalysts for the glycosylation of protected glycals will be presented. These new catalysts are cheap and readily available, and they demonstrate an expanded substrate scope both in terms of glycal and the types of alcohol glycosyl acceptor that can be used.

These catalysts have been designed based on a significant change in our understanding of the mechanism of how these glycosylations occur. We now propose that the previously used thiourea catalysts do not operate in a double hydrogen bonding manner and will present evidence to support this hypothesis. The new mechanism brings to mind the mechanisms thought to operate in some glycosidases and has opened the way for the development of this new class of catalysts.



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FLUOROMALONYL HALFTHIOESTERS AS MASKED FLUOROACETATES IN THE FIRST ENANTIOSELECTIVE ALDOL REACTION.

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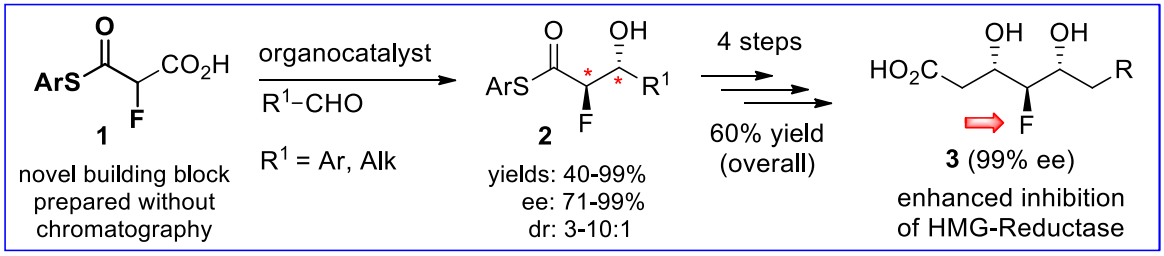
Fluorine holds an esteemed position in modern medicinal chemistry due to its unique influence on organic molecules and it is frequently used to improve activity and properties of drugs and agrochemicals. Unfortunately, the attributes that make fluorine such an exceptional pharmacological modulator also obstruct its selective introduction into complex architectures and there is a constant need for expanding the repertoire of fluorination methods and versatile fluorinated building blocks.[1]

One very long standing challenge is the enantioselective incorporation of fluoroacetate into organic molecules. Acetate itself is one of the most fundamental building blocks in nature and organic synthesis, and aldol reactions of acetate derivatives are reliable tool to access polyketide architectures. Catalytic asymmetric aldol reaction of fluoroacetate would therefore enable the controlled incorporation of fluorine at defined positions within the medicinally important compounds, thus enhancing their activity and improving their properties.

We have developed an efficient and chromatography-free synthetic pathway to novel fluoromalonic acid halfthioesters **1** (FMAHTs),[2] which serve as masked fluoroacetates in an aldol reaction. Broad range of aldehydes reacted with FMAHTs under mild organocatalytic conditions, making long sought-after, fluoroacetate aldol products **2** accessible in an enantioenriched form for the first time.[3] To demonstrate the practical utility of our methodology we prepared a fluorinated-derivative **3** of one of the current drugs, which is prescribed to treat hypercholesterolemia. Such derivatives with fluorinated side chain have so far not been accessible but were proposed to enhance the activity.[4] Indeed, we observed a boost in HMGR inhibition by the introduction of fluorine into this particular position.



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HIERARCHICAL ZEOLITES: A GREEN ALTERNATIVE TO CONVENTIONAL FRIEDEL-CRAFTS ACYLATION OF HETEROAROMATICS

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Friedel-Crafts acylation is an important industrial reaction to produce reaction intermediates of pharmaceuticals, fragrances, dyes, flavors and agrochemical products. Traditionally, this reaction is performed at high temperatures with large amounts of homogenous catalysts, such as $AlCl_3$ and $FeCl_3$ that are harmful to the environment. Zeolites are proposed as alternative catalysts[1], however, the purely microporous nature of these materials limits its application due to mass transfer limitations and accessibility to the active sites. The use of hierarchical zeolites, possessing two levels of porosity, the native micropores and an additional mesopore system, is a promising solution.

In this study, three commercial zeolite structures, BEA (Si/Al=12.5), MOR (Si/Al=10) and MFI (Si/Al=15), were submitted to desilication treatments with NaOH using previously optimized protocols.[2] In some cases, a subsequent acid treatment with HCl was made. The XRD diffraction patterns showed that the modified materials preserve the crystallinity whereas the low temperature N_2 adsorption isotherms revealed the development of mesoporosity. The catalytic behavior was investigated in the acylation of furan by acetic anhydride (molar ratio 1:5), using 150 mg of zeolite sample, at 60 ºC. The reaction mixture was analyzed by GC and the results are expressed as yields of 2-acetylfuran *vs.* reaction time. When comparing the three zeolite structures, higher yields were obtained for BEA. Fig. 1 shows the catalytic results obtained for commercial (BEA), desilicated (BEA_D) and desilicated + acid treated (BEA_D/AT) samples.

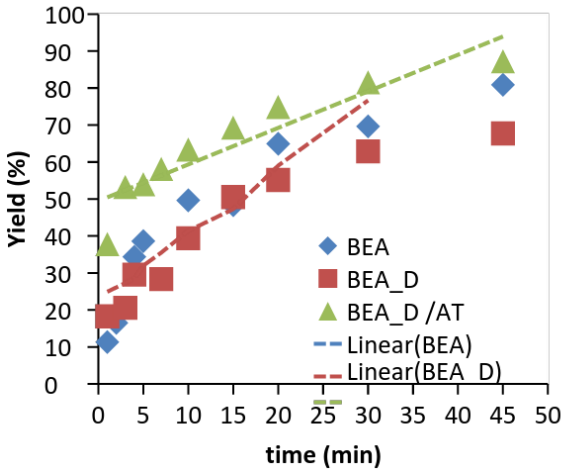

Figure 1. Yield of 2-acetylfuran *vs.* reaction time.

The results obtained show that the desilication treatment is not enough to improve the catalytic behavior (BEA_D) due to possible deposition of extra-framework species deposited at the pore mouths of the zeolite. These species are removed upon acid treatment (BEA_D/AT) improving the mass transfer and the access to the active sites, with consequent higher yield of 2-acetylfuran.

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MECHANISTIC INVESTIGATIONS AND KINETIC MODELLING OF THE DIRECT ALKYLATION OF BENZYLIC AMINES REVEAL A SURPRISING ROLE OF K_2CO_3

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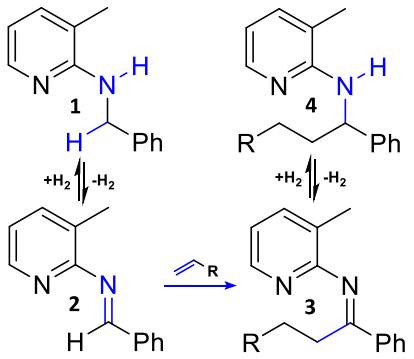
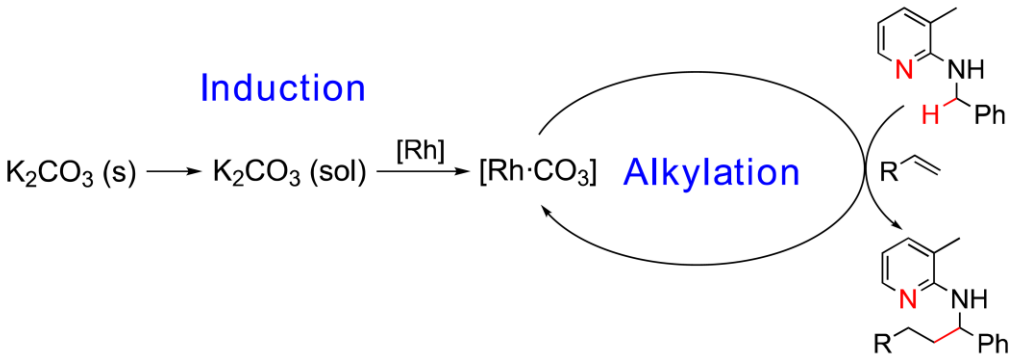
Within this work a Rh(I)-catalyzed direct C-H alkylation of benzylic amines with alkenes co-catalyzed by K_2CO_3 was studied as a benchmark reaction to gain insight into the main kinetic influence factors associated with heterogeneous bases in metal-catalyzed reactions and to elucidate one of the associated underlying reaction mechanisms. Even though formally an C(sp^3)−H activation, this reaction actually proceeds via imine intermediates and, hence, via C(sp^2)−H activation. To proof this hypothesis, series of synthetic experiments were carried out which allowed us to show that the formation of **4** from **1** actually proceeds via intermediates **2** and **3**, which are interestingly detected only in trace amounts in the reaction mixture.[1]



Additionally, to get further insight into the reaction mechanism, kinetic experiments were carried out using the method of initial rates. There, an interesting influence of the base was observed showing that K_2CO_3 is actually only needed at the beginning of the reaction to form a catalytically active species. However, the reaction rate is dependent on the amount and on the source of base, respectively its specific surface area, to some extent, which will be elaborated in this contribution. Furthermore, the reaction shows a primary kinetic isotope effect of 4.3 at the benzylic C−H position together with a reversible H−D exchange at the same position, which indicates that there are at least two distinct steps in which the corresponding C−H bonds are broken. The presented transformation shows an interesting side product profile as well, indicating that the catalyst is not only capable of activating C-H but also C-C bonds. Based on our results we were able to propose a kinetic model of this direct alkylation which is in agreement with all our experimental findings.



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TIN(IV)TRIFLIMIDATE $Sn(NTf_2)_4$: A MAGIC LEWIS SUPER ACID FOR THE CHALLENGING DIRECT α-AMIDOALKYLATION OF KETONES AND ALDEHYDES

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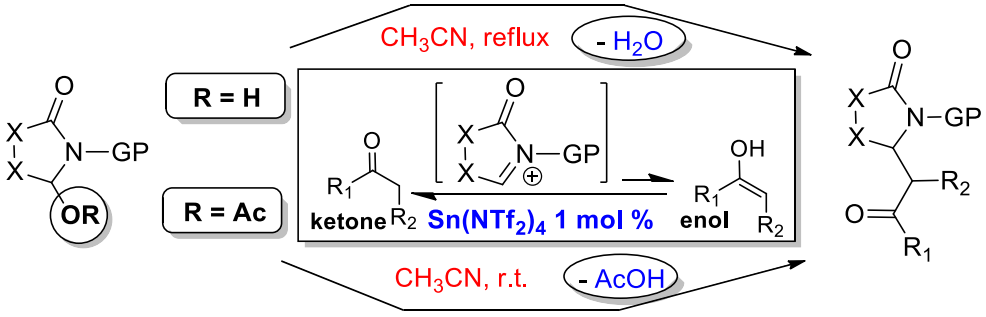
The development of catalytic S_N1-type direct alkylations of unmodified donor carbonyl components (ketones and aldehydes), belongs to the current topics of high interest in contemporary organic synthesis.[1] Unquestionable breakthroughs have recently been achieved in this field notably by enantioselective organocatalysis,[1] however, severe limitations still persist with most of the known methodologies specifically addressing highly and well activated pro-electrophiles that afford strongly and well stabilized carbenium intermediates. The extension to more challenging pro-electrophiles *i.e.* precursors of more reactive carbenium intermediates, such as heteroatom-stabilized carbocations, *viz.* oxonium ions[2] and *N*-acyliminium ions[3] is quite rare. Owing to our continuous interest in developing catalytic methods in *N*-acyliminium ion chemistry,[4] we became attracted to investigate a catalytic direct Mannich type reactions of N,O-acetals with ketones and aldehydes.

This work details our efforts in this endeavor, which have led to the development of two complementary *room temperature* and *thermal* catalytic direct α-amidoalkylation of ketones and aldehydes using 0.5-2 mol % of the Lewis superacid reagent $Sn(NTf_2)_4$ as an optimal catalyst. The two approaches are based on a rational design that itself builds on an empirical reactivity scale of both subset of reaction partners, which we have established in an preliminary optimization study. The room temperature protocol addresses mainly the combinations of the most reactive ketones and *N*-acyliminium ion precursors (typically ***acetoxy lactams*** rather than alkoxy lactams and hemiaminals), whereas the thermal version is useful for the most stimulating couplings of least nucleophilic ketones with the less reactive hemi aminals (***hydroxy lactams***), while additionally showing improvement of the step and atom-economy with release of water as the by-product.



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NOSYLATE DERIVATIVES IN PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

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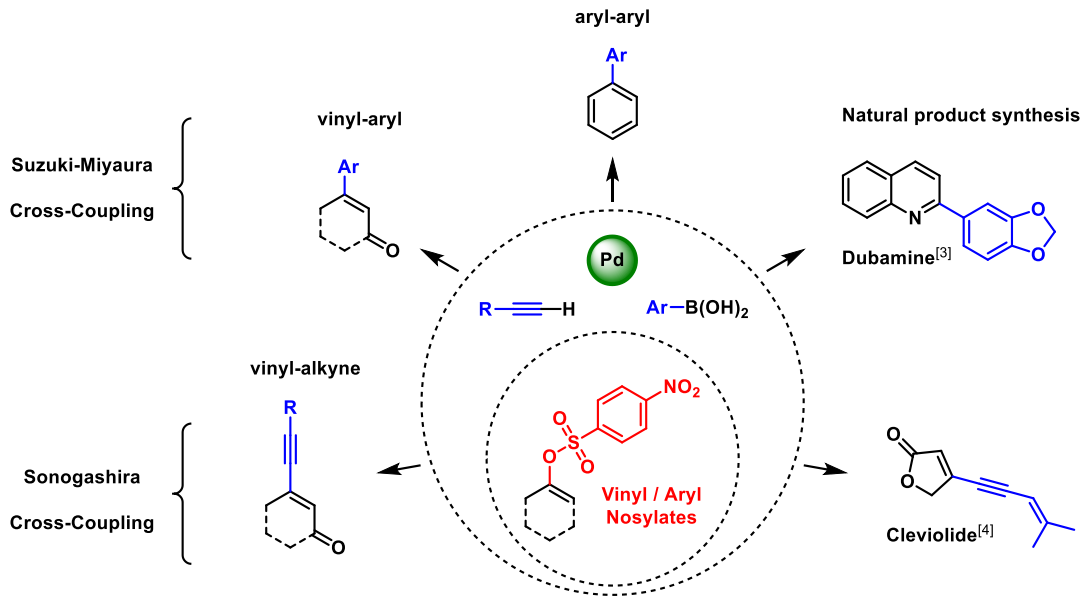
Palladium-catalyzed cross-coupling reactions are one of the most popular and powerful transformations able to build carbon–carbon bonds or carbon–heteroatom bonds. They have been extensively used since their discovery, even in industry. To reach this popularity, the cross-coupling processes were constantly modified and improved. In our Laboratory, we focused our efforts on the development of a novel leaving group – nitrobenzenesulfonates (nosylates) – and we demonstrated that they exhibit all the required properties to be engaged in various palladium-catalyzed cross-coupling reactions.[1] This preliminary study showed that nitrobenzenesulfonates are a stable and an inexpensive leaving group that allows for rapid and very efficient transformations in mild conditions with excellent yields. Nowadays, this electrophilic partner is a useful alternative to other sulfonate derivatives most commonly used.

In this communication and in the continuity of our work, we describe in more detail the scope and the limitations of the preparation of nosylate derivatives and their use in Suzuki–Miyaura[2] and Sonogashira cross-couplings.



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ONE POT PROTECTION OF DISACCHARIDES CATALYZED BY IRON(III) CHLORIDE AND APPLICATION TO A TRISACCHARIDE

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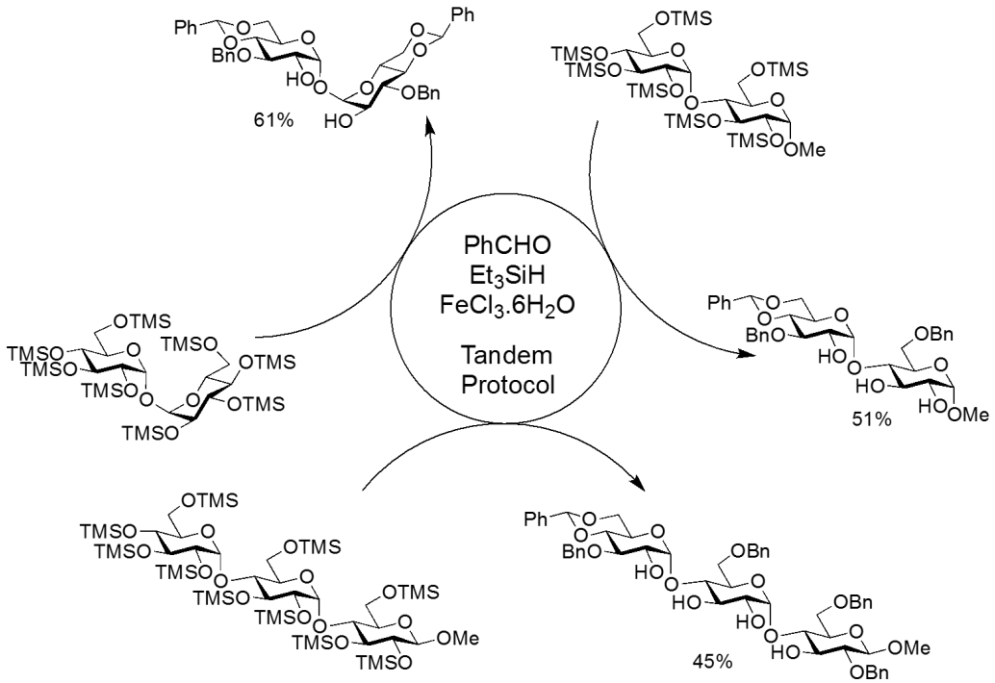
In the last decade, interest in one-pot procedures for the synthesis of complex bioactive compounds has grown dramatically.[1] Among these procedures, tandem protocols are very attractive, by limiting the time-consuming isolation and purification steps of intermediates and are of major importance in carbohydrate chemistry. We have recently reported such procedures for the regioselective and orthogonal protection of D-glucose derivatives, catalyzed by Lewis acids, based on acetalation and reductive etherification.[2] In these studies, we found $FeCl_3.6H_2O$ to be the most effective catalyst for the regioselective protection of disaccharides, with the example of the C_2 symmetric trehalose.[2b, 3] We will present more extensive results employing the $FeCl_3.6H_2O$-catalyzed tandem protection to non symmetric dissaccharides and will report one example of regioselective protection of a trisaccharide.



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SIMPLE HETEROARENIUM SALTS: ORGANOCATALYTIC TOOL FOR ACTIVATION OF HYDROGEN PEROXIDE IN OXIDATIONS

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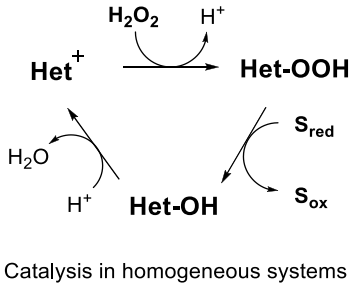
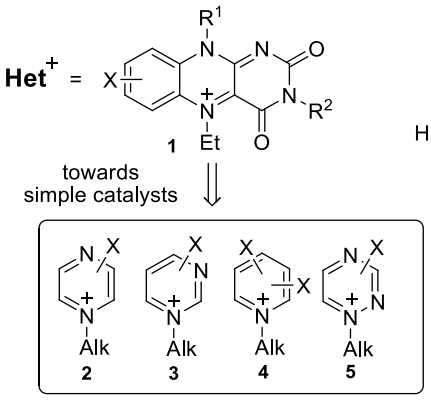
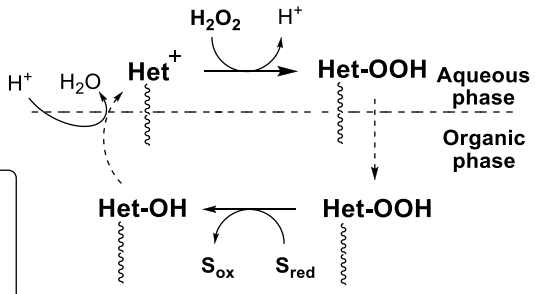
Hydrogen peroxide is an inexpensive and environmentally benign oxidizing agent producing water as the only by-product.[1] Despite its high oxidation potential, hydrogen peroxide requires activation for most reactions with organic substrates due to relatively high activation barriers. Various catalytic systems for oxidations with hydrogen peroxide have been developed; the majority of these are based on transition metal complexes forming peroxo metal species with significantly higher reactivity.

Biomimetic oxidations utilizing flavin-hydroperoxide formed *in situ* from the corresponding flavinium salt **1** and hydrogen peroxide belong among efficient organocatalytic procedures used for various types of oxygenations, namely sulfoxidations, *N*-oxidations, Baeyer-Villiger oxidations, hydroxylations of arylboronic acids or even insertion of oxygen into methyl-rhenium bond.[2] Recently, we have found that the ability to form reactive heterocyclic hydroperoxides is general property of electron-defficient heteroarenium salts, e.g. simple salts **2 – 5**, which thus can act as efficient oxidation catalysts.[3,4] The catalytic efficiency of heteroarenium salts strongly depends on the structure of heteroaromatic nuclei, type and position of substituents, alkyl group and counter-anion. This new concept for hydrogen peroxide activation and investigation of structure vs catalytic activity relationship among heteroarenium catalysts will be presented with the regard to the applications in chemoselective and stereoselective sulfoxidations. We found amphiphilic homologues of heteroarenium salts can act as catalysts in two phase oxidations[5] as they i) activate hydrogen peroxide and ii) enable peroxide species to achieve lipophilic substrate in organic phase. This new concept of PTC in oxidations will also be discussed.



Catalysis in homogeneous systems





PTC catalysis with amphiphilic salts

Aknowledgements: This work was supported by the Czech Science Foundation (reg. No. P207/12/0447).

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SYNTHESIS OF N-ACYL HYDRAZONES WITH ANTITUMORAL ACTIVITY THROUGH NHC CATALYSED MANIPULATION OF 5-HYDROXYMETHYL FURFURAL

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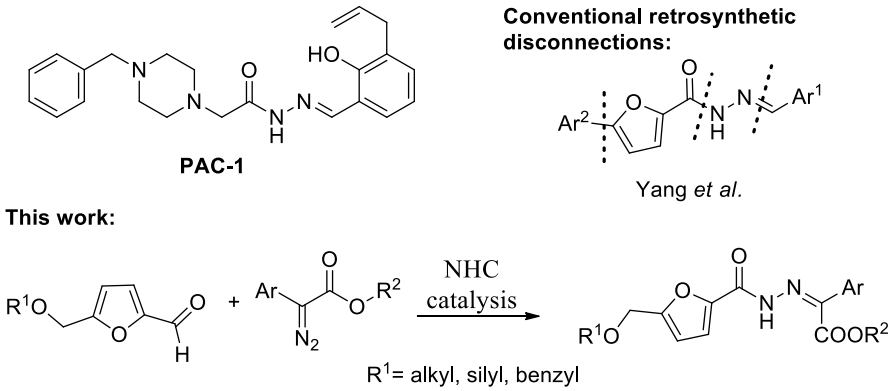
Small organic molecules having hydrazones moieties have been shown to have biological activities, such as antimicrobial, anti-inflammatory, antiviral and antitumoral activities.[1] An example is the N-acyl hydrazone PAC-1 (Scheme 1) that advanced for clinical trials as a potential antitumoral agent that induces apoptosis, through the activation of procaspase-3 enzyme interfering in the zinc-mediated inhibition pathway. The rational for this mechanistic mode of action is due to the presence of phenol as a Lewis basic site, which allows coordination to zinc ions.[2]

The most widely used method for the synthesis of N-acyl hydrazones involves a multi-step synthesis that culminates in the condensation of aldehydes or ketones with N-acyl hydrazides (as shown in the retrosynthetic disconnections, scheme 1). Herein, it is described our findings regarding the use of N-heterocyclic carbenes as suitable organocatalysts to transform directly HMF and its derivatives directly into N-acylhydrazones, via a nucleophilic *umpolung* addition of aldehydes to diazo compounds (Scheme 1). This methodology gave access to a sample library of N-acyl hydrazones incorporating 5-hydroxymethyl furfural moiety with potential antitumoral activity. The presence of several oxygen atoms in the HMF moiety offers the possibility for zinc coordination, hence the biological activity was evaluated in human cancer cell lines from breast (MCF-7), lung (NCI-H460) and colon (HT-29) origin.[3]



Scheme 1. Known N-acyl hydrazones with antitumoral activity and usual retrosynthetic disconnections vs the use of NHC organocatalysis in the synthesis of novel HMF-based N-acyl hydrazones.

Acknowledgements: Trindade thanks to FCT for funding (SFRH/BPD/73932/2010, PTDC/QUI-QUI/119823/2010, RECI/CTM-POL/0342/2012).

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COMPARISON OF ALLOXAZINE AND DEAZAFLAVINE CATALYSTS IN VISIBLE LIGHT [2+2] PHOTOCYCLOADDITIONS

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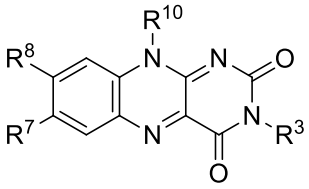
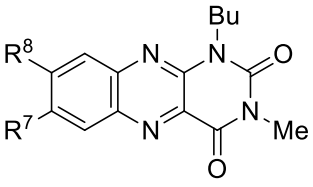
1-Butyl-7,8-dimethoxy-3-methylalloxazine (**2**), derivative of natural flavins[1] **1**, was shown to allow an efficient cyclobutane ring formation by an intramolecular [2+2] cycloaddition of both styrene dienes, considered as electron-rich substrates, and electron-poor bis(arylenones), presumably proceeding by an energy transfer mechanism.[2] Thanks to its versatility and its utilisation of a combination of photoactive organocatalyst and visible light, the system with flavin **2** distinguishes itself from those already published for visible light [2+2] photocycloadditions which are still mostly the domain of noble metal complex photocatalysts.[3] We found also other alloxazine derivatives (e.g. **3**) and deazaflavines (e.g. **4** and **5**) are able to mediate photocycloadditions by similar way. The catalysts will be compared with regard to the efficiency, substrate scope and stereoselectivity.



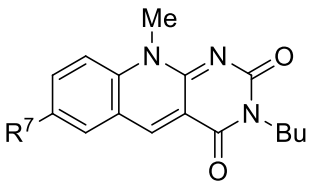
flavins (isoalloxazines)

1: R^3 = H, R^7 = R^8 = Me, R^{10} = $CH_2(CHOAc)_3CH_2OAc$, λ_{max} = 441 nm



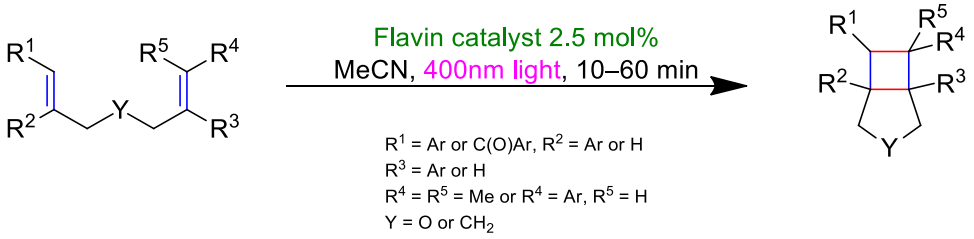
alloxazines

2: R^7 = R^8 = OMe, λ_{max} = 391 nm
3: R^7 = R^8 = H, λ_{max} = 380 nm



deazaflavins

4: R^7 = H, λ_{max} = 400 nm
5: R^7 = Br, λ_{max} = 409 nm



Aknowledgements: This work was supported by the Czech Science Foundation (reg. No. 14-09190S).

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SYNTHESIS OF TRIFLUOROMETHYLATED ALLENES BY GOLD-CATALYZED HYDRIDE SHIFT

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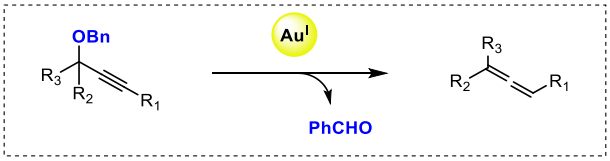
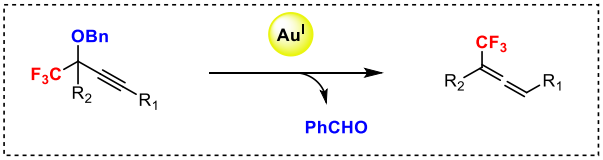
Trifluoromethylated compounds have gained a considerable interest during the last years, due to their application in medicinal chemistry and in agrochemistry. Thus, many methods were developed to incorporate a trifluoromethyl group in molecules.[1]
Besides, allenes are useful intermediates in organic synthesis thanks to their stability in standard conditions and their reactivity towards several functional groups. Thus, trifluoromethylated allenes are interesting potential trifluoromethyl-containing reagents in order to synthetize various fluorinated moieties. To our knowledge, only a few methods allow the synthesis of such allenes.[2]
Recently, Gagosz described the 1,5-hydride transfer on benzylated propargylic alcohols to synthetize substituted allenes through a gold-catalyzed cationic mechanism (Scheme 1).[3] Although the scope of the reaction was widely studied, the application of this reaction on trifluoromethylated analogues hasn't been investigated yet.



Scheme 1. Gold-catalyzed hydride transfer to access allene moieties

Herein, we describe the synthesis of trifluoromethylated allenes with this methodology, allowing the transformation of easily accessible trifluoromethylated benzylated propargylic alcohols into trifluoromethylated allenes (Scheme 2). The optimization and the scope of the reaction are presented, such as the potential reactivity of the obtained allenes.



Scheme 2. Synthesis of trifluoromethylated allenes using gold catalysis

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ORGANOCATALYTIC BIOMIMETIC APPROACH TO α-AMINOPHOSPHONATES

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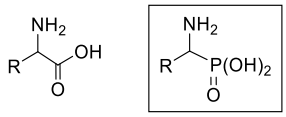
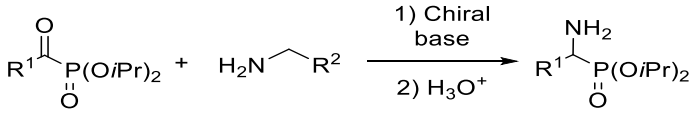
α-Aminophosphonates and α-aminophosphonic acid as an isoelectronic analogues of the corresponding α-amino acids have received considerable interest over the years.[1] They have been isolated from natural sources and exhibit significant biological activity such as antibacterial, anti-viral, antifungal or anticancer.[2]



As a consequence, they have been a target of numerous synthetic endeavors and several routes for their preparation have been established.[3] Since the biological activity of α-aminophosphonic acids and their derivatives is related to the absolute configuration of the stereogenic center located at the α-position to the phosphorus, enantioselective methods of their preparation are of great importance.[4]
Herein, we report a novel biomimetic[5] approach to biologically relevant α-aminophosphonates **3** using readily available acyl phosphonates **1** and amine **2** as starting materials. The developed synthetic strategy benefits from the high efficiency, and the optically active target products are obtained in a highly enantioselective manner.



1 **2** **3**

Aknowledgement: This work was realized within Lider programme from the National Center for Research and Development, Poland (NCBR, grant number LIDER/01/87/L-3/11/NCBR/2012).

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NEW ENANTIOSELECTIVE STRATEGIES FOR THE SYNTHESIS OF α,α-DISUBSTITUTED α-AMINO ACID DERIVATIVES

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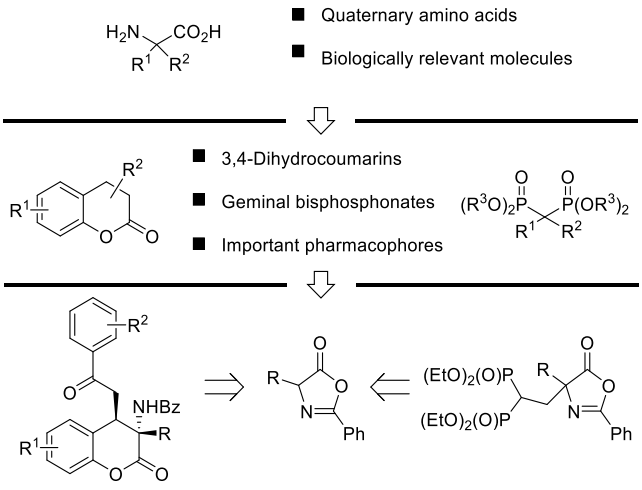
Quaternary amino acids constitute an interesting group of biologically relevant molecules widely employed in the target-oriented synthesis.[1] In recent years intensive development of methods for the synthesis of optically active α,α-disubstituted α-amino acids is observed.[2] α-Substituted azlactones constitute an important group of quaternary amino acid precursors that have found widespread applications in a contemporary organic synthesis.[3] Geminal bisphosphonates and 3,4-dihydrocoumarin moieties are privileged structural motives in medicinal chemistry and development of methods for their stereoselective preparation is receiving increasing attention of the chemical community.[4,5]
Herein, we report our studies on the synthesis quaternary amino acids containing either 3,4-dihydrocoumarin or geminal bisphosphonate structural motives incorporated.[6,7] Michael addition of α-substituted azlactones to tetraethyl ethene-1,1-diylbis(phosphonate) and 2-hydroxychalcone constitutes a key step in the developed synthetic strategies. Main benefits of the approaches relate to their high efficiency and operational simplicity.



Aknowledgements: The research was realized within the Lider programme from the National Center for Research and Development, Poland (NCBR, grant number LIDER/01/87/L-3/11/NCBR/2012).

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ORGANOCATALYTIC APPROACHES TO α-ALKYLIDENE-KETONES AND LACTONES

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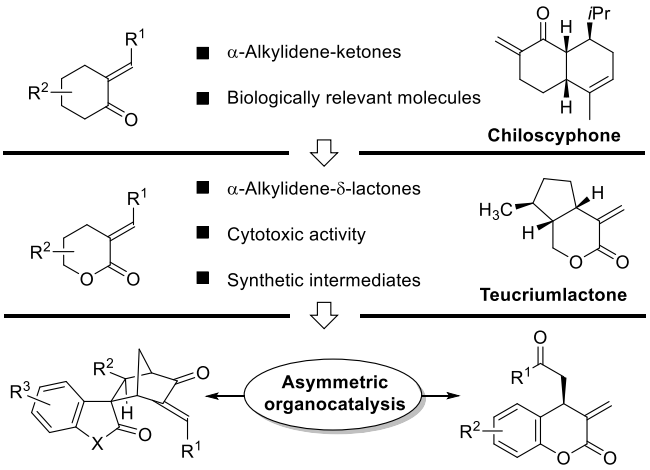
α-Alkylidene-ketone and lactone framework constitutes a privileged scaffold present in numerous natural products and pharmacologically active compounds.[1] Chiloscyphone,[2a] a naturally occurring sesquiterpene or Teucriumlactone are selected representatives of these classes of compounds.[2b] The synthetic relevance of α-alkylidene-ketones and lactones has been also confirmed.[3] In particular their ability to act as efficient Michael acceptors is well recognized. Given the biological activity and possible synthetic applications of α-alkylidene-ketones and lactones, the development of methods enabling their efficient preparation in an enantioselective fashion is of high importance to the chemical community.

Herein, we report novel enantioselective strategies for the synthesis of bicyclic to α-alkylidene-ketones and α-methylidene-δ-lactones.[4] The devised approaches utilize readily available chiral organocatalysts to control stereochemical reaction outcomes. Operational simplicity, efficiency and high enantio- and diastereoselectivities are the main benefits of the developed strategies.



Aknowledgements: This work was realized within the Homing Plus programme of Foundation for Polish Science, co-financed from European Union, Regional Development Fund.

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RITTER REACTION IN LIQUID SULFUR DIOXIDE

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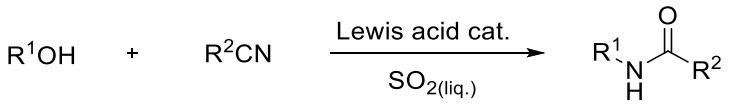
Ritter reaction is associated with a one-pot process for amide bond formation, that involves nitrile and a group, capable of giving a relatively stable carbenium ion (originally - alcohol or alkene) in strongly ionizing acidic medium.[1] The classical Ritter reaction involves use of at least stoichiometric amounts of a corrosive Brønsted acid (i.e., conc. H_2SO_4), thus often limiting its applicability to compounds containing acid labile functional groups.[2] Nevertheless, because of its atom economy and easy application Ritter reaction proved to be useful in synthesis of various biologically active molecules and drugs.[3] Over past two decades a huge progress has been made in development of catalytic variations of Ritter reaction.[4] Sulfur dioxide is not only considered to be a useful building block in synthetic organic chemistry but also can be easily liquefied to give colorless liquid, that in turn can be utilized as commercially acceptable solvent.[5] Unique characteristics of liquid sulfur dioxide ($SO_{2(liq.)}$) as a reaction medium has been previously observed.[6] One of such properties that we found particularly useful in context of Ritter reaction is the ability of $SO_{2(liq.)}$ to facilitate formation of carbenium ions.[7]
Hence we have found that the Ritter reaction proceeds well in $SO_{2(liq.)}$ (Scheme 1). Various Lewis and Brønsted acids were tested for their ability to promote this transformation in $SO_{2(liq.)}$. Reactivity of various alcohols towards Ritter reaction in our newly developed reaction conditions was also evaluated. The expected amides were obtained in good yields.



Scheme 1. Ritter reaction in liquid sulfur dioxide

Relatively low catalyst loading and activation of secondary alcohols towards Ritter reaction is a strong evidence of preferences of using $SO_{2(liq.)}$ as a solvent for transformations involving carbocation intermediates.

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GOLD(I)-CATALYZED MULTICOMPONENT [2+2+2] CYCLOADDITION BETWEEN ALLENAMIDES, ALKENES AND ALDEHYDES

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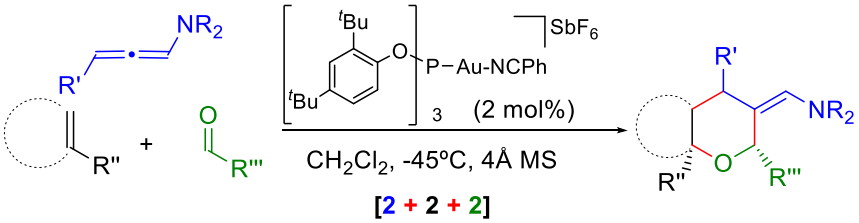
In recent years there have been extraordinary advances in the development of Au-catalyzed processes. In this context, our group has demonstrated the possibility of using allenamides as two carbon-atom components in intermolecular Au-catalyzed [4 + 2] and [2 + 2] cycloadditions with dienes and alkenes respectevly.[1] We have also developed a cascade cycloaddition between allenamides and carbonyl-tethered alkenes that affords oxabridged medium-sized carbocycles.[2]

Considering the high efficiency of the latter process, we wonder whether a fully intermolecular version involving three different π-unsaturated components could be achieved.[3] Herein we demonstrate the feasibility of such a multicomponet process, that had revealed to be highly regio- and chemoselective. The method works with different types of allenes, alkenes and aldehydes to give 2,6-disubstituted tetrahydropyrans. Additionally, we also disclosed a preliminary study of an enantioselective version.



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PHOTOCHEMICAL ENANTIOSELECTIVE β - ALKYLATION OF ENONES BY MEANS OF IMINIUM ION ACTIVATION

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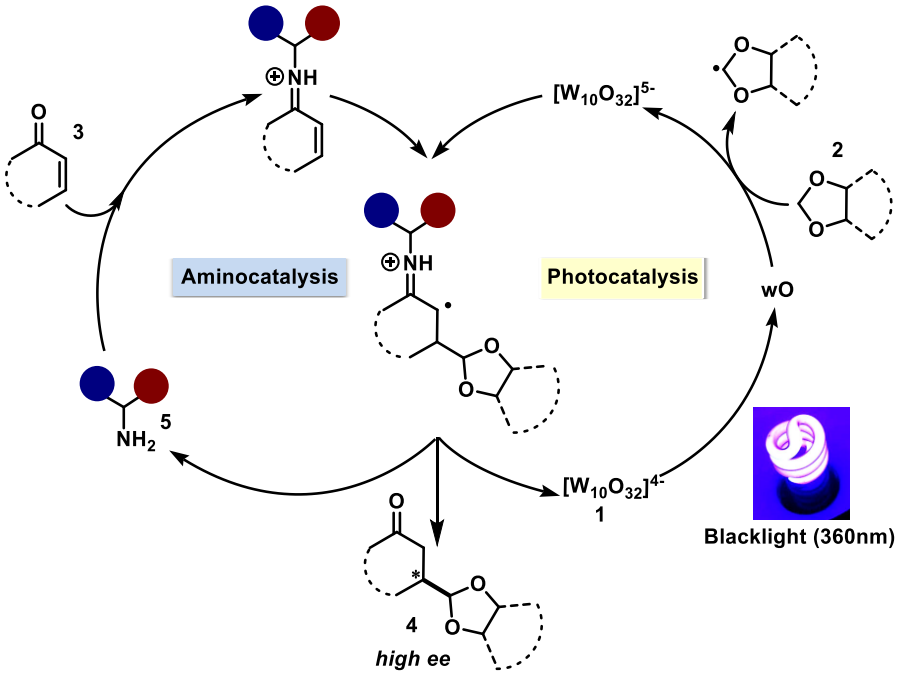
The ability of the decatungstate anion **1** to absorb UV (ultraviolet) light and produce (*via* LMCT and a short lived excited state) wO is well established.[1] This reactive species (wO) can efficiently generate alkyl radicals through hydrogen atom abstraction from alkanes.[2] Despite the extensive work in this field, an asymmetric transformation has yet to be developed.

Merging the ability of chiral amines to generate a chiral iminium ion intermediate,[3] and the ability of wO to generate alkyl radicals, we developed an asymmetric radical conjugate addition of benzodioxolanes **2** with unsaturated ketones **3**. The β-alkylated products **4** were obtained in good yield and high enantioselectivity using the tungsten-based photocatalyst **1** and a newly designed chiral aminocatalyst **5.**

The possibility of using open-shell species in combination with iminium ion activation opens up new opportunities for the design of enantioselective radical conjugate additions.



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OVERCOMING INHERENT LIMITS IN FRUSTRATED LEWIS PAIR CATALYSIS: MOISTURE TOLERANT HYDROGENATIONS

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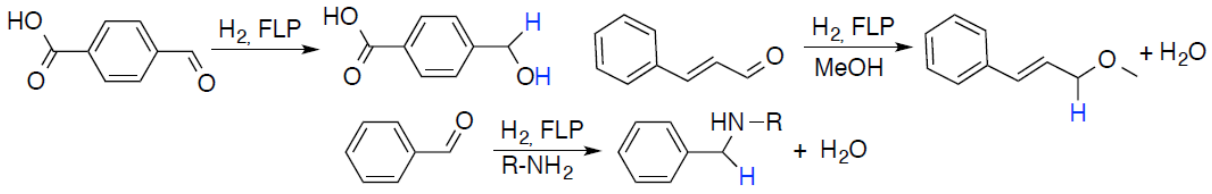
The frustrated Lewis pair (FLP) chemistry, introduced by Stephan and coworkers, is a new paradigm in small-molecule activation and catalysis.[1] This approach employs sterically encumbered Lewis acidbase pairs that impedes stable Lewis adducts formation. The FLP chemistry has actually empowered main group elements to emulate the cooperative donor-acceptor properties of transition metals, and it has significantly expanded the capacity of bifunctional, cooperative catalysis.

The FLP-catalyzed hydrogenation, a striking and emblematic application of the field, is undergoing a surge of upheaval that is largely fueled by the aspirations to develop metal-free, disruptive hydrogenation technology. Despite the many advances, the scope and practicality of FLP mediated hydrogenation still lag behind the transition metal-based strategies. Because of the appreciable, hardtype Lewis acidity of the boron center, the FLP catalyst improvement always confronts with the dilemma of substrate and/or product inhibition and moisture sensitivity. As such, the substrate scope is bounded as certain functionalities are not tolerated, and the hydrogenation process requires the rigorous exclusion of water. This restriction represents a considerable synthetic hurdle that must be overcome to realize the full potential of FLP catalysis.

So far, two key strategies have been successfully implemented to improve functional group tolerance: the mitigation of electron-deficiency of the boron center that tempers the strength of competing dative bonds,[2] and the size-exclusion approach introduced by us [3], that retards the binding to Lewis acidic center via enhanced sterical repulsion (F-strain). Although the size-exclusion developments provided Lewis acids that can markedly improve the functional group tolerance in hydrogenation, they still require rigorously dried solvents and reagents. Intrigued by the tempting prospect of moisture tolerant FLP catalysis, we have recently developed an easily accessible, bench-stable borane for frustrated Lewis pair catalyzed reduction of aldehydes, ketones and enones. The deliberate fine-tuning of structural and electronic parameters of the Lewis acidic component and the choice of Lewis base resulted in the first moisture and functional group tolerant FLP catalyst.[4] These new catalysts also allowed us to develop the first metal-free reductive alkylation and reductive amination reactions of aldehydes and ketones.[5]



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CHIRON BASED APPROACH TOWARDS THE SYNTHESIS OF 2, 5 DISUBSTITUTED PYRROLIDINES AND THEIR APPLICATIONS IN THE SYNTHESIS OF NATURAL PRODUCTS AND ORGANOCATALYSIS

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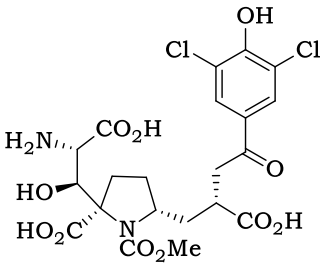
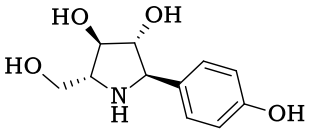
2, 5 Disubstituted pyrrolidines are key synthetic intermediates of various natural products like kaitocephalin[1] codonopsinol, preussin, radicamine etc. They are also explored as organocatalyst in asymmetric reactions. Herein we report a chiron based approach for the synthesis of 2, 5 disubstituted pyrrolidines from glutamic acid and its application for the concise and stereocontrolled formal synthesis of kaitocephalin and a number of enantiomerically pure cis/trans 5 substituted proline analogues. We have tested the synthesised molecules as organocatalyst for aldol reactions mannich reactions, α-aminoxylation of ketones and michael additions. We were successful in achieving greater stereoselectivity and efficiency than proline in many of the reactions. Our strategies and results are presented in the poster.

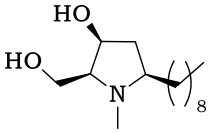
Natural products containing 2, 5 disubstituted pyrrolidine.



Kaitocephalin

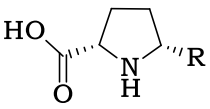


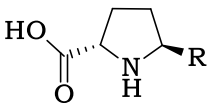
Radicamine B



(+)-Preussin

5 Substituted proline analogues synthesised as catalyst.





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ASYMMETRIC SYNTHESIS OF TETRASUBSTITUTED α-AMINOPHOSPHONIC ACID DERIVATIVES

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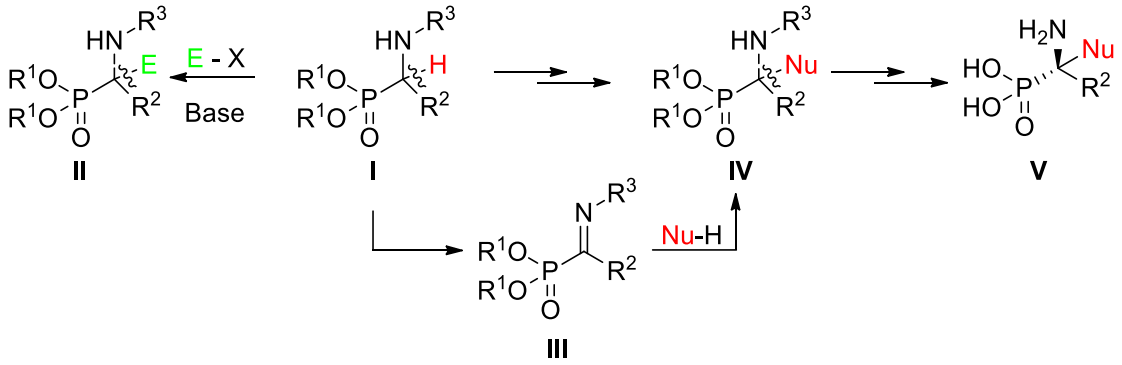
Aminophosphorus derivatives constitute a significant family of compounds in Organic and Medicinal Chemistry,[1] and interest is especially focused on the α-aminophosphonates. The biological potential of α-aminophosphonates has aroused considerable attention in the development of improved methods for their synthesis.[2] However, few alternatives have been described for the preparation of α-aminophosphonates containing tetrasubstituted α-carbons.[4]

In this context, some limited examples can be found in the literature, reporting the substitution of a hydrogen atom by an electrophilic alkyl group in a trisubstituted α-aminophosphonate **I** to afford tetrasubstituted α-aminophosphonates **II**.[3] We report in this communication a new route for the substitution of a hydrogen atom in a tertiary α-aminophosphonate by a nucleophilic reagent to obtain quaternary α-aminophosphonates **IV** which may be considered as the complementary process ("umpolung reaction") of the electrophilic substitution in the trisubstituted α-carbon of a α-aminophosphonate. This approach is very advantageous if compared to the complementary method since still allows the functionalization using, for example, nucleophilic aryl groups, not as easily available if electrophilic reagents are used.



The key step in this approach is the generation of α-ketiminophosphonates **III** through a formal oxidation of the parent α-aminophosphonates **I**. The subsequent addition of nucleophilic reagents to species **III**, applying either diastereoselective or asymmetric catalytic strategies, allows the preparation of a bunch of optically active tetrasubstituted α-aminophosphonic acid derivatives **V**.[4]

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DECARBOXYLATIVE ASYMMETRIC ALLYLIC ALKYLATION: ENANTIOSELECTIVE SYNTHESIS OF α-ARYLATED DIHYDROCOUMARIN

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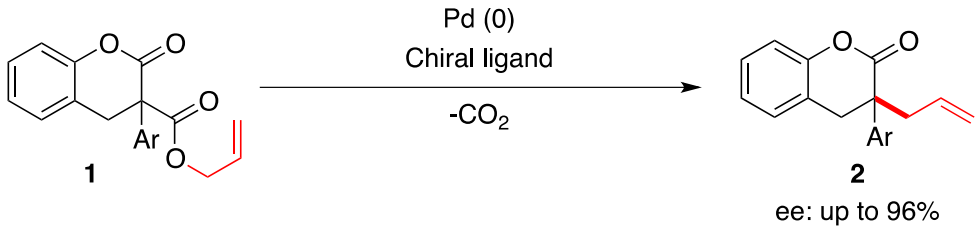
Coumarins are ubiquitous in nature and show a broad range of biological activity.[1] In the past decade, Pd-catalysed decarboxylative asymmetric allylic alkylation (DAAA) has become one of the most successful approaches for the construction of enantioenriched α-quarternary carbonyl compounds.[2,3] As part of our focus on the enantioselective synthesis of sterically hindered α-aryl carbonyl compounds within our research group,[4,5,6] we aimed to explore the DAAA of α-aryl dihydrocoumarin.



The key step in the synthesis of the susbstrate **1** is a direct α-arylation of a 1,3-dicarbonyl system using aryllead triacetate reagents. A seris of sterecally hindered aryl containing dihydrocoumarin compounds were sucessfully prepared and subjected to the DAAA reaction and the corresponding allylated products were obtained in 85-91% yields with ee's up to 96%.

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ENZYMATIC KINETIC RESOLUTION OF SECONDARY ALCOHOLS VIA AN IONIC ANHYDRIDE GENERATED *IN SITU*

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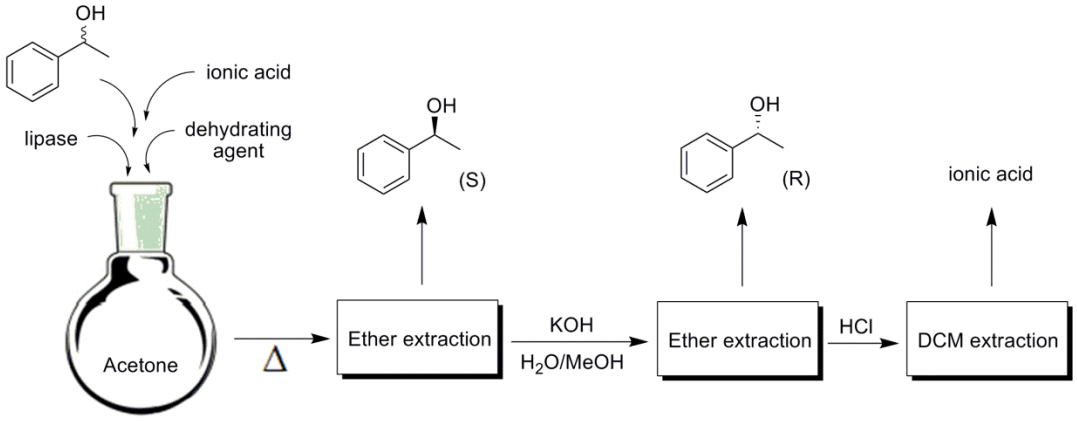
In the last decades the demand for optically pure compounds has increased tremendously, stimulated above all by the pharmaceutical industry. Among several available methods for the preparation of desired enantiomers, enzymatic kinetic resolution (EKR) is one of the most robust and practical ones. However there are some limitations, such as the need of a large excess of acylating agent to achieve the desired conversions or the production of toxic and explosive byproducts, as for instance in the case of the commonly used vinyl esters. Another limitation is the separation of each enantiomer (one as alcohol, the other as an ester). This usually requires a chromatographic step which represents a serious drawback in large scale use.[1,2]

Over the years our research group has developed several strategies that circumvent the common EKR limitations. Herein we describe our most recent work based on the use of an ionic anhydride as acylating agent. Previously we have described the synthesis of an ionic anhydride and its successful application in EKR of secondary alcohols.[3] However the anhydride synthesis/purification is time consuming and needs to be performed in close timeframe to the EKR in order to avoid anhydride degradation over time. With this in mind we explored the regeneration of the anhydride. To our delight we observed that the ionic anhydride can be prepared in situ, from the respective ionic acid and a dehydration agent, in the presence of a lipase without hampering its catalytic activity. This methodology allows the isolation of each enantiomer without any chromatographic step, and the reuse of both biocatalyst and acylating agent.



Acknowledgements: We are grateful for financial support from Fundação para a Ciência e Tecnologia (FCT) through the grant SFRH/BD/93049/2013 and the project PTDC/QUI-QUI/119210/2010.

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CATALYTIC SCANNING PROBE MICROSCOPY: HOW TO PERFORM ORGANIC CHEMISTRY WITH A MICROSCOPE

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Scanning probe (STM and AFM) nanolithography belongs to the most important methods for creation of nanoobjects on the surface with sub-100 nm resolution. It is generally based on the direct diffusion transfer (Dip-Pen nanolithography) and mechanic or electrical destruction of the surface. Recently, catalytic Scanning Probe Lithography (cSPL) has emerged as a complementary method where catalyzed chemical surface modifications were achieved using AFM probes coated with metals (Pd and Pt – azide hydrogenation[1] and alkene hydrosilylation[2]), metal oxides (Cu_2O, alkyne-azide "click" reaction[3]) and absorbed metal nanoparticles (Pd NPs, Suzuki and Heck cross-coupling[4]).

We report herein the first use of the AFM tip with immobilized homogeneous catalyst for spatially controlled epoxidation of the surface terminal alkene groups (Fig. 1).[5]

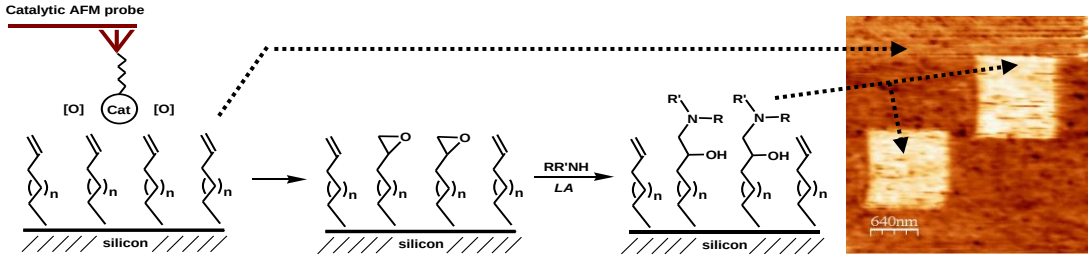

Figure 1. AFM topography image of the surface after local epoxidation of two 1 x 1 µm squares on the alkene terminated SAM followed by ring opening reaction with a secondary amine.

The local epoxidation of terminal alkene Self-Assembled Monolayer (SAM) was carried out in an oxidative liquid medium at the contact between the catalytic AFM probe and the surface. It was followed by derivatization of the resulting epoxide with a secondary amine in the presence of a Lewis acid (Fig. 1). AFM topography images showed unambiguously a well-pronounced surface growth in the epoxidized area only. The height of the objects matched with the length of the amine indicating the controlled formation of localized aminoalcohol domains on SAM. The concept used in this work could be attractive for the controlled 3D fabrication of various types of nanodevices.

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FROM FATTY ESTERS TO PEG CARBOXYLATES AS ACYLATING AGENTS – ATTRACTIVE BIOCATALYTIC APPROACHES TO OBTAIN ENANTIOMERIC PURE *SEC*-ALCOHOLS

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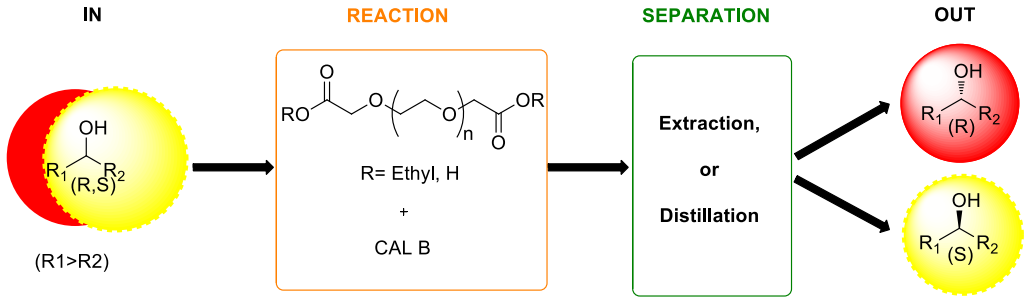
Enantiomerically pure *sec*-alcohols are important building blocks in organic chemistry, especially due to their biological relevance and versatile functional group transformation. In several cases both enantiomers are important, the resolution of racemic alcohols is an attractive approach. Our quest has been the development of appealing, competitive and more sustainable processes for the enzymatic-resolution of secondary alcohols. Consequently, our effort have been made on the development of new strategies for the one-pot resolution-separation of free sec-alcohols by the use of new acylating agents.[1] The resolution-separation is based on the selective reaction of one alcohol enantiomer with acylating agent, where one enantiomer stays in medium, leaving the other enantiomer free to be removed. The anchored enantiomer can be isolated by a second enzymatic reversible reaction. With this approach is possible to obtain both free enantiomers using only the biocatalyst and a more sustainable acylating agent. The main advantage of this approach is the possibility to overcome the limitations of the common existing technology, specifically the use of chromatography separations, the use of organic solvents and post-chemical transformations for the isolation of free enantiomers. This methodologies are quite simple, robust and reliable allowing the reuse of the medium and enzyme. Herein, is presented different strategies developed for the enzymatic one-pot resolution-separation of several sec-alcohols.



Scheme 1. Methodology for separation-resolution of secondary alcohols.

Acknowledgements: We thank Fundação para a Ciência e Tecnologia (SFRH/BPD/98053/2013), PTDC/QUI-QUI/119210/2010 and PTDC/QUI-QUI/119823/2010 for the financial support and also Novozymes and Amano enzymes for their generous enzyme supply.

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SYNTHESIS OF ETHYL 3-[4-(ARYL OR HETEROARYL)-1*H*-1,2,3-TRIAZOL-1-YL]THIENO[3,2-*B*]PYRIDINE-2-CARBOXYLATES BY A CUAAC "CLICK" REACTION

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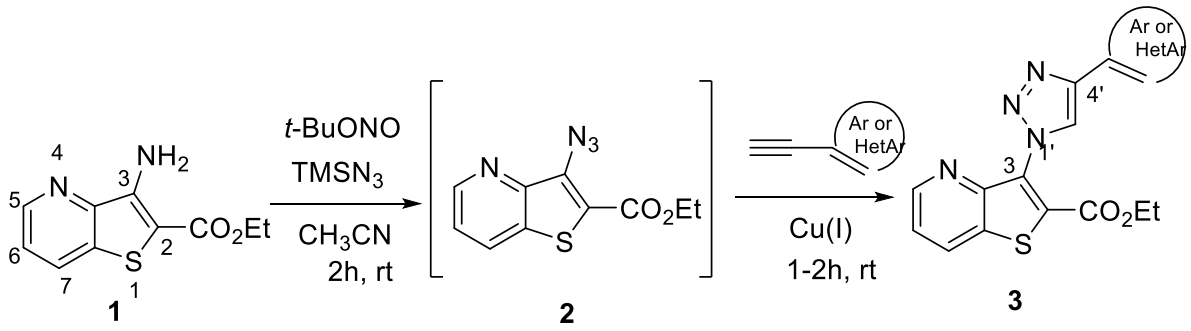
From some years now our research group has been interested in the synthesis of new thieno[3,2-*b*]pyridine derivatives, functionalized either on the thiophene or on the pyridine, that have shown to be potential antitumor compounds.[1-3] Herein we present the synthesis of 1,4-disubstituted 1,2,3-triazole linkages between the thienopyridine system in position 3 and aryl or heteroaryl compounds using a "click" reaction. These triazole derivatives are of interest for medicinal chemistry and material science.

The ethyl 3-aminothieno[3,2-*b*]pyridine-2-carboxylate (**1**) was prepared from 3-fluoropyridine-2-carbonitrile and ethyl 2-mercaptoacetate in basic medium in almost quantitative yield. The intermediate azide **2** (Scheme) was prepared reacting amine **1** with *tert*-butyl nitrite and azidotrimethylsilane ($TMSN_3$).[4] The corresponding 1,4-disubstituted 1,2,3-triazoles **3** were then obtained by a copper(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) "click" reaction (Scheme). Compounds **3** were prepared in high yields without the need of chromatographic purification, in low total reaction times (3-4h) at room temperature and using our optimized and general reaction conditions. The optimization of the reaction conditions concerning the copper species, base, additives and their amounts will be presented and discussed.



Scheme 1

Compounds **3** were fully characterized by m.p., ^{1}H and ^{13}C NMR and HRMS or Elemental Analysis. The intermediate azide **2** was isolated once and was also fully characterized.

To our knowledge it is the first time that a 1,4-disubstituted 1,2,3-triazole moiety is prepared from a 3-aminothieno[3,2-*b*]pyridine system using a CuAAC stepwise one pot procedure.

The antitumor properties of the new compounds **3** will be studied against several human tumor cell lines in collaboration with other research groups.

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PALLADIUM-CATALYSED DECARBOXYLATIVE ASYMMETRIC PROTONATION (DAP) AND ALLYLIC ALKYLATION (DAAA)

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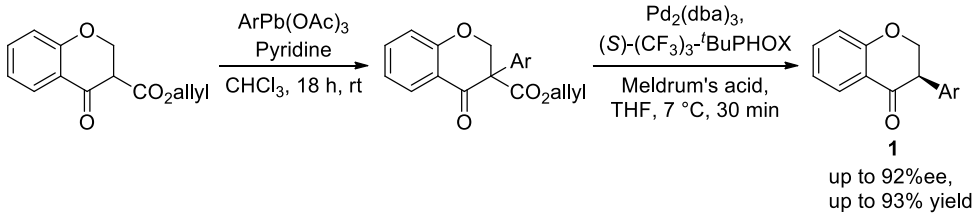
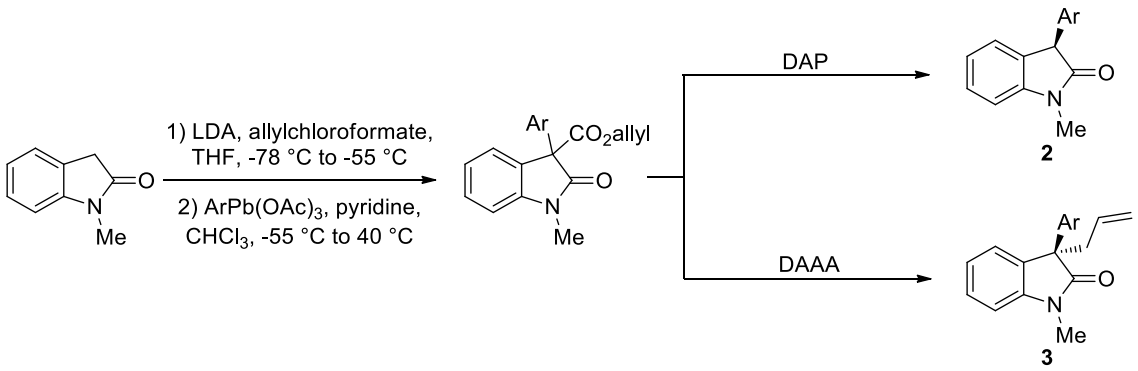
Asymmetric transition metal-catalysed transformations have emerged as a powerful tool for the generation of stereocentres on the α-position of carbonyls.[1] However, one area in which this has proved more challenging is the formation of a tertiary centre containing an aryl group, mainly due to lability of the resulting stereocentre. Recently, Stoltz reported a Pd-catalysed decarboxylative asymmetric protonation of α-alkyl and α-benzyl ketones.[2,3] Our research group has further developed this methodology to generate sterically hindered tertiary α-aryl ketones in the first catalytic asymmetric synthesis of isoflavanones **1** (Scheme 1).[4]



Scheme 1. The first catalytic asymmetric synthesis of isoflavanones **1**

Oxindoles are important scaffolds in many biologically active molecules.[5] The vast majority of these include substitution at the 3-position. The focus of the current project is to expand the decarboxylative protonation to the asymmetric synthesis of sterically hindered α-aryl oxindoles of type **2**. We also aim to investigate the influence of the steric bulk of the aryl group on the enantioselectivity of the related allylation to form oxindoles of type **3**. This poster will highlight our recent progress in this area.



Scheme 2. Catalytic asymmetric synthesis of sterically hindered α-aryl oxindoles of type **2** and **3**

References:

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IN PURSUIT OF A NOVEL IMIDATE-BASED SALEN-TYPE LIGAND CLASS

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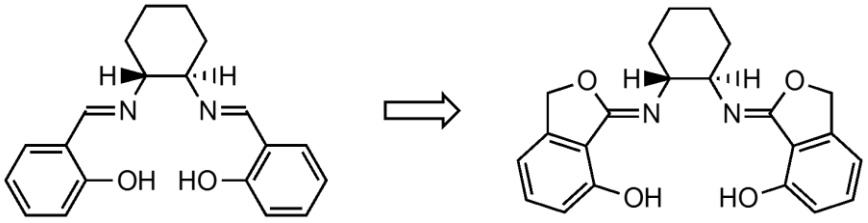
An increasing ecological awareness and global competitiveness have challenged the chemical industry towards a higher level of sustainability through innovation and technology. In research, the majority of topics on sustainable process development deals with catalysis.[1] Furthermore, in organic synthesis, transition metal catalysis already plays a vital role in the synthesis of biologically active compounds.[2]



L_1 L_2

Bisimidate ligand L_2 shows striking similarities with Salen ligands (L_1). We reasoned that this could open new opportunities for our already well-established imidate ligand family.[3] Nevertheless, the applicability of this ligand in the Mn^V-catalyzed asymmetric epoxidation reaction turned out to be more complicated than expected.

In this communication, the search towards an effective novel imidate-based Salen-type ligand class will be discussed from a ligand design point of view.

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STUDIES ON THE ALKYLATION OF OXINDOLES USING NOVEL ASYMMETRIC PHASE-TRANSFER CATALYSTS

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An oxindole skeleton bearing a *tetra*-substituted stereogenic centre at the C-3'-position is a privileged heterocyclic framework ubiquitous in many natural alkaloids and molecules of pharmaceutical interest.[1] The synthesis of these structural motifs still remains a challenge for synthetic chemists but advances have been made in recent years.[2-4] The broad therapeutic potential of the multifunctionalised chiral spirooxindoles renders them a very desirable synthetic target. Examples of pharmaceutically active spirooxindoles are presented below in Figure 1.

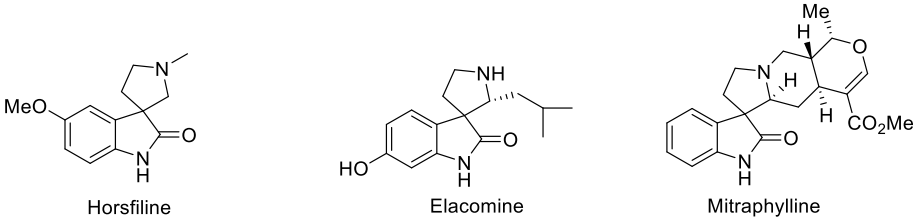

Figure 1. Pharmaceutically active spirooxindoles

In this project we aim to synthesise a diverse catalogue of oxindoles by alkylating a novel oxindole structure with a range of electrophiles. The reaction will be promoted by a new class of asymmetric phase-transfer catalysts based on cinchona alkaloids (Figure 2). We hope to learn what influences enantioselectivity in the process. We also aim to synthesise oxindoles containing a quaternary all-carbon stereogenic centre, which could be further manipulated in a subsequent cyclisation process, resulting in a facile synthesis of a spirooooxindole.

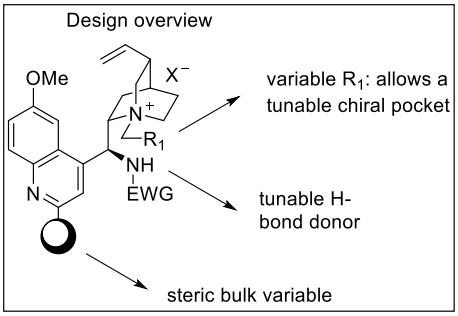

Figure 2. Catalyst design overview

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CARBOCATALYZED OXIDATIVE sp^2-sp^2 HOMOCOUPLINGS OF BENZOFUZED HETEROCYCLES

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Carbon materials, especially when partially oxidized, are known to catalyse certain reactions such as oxidative dehydrogenation of ethylbenzene to styrene.[1] Previously, we made a discovery that a heterogeneous carbon material, used initially as a gold catalyst support, had an ability to catalyse oxidative coupling of 2-aryl-indoles to 3,3'-bis(2-aryl)indoles.[2] Recently, it has been reported that *aqua regia* impregnation treatment on carbon material generates carboxylic acid groups that can act as ligands to metal nanoparticles.[3] Inspired by this, we optimized the oxidative treatment to active carbon material in respect to yield with different oxidative acid treatments. During catalyst characterisation we established a clear correlation between the catalytic activity of the studied homocoupling reaction and the amount of carbonyl functionalities on the carbon. In addition, we were able to promote oxidative homocoupling reaction of the benzofurans and benzothiofurans with stoichiometric amount of DDQ.[5] Hence, we propose that the catalytically active carbonyl groups on the oAC are in fact quinone type moieties. The study of the scope of the reaction revealed that, in addition to the indole homocoupling, oAC was able to catalyse also homocouplings 2-substituted benzofurans and benzothiofurans as well as homocoupling of 2-naphtol.[4] To the best our knowledge these are the first reported carbocatalysed C(sp^2)–C(sp^2) bond forming reactions.

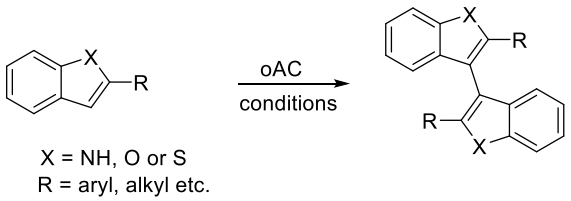

Figure 1. Carbocatalyzed 3,3'-homocoupling between 2-substituted heterocycles.

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OXIDATIVE HOMOCOUPLINGS OF BENZO-FUSED HETEROCYCLES WITH DDQ OR OXIDIZED CARBON

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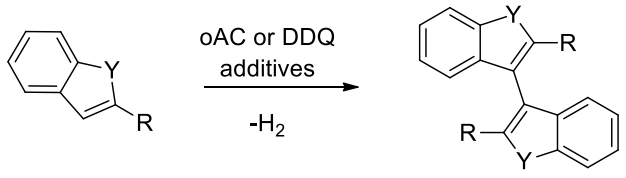
We have recently discovered that 2-arylindoles are oxidatively homocoupled to corresponding 3,3´-bi(2-aryl)indoles when heated with *aqua regia* treated activated carbon (oAC).[1]



R = various Ar and aliphatics
Y = S, O, NH, NMe

After further development of oAC we were able to improve yields compared to those originally obtained with *aqua regia* treated carbon material. Moreover, we found out that with certain additives the oxidative homocoupling can be extended to the dimerization of 2-functionalized benzofurans and benzothiofurans.[2]

During our studies we discovered that the active functional groups on oAC bear a resemblance to stoichiometric quinone type oxidants like 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). We utilized this structural analogy, and used it as a model reaction, when we investigated the homocoupling reaction mechanism with combination of experimental and computational methods.[3]

References:

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OXIDATION OF ACTIVATED CHARCOAL THROUGH ACID TREATMENTS: A SEARCH FOR AN EFFICIENT ACTIVATED CHARCOAL CATALYST FOR INDOLE – 3,3'-BIINDOLE HOMOCOUPLING REACTIONS

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Extensive research has been carried out to synthesize activated charcoal and to make oxidative post-treatments for it.[1, 2] The latter are often performed with nitric acid, which is known to produce oxygen containing functional groups on the surface and edges of the activated charcoal.[1] Generally, the activated charcoal is used as such or sometimes after oxidized treatments as a support material in heterogeneous catalysis.[3,4,5] Yet, there are only a few examples where the support itself can have some catalytic activity, even though it has been remarked that the functional groups on support could play a role in the catalysis.[3,4,6] Recently, we discovered an indole - 3,3'-biindole homo-coupling reaction that was catalyzed by oxidized activated charcoal (oAC). [5] In this study, we have further investigated the charcoal oxidation procedure and optimized it for the homo-coupling reaction. Various conditions were used for nitric acid and *aqua regia* promoted oxidations including alterations in acid evaporation conditions. The formed functional groups on the oAC were analyzed with X-ray photoelectron spectroscopy (XPS), thermogravimetric analysis (TGA) and titrimetric methods. Highest catalytic activities were observed for the oAC, when oxidizing treatments were performed with concentrated nitric acids. A comparable activity was reached with consecutive *aqua regia* treatments. Interestingly, factors like the air pressure during evaporation of acids had a profound effect on the catalytic activity and on the functional group distribution. Titrimetric methods, TGA and XPS-measurements indicated the existence of carboxylic acids, phenols, carbonyls and possibly lactones on oAC. Proof of catalytically active groups on oAC was finally received when the catalytic activity of oAC was correlated with XPS results.

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A NEW SYNTHETIC ROUTE TOWARDS SPIROOXINDOLE CORES EMPLOYING ASYMMETRIC PHASE-TRANSFER CATALYSIS

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The spirooxindoles represent a very important class of natural products, many of which possess anti-malarial and anti-tumor activity.[1] The structural feature that makes spirooxindoles highly desirable synthetic targets is the spirocyclic quaternary stereocenter at the C-3 position.[2] The selected examples of the active spirooxindoles are shown in Figure 1.

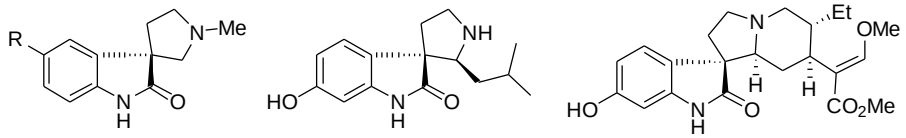

Figure 1. Representative members of spirooxindoles

Our aim is to develop a new synthetic method, combining two organocatalytic processes, i.e. traditional bifunctional asymmetric organocatalysis and phase-transfer catalysis, in the synthesis of the spirooxindole cores. The novel phase-transfer catalysts are based on the urea-derived cinchona alkaloids, which are well-known for their bifunctionality and tunability, among other advantages.[3] The synthetic route for spirooxindole core is based on the alkylation of 2-oxindole-1,3-dicarboxylate substrate with chloroacetamide in the presence of the novel phase-transfer catalyst, followed by a ring closure with subsequent reduction and deprotection, to yield a desired spirooxindole (Figure 2).

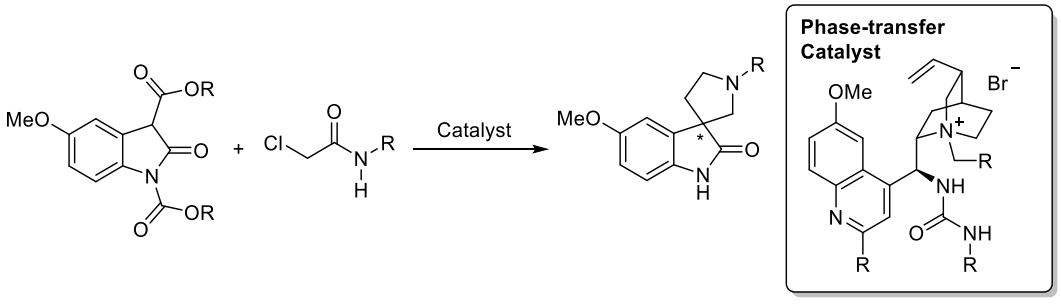

Figure 2. Design of a novel synthetic route towards spirooxindoles.

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ORGANOCATALYTIC ASYMMETRIC REACTIONS INVOLVING ENOLISABLE CYCLIC ANHYDRIDES

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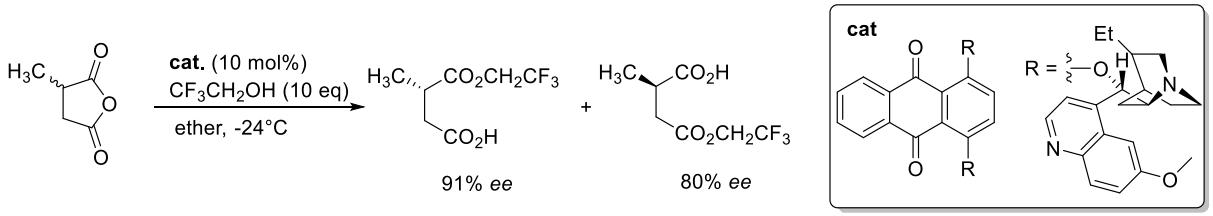
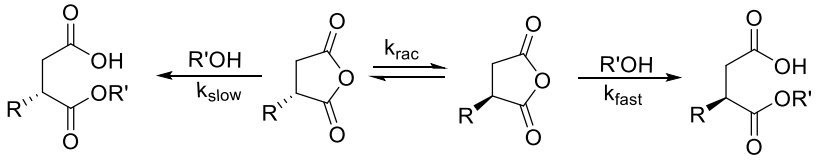
In view of the synthetic utility of optically active monosubstituted succinate monoesters,[1,2] Deng *et al*. developed a new catalytic method for their synthesis via a highly efficient parallel kinetic resolution process promoted by modified cinchona alkaloids.[3]



Our group, inspired by Deng's studies, is exploring the development of a dynamic kinetic resolution (DKR) strategy, promoted by cinchona alkaloid-derived bifunctional organocatalysts, involving racemisation of enolisable succinic anhydrides enantiomers.



Preliminary investigations were directed towards the regioselectivity of the nucleophilic addition of alcohols to enolisable anhydrides, with further studies aimed at evaluating the catalysts capability of promoting both the racemisation and the enantioselective ring-opening process.

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NEW DIRECTIONS IN THE FORMAL CYCLOADDITION REACTION BETWEEN ENOLISABLE ANHYDRIDES AND ELECTROPHILES

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We recently (2012)[1] developed the first catalytic asymmetric cycloaddition reaction between an aldehyde and homophthalic anhydride in the presence of an *ad hoc*-designed novel organocatalyst **3**, to form dihydroisocoumarin **4** structure containing two new stereocentres (Figure 1). Dihydroisocoumarins are simple derivatives of a class of natural products of considerable pharmacological activity.[2]

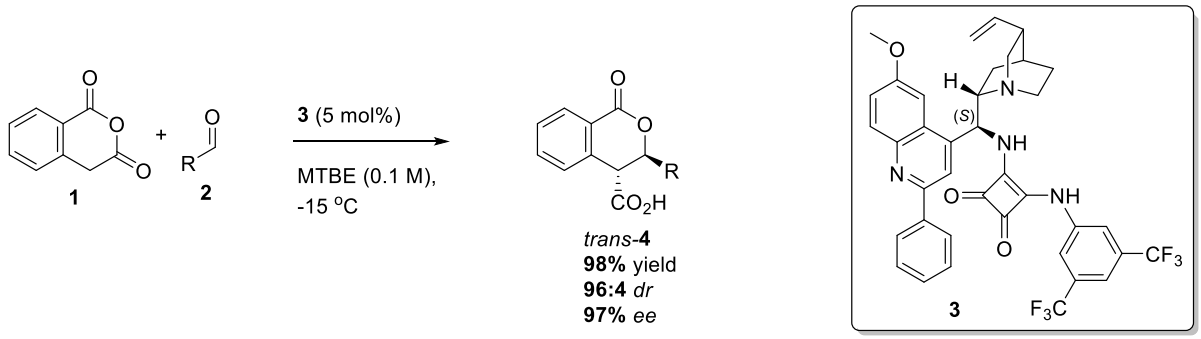

Figure 1. Preliminary studies: the first catalytic asymmetric variant (homophthalic anhydride as the enolisable anhydride)

Inspired by the successful results obtained, we are exploring a novel reaction, where a racemic *α*-branched aldehyde can be kinetically resolved by bifunctional cinchona organocatalysts, while the simultaneous formation of 3 stereocentre-containing dihydroisocoumarin acid is carried out with good diastereoselectivity and excellent enantiocontrol (Figure 2).

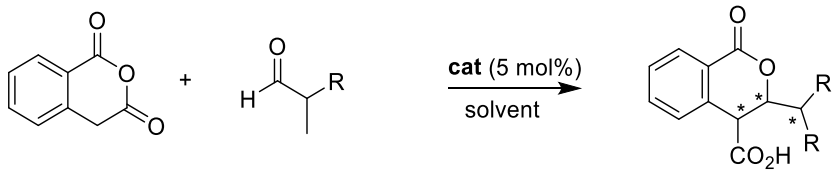

Figure 2. Cycloaddition reaction between homophthalic anhydride and *α*-branched aldehyde

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DESIGN AND SYNTHESIS OF NEW CHIRAL SO/PO BIDENTATE LIGANDS IN ORGANOCATALYSIS. A NEW APPROACH TO THE ENANTIOSELECTIVE SYNTHESIS OF BIOLOGICALLY ACTIVE CHIRAL AMINES

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Despite the historical need for and continued interest in chiral imines, their enantioselective synthesis remains a challenging task even today. In this sense, the development of new metal-free, readily available chiral catalytic systems for the enantioselective reduction of keto-imines has become an important goal in the field of asymmetric catalysis.[1] One of the organocatalytic approaches to carry out enantioselective C=N reduction involves the use of the commercially available trichlorosilane in the presence of chiral Lewis bases.

On these bases, we have synthesized a new family of chiral sulfinamide-phosphinate type **I** derivatives (figure 1) as chiral PO/SO bidentated organocatalyzers, in only two steps from the readily available enantiopure *N-tert*-butylsulfamide, (figure 1). These ligands present four diverse diversity points: the configurations at sulfur and at phosphorus, the nature of the substituent at the chiral carbon of the linker and the nature of the phosphinyl group (phosphine oxide, phosphinate or phosphonate).These ligands have been applied to the asymmetric hydrosilylation of differently substituted imines, achieving excellent chemical yields, with good to high enantioselectivities. The methodology has been successfully extended to the stereoselective synthesis of **(*R*)-NPS R568**, (figure 1), a new type of calcium receptor agonist.[2]

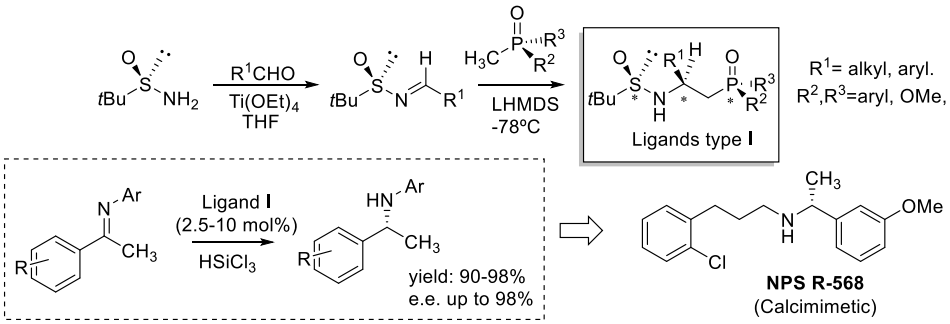

Figure 1

Acknowledgments: "Ministerio de Ciencia e Innovación" (grant Nº CTQ2013-49066-C2-2-R) and "Junta de Andalucía" (grant P11-FQM-8046).

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EXTREME HIGH-PRESSURE ACCELERATED SYNTHESIS OF NEW TRIARYLMETHANES

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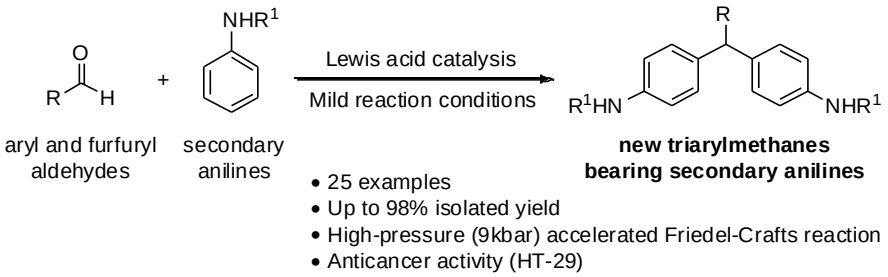
Triarylmethanes and related structures has attracted much attention in the areas of materials science and medicinal chemistry.[1] Symmetric triarylmethanes are commonly synthesized by Friedel-Crafts reaction of aromatic aldehydes with electron-rich arenes in the presence of acid catalysts at high temperatures.[1] Regarding the scope of anilines as the electron-rich arenes, the reported methodologies are mainly limited to the tertiary anilines.[2] Furthermore, the use of harsh reaction condition seems to be not compatible with acid-sensitive functional groups. Motivated by our desire to access new triarylmethanes bearing secondary anilines and acid-sensitive groups, we developed a new general and mild protocol *via* high-pressure accelerated Ytterbium-catalyzed Friedel-Crafts reaction of secondary anilines with aryl and furfuryl aldehydes, including the important biorenewable chemical platform 5-hydroxymethylfurfural (HMF)[3]. Herein we would like to present the results on the reaction conditions optimization, effect of the reaction pressure[4], reaction substrates scope, proposed mechanism based on experimental results and DFT calculations, and anticancer activity of the new synthesized triarylmethanes.[5]



Acknowledgment: We thank the Fundação para a Ciência e a Tecnologia (SFRH/BD/73971/2010 and PTDC/QUI-QUI/119823/2010), and Fundação Calouste Gulbenkian (Prémio de Estimulo à Investigação 2012) for financial support and REDE/1518/REM/2005 and the Portuguese NMR Network (IST-UTL Center) for providing access to the MS and NMR facilities.

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CATALYTIC ALKENE OXYAMINATION AND DIAMINATION WITH NITRENES

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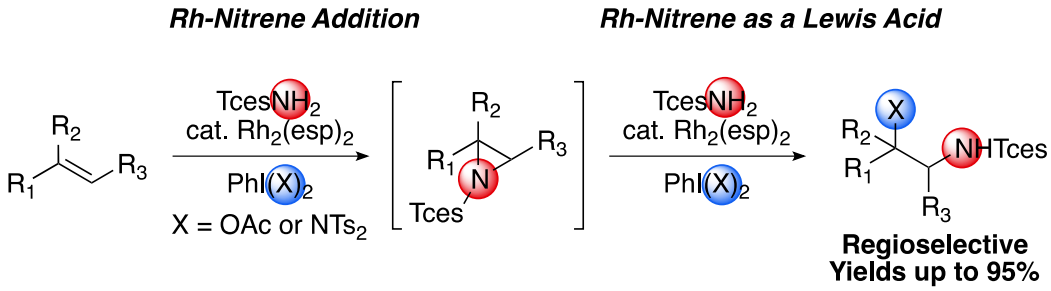
The 1,2-amino alcohol and the 1,2- diamino motifs are of utmost importance in organic chemistry. They are found in several natural products and synthetic compounds. The latter include drugs, exemplified by the recently approved antibacterial oxazolidinones, as well as the chiral ligands ubiquitous in asymmetric catalysis.[1] The prevalence of vicinal amino alcohols and vicinal diamines has been a source of inspiration for the synthetic organic chemists who have designed numerous methods for their preparation.[1,2] Alkene aminohydroxylation and diamination, in this context, provide the most direct access to 1,2-difunctionalized alkenes. Therefore, we have developed an efficient Rh(II)-catalyzed regioselective intermolecular oxyamination[3] and diamination of alkenes that provides the desired difunctionalized products in yields up to 95%. Additionally, a detailed theoretical and experimental mechanistic study revealed that this reaction involves the formation of an aziridine intermediate that undergoes *in situ* ring opening.[4] The latter is induced by an unexpected rhodium bound nitrogen species that behaves as a Lewis acid.



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CHIRAL HELICAL OLIGOTRIAZOLES AS A NEW CLASS OF ANION-ACCEPTOR CATALYSTS FOR THE ASYMMETRIC DEAROMATIZATION OF N-HETEROARENES

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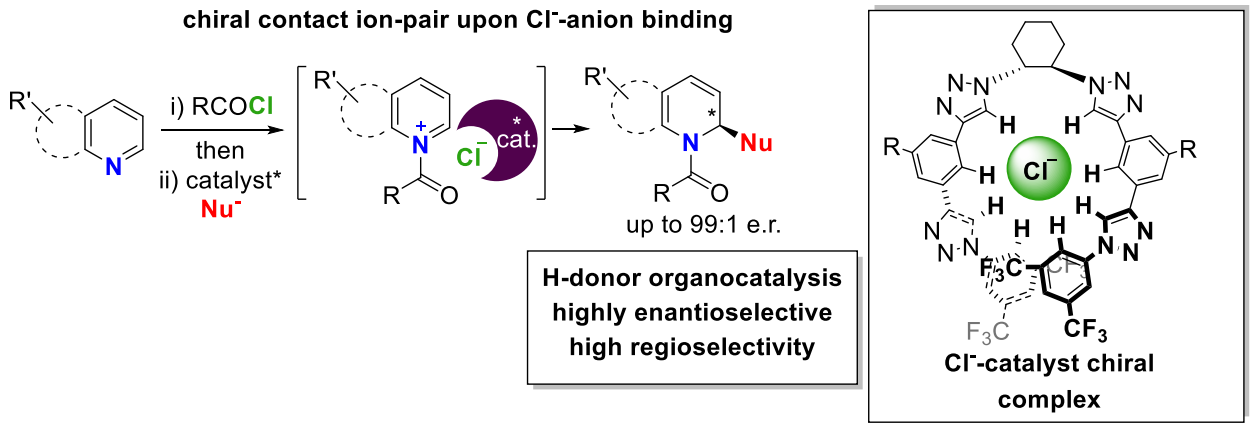
The asymmetric dearomatization of N-heteroarenes constitutes a straightforward synthetic methodology to gain bioactive and synthetic value chiral heterocycles. However, enantioselective catalytic dearomatization reactions are still rare.[1] In this regard, an interesting approach would be the use of neutral H-donor molecules as anion-acceptor catalysts.[2] However, till date essentially only chiral (thio)ureas have been efficiently employed. With the aim of providing alternative structures for anion acceptor catalysis, our group has recently developed a novel family of chiral triazoles (TetraTri) as C-H-based hydrogen donor catalysts.[3] These catalysts are able to efficiently transfer the chirality to the dearomatized products via formation of a contact chiral ion-pair complex with a preformed N-acyl ionic substrate. Herein, their outstanding performance for the asymmetric dearomatization reaction of quinolines and the more demanding simple pyridines will be presented.[3]



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METAL CONTROLLED REGIOSELECTIVITY IN THE CYCLOMETALLATION OF 2-(1-NAPHTHYL)-PYRIDINE

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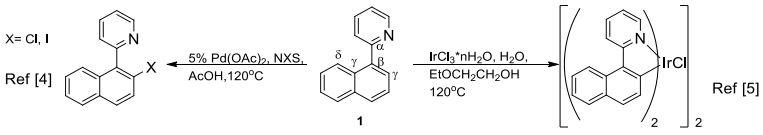
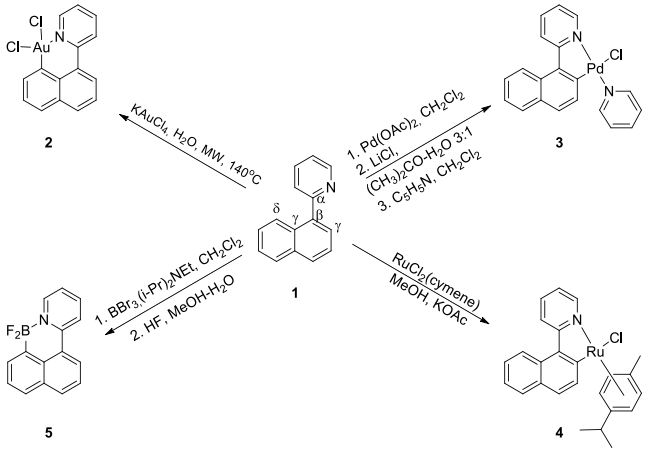
Cyclometallation is a key step in many catalytic transformations, including the reactions in the field of ligand-directed C-H activation[1]. Five-membered rings are the most common products, however, if the corresponding carbon atom is unavailable for the substitution, six-membered rings can be observed, which results in corresponding γ- and δ-selective substitutions in palladium-catalysed ligand-directed C-H activation reactions[2,3]. 2-(1-Naphthyl)-pyridine (**1**) is an interesting substrate for the cyclometallation since it contains both γ- and δ-positions available for metallation. Pd-catalysed halogenation published by Sanford[4] resulted in γ-substitution. However, the corresponding five-membered iridacycle is the only isolated metallacyclic complex of this ligand, found in literature[5].



In the course of our studies, we performed a cycloauration of **1** which resulted in an unexpected metallacycle **2** containing a six-membered ring. Cyclopalladation and cycloruthenation of **1** resulted in the formation of expected 5-membered ring-containing products **3** and **4**. Electrophilic cycloborylation with boron tribromide results in the formation of a 6-membered ring. The origins of this difference in selectivity remain unclear. Deuterium exchange studies indicate that the cycloauration and cyclopalladation are irreversible, while the cycloruthenation is reversible.



These results are promising for the development of catalytic reactions with different regioselectivities based on a choice of metal catalyst[6].

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TRANSITION METAL CATALYZED SELECTIVE 2,2,2-TRIFLUOROETHYLATION OF *N*-PYRIDYLINDOLES AND MECHANISTIC STUDY

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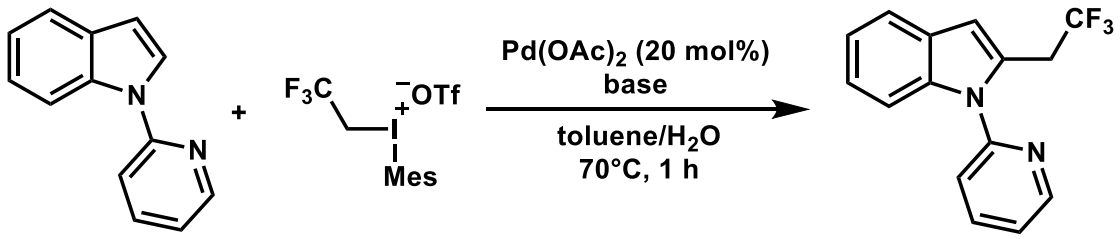
Trifluoromethyl, trifluoromethoxy and trifluormethylthio functional groups on aromatic core are often used in medicinal chemistry because of their important biological activity. However, the efficient and mild introduction of trifluoroethyl group as the desired functional group to aromatic core is still unknown. In our previous work, we have shown the mild, selective trifluoroethylation of indoles in position 3 under catalyst-free conditions. [1]

Herein, we report a novel palladium catalyzed trifluoroethylation of N-pyridylindoles using the designed aryltrifluoroethyliodonium salts. The presence of pyridine based directing group and the application of $Pd(OAc)_2$ offers the possibility to introduce the trifluoroethyl group in position 2 of the indole frame.



Several optimization studies were carried out to optimize the reaction parameters, including catalyst form, solvent, temperature and additives. The applicability of other direct groups were tested as well. Syntehtic applications of the developed methodology is also demonstrated with some examples. For the examination of the mechanism of the reaction we have prepared the complexes of the indole substrate and the catalyst.

References:

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DESIGN AND SYNTHESIS OF A PROBE AND HIGHLY BRANCHED ORGANOCATALYSTS FOR SITE–SELECTIVE TRANSFORMATIONS

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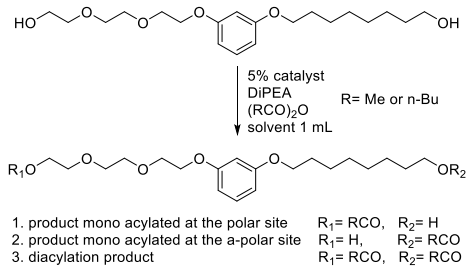
Natural products are often used as starting materials for the design of new bioactive molecules. Such structures frequently contain several very similarly reactive functional groups, and thus it can be difficult to cause only one of the groups to be functionalized selectively. The use of site-selective strategies could facilitate natural product modifications and be highly valuable in accessing semi-synthetic materials in the field of life sciences.[1,2]

Site-selective acylation organocatalysts are a promising approach for preparing derivatives of polyhydroxylated natural products. For this purpose, we synthesized a molecular probe for acylation reaction that includes two reactive sites, which are situated in different environments (polar and lipophilic). Such design allows to examine the tendency of various catalysts to perform acylation at a specific site (Scheme 1).

Following the unique structure and the dendritic effects of dendrimers, previously synthesized in our group, we envisaged using the dendritic architecture in order to create a catalytic pocket of a specified polarity that resembles enzymatic active sites in its selectivity. Thus, we conceived a catalytic system composed of a dendrimer that incorporates a polar imidazole active site in the interior and an a-polar periphery that will create a hydrophobic envelopment of this catalytic site. We presume that the polarity differences between the dendrimer regions will impact the probe access path into the catalytic pocket and, consequently, allow a preferred reaction at a particular site.

First to second generation catalysts (Figure 1) were synthesized, examined under several standard sets of conditions and compared to a simple non dendritic analogue (Scheme 1). The findings revealed a strong solvent effect that masks the polar gradient effect of the catalysts. However, we discovered that the use of an appropriate acylation reagent can intensify the latter effect, making it visible in spite of the former effect. As long as the catalytic site is enveloped by lipophilic tails the acylation of the a-polar site of the probe will be preferred.



Scheme 1

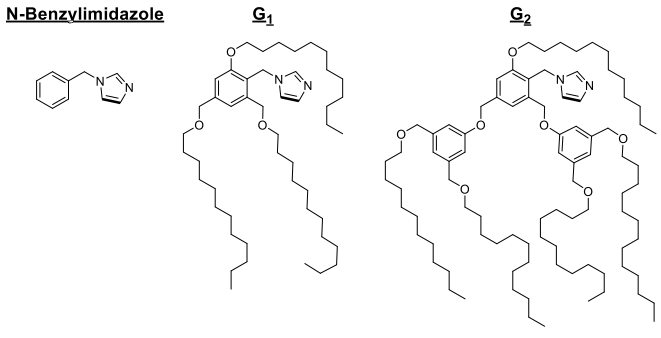


Figure 1.

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TANDEM CATALYTIC C(sp^3)-H AMINATION/SILA-SONOGASHIRA-HAGIHARA COUPLING REACTIONS WITH IODINE REAGENTS

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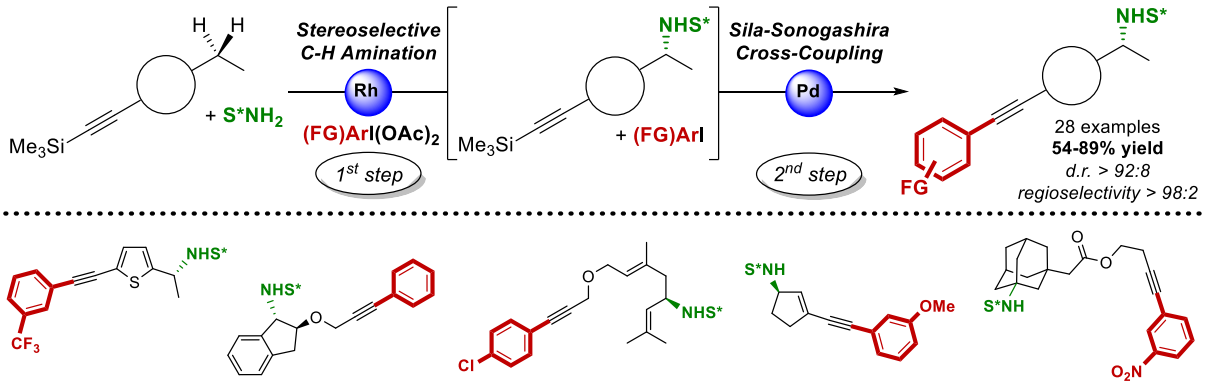
The last two decades have witnessed major developments in the chemistry of hypervalent iodine compounds.[1] Generally derived from iodobenzene, these are non-toxic and versatile reagents, which can perform selective transformations in organic synthesis.[2] Of particular relevance is the emergence of iminoiodinanes as nitrene precursors in the presence of metal complexes,[3] which has culminated in the discovery of catalytic C(sp^3)–H amination.[4] However, a key problem often associated with hypervalent iodine chemistry is the low atom economy resulting from the generation of stoichiometric amounts of iodobenzene. A sustainable solution would be to recycle the iodoarene side-product via a tandem catalysis, thus providing a rapid access to new molecular building blocks while reducing the production of waste derived from hypervalent iodine reagents. It should be noticed that such a valuable alternative has never been described in the literature, until now.

In this context, we wish to report the first example of iodoarene recycling, by a sequence of C(sp^3)–H amination/Sila-Sonogashira-Hagihara cross-coupling. The overall process first involves an iodine(III) oxidant, which generates an iodoarene by-product that is used *in situ* as a coupling partner in the second step. This sequential methodology allows the regio- and stereoselective preparation of various complex aminated molecules in good to excellent yields.[5]



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DESIGN OF 2,5-DISUBSTITUTED PYRROLIDINE CATALYSTS FOR THE ENANTIOSELECTIVE REACTION BETWEEN SILYL-KETENE THIOACETALS AND ACROLEIN: STRAIGHTFORWARD ACCESS TO CHIRAL METHYLS.

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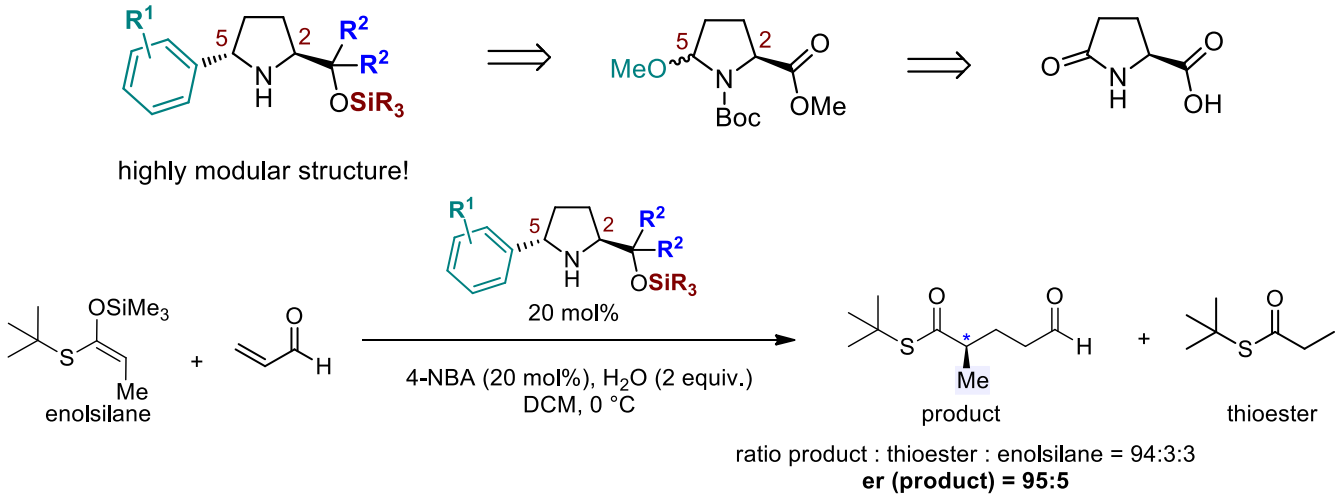
Stereocenters bearing methyl or ethyl groups are present in numerous biologically active natural products, especially those of polyketide origin. In total synthesis, these stereocenters are usually introduced by using the chiral pool or a stoichiometric amount of a chiral auxiliary (Myers and Evans alkylations, Brown crotylation…). However, practical catalytic enantioselective solutions to the "methyl stereocenter problem" have remained elusive.

In order to tackle this challenge, we have envisaged the iminium-catalyzed reaction between silyl ketene thioacetals and acrolein. The resulting thioesters can further be chemoselectively modified to generate esters, ketones, amides, and aldehydes. To control the enantioselectivity of the process, the design of a new iminium catalyst was required. Starting from readily available pyroglutamic acid derivatives, we have been able to develop a novel class of *trans*-2,5-disubstituted pyrrolidines as highly enantioselective iminium catalysts for this reaction. Systematic tuning the electronic properties of the substituents on the pyrrolidine backbone turned out to be essential for the optimization of the enantioselectivity.



Scheme 1. Synthesis of new iminium catalysts and application in the organocatalytic enantioselective reaction between silyl ketene thioacetals and acrolein.

In this presentation, the development of the methodology, the substrate scope, as well as its application to the access of valuable synthetic intermediates will be discussed.

TOWARDS A UNIVERSAL ORGANOCATALYST FOR THE SYNTHESIS OF ENANTIOENRICHED PHENYLALANINE DERIVATIVES BY ENANTIOSELECTIVE DECARBOXYLATIVE PROTONATION

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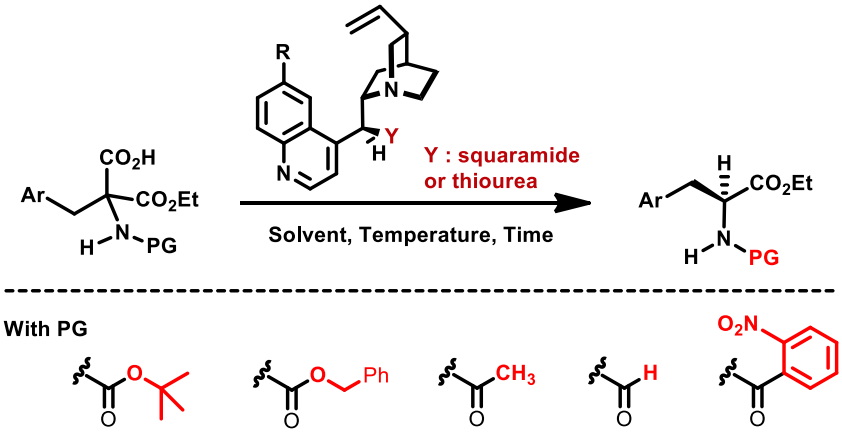
The enantioselective synthesis of amino acids is a highly developed area of research due to the ubiquity of these small molecules in natural products. Recently, our group has developed an efficient methodology to promote the formation of carbon-carbon bond or carbon-hydrogen bond by an organocatalyzed aldolisation or protonation reaction.[1] In this context, our project aims at developing a versatile access to enantioenriched non-proteogenic amino acid derivatives, using enantioselective decarboxylative protonation.

The establishment of this methodology requires the preparation of a racemic functionalized hemimalonic acid using a minimum number of steps. A chiral amine synthesized from a cinchona alkaloid will lead to an asymmetric decarboxylative protonation of these substrates. To date, thioureas derived from these alkaloids promote the decarboxylation of cyclic α-aminomalonates with good yields and excellent enantioselectivities.[2] Nevertheless, a stochiometric amount of base is required in this case. This new study aims to provide an original pathway to phenylalanine derivatives under catalytic conditions and compare the efficiency of squaramides and thioureas. This presentation summarizes our efforts to establish an enantioselective synthesis which has the advantages of being fast, efficient and flexible. A comprehensive study of reaction parameters including the nature of the *N*-protecting group (PG) is underway in the specific case of these acyclic substrates.



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ENANTIOSELECTIVE ORGANOCATALYTIC AMINATION OF PYRAZOLONES

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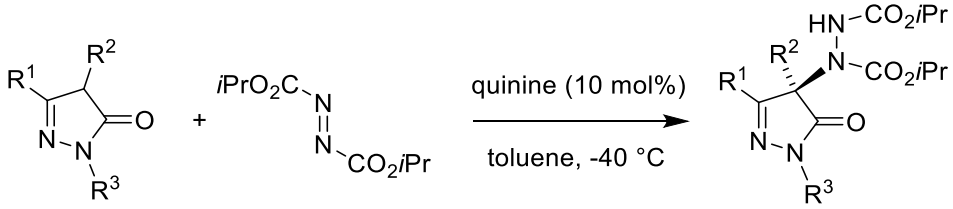
Pyrazolone derivatives are common structural motifs which exhibit a variety applications as pharmaceutical candidates and biologically active components.[1] Despite the importance of these compounds, there are a few methodologies leading to pyrazolones in asymmetric form. We have focused on the α-amination reaction with azodicarboxylates catalyzed by *Cinchona* alkaloid for enantioselective C−N bond formation providing quaternary stereogenic center at the C4 position.[2]



R^1 = Me, Et
R^2 = Me, Et, allyl, 1-naphthyl, EWG-aryl, EDG-aryl, furyl, thienyl
R^3 = *t*Bu, Ph

Figure 1. Amination of pyrazolones catalyzed by *Cinchona* alkaloid.

The aminated products were obtained in high yields and in good to excellent enantioselectivity. This procedure is versatile for a wide range of substrates and represents straightforward way to α-amino 4-substituted pyrazolones using available catalyst with no additional requirements.

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C – DOMINO REACTIONS

DE NOVO BRANCHING CASCADES FOR STRUCTURAL AND FUNCTIONAL DIVERSITY IN SMALL MOLECULES

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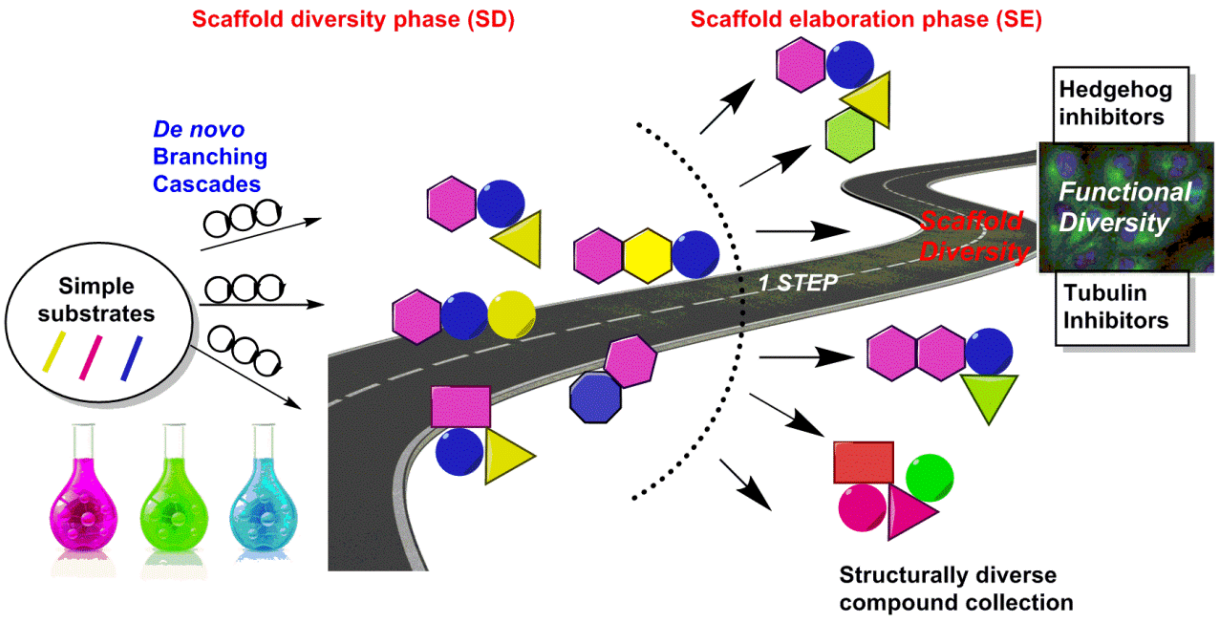
Nature displays its amazing ability to assemble a limited pool of simple building blocks into structurally and functionally diverse natural products.[1,2] In contrast to nature´s *de novo* and divergent biogenesis of secondary metabolites, laboratory synthesis of structurally diverse scaffolds is often a multi-step and tedious process that renders the compound library synthesis highly challenging and expensive endeavor. Here we present the *de novo* branching cascades strategy,[3] where simple acyclic substrates are transformed into appreciable scaffold diversity following different cascade reactions to create various distinct molecular frameworks in a scaffold diversity phase. Later, the scaffold elaboration phase introduces further complexity to the scaffolds by creating a number of chiral centres and incorporating new hetero- or carbocyclic rings. A compound collection of sixty one molecules representing *17 different scaffolds* is built up that delivers a potent tubulin inhibitor, as well as inhibitors of the Hedgehog signalling pathway.[4] This work highlights the immense potential of cascade reactions to deliver compound libraries enriched in structural and functional diversity.



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MAXIMUM DOMINO FOR MINIMUM HELICENE

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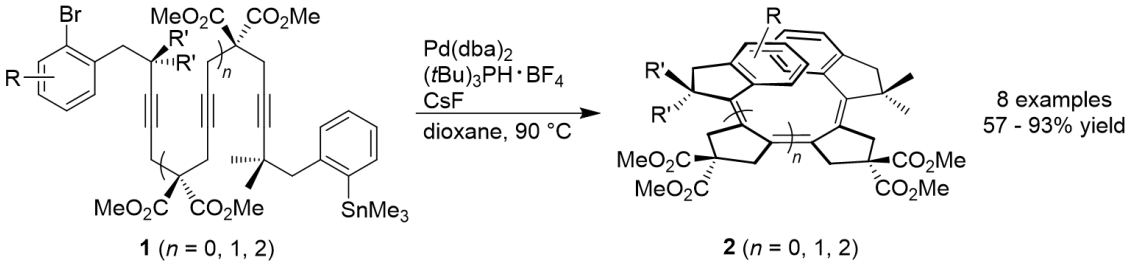
π-Helicenes consist typically of ortho-fused aromatic units, whereby the helical screw-shaped topology can be traced back to steric hindrance of the terminal rings. Therefore these structures are chiral although no asymmetric carbon atoms are present. Since the first helicene, an aza[5]helicene, was reported in 1903,[1] the attention for these fascinating compounds raised dramatically because of their unique structural and optical properties. For example optical rotation values higher than several thousand degrees are not rare and furthermore they have become model compounds for measuring the deformation of a π-system by computing and determining the energy of racemization. As a consequence, in the last decades numerous synthetic routes to access helicenes have been developed.[2]

Almost all of these synthetic methods are directed to questions such as incorporating heteroatoms and/or elongating the π-system whereas the idea to truncate the π-system of a helicene to its minimum has not been addressed so far. Therefore we investigated an approach to access these entities by a palladium-catalyzed domino cascade starting from easily available linear oligoyne chains **1** with arene units at the two termini (Scheme 1).[3] Exposed to the reaction conditions, the domino precursors first undergo several carbopalladation steps depending on the length of the oligoyne chain and then a final Stille cross-coupling terminates the domino sequence. Since the substrates differ in the length of the carbon chain, various differently sized π-helicenes **2** were obtained in yields ranging between 57 and 93%. A scaffold consisting of an *all*-s-*cis* all-*Z* oligoene chain is obtained; the π-system is truncated to its minimum.



Scheme 1. Access to π-helicenes by a multiple domino carbopalladation/Stille approach.

The helical topology was unequivocally confirmed by X-ray crystallography and CD spectroscopy.

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THREE-COMPONENT SYNTHESIS OF $\beta^{2,3}$-AMINO ESTERS: NEW DEVELOPMENTS AND USE AS TEMPLATES IN POST-CONDENSATIONS

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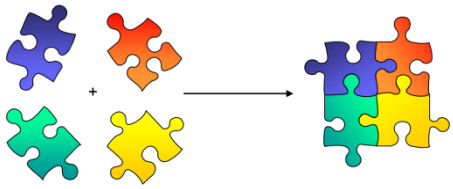
Multicomponent reactions are among the most efficient processes in synthetic organic chemistry since they rapidly increase molecular complexity starting from simple substrates (scheme 1). They are also more economical and environmentally-friendly than classical organic reactions and since they allow a straightforward access to large libraries of compounds, they represent a valuable tool for pharmaceutical industries, especially for high-throughput screening.



Scheme 1

In the past few years, our group has been involved in the development of cobalt-catalyzed multicomponent reactions involving in situ-generated organometallic reagents. This methodology was successfully applied to the preparation of various backbones like e.g. diarylmethylamines,[1] γ-lactones[2] or α-amino esters.[3]

In this communication, we report recent progress in the field by describing novel conditions for the straightforward synthesis of β-hydroxy- and $\beta^{2,3}$-amino- esters under very mild conditions, starting from organic halides, aldehydes or imines, and Michael acceptors. We also describe our contribution to the formation of various pyrrolidines using one-step post-condensations of the prepared backbones.

References:

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THE MICROWAVE-ASSISTED ORGANOCATALYZED REARRANGEMENT OF PROPARGYL VINYL ETHERS TO SALICYLALDEHYDES DERIVATIVES

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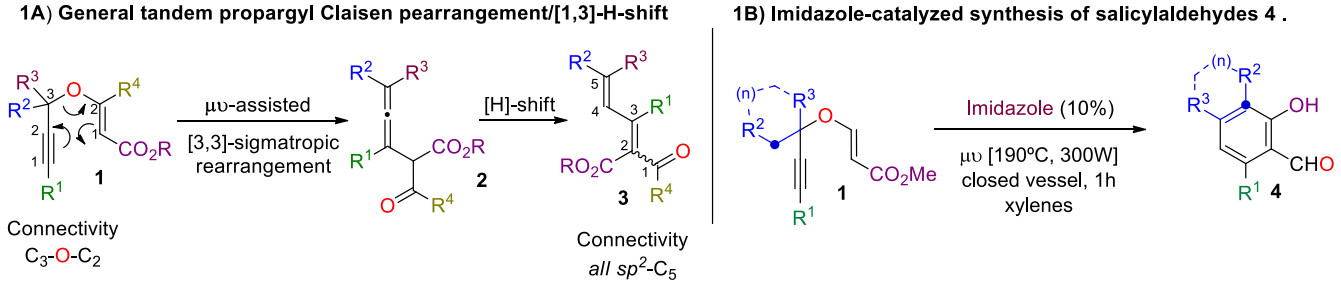
Propargyl vinyl ethers **1** constitute a privileged group of small size, densely functionalized and readily accessible linear scaffolds. The main key to the chemical reactivity encoded in these structures is the [3,3]-sigmatropic rearrangement (propargyl Claisen rearrangement) shown in Scheme **1A**,[1] which takes place irreversibly and under thermodynamic control to generate the allene **2** which isomerizes to dienal **3**. We have developed a microwave-assisted, catalytic (imidazole 10 mol-%) and scalable methodology to transform these allenes into salicylaldehyde motives supported on a broad range of topologies, which spanned from simple aromatic monocycles to complex fused polycyclic systems.[2] The reaction manifold is depicted in Scheme **1B**. We have performed a theoretical study of this reaction which is in full agreement with the observed experimental results. The reaction scope and the proposed mechanism will be commented in our presentation.



Scheme 1

Acknowledgements: This research was supported by the Spanish Ministerio de Economía y Competitividad (MINECO), and the European FEDER and Regional Development Fund (CTQ2011-28417-C01-02). L. Cotos and D.M. thank MICINN and CSIC for a FPI and a JAE-PRE grant respectively.

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[1] D. Tejedor, G. Méndez-Abt, L. Cotos, F. García-Tellado, *Chem. Soc. Rev*. **2013**, *42*, 458-471.

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STEREOSELECTIVE DOMINO SYNTHESIS OF ANTIBACTERIAL DIHYDROPYRAN EMBELIN DERIVATIVES

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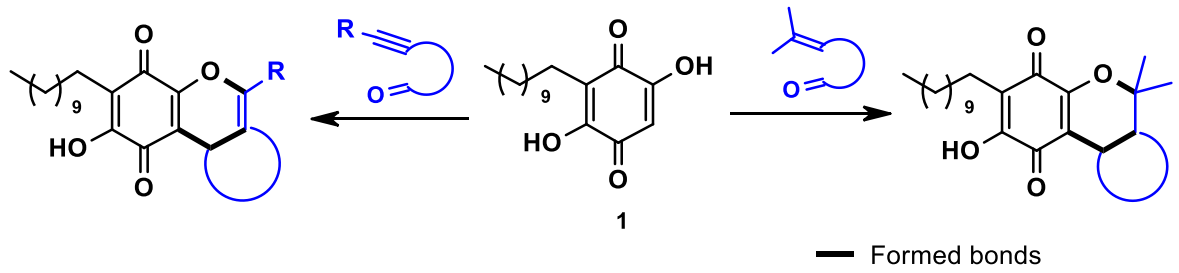
Embelin (2, 5-dihydroxy-3-undecyl-[1,4]benzoquinone) (**1**) is found to be the active principle of the species *Embelia ribes*. This compound displays many biological activities, including antitumor, antihelmintic, antifertility, analgesic, anti-inflammatory and antibacterial effects.[1] All these bioactivities make embelin an interesting scaffold for medicinal chemists.[2]

Herein, we report the synthesis of new embelin derivatives following a direct and highly efficient approach based on a domino Knoevenagel intramolecular hetero Diels-Alder reaction[3] from natural embelin (**1**) using unsaturated aliphatic and aromatic aldehydes such as *O*-prenyl and *O*-propargyl salicylaldehydes in the presence of organocatalysts (EDDA or L-proline).

Some of the obtained compounds were active and selective against Gram-positive bacteria, including multiresistant *Staphylococcus aureus* clinical isolates.



Acknowledgments: We thank MINECO (SAF2012-37344-CO3-01) and EU Research Potential (FP7-REGPOT-2012-CT2012-31G37-IMBRAIM) for financial support.

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DOMINO DIELS-ALDER REACTIONS OF OLIGOFURANS WITH ARYNES

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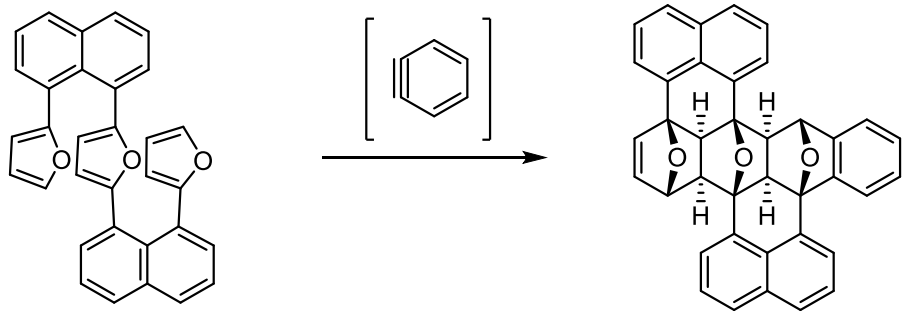
The Diels-Alder reaction of furan with benzyne is probably the most popular reaction in aryne chemistry, and it has been extensively used in order to obtain complex molecular structures. In this contribution we describe stereoselective domino cycloadditions of arynes with oligofurans linked by rigid naphthalene tethers. For example, trisfuran **1** reacts with benzyne in a tandem cascade [4+2]/[4+2]/[4+2] cycloaddition to afford adduct **2** in a good yield.[1] Remarkably, this transformation involves the stereoselective formation of six new carbon-carbon bonds and ten adjacent stereocenters! Moreover, these aryne adducts have been transformated into extended perylene derivatives by deoxygenation and aromatization with HCl/EtOH.



1 **2**

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INTRAMOLECULAR [3 + 2] CYCLOCONDENSATION OF ALKENES WITH INDOLIDENES AND INDOLIDENIUM CATIONS

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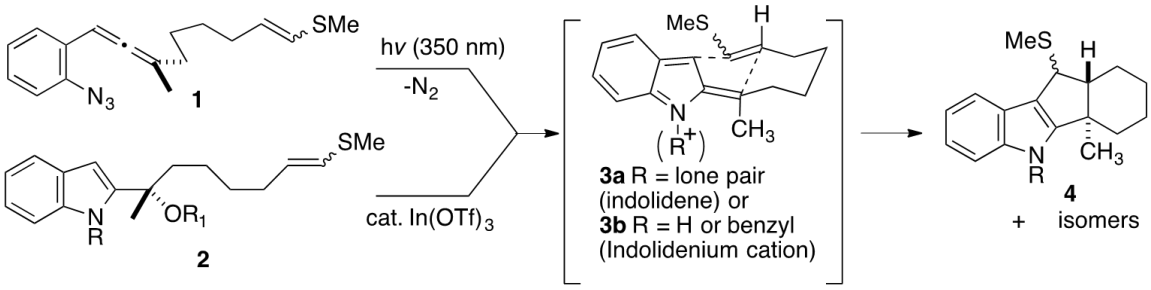
Two intramolecular cyclization approaches using indolidene/indolidenium chemistry generates tetracyclic cyclopentannelated indole architectures (**4**), which are characteristic of the fischerindole and indolosesquiterpene families of natural products.[1] A cyclization cascade initiated by the irradiation of allenyl azide **1** is presumed to go through an indolidene intermediate (**3a**), which is trapped by a pendant alkenyl sulfide nucleophile. A Lewis acid-mediated cationic cyclization results from the reaction of a putative indolidenium cation (**3b**) and a tethered alkenyl sulfide nucleophile. In both cases, regiochemical and stereochemical issues arise and our efforts to favor the desired isomer **4** are discussed.



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Cu(I)/Cu(II) ASSISTED TANDEM CATALYSIS: THE CASE STUDY OF ULLMANN/CHAN-EVANS-LAM N^1,N^3-DIARYLATION OF 3-AMINOPYRAZOLE

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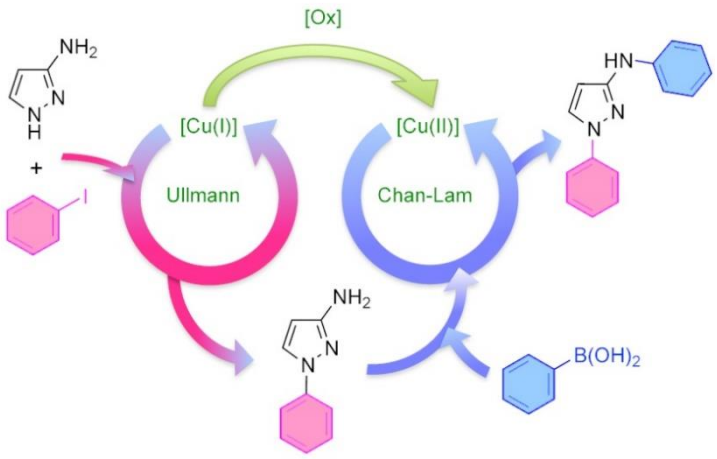
Transition-metal-catalyzed domino processes are recognized as powerful tools for sustainable organic chemistry, allowing atom and step economy.[1] Among the various domino reactions subclasses,[2] assisted tandem catalysis recently emerged as a resourceful strategy.[2c,3] This kind of process relies on the use of a single metal source to perform mechanistically distinct catalytic cycles, thanks to the *in situ* modification of the active catalyst during the reaction. This key event is mostly triggered by redox species in order to change of the metal's oxidation state and thus its reactivity. To date assisted tandem catalysis processes have only been reported for Ti, Ru and Pd complexes.

In this communication we will describe the successful development of the first assisted tandem copper-catalyzed process. As a case study, we achieved the selective N^1,N^3-diarylation of 3-aminopyrazole through a one-pot Ullman/Chan-Evans-Lam sequence.[4]



One Pot, a single copper source !

This three components one-pot reaction should be a valuable tool for medicinal chemistry that often requires efficient strategies for the regio- and/or chemoselective N-arylation of nitrogen containing heterocycles.

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D – MEDICINAL CHEMISTRY

STRUCTURE-BASED DESIGN OF INHIBITORS TARGETING SHIKIMATE KINASE, AN ESSENTIAL ENZYME FOR BACTERIAL SURVIVAL

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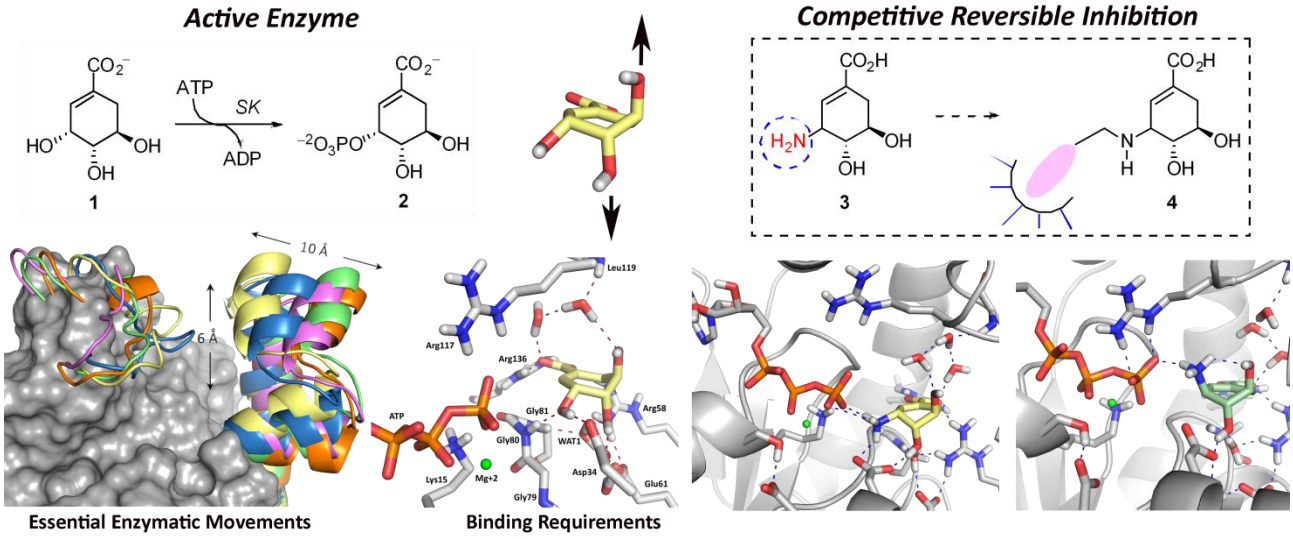
The increasing development and spread of resistance to current antibiotics have turned ordinary bacterial infections into illnesses that cannot be controlled. Infections from resistant bacteria are now too common and some pathogens have even become resistant to multiple types of antibiotics. Therefore, there is an urgent need for the discovery of novel drugs and therapies to treat antibiotic-resistant infections and, in particular drugs that target novel essential processes for bacterial survival. Targeting of new pathways will likely play an important role in the discovery of new antibiotics to combat the growing problem of antibiotic-resistant bacteria. Among the processes that have proven to be essential in certain microorganisms highlights the shikimic acid pathway, in which chorismic acid is biosynthesized. This compound is the precursor in the synthesis of aromatic amino acids and folate cofactors, ubiquinone and vitamins E and K.

In our research group we are studying the possible development of new antibiotics by the selective inhibition of the fifth enzyme of the shikimic acid pathway, shikimate kinase (SK, *aroK* gene). SK catalyzes the stereospecific phosphorylation of the C3 hydroxyl group of shikimic acid (**1**) by transferring the γ-phosphate group of ATP to the hydroxyl group to provide shikimate 3-phosphate (**2**) and ADP. It is an essential enzyme in relevant pathogenic bacteria such as *Mycobacterium tuberculosis*, *Helicobacter pylori* and *Pseudomonas aeruginosa,* but do not have any counterpart in human cells. Here we report results from NMR, biochemical and Molecular Dynamics simulation studies that help to understand the catalytic mechanism of the SK enzyme.[1] Based on these results, several competitive inhibitors of the enzyme, namely compounds **3** and **4**, were designed. Our recent results on this project will be presented.



Aknowledgements: Financial support from the Spanish Ministry of Economy and Competitiveness (SAF2013-42899-R), Xunta de Galicia (GRC2013-041) and the European Regional Development Fund (ERDF) is gratefully acknowledged. VP and EL thank the Spanish Ministry of Economy and Competitiveness and Xunta de Galicia for their respective FPI and Posdoc fellowships.

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STRUCTURE-BASED DESIGN OF *HELICOBACTER PYLORI* TYPE II DEHYDROQUINASE INHIBITORS

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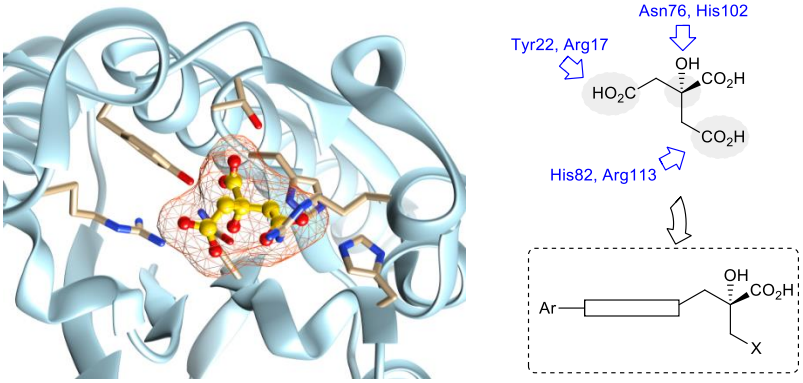
In recent years a great deal of effort has been focused on the development of inhibitors of the enzymes involved in the biosynthesis of the aromatic amino acids. This is because these enzymes are present in bacteria, fungi, higher plants and certain apicomplexan parasites, but they are absent in mammals. Among them, particular attention has been paid to the inhibition of the third enzyme in the pathway, the type II dehydroquinase (3-dehydroquinate dehydratase, EC 4.2.1.10, DHQ2) as a potential target for the development of anti-tubercular drugs as well as for the treatment of infectious diseases caused by *Helicobacter pylori,* which is the causative agent of gastric and duodenal ulcers, which has also been classified as a type I carcinogen. As a result, numerous inhibitors of this target have been developed, including analogs of the natural substrate and mimetics of the intermediate of the enzyme-catalyzed reaction. The resolution of crystal structures of several DHQ2/inhibitor binary complexes has undoubtedly been very important for this success, not only for the development of inhibitors of improved activity but also to gain a deeper understanding of its dehydration mechanism and the binding requirements of the DHQ2 enzyme.[1] These data allowed us the development of QSAR models for the DHQ2 enzymes from *H. pylori* and *M. tuberculosis* that aided in rationalizing the determinants of binding affinity and in understanding the differences between the two enzymes.[2] In particular, for *H. pylori* DHQ2 these studies suggested that enzyme inhibition might be enhanced by promoting interactions between the ligand and residues located at the 'bottom' of the interface between chains, and avoiding contacts with residues located at the 'upper part' of the interface. Bearing in mind this fact and considering the binding mode of citrate in the previously reported crystal structure of *H. pylori* DHQ2 (PDB entry 2XB9[3]), we have investigated the structure-based design of new citrate analogs as potential competitive reversible inhibitors of this enzyme. In this communication, we will present our latest results in this project.



Aknowledgements: Financial support from the Spanish Ministry of Economy and Competitiveness (SAF2013-42899-R), Xunta de Galicia (GRC2013-041) and the European Regional Development Fund (ERDF) is gratefully acknowledged. AR thanks the Spanish Ministry of Economy and Competitiveness his FPI fellowship.

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DNA CROSS-LINKING AGENTS AS PAYLOADS FOR NEW GENERATION ANTIBODY-DRUG CONJUGATES FOR THE TREATMENT OF HER-2 POSITIVE BREAST CANCER

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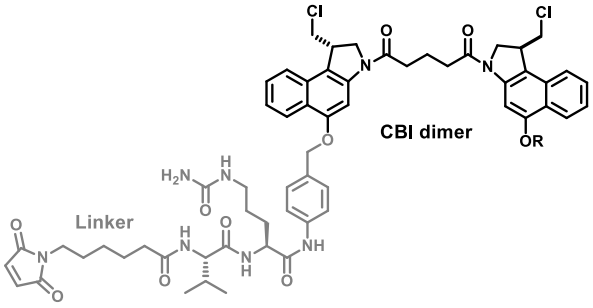
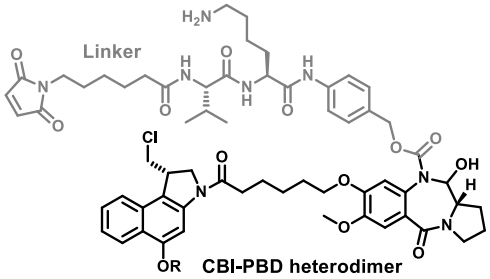
There is a current need for the development of new anti-cancer therapeutics that show high anti-tumour efficacy while reducing the toxicity to normal cells. A novel approach to cancer treatment is the combination of monoclonal antibodies (mAbs), which target antigens selectively expressed on the surface of cancer cells, with the high efficacy of cytotoxic drugs. This strategy allows selective delivery of a potent anti-cancer agent to tumours, limiting systemic exposure. The antibody-drug conjugates (ADCs) consist of a targeted mAb, a potent cytotoxic drug and a linker between those two components. The choice of the drug and the design of the linker are both critical for success. The linker should be stable in circulation and is selected according to the tumour type, the chosen cytotoxin and its ability to be cleaved in the target cell. The drug payload should exhibit very high cytotoxicity (IC_{50} usually in the pM range) across a range of human tumour cell lines. To date, there are over thirty ADCs in clinical development, and two have received FDA approval.

New drug payloads with a novel mode of action are currently needed, due to arising resistance against the first generation ADCs using anti-microtubule inhibitors as cytotoxic agent. Chloromethylbenzindolines (CBIs) and pyrrolobenzodiazepines (PBDs) are both sequence-selective DNA minor grove alkylators. CBI dimers and CBI-PBD heterodimers cross-link DNA and exhibit very high potency across a range of human cancer cell lines, the CBI dimer being exceptionally potent, in the fM range for the HL-60 cell line.





This presentation will report the synthesis of CBI dimers and CBI-PBD heterodimers and prodrugs, functionalised with appropriate linkers. These were conjugated to HER-2 and CD-22 specific mAbs. *In vivo* studies showed high efficacy for HER-2 directed ADCs, with the CBI-PBD heterodimer being more active than the CBI dimer payload in the ADC. These DNA cross-linking agents show promising activity and may have potential as second generation anti HER-2 ADCs.

SYNTHESIS OF CHEMICAL PROBES TO INVESTIGATE THE MECHANISM OF PhzA/B

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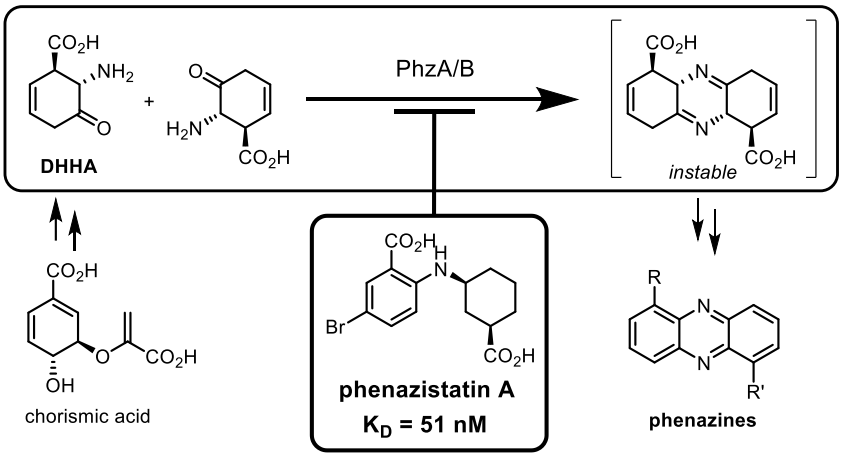
Phenazines represent an abundant class of bacterial pigments that are mainly synthesized by *Pseudomonas* and *Streptomyces* strains. Phenazines act as virulence factors and trigger tissue damage in human infectious disease. As a result of their capability to reduce molecular oxygen to toxic reactive oxygen species (broad-spectrum antibiotic activity) they furthermore provide bacteria with a competitive advantage. Phenazine biosynthesis is coupled to the shikimate pathway and the enzyme PhzA/B is therein believed to catalyze a twofold head-to-tail condensation of two *trans*-2,3-dihydro-3-hydroxyanthranilates (DHHA).[1] Inhibition of PhzA/B is assumed to have a bactericidal effect caused by accumulation of the unselectively reactive DHHA and might represent an novel antibiotic target for the treatment of *P. aeruginosa* infections.

Product analogues were synthesized and tested for their affinity to PhzA/B with Isothermal Titration Calorimetry (ITC) and protein-ligand complexes were generated by soaking experiments, thus elucidating the general binding mode.[1,2] Surprisingly, PhzA/B was the first enzyme being described that can host both enantiomers of a racemic mixture simultaneously.[3] This observation might offer new drug-discovery opportunities, following the idea of fragment-based drug discovery. Design of inhibitors for this promiscuous active site led to the discovery of phenazistatin A, exhibiting an affinity of 51 nM.



Scheme 1. Inhibition of PhzA/B in phenazine biosynthesis and the inhibitor phenazistatin A

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CATALYTIC AND BIOLOGICAL ACTIVITY OF CHIRAL AMIDES AND SULFONAMIDES BASED ON 2-AZABICYCLOALKANE SKELETON

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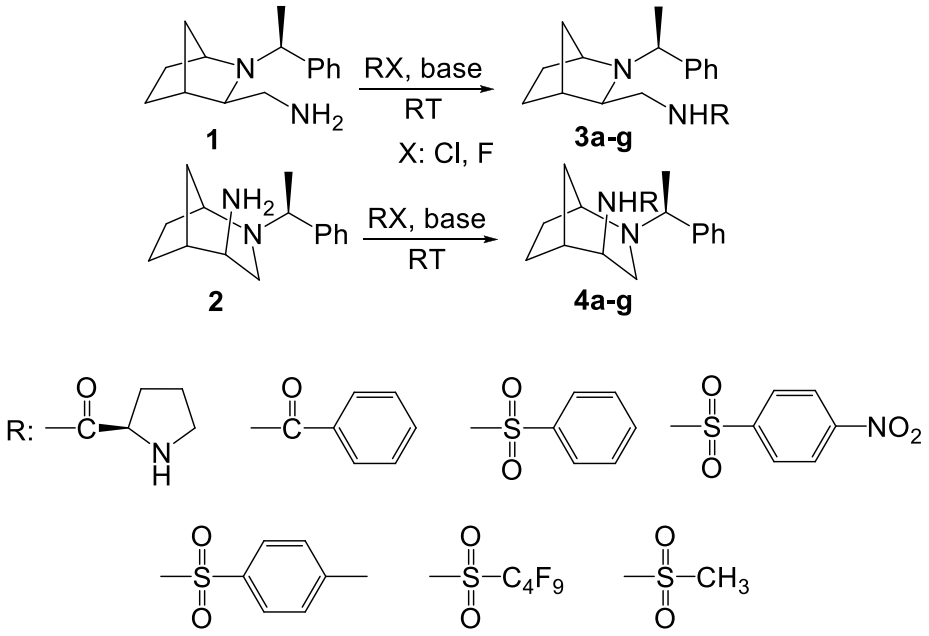
Various derivatives of 2-aza-bicyclo[2.2.1]heptane and 2-azabicyclo[3.2.1]octane have been recognized as biologically active compounds or precursors of pharmaceuticals.[1-3] They have also found numerous applications as selective ligands and organocatalysts in many asymmetric transformations.[4-5] The stereoselective *aza*-Diels-Alder reaction between dienes and chiral imines is applied as a highly efficient method for the preparation of 2-azanorbornanes, while ring expansion of 2-azanorbornyl alcohol under Mitsunobu reaction conditions yields bridged azepane derivatives.[6] In this contribution, a synthesis of a series of new azabicycloalkane derivatives is presented (*exo* and *endo* epimers), including chiral amides and sulphonamides.



The obtained compounds **3a–g** and **4a–g**, after a full physicochemical characterization, have been tested for their biological and catalytic activity.

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CYCLIC *iso*DGR AND RGD PEPTIDOMIMETICS: INTEGRIN ANTAGONISTS AND TUMOR-HOMING DEVICES

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Integrins are a large family of cell adhesion receptors composed of two non-covalently bound α and β transmembrane glycoproteins and are involved in physiological and pathological processes.[1] Several integrins, including $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_5\beta_1$, and $\alpha_{IIb}\beta_3$, recognize endogenous ligands using the tripeptide sequence Arg-Gly-Asp (RGD) and its mimic *iso*Asp-Gly-Arg (*iso*DGR).[2] Four *cyclo*[DKP-*iso*DGR] integrin ligands have been synthesized and their ability to bind $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrins has been studied.[3] At least one low-nanomolar ligand was identified, namely ***cyclo*[DKP3-*iso*DGR]**, which is, to the best of our knowledge, the most potent *iso*DGR $\alpha_V\beta_3$ integrin ligand reported so far (Figure 1). The biological activities of ligands ***cyclo*[DKP3-RGD]** and ***cyclo*[DKP3-*iso*DGR]**, bearing the same bifunctional diketopiperazine (DKP) scaffold and showing similar $\alpha_V\beta_3$ integrin binding values, were compared in terms of their cellular effects in human U373 glioblastoma cells. They displayed overlapping inhibitory effects on the FAK/Akt integrin activated transduction pathway and on integrin mediated cell infiltration processes, and qualify therefore as integrin antagonists. With the aim of exploiting the tumor-homing potential[4] of ***cyclo*[DKP3-*iso*DGR]**, a cyclic *iso*DGR peptidomimetic displaying a proper handle for conjugation to cytotoxic agents has been developed.

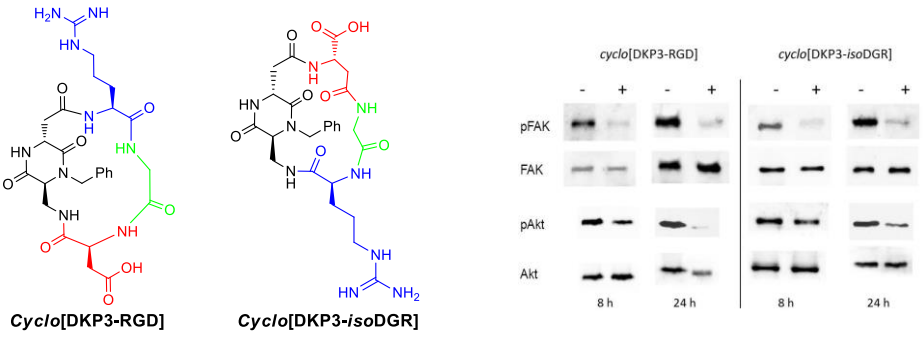

Figure 1. ***Cyclo*[DKP3-RGD]** and ***cyclo*[DKP3-*iso*DGR]** integrin ligands and inhibition of FAK/Akt phosphorylation in human U373 glioblastoma cells (western blot analysis).

Acknowledgements: we thank Fondazione CARIPLO (Project RE-D DRUG TRAIN2010–1373) for a research grant (to U.P.) and a PhD fellowship to S.P.. We also gratefully acknowledge Ministero dell'Università e della Ricerca for financial support (PRIN project 2010NRREPL).

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FRAGMENT LINKING OF INHIBITORS OF THE ASPARTIC PROTEASE ENDOTHIAPEPSIN FACILITATED BY PROTEIN-TEMPLATED CLICK CHEMISTRY

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Fragment-based design (FBD)[1] enables the design of bioactive compounds. Whereas there are numerous reports on FBD using optimization of a hit by fragment growing/optimization, fragment linking is rarely used.[2] Protein-catalyzed click chemistry is a hit-identification strategy, in which azides and alkynes are assembled irreversibly to the corresponding triazoles.[3]

We have demonstrated that fragment linking and protein-catalyzed click chemistry constitutes an efficient hit-identification strategy. Using co-crystal structures of the aspartic protease endothiapepsin and fragments,[4] we have designed a library of inhibitors generated from alkynes and azides and used protein-catalyzed click chemistry to identify potent inhibitors, which were characterized by UPLC-TOF/SIM.

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SYNTHESIS OF NOVEL FUSED 1,4-DIHYDROPYRIDINES AS SYNERGISTS WITH 5-FLUOROURACIL

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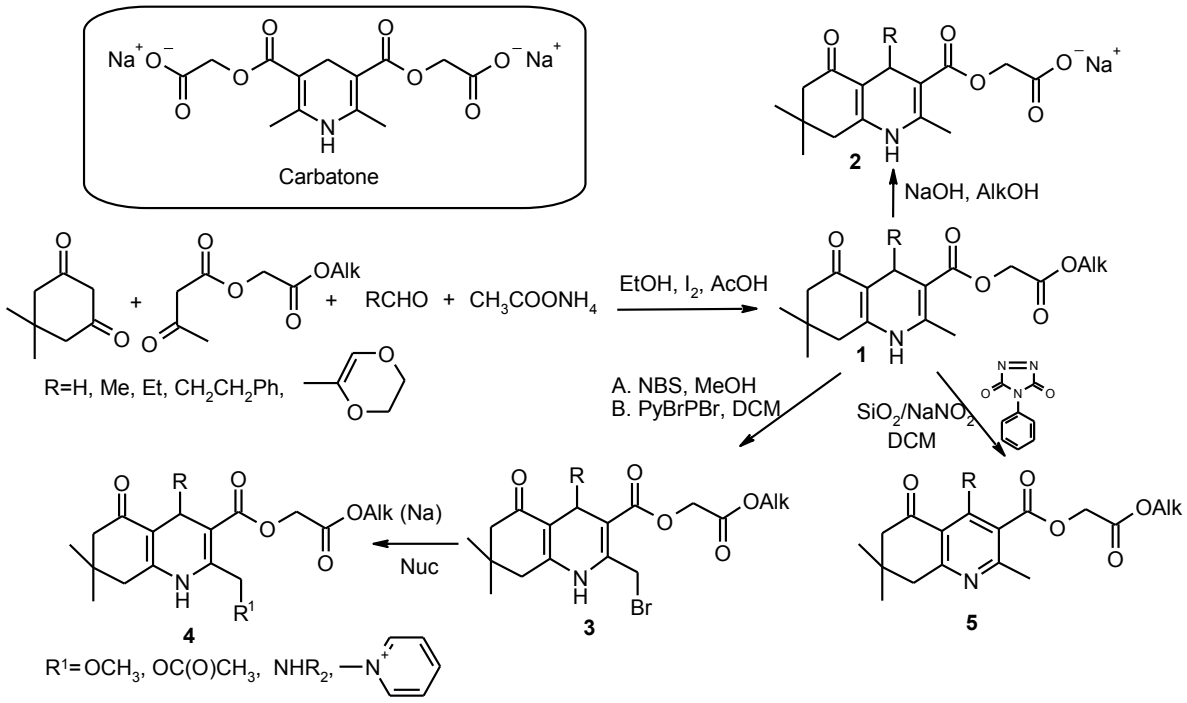
The 1,4-dihydropyridines (DHPs) comprise a class of drugs possessing a wide variety of biological and pharmacological activities. Recently we have found that disodium 2,6-dimethyl-1,4-DHP-3,5-biscarbonyloxyacetate (carbatone) and its 4-alkyl derivatives increase antitumour activity of 5-fluorouracil [1]. On the other hand, β-annelated 1,4-DHPs bearing a condensed cyclohexenone or piperidine-2-one ring are reported as TGF/Smad inhibitors that stimulate cardiomyogenesis of pluripotent stem cells [2].

In the course of our program focused on the elaboration of novel efectors of anti-cancer drug activities, here we report the four-component synthesis of alkoxycarbonylmethyl 5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates **4** comprising various substituents in 2- and 4- position. The water soluble form **2** was easily prepared in alkaline medium. 2-Bromomethyl derivative **3** proved to be a key intermediate to install several nucleophylic functional groups in 2- position.



The synergistic effect of the synthesized hexahydroquinolinones and 5-FU was evaluated in *in vitro* experiments on the MDA cell line.

Acknowledgement: this study was supported by the ESF project *1DP/1.1.1.2.0./13/APIA/VIAA/011.*

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SYNTHESIS AND EVALUATION OF GALLINAMIDE A ANALOGUES AS ANTIMALARIAL DRUG LEADS

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Isolated from marine cyanobacteria of the genus *Schizothrix*, gallinamide A[1] (**1**, Fig.1) is a depsipeptide natural product that shares many structural features with a number of potent cytotoxic agents, including the dolastatins[2]. These molecules have been reported to possess antimalarial activity against chloroquine-resistant *Plasmodium falciparum*, the etiological agent of malaria, while exhibiting low cytotoxicity against human cell lines[1]. The interesting pharmacological properties of gallinamide A prompted us to investigate this natural product as an antimalarial drug lead. The total synthesis[3] and stereochemical assignment of gallinamide A[4] was first carried out over seven steps in the longest linear sequence. This synthesis was amenable to the preparation of structural analogues (Fig.1), a number of which exhibited more potent antimalarial activity than the gold-standard malaria drug chloroquine against *P. Falciparum*[5]. A second generation library of analogues has also been generated through the development of a novel solid-phase elongation and cyclisation approach that has enabled more detailed structure-activity relationships to be established for the natural product analogues.

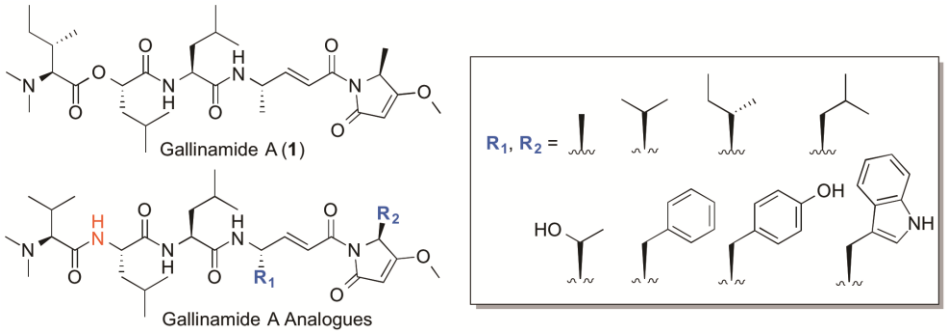

Figure 1. Gallinamide A (**1**) and first generation of structural analogues.

Finally, we have been able to show that these natural product analogues exhibit antimalarial activity through the inhibition of the food vacuole falcipains, cysteine protease enzymes in *P. falciparum* responsible for the degradation of host hemoglobin. This work has provided an opportunity to design and synthesize novel antimalarial drug leads, based on the Gallinamide A scaffold, that operate by novel modes of action to current therapies for which significant resistance has emerged.

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^{18}F-RADIOLABELLING OF MEDICINALLY-RELEVANT HETEROCYCLIC MOTIFS

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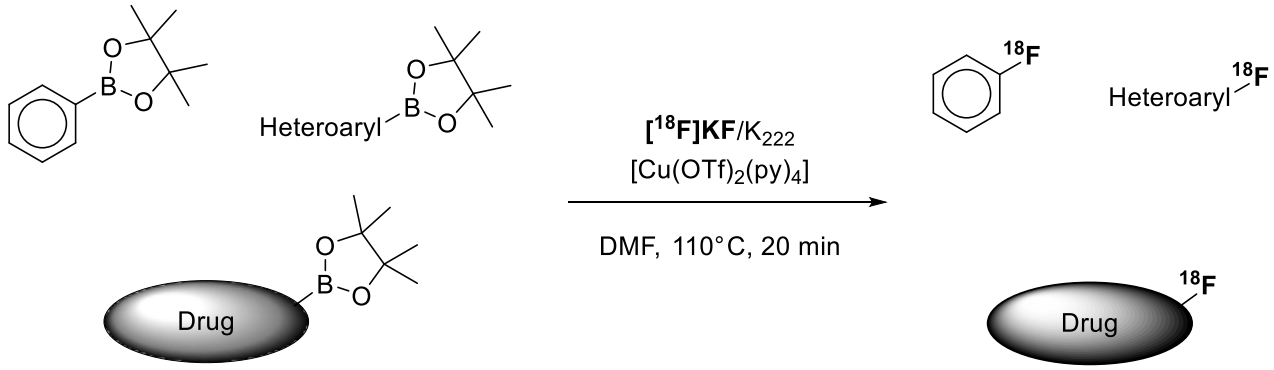
Positron Emission Tomography[1] (PET) allows the non-invasive imaging of cancer and neurodegenerative diseases such as Alzheimer's and Parkinson's.[2] This technology is also of great importance in drug development by studying the biodistribution and pharmacokinetics of drug candidates *in vivo*.
In this context, the synthesis of ^{18}F-labelled arenes is of particular importance due to the prevalence of this motif in pharmaceuticals, but there is still a lack of a general and easily applicable method to synthesise these.[3] In the last years, new groundbreaking methods emerged for the ^{18}F labelling of arenes using transition-metal mediated methods or umpolung approaches directed towards either the substrate[4] or the fluoride source.[5] Recently, we reported a Cu-mediated process for the labelling of aromatic compounds, starting from readily available and bench-stable aryl boronic esters and the nucleophilic [^{18}F]fluoride.[6] In this presentation, we will show a comprehensive study delineating the robustness of this method concerning heterocycles and heteroarenes and the application of this labelling method on these two classes of molecules, as they are of pivotal importance in drug discovery and development.



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MEDICINAL CHEMISTS TO AID THE COMMUNITY FOR OPEN ANTIMICROBIAL DRUG DISCOVERY

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The antibiotic pipeline is broken, with a dearth of new antibiotics, a collapse in pharmaceutical company research[1], and the exhaustion of chemical diversity contained in pharma libraries. “The low hanging fruit from the antibiotic tree has probably already been picked and new sources of compounds are needed.”[2] We believe that there is an untapped resource contained in the laboratories of synthetic organic chemists; synthetic compounds prepared for other projects that have never been tested for their antimicrobial potential. These compounds, which are sitting at the back of benches and freezers, may have been synthesised to validate new synthetic routes, develop new methodologies, or create unusual structures. A global screening initiative will uncover this significant and rich chemical diversity held outside of corporate screening collections by providing a low-barrier access to testing.

Antibacterial drugs occupy a unique property space that is different to drugs developed for other therapeutic areas, suggesting that libraries from commercially sources[3] lack the physicochemical properties ideal for activity against bacteria. There is a requirement to extend the source of chemical diversity needs to be investigated.

We have created a Wellcome Trust-supported not-for-profit Open-Access pipeline, The Community for Open Antimicrobial Drug Discovery (CO-ADD; co-add.org) initiative to provide unencumbered free antimicrobial screening for any interested researcher. CO-ADD builds upon a suite of established in vitro and in vivo assays, medicinal chemistry and core researcher expertise and aims to unearth fresh chemical diversity for the treatment of bacterial infection.

In this presentation we will discuss the properties of antibiotic-like compounds, and how the organic chemistry community can contribute to solving an imminent threat to public health.

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INDOLE-PYRIDO[2,3-*d*]PYRIMIDINE HYBRIDS: THREE-COMPONENT SYNTHESIS AND BINDING STUDIES AGAINST DOPAMINERGIC RECEPTORS

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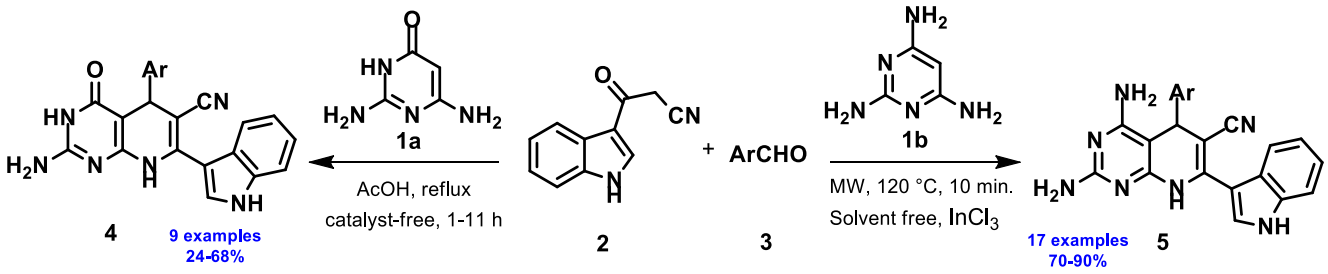
Pteridine is the heterocyclic core presents in important biological metabolites such folic acid or pterin; deazapteridine analogs, such pyrido[2,3-*d*]pyrimidine compounds exhibit relevant enzymatic activity along with for example antiproliferative propierties, such as dihydrofolate reductase (DHFR) inhibition, [1] being used e.g. in the treatment of cancer.[2,3] We are here reporting the MCR's between corresponding 4-aminopyrimidine **1a** or **1b**, 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **2** and aromatic aldehydes **3**, both at classical reflux in acetic acid and under free-solvent MWI-assisted with $InCl_3$ as a catalyst, to afford the hybrids **4** and **5**, with better results for these last environmentally friendlier conditions.



Binding studies on rat striatal membranes were used to evaluate their affinity and selectivity towards D1 and D2 Dopaminergic Receptor and establish the structure activity relationship (SAR) as dopaminergic agents on three of those compounds, displaying a remarkable selectivity for D2 receptor and low affinity for D1 receptor. A molecular modelling study was carried out, combining both Molecular Dynamics simulations with DFT calculations, to provide a clear picture of the ligand binding interactions from a structural and energetic point of view. Therefore, it is likely that compounds behave as D2 DR agonist since serine residues cluster are crucial for agonist binding and receptor activation.

Acknowledgements: DV and JT acknowledge for the financial support due by the Colombian Institute for Science and Research (COLCIENCIAS). JC and MN thank the financial support from the Consejería de Economía, Innovación y Ciencia (Junta de Andalucía) and Universidad de Jaén.

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NOVEL TRYPANOSOMATID INHIBITORS INSPIRED BY NATURE

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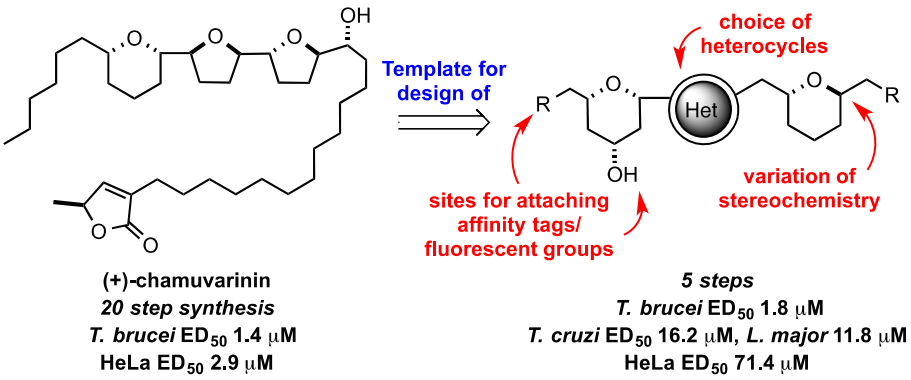
Trypanosomatids are a group of biochemically related unicellular parasites, many of which cause life threatening, debilitating disease in humans. The three major forms of Trypanosomatid disease; African sleeping sickness, Chagas disease and Leishmaniasis are caused by host infection with the parasites *T. brucei*, *T. cruzi* and *L. major* respectively. Combined, these parasites are responsible for disease in millions of people worldwide, predominantly in developing countries. Lack of financial incentive for pharmaceutical companies means there are few validated drug targets, while the currently prescribed treatments are antiquated and exhibit severe side effects.[1]



Chamuvarinin,[2] an acetogenin isolated from the roots of *Uvaria chamae*, displays single figure micromolar activity towards *T. brucei*. New rapidly assembled THP-triazole-THP analogues were designed on the basis of molecular modeling of the central tricyclic core of chamuvarinin and these simplified analogues were found to kill *T. brucei*, *T. cruzi* and *L. major* at micromolar levels, highlighting the possibility of a shared mechanism of action. Significantly, select analogues also show good selectivity over mammalian cells. This paper will detail preliminary SAR studies and our work towards identifying the protein target of these novel anti-parasitic agents.[3]

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SYNTHESIS OF NEW C(4) AND/OR C(5) THIENYL SUBSTITUTED PYRIMIDINES AS POTENTIAL ANTIMYCOBACTERIAL AGENTS

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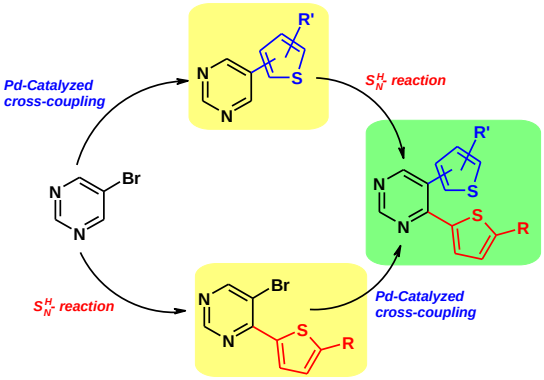
We have recently reported the synthesis of a new series of 5-arylethenyl-4-(het)arylpyrimidines, which exhibit a good level of activity against multidrug-resistant strain of *Mycobacterium tuberculosis* and a low acute toxicity [1]. Besides that, it has been observed that variation of thienyl substituents at C(5) and C(6) positions in 5-aryl-6-hetaryl substituted 1,6-dihydropyrazines derivatives affect strongly their antituberculosis activity [2]. Herein we wish to report that combination of the Suzuki cross-coupling and nucleophilic aromatic substitution of hydrogen (S_N^H) reactions proved to be a convenient method for the synthesis of C(4) and/or C(5) mono(thienyl) and di(thienyl) substituted pyrimidines from commercially available 5-bromopyrimidine. The structures of new compounds have been established unequivocally by X-ray diffraction analysis (for example, see Figure 1)



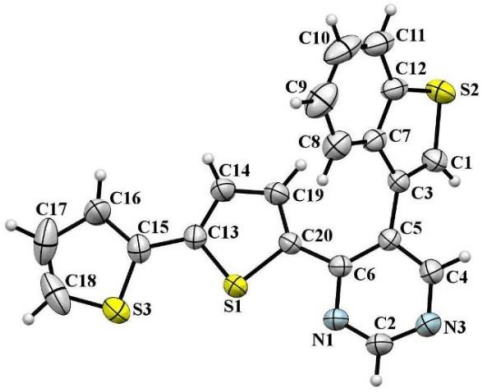


Figure 1. X-ray structure of 5-benzo[*b*]thiophen-3-yl-4-[2,2']bithiophen-5-yl-pyrimidine.

All new pyrimidines proved to be active *in vitro* in micromolar concentrations against H_{37}Rv, *avium*, *terrae*, rifampicin and isoniazid-resistance strains of *Mycobacterium tuberculosis*. Also, the experimental data concerning *in vivo* acute toxicity in mice have been obatined, thus demonstating that these compounds can be regarded as promising antituberculosis agents.

Acknowledgments: This work was financially supported by the Ural Branch of the Russian Academy of Sciences (Grant No 13-3-019-UMA), the Russian Foundation for Basic Research (research projects No. 13-03-96049-r_ural_a, 14-03-01017 A and 14-03-31040-mol_a), the Council on Grants at the President of the Russian Federation (Program of State Support for Leading Scientific Schools of the Russian Federation and Young Scientists, Grant MK-3939.2014.3).

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STUDIES ON AMINOPYRIDINES REACTIVIY TOWARDS NOVEL CYCLOOXYGENASE INHIBITORS

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Two isoforms of cyclooxygenase (COX) exist and while COX-1 is constitutive, COX-2 expression is induced during inflammatory processes.[1] Commercially available non-steroidal anti-inflammatory drugs (NSAIDs), used for the treatment of inflammation, are mostly non-selective, inhibiting both isoforms and thus revealing gastrointestinal (GI) toxicity. As a result, studies towards COX-2 selective inhibition led to a class of selective NSAIDs known as “coxibs”. Though coxib-type compounds benefit from the lack of GI toxicity, this class was recently reconsidered due to adverse cardiovascular events.[2] Therefore safer COXs selective inhibitors are needed.

Our group has been focused on the search for efficient selective inhibitors and on the disclosure of COX mechanism of inhibition.[3,4] A new generation based on the azaindole scaffold is currently under preparation starting from halogenated aminopyridines (Figure 1). Azaindoles are challenging scaffolds, due to the electron-deficient nature of the pyridine ring that modifies the π-system electronics, many classical indole synthetic methods either do not work or are not as efficient when directly applied to the synthesis of azaindole analogues.[5] Despite the fact that functionalized aminopyridines are key building blocks to achieve azaindoles, they are also challenging substrates for metal-catalyzed cross-coupling reactions and metal-catalyzed reactions, key reactions on synthetic modern methods available to date that allow the construction of bioactive and heterocyclic compounds.

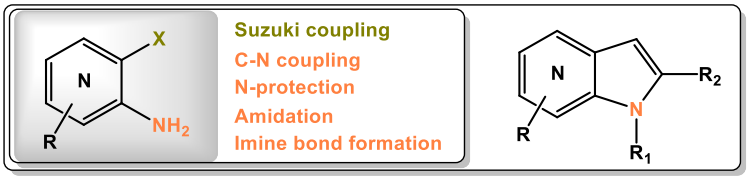

Figure 1. Chemical transformations on aminopyridines towards an azaindole library.

This presentation will focus on our recent studies on the synthetic transformations of several aminopyridines in order to achieve a suitable COX selective inhibitor.

Acknowledgements: We thank to the Fundação para a Ciência e Tecnologia for fellowship SFRH/BD/89518/2012.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF OCTAHYDROPYRAZIN[2,1-a:5,4-*a*']DIISOQUINOLINE DERIVATIVES

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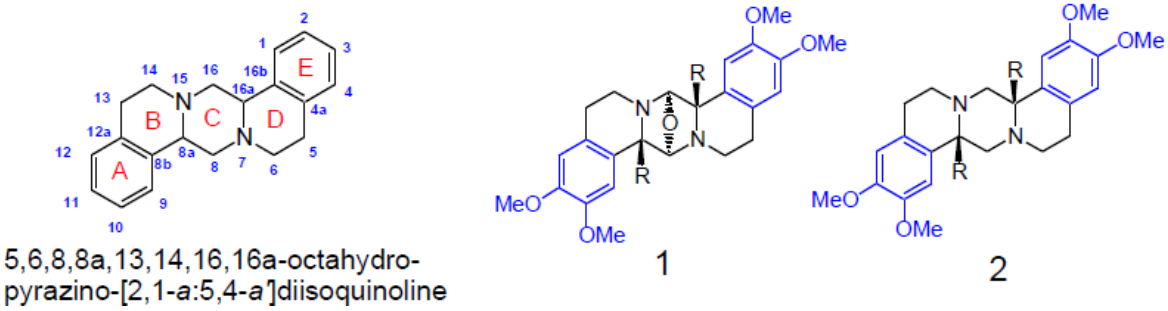
This project is focused on the search for a new anticancer drug candidate with rare octahydropyrazin[2,1-a:5,4-a']diisoquinoline skeleton (Figure 1.). Synthesized by us compounds type **1** and **2**, contain two terminal dimethoxyphenyl groups (ring A and E), therefore they are structurally related to compounds isolated from plants as berberine, erianin, combretastin, curcumine, tylocrebrine, or tylophorine. However to the best of our knowledge, compounds with such skeleton were never found in the nature. We have developed a stereoselective method for the preparation of octahydropyrazin[2,1-*a*:5,4-*a*']diisoquinoline derivatives starting from L-tartaric acid. The key steps of the synthesis involve the dimerization of an in situ generated alfa-aminoaldehyde into the corresponding cyclic bis-hemiaminal, followed by dehydration in the presence of a base to give a 7-oxa-2,5-diaza-bicyclo[2.2.1]heptane derivative, which can be regarded as a bicyclic bis-hemiaminal inner ether[1]. This general and well tested methodology was applied for the synthesis of all planned optical pure compounds. These compounds represent a new class of molecule, with a structure unambiguously established for the first time.



5,6,8,8a,13,14,16,16a-octahydro-pyrazino-[2,1-*a*:5,4-*a*']diisoquinoline

1 2

In our in vitro antitumor study, we found that novel octahydropyrazin[2,1-*a*:5,4-*a*']diisoquinoline derivatives have strong antitumor effect on human cancer cells. Our experiments carried out with flow cytometry assessment of annexin V binding and fluorescent microscopy assay revealed that these compounds inhibited the proliferation of breast cancer cells by increasing the number of apoptotic cells[2]. These results are the first to systematically characterize cytotoxicity and apoptosis induction by these compounds in comparison to etoposide and camptothecin. The results of our studies suggest that further work should be conducted to better define the limits of the structure-activity relationships among octahydropyrazin[2,1-a:5,4-a']diisoquinoline derivatives.

Acknowledgements: The authors are grateful to the National Science Centre (Grant DEC-2012/07/B/NZ7/04382) for financial support.

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SYNTHESIS OF NOVEL DIISOQUINOLINE DERIVATIVES WITH POTENT ANTIPROLIFERATE ACTIVITY

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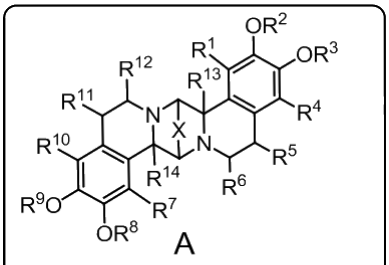
We synthesized novel diisoquinoline derivatives in both optical forms bearing a variety of substituents as presented on structure **A**. We have found that these compounds show greater cytotoxicity compared with etoposide and camptothecin in breast cancer cells. Our experiment showed that the antiproliferative effect of these diisoquinoline derivatives is independent of the estrogen receptor status of the breast cancer cells. These potent inhibitors may constitute potential pharmacological agents for the treatment of both hormone responsive and nonresponsive breast cancer cells. Understanding the mechanism of action of tested compounds is fundamental for the present project. Therefore we plan to perform detailed studies including investigations of the activity of these compounds in various cancer and normal cell lines, as well as the impact on apoptosis and signal transduction pathway. The evaluations of their bioactivity disclosed, that these compounds inhibit topoisomerase type I and II, however, the mechanism of action is not clear yet. The motivation for the present study was the hypothesis that dual inhibitors that target type I and type II topoisomerases may offer the prospect of circumventing acquired altered topoisomerase resistance associated with downregulation of a single protein, with consequential improvements in therapeutic index. The impact of substitution pattern and absolute configuration on bioactivity was analyzed to contribute to the rational design of more selective drugs to target topoisomerase proteins.



A

X = O, S

R^1-R^{12} = variety of groups, including alkyl, aryl, halogen, heterocyclic etc.

There are two apoptosis pathway: the extrinsic pathway of apoptosis and the intrinsic pathway, also called the mitochondrial pathway. As a result of excitation the extrinsic pathway follows the activation of caspase 8, whereas the initiation of the intrinsic pathway leads to the activation of caspase 9. Our results suggested that apoptosis of cells in the presence of these novel diisoquinoline derivatives follows the mitochondrial pathway, with the decrease in MMP and the activation of caspase 9. However, these compounds also activated caspase 8 suggesting that the extrinsic pathway of apoptosis might be also involved in induced cell death. Activated caspase 8 can cleave and activate effector caspase 3. The significant increase in the number of cells with active caspase 3 was observed for novel diisoquinoline derivatives in MDA-MB-231 breast cancer cells. Cytotoxic properties of these compounds in cultured human breast cancer cells correlate to their ability to inhibit topoisomerase I/II.

Acknowledgements: The authors are grateful to the National Science Centre (Grant DEC-2012/07/B/NZ7/04382) for financial support.

SYNTHESIS AND STRUCTURE OF ETHYL 4-CHLORO-7-IODOQUINOLINE-3-CARBOXYLATE, A VERSATILE BUILDING BLOCK FOR THE PREPARATION OF INHIBITORS TARGETING THE *BC1* COMPLEX OF *PLASMODIUM FALCIPARUM*

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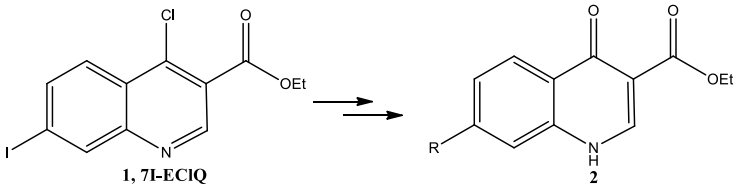
Malaria remains one of the most deadly infectious diseases in the world. With the growing emergence of resistance to existing therapies, the development of novel and better antiplasmodial drugs remains a priority.

A series of 7-substituted quinolone 3-esters **2** have been shown to be potent inhibitors of the bc1 complex of *P. falciparum*. The bc1 complex is a validated target for antiplasmodial drug design. It is a homodimeric transmembrane protein responsible for the transfer of electrons from ubiquinol to cytochrome c, together with the vectorial translocation of protons across the inner mitochondrial membrane.[1]



It has been proposed that quinolone 3-esters **2** target the Qo site of the enzyme, leading to a loss of mitochondrial function, collapse of the trans-membrane electrochemical potential and, ultimately, parasite death.[2] Docking studies have shown that the NH and the carbonyl groups of quinolones are crucial to the inhibitory activity.[3] However, compounds **2** have poor pharmacokinetic profile and the possibility of quinolone/hydroxyquinoline tautomerism may impact negatively in the pharmacodynamic profile.[4] Structure-based optimization can be achieved by altering the substituent in position 7. As such, a library of compounds **2** have been designed for SAR studies. 4-Chloroquinolines are important building blocks to achieve this goal and ethyl 4-chloro-7-iodoquinoline-3-carboxylate, **7I-ECIQ**, **1** proved to be instrumental as an intermediate for access to a range of new quinolone 3-esters **2**.

We now discuss the synthesis and detailed structure of **7I-ECIQ**, in the crystal state and as isolated molecule, studied using X-ray crystallography, matrix isolation coupled to FTIR and DFT calculations.

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NOVEL ECDYSTEROIDS DERIVATIVES AS POTENTIAL MDR MODULATORS FOR ANTICANCER THERAPY

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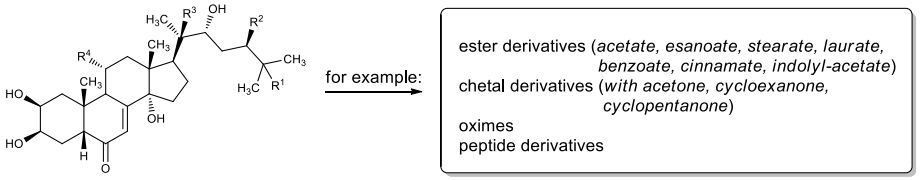
Ecdysteroids are an emerging potential class of secondary metabolites from plants for anticancer chemotherapy. They are insect steroid hormones which trigger metamorphosis in insects, for example *Drosophila melanogaster*, but they are also frequently found in plants including spinach and quinoa, where they apparently play a defensive role.[1] Positive effects of ecdysteroids on mammals have been studied over the years, so that food supplements containing ecdysteroids have been developed and supposed to be safe "green anabolics". Recent studies from Hunyadi et al.,[2] found that certain ecdysteroids, such as the most common 20-hydroxyecdysone, significantly decrease the resistance of a multi-drug resistant (MDR) murine leukemia cell line expressing the human ABCB1 transporter to doxorubicin, a known chemotherapeutic agent that is a substrate of the ABCB1 transporter. Acquisition of multidrug resistance (MDR) remains a major impediment to successful chemotherapy. MDR is considered to be a multifactorial event, including decreased drug accumulation, increased efflux, modification of drug targets and defects in cellular pathways. The ABCB1 transporter is a membrane-associated P-glycoprotein which acts as drug efflux pump with broad substrate specificity.



20-Hydroxyecdysone ($R^1 = R^3 = OH$, $R^2 = R^4 = H$)
Ponasterone A ($R^1 = R^2 = R^4 = H$, $R^3 = OH$)
Makisterone A ($R^1 = R^3 = OH$, $R^2 = CH_3$, $R^4 = H$)
Ecdysone ($R^1 = OH$, $R^2 = R^3 = R^4 = H$)
Ajugasterone C ($R^1 = R^2 = H$, $R^3 = R^4 = OH$)

Aiming to investigate the potential useful role of ecdysteroids as MDR modulators, we pursued the synthesis of a small library of derivatives, focusing on a wide range of naturally occurring minor ecdysteroids, besides the well known 20-hydroxyecdysone. Among them, we are evaluating in particular ponasterone A, because of its unique capacity of interaction with the mammalian expression system, recently resulting in the development of ponasterone A-based useful tools for modulating gene expression in mammalian cells and transgenic animals.[3] In order to deepen understanding of the key role of polarity in determining the MDR modulation, we applied various functional groups modifications, mostly by means of esterification and protection of all or selected hydroxyl groups. We also developed innovative structural modifications, involving the cholesterol-originated side-chain and the ecdysteroid characteristic 7-en-6-one (α,β-unsaturated ketone) functional group in the B-ring. Biological evaluation of all synthesized compounds as resistance modulators, also in combination with well assessed drugs, is currently underway, as well as computational docking studies on selected molecules, aimed to characterize the substrate-binding site interaction within the human P-glycoprotein homology model structure.

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SYNTHESIS OF NEW NTS2 SELECTIVE NT(8-13) PEPTIDE ANALOGUES BY INCORPORATION OF A Cᵅ-TETRASUBSTITUTED AMINO ACID BY USING SPPS

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The tridecapeptide pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH is known as neuropeptide neurotensin,[1] which is located and produced in the gastrointestinal tract, the central nervous system and the brain.[2] Acting as a neuromodulator, a wide range of biological functions are mediated by the binding of neurotensin to three different neurotensin receptors (NTS1, NTS2, NTS3) which are known so far. For example, the different physiological effects, which are associated with NTS2 are hypothermia,[3] antipsychotic properties[4] and the promotion of μ-opioid-independent antinociception[5] as an important part in the modulation of tonic pain sensitivity.[6] Investigations proofed that the C-terminal fragment NT(8-13) is representing the pharmacological active part[7] of neurotensin and therefore the most applied lead structure for the development of NTS1 as well as NTS2 selective ligands as therapeutic agents or for the use in imaging.

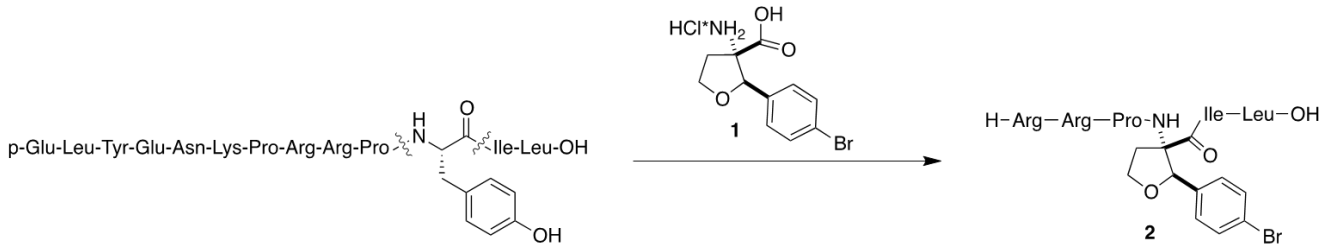

Figure 1. Incorporation of compound **1** as modification of NT (8-13) leading to the target structure **2**

We synthesised of a small peptide library incorporating the unnatural amino acid HCl*H-TAA-Br **1** by solid phase supported peptide synthesis. The tetrahydrofuran amino acid[8] **1** is used to replace Tyr^{11} leading to new NT(8-13) peptide mimetics (Figure 1). Biological investigations employing a radio ligand binding assay were performed revealing selectivity towards hNTS2.

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AZAHETEROCYCLIC AND ALIPHATIC THIOLS IN THE DESIGN OF NITROSYL FERREDOXIN MIMETICS - NEW CLASS OF MEDICINES FOR THERAPY OF SOCIALLY SIGNIFICANT DISEASES

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Nitric monoxide (NO) therapy is the newest approach to the treatment of socially important diseases all over the world. Nitric oxide (NO) is a multi-functional molecule able to interact with many cellular targets. Considerable experimental material has been accumulated, which demonstrates that NO participates both in the development of pathologic processes, and in their correction by chemotherapeutic methods [1-4]. In addition to many studies aimed at the search for compounds-traps for the excess NO, the interest is growing to the search for new classes of compounds that generate NO, which could be the base for a new generation of medications easily delivering NO to biologic targets.

Functional thiols having a high coordination activity, antineoplastic (especially the thioderivatives of benzimidazole, benzotiazole, pyridine, pyrimidine, etc.) and cardioprotective (penicillamine, glutathione, thiosulfate, etc.) effects were used for the isolation of mimetics of nitrosyl non-heme proteins active sites [5].

Fundamental researchs of the structures and properties including pharmacological activity of these compounds in the solid phase and in the solutions were performed. High anticancer activity *in vitro* and *in vivo* has been first shown for a series of nitrosyl iron complexes. Functional sulfur-containing ligands in these complexes are reversible inhibitors for synthesis of cellular DNA, and they suppress the growth of tumors of various genesis, while the NO group, being the second component of the hybrid complex, is a key signal molecule that controls the tumor growth [6-9]. On the models of ischemic and reperfusion injury of Wistar rats' heart, it has been shown that some nitrosyl iron complexes have cardioprotective effect [10,11].The functions of NO in the regulation of the reversible processes of Fe-S cluster assembly in proteins and the formation of *Escherichia coli* biofilms have been investigated.

Nitrosyl complex with cysteamine in physiological concentrations suppressed the formation of mature biofilms, and the activity of this compound was comparable to that of antibiotic ciprofloxacine as positive control [12].

The work has been performed under financial support of Program of the Presidium of RAS No.24.

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SYNTHESIS AND ANTI-LEISHMANIAL ACTIVITY OF SELECTED TETRAOXANES

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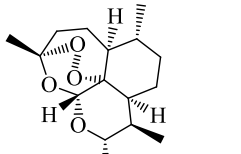
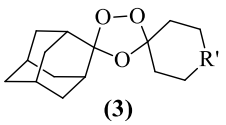
Leishmaniasis, a protozoal tropical disease, is the most prevalent vector-borne infectious disease after malaria. Leishmania spp are the causative agent of human and canine leishmaniasis[1]. Currently available drugs (e.g. pentavalent antimonials, paromomycin, liposomal amphotericin-B and miltefosine) are expensive, show toxicity to the host and declining efficacy, mostly due to increasing selection of resistance[2]. According to WHO, the development of safe and cost-effective drugs against leishmaniasis is of upmost urgency.

Artemisinin and derivatives (ART's) (1,2) exhibit high anti-protozoan activity against *Plasmodia* spp. and low toxicity to the host. These compounds and are widely known antimalarial drugs. It is proposed to earlier studies demonstrated the activity of fluoro-artemisinins against promastigote forms of *Leishmania donovani*[3]. However, no activity was perceived against corresponding intramacrophage amastigote forms. In a recent investigation it was the susceptibility of *Leishmania infantum* life stage forms (promastigote and amastigote) to selected trioxolanes (3) with known antiplasmodial activity. The compounds tested exhibited similar activity and lower cytotoxicity than AmphB, demonstrating the potential of the peroxide chemotype as a tool for leishmaniasis chemotherapy in mammalian host[4]. We now report on the synthesis and activity of a representative library of 1,2,4,5-tetraoxanes (4) against axenic and intramacrophage amastigote forms of *Leishmania donovani*.



R=CH_3 **(1)**; OR

$COCH_2CH_2COONa$ **(2)**



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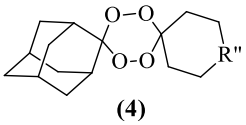

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Acknowledgements: CCMAR/UAlg, 'Fundação para a Ciência e a Tecnologia' (FCT), FEDER, through projects PTDC/QUI-BIQ/112943/2009 and Pest-C/MAR/LA0015/2013.

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FROM CHITIN TO BACTERIAL PEPTIDOGLYCAN: AN UNEXPLORED CHEMOENZYMATIC APPROACH

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Peptidoglycan (PGN), a major component of the bacterial cell wall, is made of repeating N-acetylglucosamine (NAG) - N-acetylmuramic (NAM) disaccharide units, linked via [NAG-(β-1,4)-NAM] linkage, with a pentapeptide attached to the D-lactyl moiety of each NAM. The structure of the PGN macromolecule determines bacteria shape and provides the mechanical strength required to resist osmotic challenges[1]. Most important, the synthesis and composition of the PGN is associated with expression of bacterial resistance to different antibiotics and with a variety of host/bacteria interactions.

The determination of the role of PGN in host disease has been hampered by the lack of pure and homogeneous polymerized PGN. We are addressing this problem by chemically synthesizing PGN polymers. There are two major obstacles for this synthesis: (i) the presence of a β-1,4 glycosidic bond, as it becomes necessary to perform multistep synthetic sequences to obtain a regio and stereoselective assembly of glycosidic bonds which is crucial for biological activity and (ii) the difficulty in obtaining sufficient long PGN fragments to replace samples of biological origin. Therefore, we and others have restricted our studies to the use of small PGN fragments [2], isolated from bacteria, or of expensive low-molecular weight synthetic PGN monomers and dimers whose synthesis requires 37 synthetic steps [3].

Our strategy consisted on establishing a large-scale chemoenzymatic route capable of converting chitin into PGN polymers of different composition. Chitin is a β-1,4-linked NAG biopolymer and it can be modified into PGN by linking a lactate unit in alternating NAG units to which peptides may be connected. This results in a polymer possessing the glycosidic bonds with the correct regio and stereoselectivity as they were originally present in the chitin substrate.

This presentation will focus on our recent strategy to assemble PGN surrogates of homogenous composition from chitin, involving a chemoenzymatic approach.

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INVESTIGATION OF THE INTERACTION OF VANCOMYCIN WITH SYNTHETIC BACTERIAL MUROPEPTIDES

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Vancomycin is a member of the glycopeptides family antibiotics considered a last-resort agent in the treatment of infections caused by Gram-positive bacteria.[1] In order to find new agents to combat bacteria resistance it is important to understand the details of the mechanism of action of glycopeptides antibiotics.[2] Those antibiotics prevent the formation of peptidoglycan (PGN), the major component of the bacterial cell wall which is constituted by a glycan chain of alternating β(1→4)-linked *N*-acetylglucosamine (GlcNAc) and *N*-acetylmuramic acid (MurNAc), cross-linked by short peptide bridges.[3]

It is well established that the replacement of the last amino acid in the peptide chain linked to the MurNAc moiety changes the interaction with the glycopeptides antibiotics. So far the interactions studies have been limited to the use of *N*-protected dipeptides and tripeptides.[4] In order to clarify how the different compositions of the bacterial peptide chain and carbohydrate unit affect the recognition by vancomycin we have developed a study involving synthesis and screening of small bacterial muropeptides.

We have been dedicated to the synthesis of glucosamine disaccharides and GlcNAc-MurNAc moieties.[5] Herein we will present our studies on the interaction between vancomycin and the synthesized muropeptides.

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PHOTODYNAMIC PHTHALOCYANINES AND AZAPHTHALOCYANINES FOR CONJUGATION WITH OLIGONUCLEOTIDES AS POTENTIAL THIRD GENERATION PHOTOSENSITIZERS

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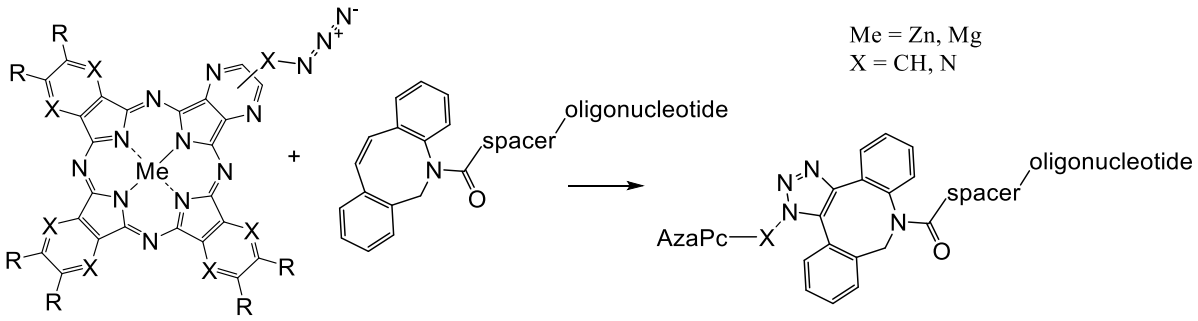
Photosensitizers are molecules with low dark toxicity able to produce toxic oxygen species after excitation by light of appropriate wavelength. Excellent photochemical and photophysical properties, especially capability of high singlet oxygen production, make phthalocyanines (Pc) and their aza-analogues (AzaPc) very efficient photosensitizers[1]. Moreover, Pc and AzaPc show high fluorescence quantum yields, which can be employed in molecular biology based diagnostic methods. To target a specific tissue, photosensitizers and fluorophores are often modified with appropriate moiety. One possibility is attaching a synthetic oligonucleotide as a tool targeting either a complementary sequence (in case of antisense technology) or even almost any structure (in case of an oligonucleotide aptamer). While *in vivo* kinetics of such photosensitizer conjugates is problematic, *ex-vivo* treatment can be feasible.

Azido group modified non-symmetrical AzaPc of AAAB type bearing various peripheral substituents were synthesized using statistical condensation. Their conjugates with oligonucleotides were prepared by solid phase labeling of oligonucleotides, which is highly advantageous considering the purification of the product and possibility to use water insoluble photosensitizer molecule. Several variations of Huisgen cycloaddition "click" method were employed for the conjugation finding the copper free azide-cyclooctyne click chemistry[2] to be the most efficient.



Photophysical and photochemical properties of the prepared AzaPc-oligonucleotide conjugates were tested in water solutions to examine their potential for use in biological environment.

Aknowledgements: The work was supported by Czech Science Foundation, project No. 13-27761S.

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RIBOSOME TARGETING ANTIBIOTICS AS SCAFFOLDS FOR NOVEL BACTERIAL MEMBRANE DISRUPTORS

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Infections caused by drug resistant and slow-growing bacteria are increasingly becoming a one of the greatest challenges of worldwide health organizations. The decrease in the efficacy of a large percentage of the current repertoire of clinically used antibiotics against these types of infections emphasizes the need for the development of novel antimicrobial agents that will effectively eradicate a broad spectrum of bacteria regardless of the bacterial cell cycle stage. To date, the concept of disrupting bacterial membranes as a strategy to develop antibiotics has been poorly exploited even though such antibiotics should be un-affected by the bacterial cell cycle and its intracellular resistance mechanisms, and therefore offer a solution to persistent infections.

In this study we used the ribosome targeting aminoglycoside antibiotic tobramycin, as a scaffold for the synthesis of novel bacterial membrane disruptors. We designed antimicrobial cationic amphiphiles by varying several structural parameters: the length of the hydrophobic residues attached to the aminoglycoside, the type and number of hydrophobic residues, the hydrophobicity/hydrophilicity ratio and the linkage between the hydrophobic and hydrophilic parts.[1-4]

Antimicrobial activity, membrane selectivity and structure activity relationship were studied. Some of the cationic amphiphiles in this study demonstrated marked antimicrobial activity against a broad selection of Gram-positive and Gram-negative pathogens. These compounds, which no longer target the ribosome, were well over an order of magnitude more potent against the tested pathogens than the parent antibiotic tobramycin and the membrane-targeting antimicrobial peptide mixture gramicidin D that are in clinical use.

The results of this study demonstrate that it is possible to design aminoglycoside-base membrane targeting antibiotics which demonstrate enhanced selectivity to bacterial membranes.

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EN ROUTE TO PROTEASE-TRIGGERED CARBON MONOXIDE RELEASING MOLECULES

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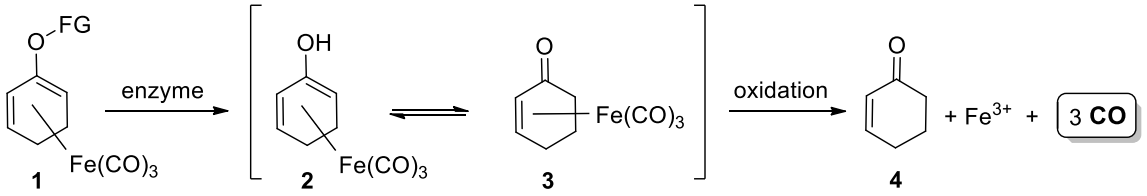
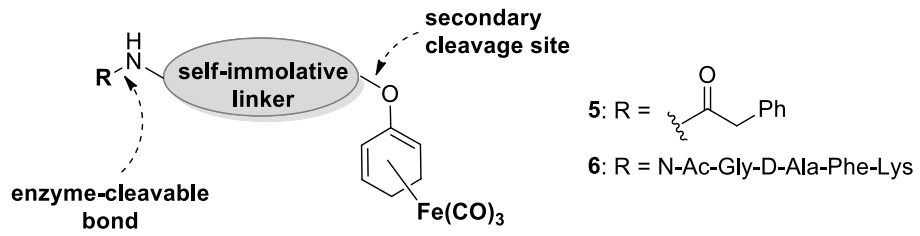
Carbon monoxide is an essential biological signaling molecule, which is endogenously produced in humans.[1,2] The potential of CO as a therapeutic agent is evidenced by its pronounced anti-inflammatory, cytoprotective, and anti-hypertensive activity.[1] However, the pharmacological use of gaseous CO is hampered by a high risk of intoxication and a lack of tissue selectivity.[1] CO-releasing molecules (CORMs) have recently emerged as potential tools for the *in vivo* administration of CO.[3,4] In the search for tissue or cell-specific CORMs we recently introduced η^4-acyloxy-cyclohexadiene-$Fe(CO)_3$ complexes as enzyme-triggered CORMs (ET-CORMs).[5,6] These compounds release their CO load after activation by a hydrolytic enzyme.



Basing on the presented concept, current research efforts are aimed at the development of protease-triggered CORMs, as modifications in proteolytic activity are known to be associated with diseases like cancer, rheumatoid arthritis and cardiovascular disorders.[7] As model systems, a series of penicillin G amidase-cleavable compounds with a general tripartite structure **5** was synthesized. The expected amidase-triggered decay associated to the release of CO was confirmed by HPLC studies, headspace GC CO release measurements as well as in a cell-based assay.



The synthesis of more advanced derivatives of type **6** carrying a plasmin or cathepsin B-specific oligopeptide specifier was also achieved recently.

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GLYCOSYLATED NAPHTHALIMIDES AS ENZYME ACTIVATED ANTI-CANCER THERAPEUTICS

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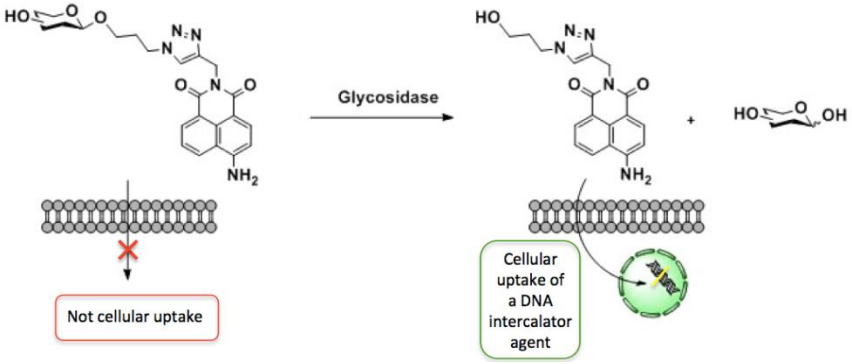
Carbohydrates are ubiquitous in nature and play a fundamental role in a wide range of biological processes including cell-cell recognition, signalling and inflammation.[1] Several carbohydrate-based drugs have been developed as effective cancer therapies.[2] Naphthalimides are well known to behave as DNA intercalators; capable of disrupting the DNA structure and inhibiting topoisomerase II activity, making them feasible anticancer drugs candidates. Due to their interesting fluorescence properties they have also been studied intensively over the last years as fluorescent tags, chemo sensors and dyes.[3]

A family of glycosylated naphthalimides has been synthesised and tested for anti-cancer activity *in vitro*. The glycoconjugates do not undergo endocytosis directly; instead, a novel glycosidase activated drug-release mechanism was employed to release the active naphthalimide substrate, which is rapidly endocytosed by cancer cells.



The fluorescence properties of the naphthalimides allow the cell uptake to be monitored. It has been observed that the naphthalimide moiety undergoes intercalation in nuclear DNA of cancer cells following endocytosis. The biological behavior of these compounds has been studied in three different cell lines that express specific carbohydrate receptors to identify possible lectin-dependent behavior.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF LANTHANIDE-BASED PROBES FOR THE DETECTION OF GLYCOSIDASE ENZYMES

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In nature, the hydrolysis of glycosidic bonds is catalysed by a class of enzymes known as glycosidases. These enzymes increase the rate of hydrolysis rate by 10^{17} fold when compared to spontaneous hydrolysis events and they exhibit exquisite substrate selectivity.[1] Approximately 3% of the human genome is dedicated to encoding these carbohydrate active enzymes which highlights their biological importance.[2] The realisation of glycosidases' dominant role in many biological and industrial processes has boosted research into the development of techniques to accurately detect and profile these enzymes so as to improve understanding of their function.

Lanthanide-based probes are highly sensitive and can be used to detect enzyme activity *in vitro*.[3] The intricate optical and spectroscopic properties of the lanthanides make them useful spectroscopic handles for probing such interactions. The lanthanides display many desirable photophysical properties including long wavelength emission and long lived excited states which renders them ideal for biological applications.

We have prepared and evaluated a range of glycosylated lanthanide-based probes for the detection of glycosidases. In this work, we present an array of novel, bio-responsive probes possessing a carbohydrate group conjugated to octadentate Tb(III) cyclen complex. Upon action of a glycosidase enzyme, hydrolysis of the glycosidic linkage occurs, releasing the free saccharide with concomitant modulation of the lanthanide luminescence.

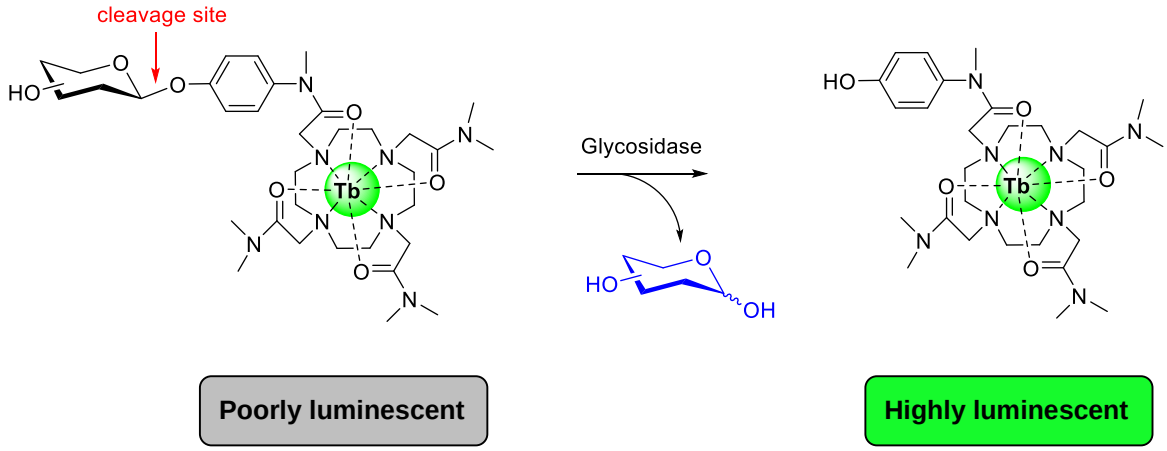

Figure 1. Schematic representation of probes for the detection of glycosidase enzymes.

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PREPARATION OF GLYCONANOPARTICLES DISPLAYING *p*-HBAD GLYCANS AS VACCINE CANDIDATES AGAINST MYCOBACTERIUM TUBERCULOSIS

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Tuberculosis is a global pandemic caused by *mycobacterium Tuberculosis* infecting 9 million people and killing 1.5 million people annually.[1] Currently the only vaccine available for the disease is the Bacillus Calmette-Guérin (BCG) vaccine, which has variable efficacy. There is emerging interest in the field of immunology towards the development of glyconanoparticles as vaccines. The *para*-hydroxybenzoic acid derivatives (*p*-HBADs) produced by *mycobacterium Tuberculosis* have been found to induce immune response *in vitro*.[2]

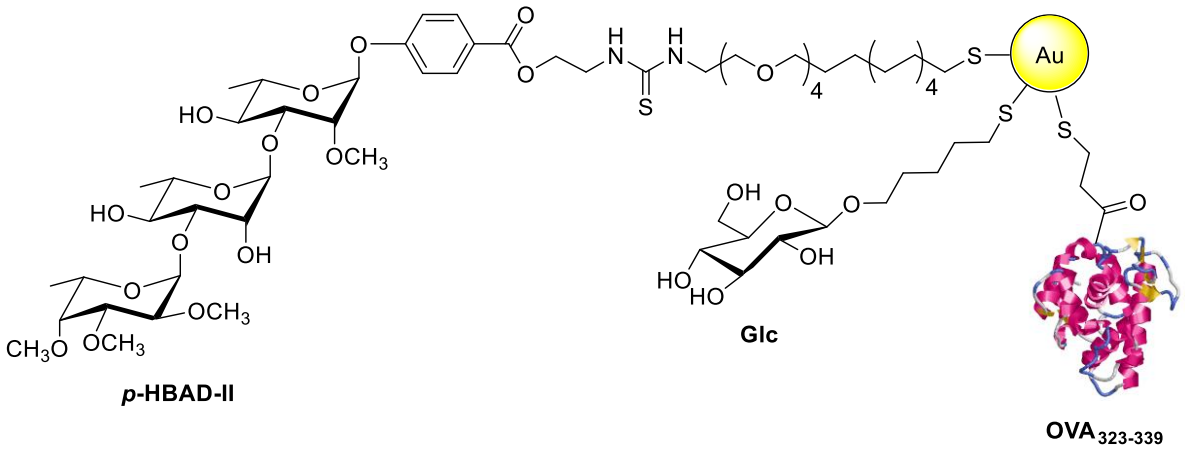

Figure 1. Schematic representation of the glyco-AuNP surface containing *p*-HBAD-II, glucose and T-helper ovalbumin 323-339 peptide $OVA_{323-339}$.

The *p*-HBAD glycans produced by *mycobacterium Tuberculosis* were prepared *via* an efficient synthetic route. The synthetic *p*-HBADs were conjugated to a linker displaying a terminal thiol residue suitable for array on gold nanoparticles.[3] An immunologically active T-helper ovalbumin 323-339 peptide $OVA_{323-339}$ was incorporated onto the surface of the gold nanoparticles to allow for T-cell activation.[4] The immunomodulatory effects of these functionalised nanomaterials on the production of inflammatory cytokines was investigated.

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ANTIPLASMODIAL ACTIVITY AND COMPUTACIONAL STUDIES OF NEW BIFLAVONOID DERIVATIVES

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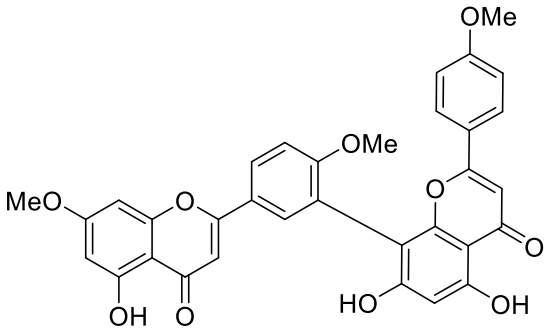
Malaria is a major global disease caused by parasites of the genus *Plasmodium* mainly affecting people living in the least developed countries. In 2012, more than 200 million cases of malaria were reported, resulting in approximately one million deaths. *Plasmodium falciparum* infection is the biggest cause of mortality although other malarias contribute significantly to the considerable humanitarian and economic burdens in malaria endemic regions.[1] Because of parasites have developed resistance to all historically used antimalarials, and in the absence of effective antimalarial vaccines, low molecular weight antimalarial drugs are important weapons against the disease.[2]

In this sense the bisflavonoid sciadopitysin isolated from *Retrophylum* rospigloisii[3] presents a high antiplasmodial activity against F-32 Tanzania (chloroquine sensitive) strains of *Plasmodium falciparum*. From this natural biflavonoid a series of derivatives were prepared in order to evaluate the role of the different substituents in the activity. In this communication we report the results obtained and we also include molecular computacional studies.



Acknowledgments: We thanks MINECO (SAF2012-37344-CO3-01) and EU Research Potential (FP7-REGPOT-2012-CT2012-31G37-IMBRAIM) for financial support.

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BASHY COMPLEXES: CONSTRUCTION AND CHARACTERIZATION OF BORONIC ACID BASED FLUORESCENT DYES

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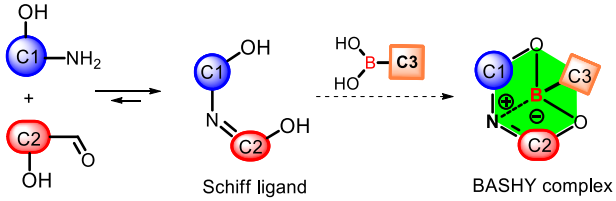
Organic fluorescent dyes have gathered the attention of a diverse community of researchers in fields as plastic electronics and theranostics. Highly fluorescent compounds as borondipyrromethene (BODIPY) chromophores have been extensively used in different applications due to a remarkable combination of photophysical properties.The success of BODIPY derivatives triggered the engineering of fluorescent molecules featuring a central boron(III) atom coordinated to bidentate ligands. Boron will improve the ligand's stability and enhance the construct planarity, conjugation and charge transfer throughout the π-system.[1]

Boronic acids (BAs) are known to form fluorescent complexes upon binding with bidentate ligands. However, this coordination is reversible and the constructs lack the stability required to be used as dyes. Otherwise, BAs generate more stable complexes with tridentate ligands, though these boronates are often poorly fluorescent because the central boron atom adopts an out of plane tetrahedral geometry that compromises the ligand's planarity.[2]

Based on our experience in the preparation of boronates from schiff ligands, we expect to overcome the aforementioned issues, since the modular construction of schiff ligands maybe be specifically engineered to accommodate BAs in the form of a configurationally stable π-conjugated complex. Herein, we present a new class of fluorescent boronate complexes, boronic acid salicylidenehydrazone (BASHY) which were construct in an one pot fashion from 3 different modules (scheme 1).[3]



Scheme 1. Construction of BASHY complexes.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (SFRH/BD/94779/2013).

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NEW RUTHENIUM(II) COMPLEXES AS GOOD COLORECTAL ANTICANCER AGENTS

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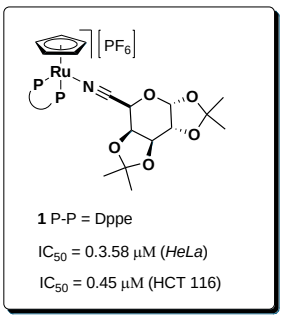
Colorectal cancer is the second most common cancer in developed countries, and a major cause of cancer-related deaths worldwide. The development of new metallodrugs with high antitumor activity, low toxicity is highly desired and it is also a challenge in drug design.

In last years, ruthenium complexes appear as an excellent alternative to Pt metallodrugs due to their lower general toxicity attributed to the higher specificity of the Ru complexes for cancer cells comparing with healthy tissue.[1]

Recently, we synthesized several ruthenium(II) complexes bearing carbohydrate moieties such as complex **1** that showed good cytotoxicity on *HeLa* cancer cells (cervical carcinoma) with IC_{50} value in the low micromolar range, better than cisplatin.[2] We also demonstrated that a variety of ruthenium(II) complexes containing a carbohydrate moiety such as complexes **1** and **2** are good colorectal anticancer agents.[3]

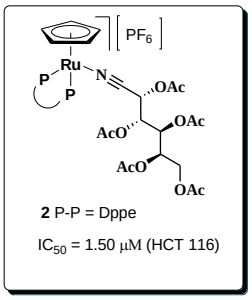
In continuation of our work, in this communication we report the synthesis and cytotoxicity, on HCT116 colorectal cancer cells, of new ruthenium(II) complexes with different nucleosides and drug moieties such as the 5-Fluorouracil (5-FU), which has been largely used in the treatment of various cancers, including colorectal cancer.



1 P-P = Dppe

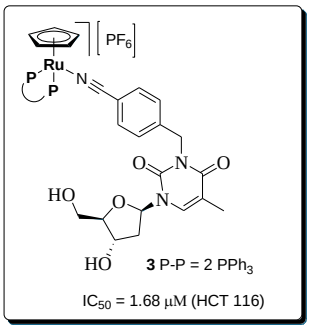
IC_{50} = 0.3.58 μM (*HeLa*)

IC_{50} = 0.45 μM (HCT 116)



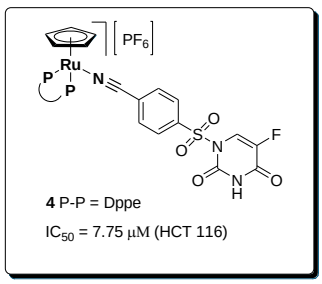
2 P-P = Dppe

IC_{50} = 1.50 μM (HCT 116)



3 P-P = 2 PPh_3

IC_{50} = 1.68 μM (HCT 116)



4 P-P = Dppe

IC_{50} = 7.75 μM (HCT 116)

Acknowledgments*:* This research was supported by FCT through projects PTDC/QUI-QUI/102114/2008 and PTDC/QUI-QUI/110532/2009 and annual funds UID/QUI/00100/2013. PRF and DMP (SFRH/BD/96517/2013) thank FCT for grants.

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ANTIMICROBIAL ACTIVITY AND TOXICITY EVALUATION OF CHOLINE ANALOGUES

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Choline is a building block for cell membrane formation[1,2] and for the synthesis of the neurotransmitter acetylcholine.[2] The choline-based ionic liquids (ILs) has raised particular attention in the design of "greener" ILs.[1,2] Such evaluation has been documented in literature for some ILs and the marine bacteria *Vibrio fischeri* has been a common model used for assessment of their impact in the aquatic environment.[3,4] Data shows that toxicity is highly dependent on the structural modifications of the cholinium, namely alkyl chain length, number of hydroxyethyl groups and insertion of carbon–carbon multiple bonds, and that dicationic compounds induced a significantly lower toxicity than their monocationic counterparts.[3] Human cell lines as HT-29 and CaCo-2 have been applied for studying of ILs toxicity in human beings.[5] Additionally, the study of choline-based ionic liquids with the magnetic anions $[FeCl_4]$, $[GdCl_6]$, $[CoCl_4]$ and $[MnCl_4]$ has also been studied by our group and resultant data shows that $[FeCl_4]$ followed by $[GdCl_6]$ are the best magnetic anions.[6] Such guidelines are important to direct the design of safer choline-based ILs.

In addition, several reports on the literature have demonstrated that choline-based ILs can exert a broad-spectrum of antimicrobial activity including Gram-positive and Gram-negative bacteria.[1] In this view, we have tested the toxicity and antimicrobial activity of a wide range of choline-based ILs synthesized through alkylation of the amine with the correspondent halide in MeCN. The antimicrobial and the toxicity results were correlated with each other resulting in the discovery of interesting low toxic ILs with a high antimicrobial activity.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (SFRH/BPD/73822/2010, SFRH/BPD/88666/2012 and PTDC/QEQ-PRS/2824/2012).

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DESIGN OF UREA-BASED ANION RECEPTORS WITH ANTICANCER PROPERTIES

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Channelopathies are diseases caused by genetic mutations of the proteins responsible for the regulation of the ion transport in cells.[1] For instance, a chloride transport deficiency is expressed in cystic fibrosis (CF), which is the most common life-threatening genetic disease in humans.[2] In addition, there are several studies that infer a link between anion transport and anticancer activity, for instance, it is known that the activation of K^+ and Cl^- efflux channels originate a cell volume decrease, inducing apoptosis of cancer cells.[3]

On the other hand, Ataluren (Translarna™, Figure 1) is a small molecule, incorporating 1,2,4- -oxadiazole ring, is currently in phase III clinical trial in the USA and recommended for approval in the EU for CF.[4–7] Inspired in this drug-like molecule, we have devised two series of small anion receptors composed of urea binding moiety linked by the ethylenediamine to an amide binding unit decorated with 1,3,4-oxadiazole or 1,2,4-ozadiazole rings (Figure 1, **1** and **2**, respectively). Herein, we report the synthesis and binding affinity of these receptors for biological anions (chloride and bicarbonate) together with their transmembrane anion transport and cytotoxicity properties against human cancer cell lines.

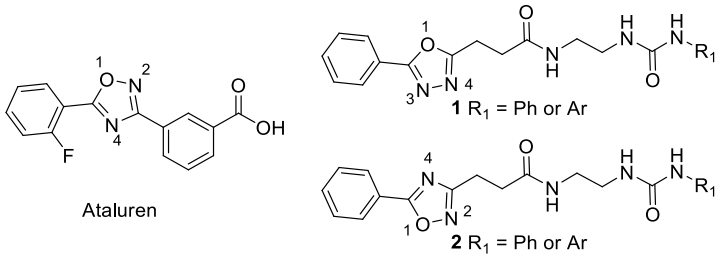

Figure 1

Acknowledgements: This work was financially supported by National Funds through FCT under projects PTDC/QUI-QUI/101022/2008 and PEst-UID/MULTI/00612/2013. J.M. Caio also thanks FCT for his PhD fellowship SFRH/BD/66789/2009.

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2,4-DISUBSTITUTED CYCLOPENTENONES AS ANTIPROLIFERATIVE AGENTS: DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES AND BIOLOGICAL ACTIVITY

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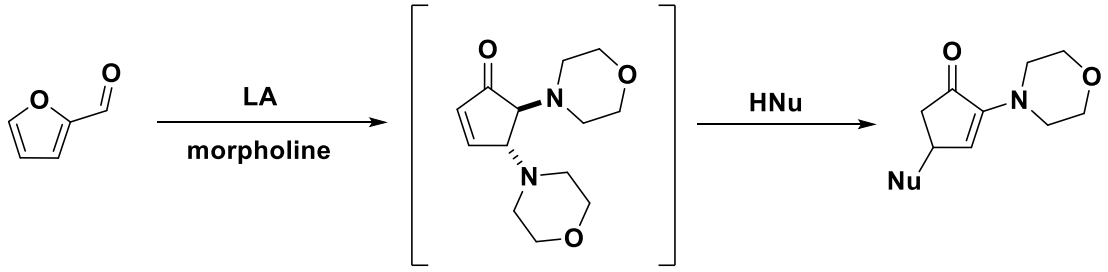
Bifunctionalised cyclopentenones are versatile building blocks for the synthesis of natural products. In particular, C-2 amino[1] and C-2 hydroxy cyclopentenones.[2] Additionally, cyclopentenone scaffold has been described as a transcription factor – NF-□B inhibitor, leading subsequently to the apoptosis of estrogen receptor-negative breast cancer cells; and inhibit the growth of both melanoma and NSCLC cells.[3]

Due to the great relevance of this core and based on the recent work developed by Batey *et al*.,[4] where it is described a one-step conversion of 2-furaldehyde to trans-4,5-diamino cyclopentenones *via* electrocyclic rearrangement of an intermediate enamine, and also based on our previous work,[5] an efficient method for synthesis of carbocycles, including 2,4-bifunctionalised cyclopentenones from 2-furaldehyde (Scheme 1) will be present as well as the anti-proliferative activity towards a cell lung cancer (NCI-H460) and other cancer cell lines from breast (MCF-7, MDA-MB-231) and colon (HT-29).



Scheme 1. Synthetic approach for the synthesis of 2,4-disubstituted cyclopentenones.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (SFRH/BPD/75045/2010, SFRH/BPD/73822/2010, PTDC/QUI-QUI/119823/2010).

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SYNTHESIS OF MOLECULAR PROBES TOWARD DISEASE BIOMARKER DISCOVERY

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Advances in biomarker discovery are closely related to the technological development of powerful analytical tools. Nevertheless, there is a substantial translational gap from biomarker discovery to their clinical applications and only a few receive regulatory approval every year. Activity-based protein profiling has emerged as a powerful technique for proteome analysis and, unlike classical proteomics, allows the quantification of enzymes in their active catalytic state by covalent attachment of a synthetic probe to the enzyme active site. Proteases are the largest family of enzymes and comprise an estimated 2% of the human genome being involved in a wide range of biological processes. Hence, the adequate design of specific targeted molecular probes may lead to selective, efficient and easy to handle assays for biomarker discovery and validation.[1]

Chronic obstructive pulmonary disease (COPD) is the third leading cause of dead worldwide and Human Neutrophil Elastase (HNE) is a serine protease that plays an important disruptive role in the onset and progression of this disease, leading to lung tissue damage.[2] HNE specific activity is then clinically relevant for the diagnosis and prognosis of COPD, and adequate chemical probes can be designed to quantify the active catalytic state of these enzymes. On the basis of this work is the rational design, synthesis and evaluation of activity-based probes targeting HNE toward the pioneer application to COPD proteome analysis, with the ultimate goal of validating HNE as COPD potential diagnostic tool. Proof-of-concept using clickable `4-oxo-β-lactam-based probes (Figure 1) showed that inhibitory activity of the 4-oxo-β-lactam (potent covalent HNE inhibitor) was not affected by incorporating the tag and, more importantly, internalization in human neutrophils and selective detection of HNE in a large excess of cell lysate proteins was observed. Further synthetic studies on the chemical warhead, linker and tag optimization to target HNE and other serine proteases will be presented.

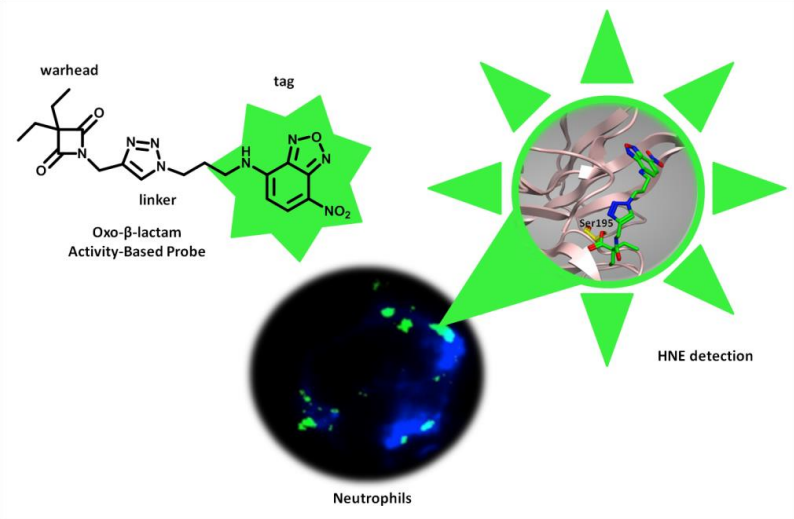

Figure 1. Activity-based probe for human neutrophil elastase related proteomes.

Aknowledgements: E.F.P. Ruivo acknowledges a research grant awarded by Fundação AstraZeneca Innovate Competition (Portugal). S. D. Lucas is a FCT Investigator (IF/00472/2014).

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SELECTIVE INHIBITION OF BACTERIAL TOPOISOMERASE I BY ALKYNYL BIS-BENZIMDIAZOLES

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New approaches for the discovery of antibacterial drugs are paramount to our efforts in the continuing fight against bacterial resistance. In this regard, enzyme inhibitors that selectively target a bacterial enzyme over their human counterpart offer unique opportunities for such selective inhibition approaches. Bacterial DNA topoisomerases are one such class of enzymes that help in regulating DNA topology. The cellular functions of topoisomerases include relaxing supercoils in DNA as well as introducing supercoils to their DNA substrates. These functions of DNA topoisomerases can be used to develop anticancer or antibacterial agents.

The therapeutic interest in the development of small molecules as inhibitors of DNA topoisomerase lies in their ability to act as both cleavable complex stabilizing agents as well as in their ability to bind at the ATP binding site.

We have performed the synthesis, nucleic acid binding, topoisomerase I activity, and antimicrobial activity of functionalized bisbenzimidazoles. The addition of alkyne functionalized alkyl chain converts Hoechst 33258 from a non-selective topoisomerase (bacterial and human) inhibitor to a highly selective bacterial topoisomerase I inhibitor. The results obtained opens up a new approach to targeting bacterial topoisomerases and the potential role of a hydrophobic pocket in the DNA–E. coli topoisomerase I complex.

KINETIC STUDY OF MINERAL ACID-CATALYZED CONVERSION OF 7-ETHYLTRIPTOPHOL TO METHYL ESTER OF ETODOLAC

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Etodolac, 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetic acid is a non-steroidal antiinflamatory antirheumatic drug. A key intermediate in the synthesis of Etodolac is its methyl ester which can be obtained by oxa-Pictet-Spengler reaction, starting from 7-ethyltriptophol. Pyrano[3,4-*b*]indole ring is closed in the reaction of 7-ethyltriptophol and β-ketoester, methyl 3-oxo-pentanoate. For the preparation of oxacycle (pyranic ring) different Brönsted and Lewis acids can be employed.[1] Typically, aqueous hydrochloric or sulfuric acid, as well as boron trifuoride etherate, gasous hydrochloride, *p*-toluensulfonic acid, zink chloride, aluminium chloride and tin(IV) chloride in organic solvents are used to promote the reaction. Catalyst such as boron trifuoride etherate is expensive and is stable only in a perfectly anhydrous environment, which is difficult to manage, especially in productions on a larger scale. Therefore, the processes in which inorganic mineral acids can be used are preferred.[2] We report the kinetic study of conversion of 7-ethyltriptophol to methyl ester of Etodolac in methanol in the presence of concentrated hydrochloric and sulfuric acids. In order to optimize the synthetic procedure, kinetic profiles of reactions promoted with different molar ratios of acids (with respect to the β-ketoester) were determined using HPLC as a method of choice.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF STABLE HETEROAROMATIC LIPOXIN A_4 ANALOGUES

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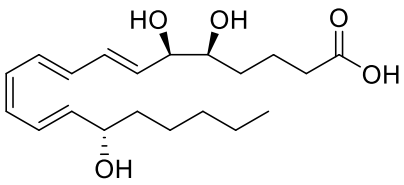
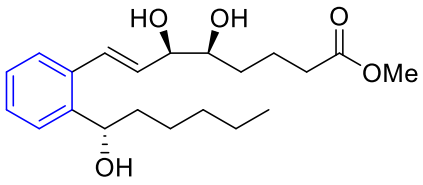
Lipoxins are trihydroxytetraene-containing eicosanoids that are biosynthesised from arachidonic acid by lipoxygenase enzymes and possess potent and selective anti-inflammatory activity. There are two native lipoxins; LXA_4 and LXB_4. These were first isolated from human leukocytes by Serhan and Samuelsson in 1984.[1] They activate the ALX receptor on polymorphonuclear leukocytes (PMNs) and monocytes preventing the migration of neutrophils to sites of inflammation thus acting as stop signals. Due to this anti-inflammatory activity, lipoxins are of interest as potential drug candidates for inflammatory diseases such as asthma, rheumatoid arthritis, atherosclerosis, psoriasis, periodontal disease and cystic fibrosis.[2]

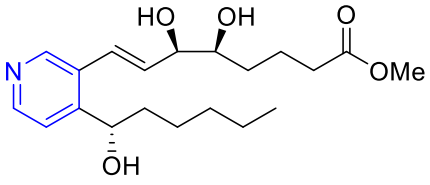
LXA_4 is rapidly metabolised *in vivo* and in an effort to prevent this, recent research has been carried out towards the development of more stable analogues.[3] Substantial work has been carried out by our research group in this area, with the successful synthesis of stable benzene and pyridine analogues.[4,5] These analogues were found to significantly increase phagocytosis of apoptotic PMN's compared to native LXA_4 and to supress key cytokines involved in inflammatory diseases.



LXA_4



Benzene Analogue



Pyridine Analogue

Our research group is carrying out an extensive SAR lipoxin programme in an effort to design and develop further analogues with increased potency and stability. This poster will outline the synthesis of some novel heteroaromatic LXA_4 analogues which features a Suzuki-Miyaura cross-coupling and an asymmetric hydrogenation as the key reactions. The preliminary biological evaluation of these analogues will also be presented.

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SYNTHESIS AND SAR OF IONIZABLE 1,3,4-OXADIAZOL-2(3*H*)-ONES AS PERIPHERALLY SELECTIVE FAAH INHIBITORS WITH IMPROVED AQUEOUS SOLUBILITY

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Fatty acid amide hydrolase (FAAH) is a member of the extensive family of serine hydrolases[1] that catalyses the degradation of lipid signalling fatty acid amides such as oleamide and anandamide (AEA).[2] AEA binds and activates both central (CB_1) and peripheral (CB_2) receptors of the endocannabinoid system (ECS) and potentially has clinical relevance in a wide range of diseases and pathological conditions. The biological action of AEA is quickly terminated by FAAH. Therefore, inhibition of FAAH could prolong the beneficial effect of AEA. Recently, our group described a series of 3-phenolic and 3-catecholic 5-phenoxy-1,3,4-oxadiazol-2(3*H*)-ones possessing *in vivo* FAAH inhibition in mice[3]. Several of the disclosed compounds such as **1** (Fig. 1) showed peripherally selective inhibition of FAAH that may be particularly beneficial for the treatment of certain cardiovascular diseases such as hypertension and heart failure.

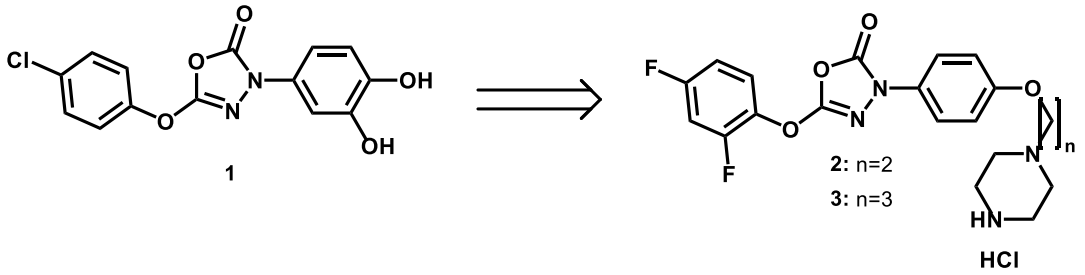

Figure 1

Herein, we report synthesis and structure activity relationships (SAR) of novel 5-(2,4-difluorophenoxy)-3-aryl-1,3,4-oxadiazol-2(3*H*)-ones that display improved physicochemical properties over catecholic compound **1** and are suitable for formulations for topical or inhaled administration. These molecules such as **2** and **3** (Fig. 1) could prove beneficial for the treatment of certain respiratory and ocular disorders in which FAAH plays a role. *In vivo* efficacy of the new compounds will be presented.

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ON THE FIELD OF METALLODRUGS: NOVEL RUTHENIUM(II) COMPLEXES WITH THIOSEMICARBAZONES

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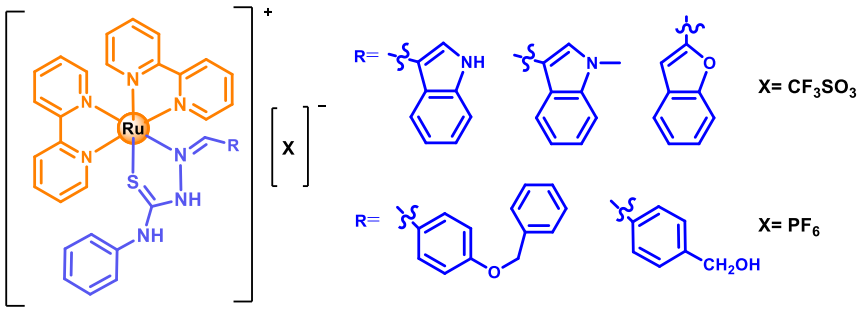
Cancer is the second largest cause of death in developed countries. Two in every five people born today will be diagnosed with cancer at some time during their life, and one of them will effectively perish from that condition. According to the World Health Organization, cancer mortality is projected to rise to over 13.1 million people in 2030[1]. Cisplatin and analogues are, to date, the only metal-based chemotherapeutics approved worldwide for clinical use. Although highly effective, dose-limiting side effects and the development of resistance to treatment severely limit their clinical value. Ruthenium-based compounds are a recognized effective alternative, typically offering a wider spectrum of activity and the potential to overcome tumor platinum-resistance, as well as different mechanisms of action and a lower toxicity in general[2].

Research in this field has been quite extensive and several families of Ru(II) and Ru(III) compounds have been developed. In the search for metal-based agents with suitable stability and solubility in aqueous media, octahedral 'Ru(NN)$_2$L' complexes (NN being a polypyridyl-type ligand) have shown an interesting profile, their therapeutic activity being to some extent modulated by the ligand L, especially if it exhibits biological activity on its own. In this context thiosemicarbazones (TSCs), particularly those including heterocyclic moieties, possess a broad range of biological activity, such as antimalarial, antimicrobial, antifungal and antitumor properties[3], and can be used as the bidentate ligand L[4].

In this work five new aromatic TSCs were synthesized and used in the preparation of novel ruthenium(II) complexes of the type [Ru(*NN*)$_2$(TSC)][X] (*NN*=2,2'-bipyridyl; X=PF_6^-, $CF_3SO_3^-$) – see Figure. All ligands and complexes were fully characterized by NMR, IR, UV-Vis, ESI-MS, Elemental Analysis and Cyclic Voltammetry. Their anti-cancer activity was evaluated *in vitro* against ovarian adenocarcinoma and triple-negative breast human cancer cells. We present herein our preliminary results on these new highly promising agents.



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SYNTHESIS AND BIOLOGICAL PROFILE OF NOVEL PYRANOSYL ISONUCLEOSIDES

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Isonucleosides, regioisomers of nucleosides comprising the nucleobase linked to the sugar moiety at a non-anomeric position, have attracted much interest due to their potential to exhibit antiviral and antitumor activities.[1,2] Such molecules have the propensity to interfere in biological processes in which natural nucleosides are involved, such as nucleic acid synthesis and cell division, which are deregulated in diseases such as cancer or viral infections.[3,4] Moreover, these nucleoside analogs present better stability towards enzymatic hydrolysis that their natural counterparts.
In the reported isonucleosides, the nucleobase is linked at C-2 or C-3 to the sugar backbone, especially furanose units. Hence, we were motivated to explore other positions of the sugar moiety for the coupling of a nucleobase towards new types of isonucleosides.

In this communication, the synthesis of 6´-isonucleosides (Fig. 1), embodying purine or pyrimidine motifs, as well as triazole-containing derivatives is presented. The synthetic methodologies included the Mitsunobu coupling of partially protected glycosides containing a free OH-6 with a nucleobase or the Cu(I)-catalyzed sugar azide-alkyne cycloaddition. Variations on the substitution and on configuration of the sugar moiety were made, extending the panel of compounds for further bioactivity screening.

The compounds were subsequently evaluated for their ability to inhibit cyclin-dependent kinase-2, which is a therapeutic target for cancer,[5] and for their cytotoxicity on a panel of tumour and healthy cells. In order to have a broader knowledge on the compounds' biological potential, cholinesterases were also included in the inhibition assays. The synthetic work and the results of the bioactivity assessment will be revealed and discussed herein.

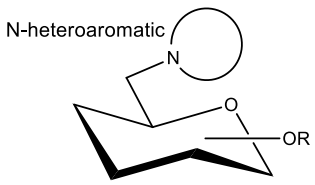

Figure 1. General structure of the synthesized 6´-isonucleosides.

Acknowledgements: The authors thank Fundação para a Ciência e a Tecnologia for funding through the projects IF/01488/2013 and UID/MULTI/00612/2013 and for the research grant to Daniela Batista.

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IBUPROFEN AND NAPROXEN IONIC LIQUIDS: OLD DRUGS, NEW PROPERTIES

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Pills and tablets are the most common formulations of drugs in ambulatory regime. The majority of these contain Active Principle Ingredients (API) in solid form, which may crystallize as different polymorphic structures. As polymorphs usually present distinct efficiencies, finding ingenious ways to tackle this disadvantage is of paramount importance to the pharmaceutical industry.[1] This characteristic is very present in the non-steroidal anti-inflammatory drugs Ibuprofen and Naproxen (Figure 1), which also display very low bioavailability.[2,3]

The peculiar properties of salts of organic compounds as Ionic Liquids (ILs) have bestowed their application in several research areas, including pharmaceutical sciences. In fact, Ionic Liquids as Active Pharmaceutical Ingredients (API-ILs) have been reported as alternative pharmaceutical salts that can simultaneously reduce the formation of polymorphs and improve bioavailability.[4]

In this communication we present new API-ILs comprising Ibuprofen and Naproxen as anions combined with appropriate biocompatible methylimidazolium and tetraalkylammonium cations. The prepared API-ILs were characterized by standard spectroscopic techniques and their thermal properties were evaluated by DSC.

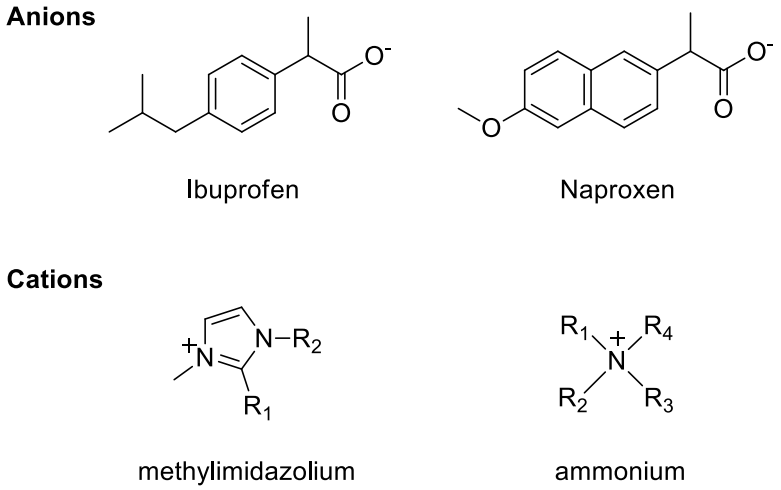

Figure 1. New API-ILs based on Ibuprofen and Naproxen.

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NOVEL MIMETICS OF SUGAR PHOSPHATES AND OF NUCLEOTIDES AIMED TO TARGET NUCLEOTIDE-DEPENDENT ENZYMES: SYNTHESIS AND DOCKING STUDIES

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Nucleotide-dependent enzymes comprise a vast array of enzymes that are involved in many fundamental biological events such as nucleic acid synthesis, cell division or metabolism. Their deregulated or abnormal activity drives the progress of various diseases and hence various enzymes of this class became important therapeutic targets. Among them, cyclin-dependent kinases (CDKs), which regulate the cell cycle by transferring a phosphate group of ATP to protein substrates, emerged as promising targets for cancer due to their overexpression and overactivity in tumor cells.[1] The known CDK inhibitors are based on aromatic or heteroaromatic motifs and only target the enzyme subpocket to which the adenine moiety of ATP binds.[2] So far, despite potent inhibition and cytotoxicity to tumor cells exhibited by some of these molecules, their significant toxicity to healthy cells limits their clinical use.[3]

In this communication we report on the development of novel mimetics of nucleotides intended to interact with the ATP-binding pocket of a CDK at the regions to which the sugar, the adenine and the phosphate system of ATP bind to the enzyme. CDK-2, whose inhibition is reported to cause selective toxicity to malignant cells [4] was the kinase targeted.

Molecules having a carbohydrate backbone, an aromatic or N-heteroaromatic moiety as well as a potential bioisostere of a phosphate group were synthesized and their interaction with the ATP binding site of the crystal structure of the activated cyclin A/CDK-2 complex were inspected by molecular docking. Simpler molecules, intended to sugar phosphate mimicry were also prepared aiming to target the enzyme at the ribose and at the phosphate regions of its ATP pocket.

In addition, a new structural framework for potential mimetics of nucleoside diphosphate sugars, which are substrates for enzymes such as glycosyltransferases, was designed. The synthesis of analogs of diphosphate-linked disaccharides and corresponding nucleoside, embodying an uncharged surrogate of a diphosphate system was carried out.

The synthetic methodologies and the results of the molecular docking studies which were performed to identify promising CDK-2 inhibitors will be presented.

Acknowledgements: 'Fundação para a Ciência e Tecnologia' (FCT) is acknowledged for funding (IF/01488/2013, IF/00472/2014 and CQB strategic project UID/MULTI/00612/2013).

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SYNTHESIS OF NEW RUTHENIUM CYCLOPENTADIENYL COMPLEXES COMPRISING CARBOHYDRATE LIGANDS AS POTENCIAL ANTITUMOR AGENTS

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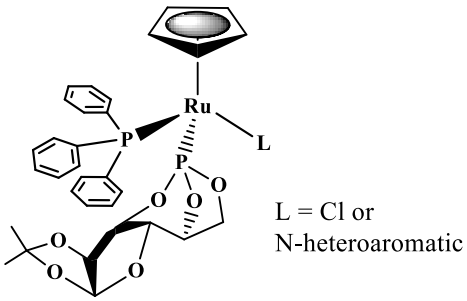
Since it was proved that ruthenium complexes are effective alternatives to platinum-based complexes for cancer chemotherapy, the study of ruthenium organometallic complexes has been an attractive topic in the search of new antitumor agents. During the recent years our group has been involved in the synthesis of new half sandwich "Ru(η^5-C_5H_5)"-derived compounds whose cytotoxicity was found, in most of the cases, better than that of cisplatin, against several cancer cell lines of typically low, medium and high resistance to metallodrugs.[1,2]

The ligands in organometallic complexes play an important role not only in the cytotoxicity but also in the lipophilicity, stability, bioavailability, and the specificity of a metallodrug. Carbohydrates are an excellent class of tunable ligands since they are often inexpensive, naturally available and can be easily modified. Besides improving compounds' solubility and biocompability, their ability to be recognized by cell-surface receptors indicate their potential to interfere with carbohydrate–protein interactions and hence to inhibit cell–cell recognition and adhesion phenomena, essential processes in cancer growth and progression.[3] Due to the high energy demand of tumours, which can only be satisfied by glycolysis, linking sugar derivatives to a metal center could be an easy way to improve the drug's cytotoxic selectivity into the tumor.[4]

Having all this issues in mind, the objective of the present work is to combine the good results of Ru(η5-C_5H_5)-based complexes with the promising features that carbohydrates can play in bioorganometallic chemistry. This work intends to reach a new family of ruthenium complexes whose main structure is represented below. The present communication reports our most recent results involving new piano stool "RuCp" derivatives with carbohydrate and N-heteroaromatic ligands. Results of the extensive characterization *via* different spectroscopic approaches (NMR, UV-vis, FTIR) will be disclosed herein.



Acknowledgments: "Fundação para a Ciência e Tecnologia" for funding through the FCT Investigador program (N.M. Xavier), SFRH/BPD/93513/2013 post-doctoral Grant (T.S. Morais) and financial support (PTDC/QUI-QUI/118077/2010, PEst-OE/QUI/UI536/2011 and UID/MULTI/00612/2013).

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GENISTA TENERA AS A SOURCE OF INNOVATIVE MOLECULAR LEADS WITH ACTIVITY AGAINST DIABETES AND RELATED AMYLOID DISORDERS: PHYTOCHEMISTRY, SYNTHESIS AND MECHANISM OF ACTION

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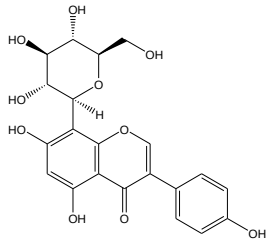
Genista tenera is an endemic plant to the island of Madeira, Portugal, which is used in folk medicine for the control of diabetes. Previous research work performed by of our group showed that its ethyl acetate and the *n*-butanol flavonoid extracts have a significant antihyperglycemic effect on STZ-induced diabetic Wistar rats as well as strong antioxidant activity [1]. The phytochemical study of the bioactive and non-toxic flavonoid extracts was evaluated by chromatographic and spectroscopic techniques and several flavonoid aglycones and flavonoid glycosides were identified [1-3]. Most of these compounds were evaluated and, particularly, 8-β-D-glucosylgenistein (**1**) – the major component of the ethyl acetate extract – was found to be an extremely potent antidiabetic that was able to decrease glucose excursion to normal values upon an oral glucose tolerance test, with concomitant increase of glucose-induced insulin secretion [4].

Optimization of the synthesis of this glucosylisoflavone is now presented in order to carry out additional biological studies for the disclosure of its mechanism of action. Molecular recognition studies of (**1**) with human islet amyloid polypeptide (hIAPP) and amyloid β 1-42 ($A\beta_{1-42}$) peptide were conducted employing Saturation Transfer Difference (STD) techniques, demonstrating that this antidiabetic lead binds to both aggregation-prone molecular species, which are major physiopathological features of type 2 diabetes and Alzheimer's disease, respectively. Moreover, Atomic Force Microscopy (AFM) and Thioflavin T (ThT) fluorescence assays revealed the remarkable ability of **1** to prevent the formation of hIAPP cytotoxic oligomers. Together, these studies rationalize the usefulness of *Genista tenera* as a medicinal plant for the control of diabetes and prevention of frequently associated neurodegenerative disorders, and reinforce the potential of 8-β-D-glucosylgenistein (**1**) as a promising multitarget antidiabetic lead for drug development.



(1)

Figure 1. 8-β-D-glucosylgenistein

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TARGETING DIABETES WITH *C*-GLUCOSYL DIHYDROCHALCONES AS POTENTIAL SODIUM-GLUCOSE CO-TRANSPORTER (SGLT) INHIBITORS

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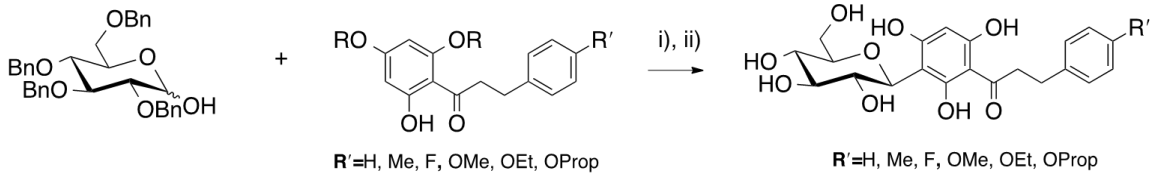
In our body kidneys are responsible for the reabsorption of glucose (> 99%). However in diabetic conditions glucose concentration is too high and the kidneys reach a threshold of reabsorption and glucose is excreted in urine (glycosuria). This process increases the osmotic pressure of the urine and promotes the inhibition of water reabsorption by the kidneys leading to an increase of urine production (polyuria) and consequently dehydration and thirst (three of the most common symptoms in early stage of diabetes).[1]

The proteins responsible for the transport of glucose into the cells are called sodium-glucose co-transporters (SGLTs). There are 6 isoforms with different sugar affinities and location. The two isoforms that transport glucose and are located in the kidneys are SGLT1 and SGLT2.[2] The inhibition of these proteins leads to a decrease in glucose reabsorption. However, SGLT1 has also affinity to galactose and its inhibition leads to gastrointestinal side effects. To avoid this problem, scientists have been searching for selective SGLT2 inhibitors in the last couple of years.[2]

Phlorizin, a dihydrochalcone glucoside, was the first SGLT1/SGLT2 inhibitor, discovered in 1835.[3] This compound did not go to clinical trials due to its SGLT1 inhibition and also because it is hydrolyzed by gastrointestinal enzymes. However, *C*-glycosyl derivatives are stable against them.

In this work we present the synthesis of a small library of *C*-glucosyl analogs of phlorizin as new potential SGLT2 inhibitors (Scheme 1). Their synthesis comprises the preparation of the glycosyl donor (2,3,4,6-tetra-O-benzyl-D-glucopyranose) and the glycosyl acceptors (dihydrochalcones) followed by the *C*-glycosylation of dihydrochalcones in the presence of catalytic amount of TMSOTf, benzyl groups' removal with Pd/C and Et_3SiH by *in situ* hydrogenation.

Their *in vitro* evaluation is currently under progress but cell viability revealed that none of these *C*-glucosyl compounds are cytotoxic in HEK293 cell line (cell viability > 95%). The aglycones (chalcones and dihydrochalcones) showed, in some cases, a slightly higher cytotoxicity with 60-70% cell viability after 24 h incubation.



Scheme 1. Synthesis of *C*-glucosyl dihydrochalcones. i) TMSOTf (0.5 equiv.), DCM/ACN, Drierite (40-60% yield); ii) Pd/C, Et_3SiH, EtOAc/MeOH (90-99% yield).

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NEW BACE1 INHIBITORS FOR ALZHEIMER'S DISEASE TREATMENT

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Alzheimer's disease (AD) is the most common dementia worldwide and at present an effective therapy is an unmet medical need. It is generally accepted that accumulation of amyloid-β protein (Aβ) in the brain parenchyma represents an early incident on a cascade of events that ends in neurodegeneration and dementia, and thus, Aβ is considered as the etiologic agent of the disease. The formation of Aβ requires the initial cleavage of the amyloid precursor protein (APP) by the β-secretase enzyme (BACE1), followed by the activity of the γ-secretase over the ensuing transmembrane fragment. So far, only one BACE1 inhibitor previously developed reached the phase II/III clinical trials. Therefore, the goal of this study is the design and development of a new inhibitor for BACE1, a key enzyme for the production of amyloid-β peptide (Aβ), which we expect will overcome some of the limitations of previous BACE1 inhibitors that hindered their clinical use.

The compounds we designed were screened for their ability to inhibit BACE1 by an in vitro cell-free assay. The compounds IC_{50} was determined and the two most promising drugs were then evaluated for their ability to inhibit BACE1 and reduce endogenous Aβ production in a cellular model of AD (Neuro-2A cells overexpressing APPswe, N2A-APPswe). The levels of secreted Aβ40 and Aβ42 as well as the levels of the soluble fragment sAPPβ were assessed by ELISA and Western blot, respectively, after incubation of N2A-APPswe cells with the compounds for 24 hours. In these conditions, we observed that 100 μM of compound 7 reduced the levels of Aβ40 and Aβ42 by about 70 % and 55 %, respectively, whereas 100 μM of compound 8 reduced Aβ40 and Aβ42 levels by about 60 %. Accordingly, both compounds induced a reduction in the levels of sAPPβ. Moreover, a 24 h incubation with the new BACE1 inhibitors (compound 7 and 8) at the concentrations used to decrease Aβ40 and Aβ42 levels, did not change cell viability as assessed by the MTT assay. Thus, the compounds did not cause cytotoxicity while reducing the endogenous Aβ production by N2A-APPswe cells. The efficacy of the selected compounds to inhibit BACE1 was also tested in the 3xTg AD mouse model. We observed that both compounds (1.25 mg/kg) reduced plasma Aβ40 by about 25-30% and, at a dose of 5.0 mg/kg, compound 7 and compound 8 reduced plasma Aβ42 by about 35-45%, as assessed by sandwich ELISA 24 h after a single administration to 4 months-old mice. Regarding brain soluble Aβ levels, 1.25 mg/kg of the compounds 7 and 8 reduced Aβ40 and Aβ42, by about 30%, 24 h after administration.

Taking into account our preliminary results, we expect to develop a new BACE1 inhibitor that will be able to delay the onset and progression of the disease since it will prevent Aβ production and the subsequent neurotoxic events triggered by Aβ accumulation.

Aknowledgements: This work is supported by FCT (R Resende's fellowship: SFRH/BPD/34712/2007; PTDC/NEU-SCC/1351/2012; UID/NEU/04539/2013; CENTRO-07-ST24-FEDER-002002), InovC, FEDER and COMPETE.

INSIGHTS INTO THE MECHANISM OF ACTION OF A GLYCOSIDE SURFACTANT

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In this work, the lead compound from a family of previously researched glycosides [1] was investigated regarding its synthesis and its antibacterial activity against *Bacillus* species.

The synthetic pathway developed involved the conjugation of L-rhamnal with the desired aliphatic chain, via glycal formation. The lead compound, namely dodecyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside (Fig. 1), was submitted to several assays, aiming to understand the mechanism of action (MoA). Studies on the bacterial vitality, viability and bacterial metabolism, (reconstruction using phenotypic microarrays Biolog®) were carried out in order to understand compounds influence on the bacterial biological system. In addition, several mutant libraries by random transposition and knock-out of specific membrane related targets, using as a model strain B. cereus ATCC 14579, were used in the search for a specific molecular target.
Also, other techniques were used in order to evaluate compound effects on bacterial sporulation cycle and on different cellular ultra-structures, using protoplasts and spheroplasts as well as imaging techniques, namely atomic force microscopy and fluorescence microscopy.

With all the different approaches applied a solid theory for the mechanism of action was achieved and will be presented and discussed.

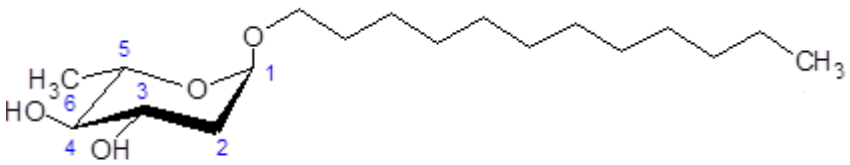

Figure 1. Structure of dodecyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside

References:

[1] A. Martins, M.S. Santos, C. Dias, P. Serra, V. Cachatra, J. P. Pais, J. Caio, V. H. Teixeira, M. Machuqueiro, M. S. Silva, A. Pelerito, J. Justino, M. Goulart, S. V. Silva, A. P. Rauter, Eur. J. Org. Chem, **2013**, 1448 –1459;

ASSESSING STRUCTURAL FEATURES OF NEW ANTIMICROBIAL DEOXY GLYCOSIDES WITH ANTI AGEING POTENTIAL

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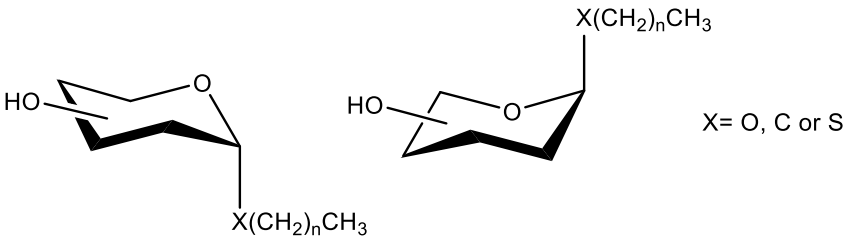
The increasing average life expectancy in developed countries led to an escalating concern regarding geriatric infectious diseases. Infections in elderly populations are known to be not only more frequent but also more severe.[1] On the other hand, emergence of antibiotic resistance encouraged chemists to explore new structures in the search of new antibiotics with new modes of action. We have introduced a new family of deoxy glycosides, some of which exhibiting a potent activity against *Bacillus* spp, in particular *B. cereus* and *B. anthracis*.[2-4] We present now a series of related alkyl O- and S-glycosides, differing in glycon configuration, deoxygenation pattern and aglycon structure, as well as their C-glycosyl counterparts (Scheme 1, structure type I), for the recognition of the structural features that determine the bioactivity. While the preparation of 2-deoxy O- and S-glycosides was accomplished from the appropriate glycal via a simple, easy to run and stereoselective reaction with triphenylphosphane hydrobromide, C-glycosyl analogues and alkyl 3-/, 4-/ and 6-deoxy glycosides were obtained via alternative but efficient synthetic methodologies.

Depending on their key structural features, these compounds demonstrate a potent activity against *B. cereus*, *B. anthracis* and *E. Faecalis*. Some of these structures were also tested for their ability to prevent conversion of PrP^{c} to PrP^{Sc} in cells, as well as for their interaction with soluble cystatin B amyloid fibrils by NMR spectroscopy. The promising results arising from the latter interaction studies show their potential for neurodegenerative diseases, opening the door to a new line of investigation, pertaining to antibiotic compounds showing neuroprotective activity

This work clearly demonstrates the uniqueness of carbohydrates which stereochemistry and chemical structure can tune the bioactivity exhibited by stereoisomers.



Scheme 1. Structure-type of the antibacterial compounds from D- and L- series.

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BUTYRYLCHOLINESTERASE AS A TARGET FOR DEGENERATIVE DISEASE THERAPIES

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Healthy ageing is a major concern worldwide mainly due to the increase in average life expectancy. The risk of being affected by a neurodegenerative disease increases dramatically with age. In particular, Alzheimer's disease (AD) is the leading cause of dementia and current treatments can only ameliorate the symptoms. While on early stages of AD, cholinergic activity is controlled by acetylcholinesterase (AChE), in later stages AChE activity is decreased and butyrylcholinesterase (BChE) is also responsible for the degradation of acetylcholine. Since most treatments for AD rely on single inhibition of AChE or dual inhibition of both enzymes, research focusing on selective BChE inhibition to access a better understanding of BChE role in AD is mandatory.[1]

Cancer is also one of the main concerns for investigators around the world that are dedicated to the search for new treatments to provide a healthy and active ageing. Not only different therapies with fewer side-effects are required but also new and more effective imaging agents for detection of malignant cells at earlier stages are required to provide a better treatment. BChE levels have been used as a biochemical marker in the management of head, neck and cervical cancer.[2]

Selective inhibitors of BChE has been a major research area of our group. We have found a new family of nucleosides embodying an unusual byciclic sugar moiety (type **I**) that demonstrated potent and selective inhibition of BChE.[3] With the goal of simplifying the structure of these nucleosides, new BChE inhibitors with general structure type **II** and **III** were synthesized exhibiting also potent activity.[4] To assess their biokinetics and potential interest as radioprobes for imaging BChE activity in AD or cancer patients, the most promising compounds were successfully radioiodinated with ^{125}I and biologically evaluated. The results will be presented and discussed.

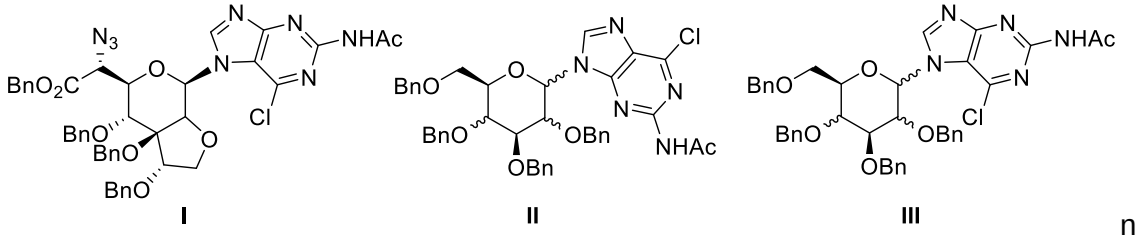

Figure 1. General structures of nucleosides

References:

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E – NATURAL PRODUCT CHEMISTRY

SYNTHESES OF SECO-PROGELDANAMYCIN ACID DERIVATIVES: STUDIES TOWARDS THE FLEXIBILITY OF THE AMIDE SYNTHASE

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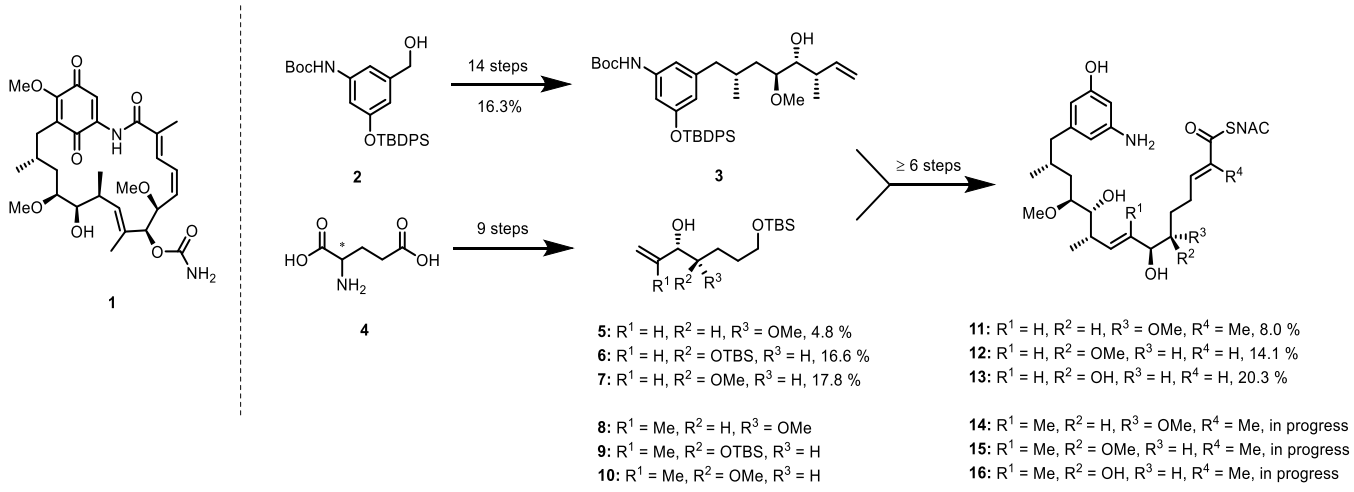
Geldanamycin (**1**, Scheme 1) is a benzoquinone ansamycin antibiotic produced by *Streptomyces hygroscopicus*. It binds to Hsp90 and inhibits its ATP-dependent chaperone activity, namely the correct folding and maturation of the client proteins. Because most of these proteins are protein kinases or transcription factors involved in the formation and progression of cancer cells, geldanamycin and its derivatives are potential anticancer chemotherapeutic agents. Unfortunately, despite its *in vitro* anticancer activity, geldanamycin has not been approved for clinical use due to hepatotoxicity and strong side effects.

To study the acceptance and biosynthetic transformation of complex substrates by the amide synthase *Gdmf* - the enzyme responsible for the macrolactamization in the biosynthesis of geldanamycin, three *seco*-progeldanamycin acid derivatives **11**-**13** were synthesized for enzyme assays. The syntheses of three other *seco*-progeldanamycin derivatives **14**-**16** are in progress (Scheme 1).



Scheme 1. Syntheses of *seco*-progeldanamycin acid derivatives.

References:

[1] a) L. Whitesell, S.L. Lindquist, *Nat. Rev. Cancer,* **2005,** *5*, 761−772; b) S. Eichner, H.G. Floss, F. Sasse, A. Kirschning A. *ChemBioChem.* **2009,** *10*, 1801-1805; c) S.Eichner, T. Eichner, H.G. Floss, J. Fohrer, E. Hofer, F. Sasse, C. Zeilinger,A. Kirschning, *J. Am. Chem. Soc.* **2012,** *134*, 1673–1679.
[2] a) M. Vogt, Umpolung von Allyl-Palladium-Komplexen und Anwendung in der Synthese von Naturstoff-Fragmenten. Ph.D. Dissertation, Leibniz Universität Hannover, Hannover, **2010**; b) J. Ermane,Syntetische und mutasynthetische Zugänge zu neuen Hsp90 Inhibitoren. Ph.D. Dissertation, Leibniz Universität Hannover, Hannover, **2013**.

CHEMICAL AND BIOLOGICAL INVESTIGATIONS OF ANSAMITOCIN-NANOPARTICLE-CONJUGATES AS MULTIFUNCTIONAL CANCER THERAPY AGENT

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Cancer is one of the most prevalent diseases nowadays but so far hardly any selective drugs against solid tumors are available. Ansamitocins are well known for their cytotoxic properties but failed in clinical trials because of severe side-effects.[1] Recently, an ansamitocin-antibody-conjugate (Kadcyla®) against breast cancer reached the market (2013).[2] Here, we present a new concept for treating cancer by combining two therapies: chemotherapy and hyperthermia. This new concept should reduce the side effects of the ansamitocins by selective release of the toxin using externally induced heat. This strategy is realized by the development of an ansamitocin-nanoparticle-conjugate that contains a thermolabile linker system (fig. 1A).[3] A second binding site on the nanoparticle provides an opportunity to additionally functionalize the nanoparticles with fluorescence markers (e.g. FTIC) or specific antibodies.

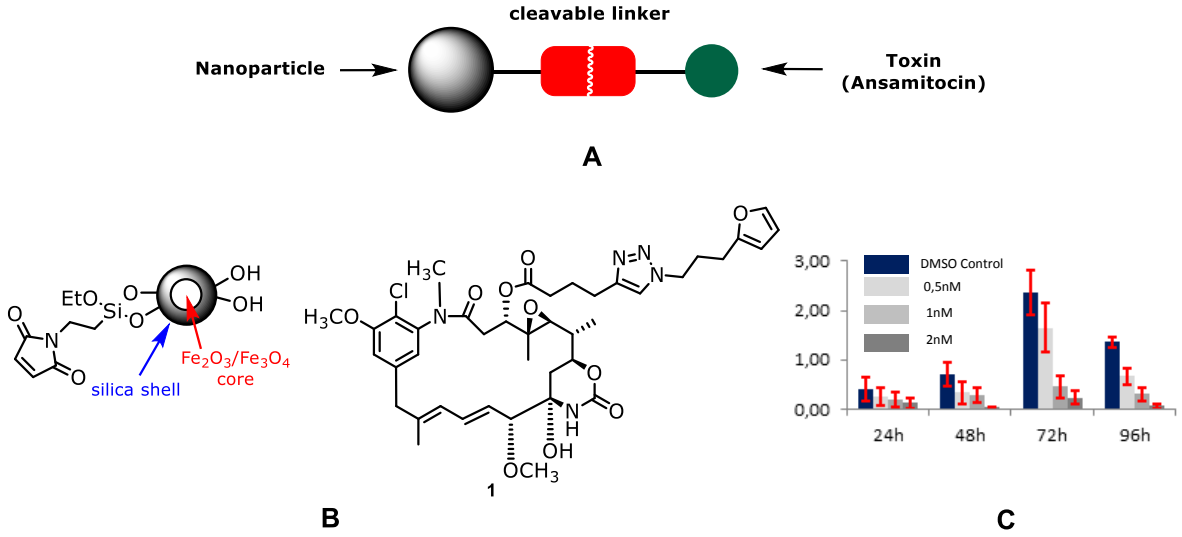

Figure 1. A: Model of the ansamitocin-nanoparticle-conjugate; B: Fragments of the conjugate after release; C: Celltests on cellline Huh7 with treatment of compound 1.

In preparation of *in vivo* mouse model tests the drug and the conjugate are actually tested against a human hepatocellular carcinoma cellline (Huh7). First tests indicate a good concentration dependent effect on the cell growth (fig. 1C).

References:

[1] M. J. Ravry, G. Omura, R. Birch, *Am J. Clin Oncol.* **1985**, *8*, 148-150.
[2] S. Girish, et al. *Cancer Chemother Pharmacol,* **2012**, *69*, 1229–1240.
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STUDIES TOWARDS THE TOTAL SYNTHESIS OF MUMBAISTATIN

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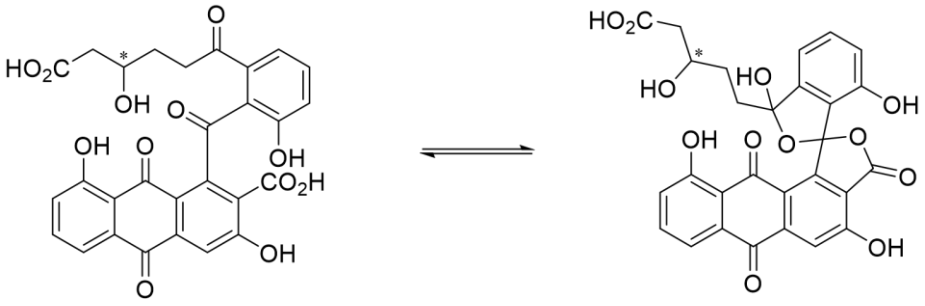
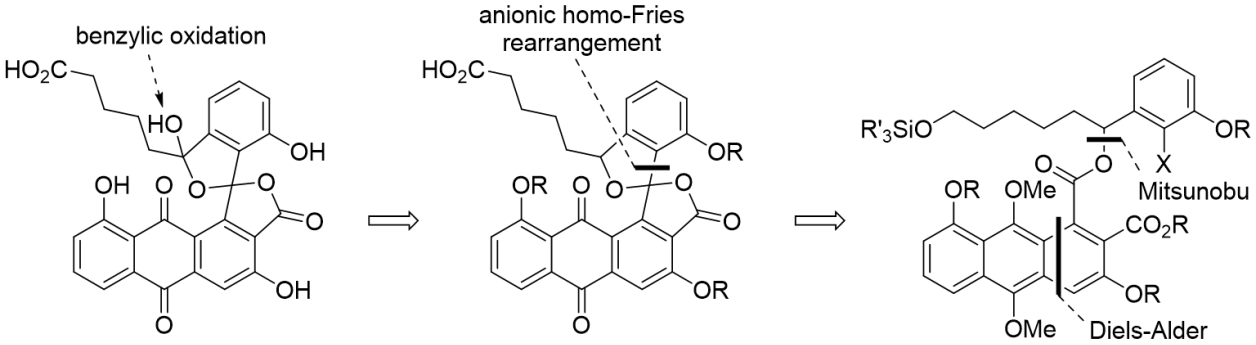
Mumbaistatin **1a** is a structurally unique polyketide and the strongest naturally occurring inhibitor of glucose-6-phosphate translocase-1 (G6P-T1) known today. This multi enzyme complex is a promising target for drugs being effective against type-2-diabetes mellitus and angiogenic processes associated with brain tumor development.[1]



1a **1b**

The structure of Mumbaistatin **1a** consists of an anthraquinone part and an arylketone part linked together by a carbonyl bridge.[2] It also shows a tetra-*ortho*-substituted benzophenone motif as core structure, which represents the major challenge in the total synthesis of the molecule. In solution the “open-form” **1a** exists in an equilibrium with the cyclised spiroketal form **1b**.



2 **3** **4**

We succeeded to synthesize a dideoxy cyclo-mumbaistatin derivative related to **1b** following the retrosynthetic strategy shown above.[3] Important steps are the benzylic oxidation of the spiroketal **3** (to give **2**) preceded by an anionic homo-Fries rearrangement of the ester **4**. The ester itself was made by a Mitsunobu reaction of a benzylic alcohol and a carboxylic acid. The anthraquinone motif itself was build up by a Diels-Alder reaction.

References:

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DIRECT OXIDATIVE COUPLING OF N-ACETYL INDOLES AND PHENOLS FOR THE SYNTHESIS OF BENZOFUROINDOLINES RELATED TO PHALARINE

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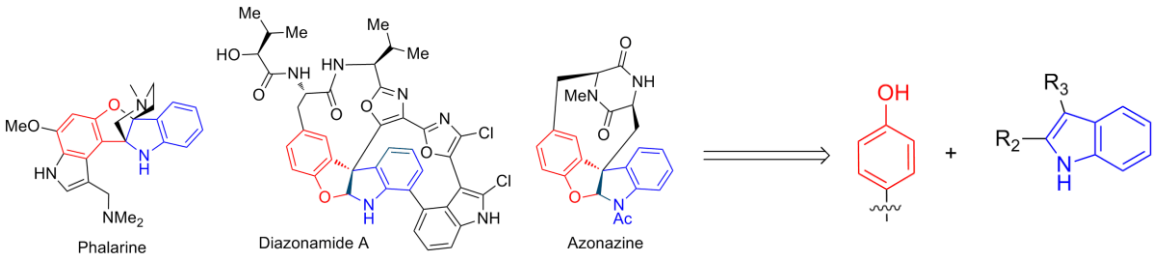
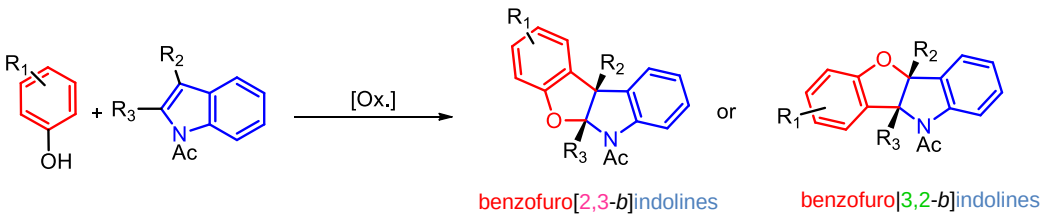
The benzofuroindoline core can be found in several natural products as phalarine, azonazine or diazonamide A and led to numerous investigations towards their syntheses. The last one has been the focus of a high number of research investigations because of its high antitumor activity (IC_{50} < 5 nm) and its intriguing structure.[1] Direct oxidative coupling between phenolic and indolic moieties has been thought to be the central part of the biogenetic scenario of the biosynthesis of benzofuroindoline-containing natural products (scheme 1).[2]



Scheme 1. Natural compounds containing benzofuroindolines core

We will present the union of phenol and *N*-acetylindole activated by $FeCl_3$[3] in oxidative conditions which lead directly to benzofuroindoline frameworks via radical intermediates (scheme 2).[4]



Scheme 2. Strategy using Indoles and Phenols

Depending on the substitution of the indole, the benzofuro[2,3-*b*]indolines or the benzofuro[3,2-*b*]indolines could be selectively obtained.

References:

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CHEMICAL COMPONENTS IN ESSENTIAL OILS FROM PLANTS OF THE GENUS ORIGANUM USED IN AN ALTERNATIVE METHOD FOR ELIMINATING BACTERIAL ACTION IN AQUACULTURES

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Antimicrobials are used in the food industry for two main reasons: to control natural spoilage processes (food preservation), and to prevent the growth of micro-organisms, including pathogenic micro-organisms (food safety). Nowadays essential oils (EO) are recognized as safe substances by the Food and Drug Administration [1] and some contain compounds which can be used as antibacterial additives [2,3]. Public concern about the use of antibiotics in livestock feed has increased, because of the emergence of antibiotic resistant bacteria and their possible transmission from livestock to humans. The aims of this study were a) to determine the chemical composition of essential oils extracted from three species of the genus *Origanum*, and b) evaluate their ability to inhibit *in vitro* bacterial strains such as *Vibrio*, isolated from aquaculture facilities, and the common microbial strains *Escherichia coli* and *Sacharomyces cerevisiae*.

The emphasis given to the *Vibrio* strains study is due to the fact that in previous studies [4] we found evidence that the aforementioned EO were able to eliminate the bacterial action in aquacultures, especially during the rearing of marine fish larvae in which high mortality rates are often observed especially during the first weeks after hatching. One of the factors likely to affect the survival of the larvae is the bacterial load associated with added live food, such as rotifers (*Brachionus* sp. and *Artemia* sp.). Opportunistic bacteria include members of group of *Vibrio*, which may prove highly virulent for the larvae. A prerequisite for the successful rearing of larvae is the control of bacterial load in live food and larval tanks.

In this project, three plant species of the genus *Origanum*, namely *O. vulgare* subsp. *hirtum* (Link) Ietswaart, *O. onites* L., and *O. marjorana* L. that belong to the Lamiaceae family were studied for their chemical composition and antibacterial activity. Essential oils of these plants were analyzed *via* gas chromatography coupled with mass spectrometry (GC-MS). The main chemical group identified in the component mixture was phenols, with thymol and carvacrol being the main constituents followed by γ-terpinene and p-cymene. The second largest group of components is that of the monoterpene hydrocarbons and oxygenated monoterpenes, followed by sesquiterpenes with β-bisabolene being the major component of this class. Caryophyllene oxide is the most abundant among oxygenated sesquiterpenes. The oils were assayed as potential antibacterial agents and were used as an alternative method for disinfection of rotifers *Brachionus plicatilis*. *In vitro* studies with several fish pathogens showed that the essential oils were able to inhibit growth of pathogens. The EOs showed antibacterial activity *in vivo* on the bacterial strains of the *Vibrio* group and contributed to the reduction of the bacterial load of the rotifers. The *O. onites* species was more effective with respect to the disinfection of rotifers.

Acknowledgements:This research has been co-financed by the European Union (European Social Fund - ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program: ARCHIMEDES III, Investing in knowledge society through the European Social Fund.

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ACETYLCHOLINESTERASE INHIBITORS FROM *PILIOSTIGMA THONNINGII* (SCHUM.)

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Bauhinia thonningii Schum., best known by its synonymous *Piliostigma thonningii* (Schum.) Milne-Redh, is widely distributed in Africa, extending from West Africa to east and southern Africa and Asia [1, 2, 3]. Its root and twig have been used for the treatment of dysentery, fever, infections, respiratory ailments, snake bites, hookworm and skin diseases [1]. The decoction of the leaves and bark is used in Africa for the treatment of wounds and ulcers, gastric and heart pain, gingivitis and as an antipyretic [3]. Previous studies on this plant had resulted in the isolation of quercetin, quercitrin, a 2-phenoxychromone: piliostigmin, *C*-methylflavonols and a two kaurane diterpenes in leaves [3, 4]. In stem bark from *P. thonningii* the D-3-*O*-methylchiroinositol and a griffonilide was isolated [6, 7] and in roots 5α-stigmasta-7,22-dien-3β-ol and four labdane-derivatives [8].

Chemical investigation of *Piliostigma thonningii* roots led to the isolation of five compounds, β-sitosterol (**1**), benzoic acid (**2**), 3-O-α-L-rhamnopyranosyl-quinovic acid (**3**), 3-O-β-D-fucopyranosyl-quinovic acid (**4**) and vincoside lactam (**5**). The crude methanolic extract and the hexane, chloroform, ethyl acetate and aqueous fractions as well as compounds **3**-**5** were evaluated for their ABTS and DPPH radical scavenging capacity, peroxide value and acetylcholinesterase inhibition activity by the Ellman's method and bioautographic assay. The extract and the fractions were also evaluated for their total phenolics contend and molluscicidal activity. The compounds presented a low ABTS and DPPH activity, compounds **4** and **5** showed AChE inhibition by the Ellman's method while by the bioautographic assay the active compounds were **3** and **4**.

Aknowledgements: This work was partially funded by the Project FCOMP-01-0124-FEDER-007430 of Fundação para a Ciência e Tecnologia (FCT) with FEDER funding and Materiais Fibrosos e Tecnologias Ambientais – FibEnTech, University of Beira Interior, 6200-001 Covilhã, Portugal. The authors are grateful to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Auxílio à Pesquisa de Alagoas (FAPEAL), and Fundação Capacitação de Pessoal de Nível Superior (CAPES) for scholarships and financial support in respect of this study.

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A CONVENIENT SYNTHESIS OF PHENOLIC COMPOUNDS SULFATE METABOLITES

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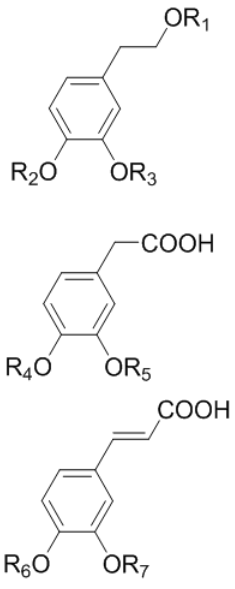
Although many studies have investigated the in vitro antioxidant properties of virgin olive oil phenolics as well as their protective effects against cell injury [1], the biological properties of these phenols in vivo depends on the extent to which they are absorbed and metabolized. In a recent work, the metabolites hydroxytyrosol (3,4-dihydroxyphenylethanol) sulfate and hydroxytyrosol acetate sulfate were found to be the most useful metabolites for monitoring the intake compliance of extra virgin olive oil, showing a significant post-treatment increase both in plasma and urine[2].

The growing interest in the bioactivity of natural polyphenols and of their metabolites requires pure metabolites to be used in bioassays and as standards in research protocols. Therefore, we report here the synthesis of several hydroxytyrosol and hydroxytyrosol metabolite sulfates achieved using a simplified protocol with improved yields. A synthetic solution based on avoidance of high temperature conditions during the synthesis and of low pressure conditions during purification has been established. Sulfates of several phenolic compounds (Table 1), namely hydroxytyrosol, hydroxytyrosol acetate, homovanillyl alcohol, homovanillyl alcohol acetate, homovanillilic acid, ferulic acid, and 3,4-dihydroxyphenylethanoic acid, were efficiently synthesized in 1-2 steps in a good yield and purified form using simple procedures. The proposed protocol was shown to be relatively fast, efficient, cheap and widely applicable to a number of catechol scaffolds.

Table 1 – Phenolic compounds sulfate metabolites

Compound	R_1	R_2	R_3
2	H	SO_3H	H
3	H	H	SO_3H
4	$COCH_3$	SO_3H	H
5	$COCH_3$	H	SO_3H
7	$COCH_3$	H	H
8	H	SO_3H	CH_3
10	$COCH_3$	SO_3H	CH_3
16	SO_3H	H	H
17	$COCH_3$	SO_3H	SO_3H
Compound		**R4**	**R5**
12		SO_3H	CH_3
14		SO_3H	H
15		H	SO_3H
Compound		**R6**	**R7**
18		SO_3H	CH_3



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REACTIVITY STUDY AND ANTIMICROBIAL EVALUATION OF DITERPENES FROM *PLECTRANTHUS MADAGASCARIENSIS*

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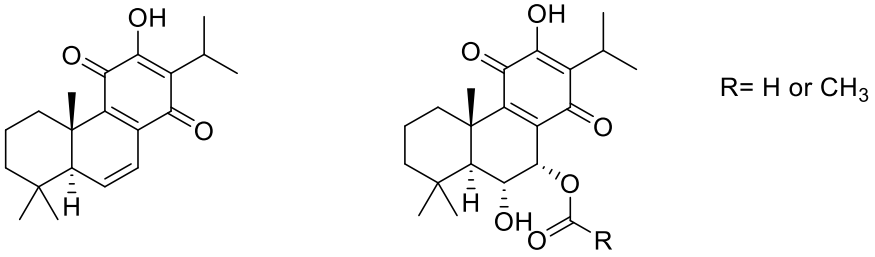
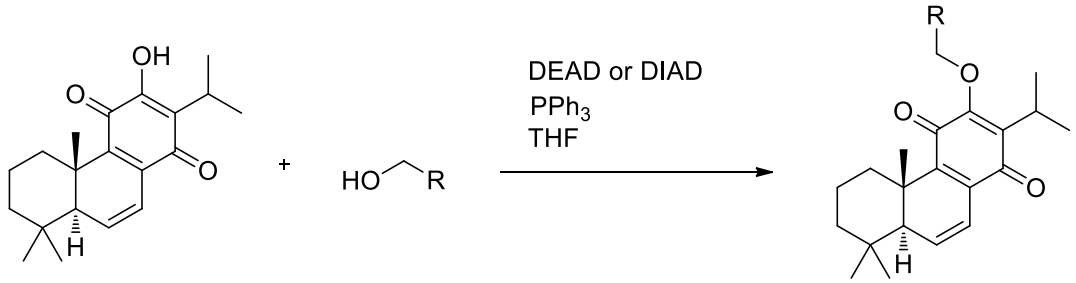
The antibiotic resistance of microorganisms is a growing problem that leads to the development of new drugs. *Plectranthus madagascariensis* is an aromatic herb vastly distributed throughout the Southeast of Africa and is often used in the treatment of wounds, virus infections and pain [1]. Previous studies on *P. madagascariensis* extracts showed a potent activity against Gram positive bacteria. The chemical profile of the bioactive ultrasound acetonic extract was analyzed by HPLC-DAD and the main components were identified as the abietane diterpenes 7,6-dihydroxyroyleanone, 7α-acetoxy-6β-hydroxyroyleanone, 7α-formyloxy-6β-hydroxyroyleanone, coleon U and a polyphenol, rosmarinic acid. The diterpenoid quinones are known for its antimicrobial activity against *Staphylococcus* and *Enterococcus spp* [2]. Using different isolation techniques, 7α-acetoxy-6β-hydroxyroyleanone **1** and 6,7-dehydroroyleanone **2** were successfully isolated and fully characterized.



1 **2**

These molecules with the hydroxyquinone structure constitute a very interesting class of compounds. Their different chemical and physical properties are very valuable in organic chemistry. The reactivity of the acidic hydroxyl group, allows its derivatization via Mitsunobu reaction (Scheme 1). Preliminary results, where the condensation of dehydroroyleanone with allyl alcohol was achieved with success (77% yield), are a driving force to further derivatizations and, consequently further antimicrobial evaluations. Also, these compounds tolerate other derivatizations with reactive groups.



Scheme 3 – Derivatization of 6,7-dehydroroyleanone via Mitsunobu reaction.

The results indicate that *P. madagascariensis* seems to be a good raw vegetal material for the isolation of lead antimicrobial compounds that could be further modulated into potential antibiotics.

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CHEMICAL SYNTHESIS AND BIOLOGY OF MARMYCIN A

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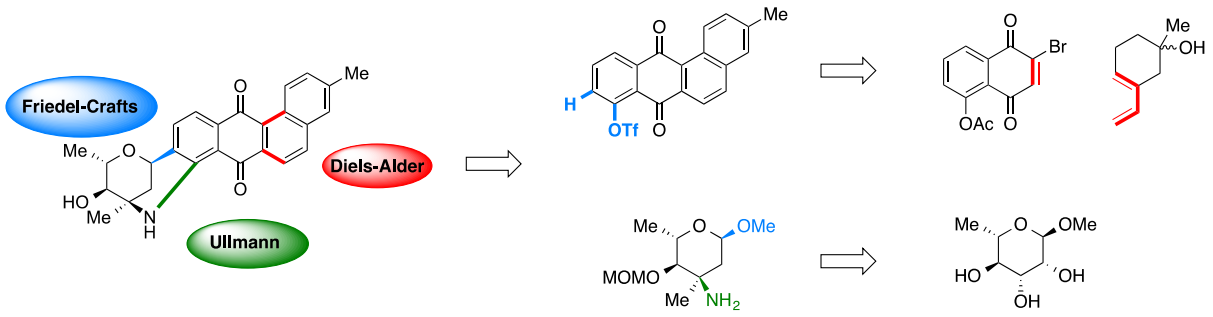
Marmycin A is an angucycline class of antibiotics recently isolated from Streptomyces-related actinomycete. [1] It is structurally unique in that it contains an angular polyaromatic scaffold, including an anthraquinone moiety and a fused sugar backbone containing a C-C and C-N junctions. [2] Interestingly this natural product exhibits potent antiproliferative properties against a range of human cancer cell lines. It is noteworthy that the structure of Marmycin A is reminiscent of the anticancer compound doxorubicin suggesting that it may operate by similar mechanisms. Nevertheless, the fact that the sugar conformation is locked and that the amine is aromatic (free base at physiological pH) suggest that Marmycin A may be more selective than doxorubicin and is therefore an interesting candidate for cancer therapy. However, preparation of samples of Marmycin A is troublesome due to difficult isolation and growth of this strain of actinomycete. [1] This issue seriously limited throughput biological investigations so far and thus prompted us to accomplish the first total synthesis of this small molecule. [3] Preliminary results on its putative biological target(s) and on its cellular mode of action at the molecular level will be similarly presented.



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STUDIES ON THE CHEMISTRY AND BIOLOGY OF FRAGIN

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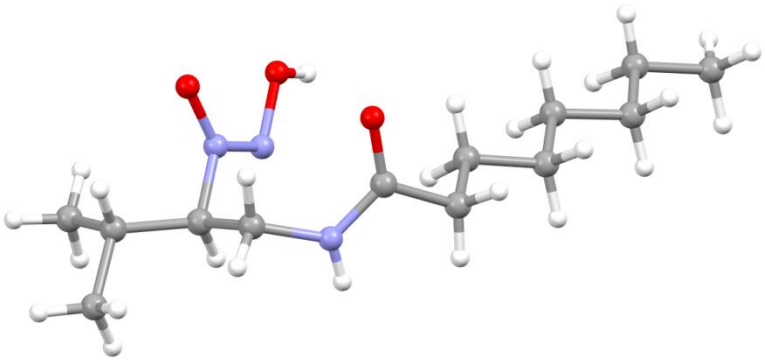
Fragin was isolated from *Pseudomonas fragi* in 1967 [1] and its constitution was established by total synthesis [2] and X-ray crystallography. [3] To date, its absolute configuration has not yet been established. The natural product possesses an unusual *N*-nitroso-*N*-hydroxylamine functional group, which is present only in few natural products, and exhibits a range of biological activities such as growth inhibitor of algae and lettuce seeds, antifungal, antimicrobial and anticancer properties. [4]



Fragin

In this communication, we report our studies on the chemical and biological properties of this natural product.

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TOTAL SYNTHESIS OF AERUGINOSIN 828A

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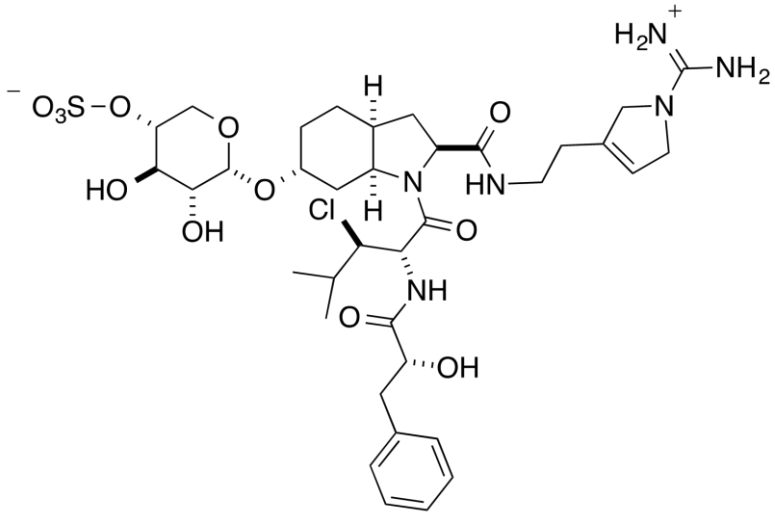
Aeruginosins constitute a family of linear modified peptides naturally occurring in cyanobacterial waterblooms. Today, over 40 compounds of this class of natural products are known. [1] Aeruginosin 828A was isolated form *Planktothrix rubescens* and it has been shown strong inhibition of thrombin and trypsin. Furthermore, aeruginosin 828A was found to be a potent biotoxin. [2]



Aeruginosin 828A

The aim of this project is to confirm the proposed structure by total synthesis. The effect of the chlorine and the sulfate residues on the biological activity should be clarified through analogue syntheses.

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TOTAL SYNTHESIS OF FIDAXOMICIN

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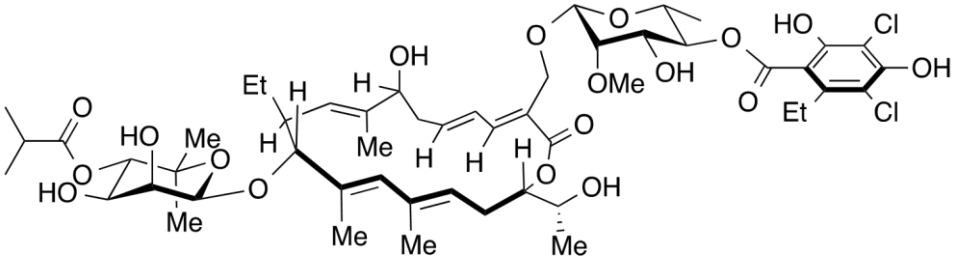
Fidaxomicin is a FDA-approved narrow spectrum antibiotic and currently used for the treatment of *Clostridium difficile* infections. This macrolide has also been found to exhibit potent biological activity against the multi-drug resistant *Mycobacterium tuberculosis*, however its poor pharmakokinetics prohibit its use as a drug. [1] Surprisingly, in spite of its significant biological properties and unique molecular structure no total synthesis of fidaxomicin has ever been reported since the first isolation in 1975. [2]



***fidaxomicin* (1)**

After our successful synthesis of the core aglycon, [3] we will present the first total synthesis of fidaxomicin. The synthetic tools achieved in the synthesis of this challenging 18-membered macrolide paves the way to generate structurally diverse analogs and could provide new insights into the structure-activity relationship.

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MUTASYNTHETIC APPROACH TOWARDS NEW HETEROAROMATIC GELDANAMYCIN DERIVATIVES

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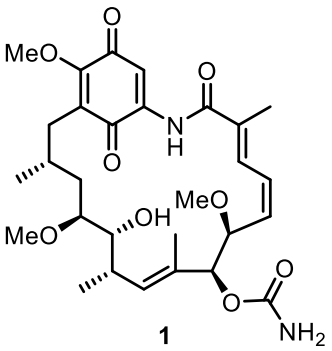
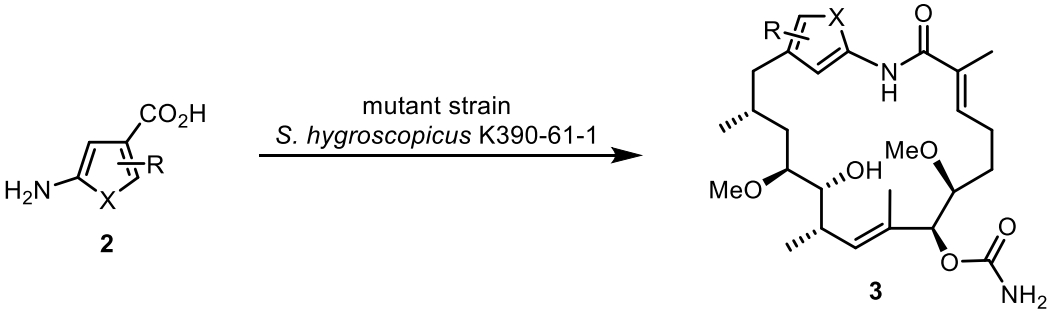


1

Geldanamycin (**1**) is a potential antitumor drug which is produced by *Streptomyces hygroscopicus*.[1] Its activity is based on the inhibition of the ATP dependent chaperone activity of heat shock protein 90 (Hsp90). Although geldanamycin (**1**) shows a high potential *in vitro*, its pharmaceutical properties prohibit clinical applications, primarily caused by the metabolism of the benzoquinone moiety.

Geldanamycin derivatives with different aromatic cores were obtained in a mutasynthetic approach.[2] A derivative incorporating a 5-membered thiophene core, derived from 5-amino-thiophene-3-carboxylic acid, shows good antiproliferative activity.

Thus the purpose of this project is to obtain a variety of 5-membered heterocyclic geldanamycin derivatives **3** with different functional groups and substitution patterns on the aromatic core by mutasynthesis (Schem).



2 **3**

Scheme 1. Mutasynthesis of geldanamycin derivatives 3.

Furthermore, we want to explore the combination of flow synthesis of mutasynthons **2** with mutasynthesis to geldanamycin derivatives **3**.

References:

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SYNTHESIS OF BICYCLIC IMINO- AND CARBASUGARS FROM CHIRAL POOL

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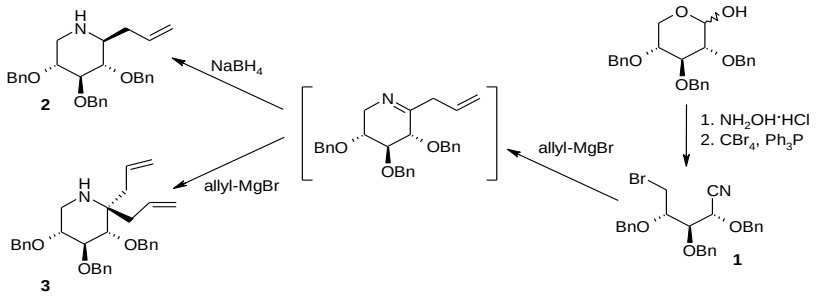
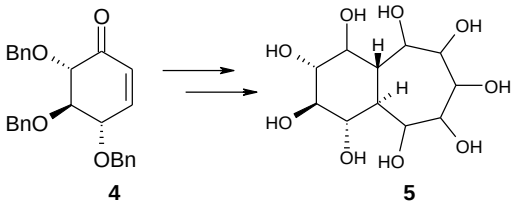
Polyhydroxylated mono- and bicyclic compounds, being structurally similar to carbohydrates, can act as glycomimetics.[1] Recently, we have developed a novel methodology enabling efficient synthesis of polyhydroxylated quinolizidines, indolizidines (such as castanospermine) and azaspiro[4.5]decanes.[2] A key step of this methodology consists in an addition of allylmagnesium bromide to ω-bromonitrile **1** (derived from D-xylose) followed by an intramolecular displacement of a bromide anion. The resulting cyclic imine was treated either with allylmagnesium bromide or with $NaBH_4$, providing 2-allylpiperidine **2** or 2,2-diallylpiperidine **3**, respectively.



Apart from the above-mentioned methodology, our group proposed, over the last several years, a highly stereoselective synthetic pathway to decalin systems.[3] However, it enables to obtain only the *cis*-decalins. Thus, we have designed a novel approach, employing the cyclohexenone derivative **4**. This stereoselective synthetic route leads to the *trans*-bicyclic systems, such as **5**.



Acknowledgements: The support from Grant: POIG.01.01.02-14-102/09 (part-financed by the European Union within the European Regional Development Fund) is acknowledged. Also, the support from National Science Center (NCN) in Poland (grant UMO-2014/13/N/ST5/00513) is acknowledged.

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APPLICATION OF A CARBANION TRANSMETALATION OF ARYL ALKYL SULFONES IN THE TOTAL SYNTHESIS OF CYCLOPENTANOID MONOTERPENES

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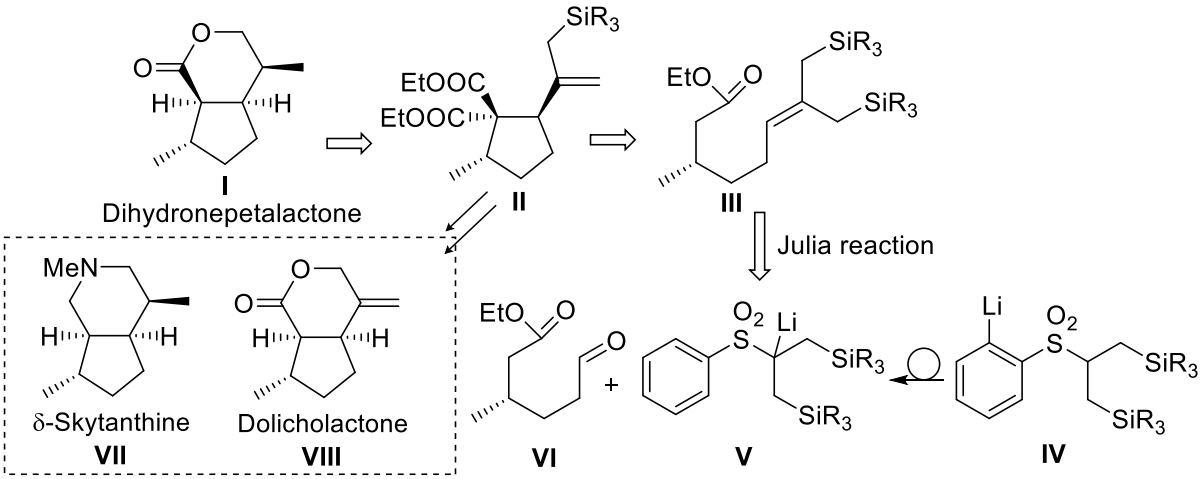
In a recently published total synthesis [1] of naturally occuring dihydronepetalactone **I**, a crucial olefin intermediate was prepared by a Wittig reaction in unsatisfactory yield and subsequent radical cyclization to **II** was not diastereoselective. The Julia reaction could be a convenient alternative for the preparation of the modified symmetric olefin **III** which might induce better selectivity during the tandem alkoxycarbonylation/oxidative radical cyclization.
The envisaged prototypical Julia olefination led instead suprisingly to directed *ortho*-metalation of □□□-disilylated sulfone.[2] The resulting aryllithium **IV** was found to rearrange subsequently completely to the initially expected sulfonylalkyllithium **V** on warming and reacted with aldehyde **VI**.



Olefin **III** was subjected to radical cyclization forming the silylated cyclopentane **II**, which serves as a unique starting point for the synthesis of a wide range of iridoids. In this contribution total synthesis of dihydronepetalactone as well as approaches leading to other cyclopentanoid monoterpenes **VII** and **VIII** with similar structural motifs will be presented.

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SHORT AND MODULAR APPROACH TO LEPADIN ALKALOIDS

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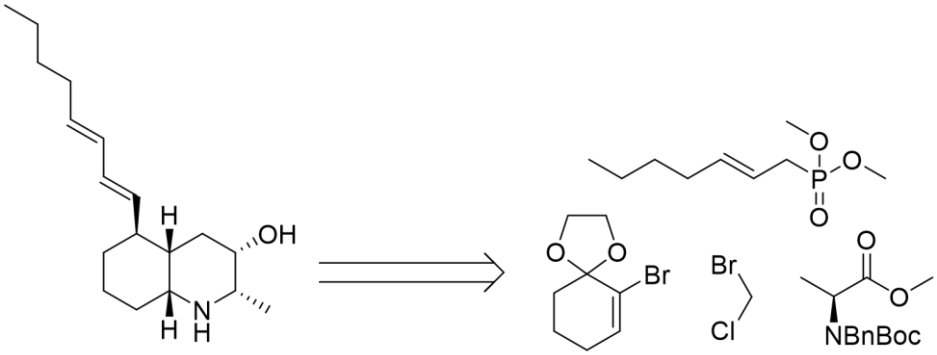
Lepadins form one of four groups of biologically distinct decahydroquinoline alkaloids. There are three stereochemical groups of lepadin alkaloids. Current state of the art strategies for lepadin alkaloid synthesis require 18-38 steps. None of these syntheses can provide practical access to lepadins to support further biological studies. Owing to our interest in C-18 amino alcohol natural product chemistry we decided to make our contribution to decahydroquinoline alkaloid research and choose lepadins as suitable targets. During lepadin alkaloid synthesis studies we have developed a unified strategy with the aim to access complete stereochemical complexity of these natural compounds in a step economic and modular fashion.



lepadin B

In this presentation the details on the development of short synthetic sequences to lepadin alkaloids including the advancement of several new methodologies during various stages of synthetic routes will be discussed.

ANTIACETYLCHOLINESTERASE AND ANTIOXIDANT ACTIVITIES OF SEVERAL *PLECTRANTHUS* SPECIES

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The genus *Plectranthus* L Herit. (Lamiaceae), with ca. 300 species of herbs and shrubs, is widely distributed in Africa, Asia, Australia and some Pacific Islands. Many *Plectranthus* species are cultivated for their edible tubers, as essential oil crops or ornamentals, while others also used in folk medicine for to treat many disorders and diseases [1]. This family has several biologic activities among which antioxidant, antimicrobial and anti-inflammatory can be mentioned. These activities are due to phenolics compound, flavonoids and tannins that they have in their phytochemical constitution [2]. To understand a little bit deeper these plants' activities, infusions of leaves of nine different species of *Plectranthus (P. ernstii*, *P. gradidentatus*, *P. lanuginosus*, *P. madagascariensis*, *P. neochilus, P. venteri*, *P. verticillatus* "Ubombo", *P. verticillatus* ""Barberton" and *P. zuluensis)* were prepared and lyophilized to yield an extract. The major components were identified by LC-MS and it was find out that rosmarinic acid was present in all extracts and in most of them was the main component. Rosmarinic acid is a typical compound from *Lamiaceae* family. The quantification of the rosmarinic acid was made by HPLC against an external standard. In this work the biological activities studied were antioxidant activity, using DPPH assay and the inhibition of acetylcholinesterase (AChE), employing the Ellman method with some adaptations [3]. The AChE inhibition activity, quantified as IC_{50} value and the antioxidant capacity of these extracts, measured as EC_{50} values, were dependent on rosmarinic acid content. Although this phenolic acid was the largest component, several flavonoids and tannins were also present. The extract from *P. zuluensis* showed the lowest IC_{50} value, 80 μg/ml and also the highest antioxidant activity, EC_{50} of 13.3 μg/ml, similar to the standard antioxidant BHT [3]. This extract had the highest rosmarinic acid concentration (362 ug/mL) but the flavonoid derivatives and tannins present in the extract may also contributed to this effect. The IC_{50} value of rosmarinic acid for AChE activity is 440 μg/mL [3] not justifying alone, by itself, the high activity found, nevertheless a high correlation between the AChE inhibition and the rosmarinic acid content was verified. These values indicate that, besides rosmarinic acid, also the flavonoids present in the extract and the tannins, although in lower amount may contribute to the enzyme inhibition activity. The total phenolic compounds and total tannins present in all the extracts were also quantified. To verify if the chemical composition of the extracts is modified during the digestion, the metabolism *in vitro* by adding gastric and pancreatic artificial juices to the extracts was analyzed. None of the extracts suffer any changes and the initial activities were kept constant.

Acknowledgements: FCT for the programmatic financing reference number: UID/MULTI/00612/2013.

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SYNTHESIS OF NEW C-13 BERBERINE DERIVATIVES

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Berberine is a natural isoquinoline alkaloid isolated from plants of *Berberidaceae*, *Ranunculaceae*, and *Papaveraceae* families, which has been widely used in traditional Chinese medicine due to its antimicrobial and antiprotozoal activity.[1] Berberine and derivatives have gained much attention in recent years owing to multiple pharmacological effects, including anticancer, antiviral and antibacterial activities.[1]

Berberine is a 5,6-dihydrodibenzo[*a,g*]quinolizinium derivative that can be functionalized at different positions on its skeleton. The typical functionalizations in berberine core are nucleophilic addition to C-8, derivatization at position C-9 and alkylation at C-13 through enamine-8-acetonyl intermediate. [2]

The derivatives resulting from alkylation in position C-13 are target of increasing research due to its high anti-cancer activity (Figure 1(a)).[1] So far, derivatizations at this position are performed by a two-step procedure: the first step requires enamine activation by nucleophilic addition at C-8 [3] or reduction of iminium functionality[4], the second step is a nucleophilic attack of the activated enamine to an electrophile, followed by restoration of the quinolizinium core aromaticity (Figure 1(b)). This derivatization method of C-13 position allows the attachment of several benzyl and alkyl electrophiles but arylation and introduction of heteroatoms is still not possible by direct C-13 derivatization of berberine. Herein we present an alternative method that will allow for the first time further derivatization of this position with a range of coupling agents using robust synthetic methodologies.

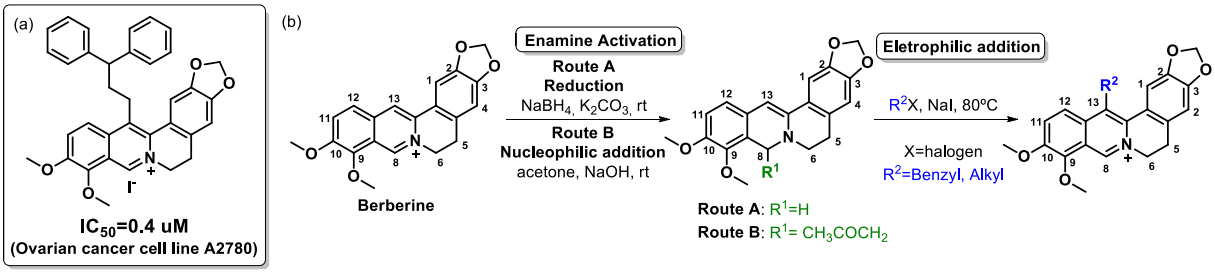

Figure 1: (a) Example of C-13 Berberine derivative with highly anticancer activity,[1] (b) Reported derivatization possibilities of C-13 position of Berberine.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (SFRH/BDP/100677/2014).

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IMPACT OF *CITRUS* PECTIN ON OENIN COPIGMENTATION MECHANISMS

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Anthocyanins have a high potential as natural colorants due to their attractive colors. Additionally they are non-toxic, non-mutagenic [1] and their pharmacological properties are also well known and account for their therapeutic use [2]. However, the use of these colorants may face some problems due to their instability. For instance, the color of anthocyanins is highly dependent on pH due to changes in the concentration of the four species present in acidic and neutral aqueous solutions [3]. Copigmentation mechanism is regarded as one factor of structure stabilization, *i.e.*, coloration of anthocyanins [4,5]. This mechanism consists of hydrogen-bind interaction and hydrophobic interactions (□-□ stacking) between the colored forms of the anthocyanins (*i.e.*, flavylium cation ion and quinoidal forms) with other colorless organic molecules (*i.e.*, copigments) [6]. Copigmentation complexes adopt a sandwich configuration (vertically stacked) that protects the flavylium chromophore from the nucleophilic attack of water, thus partially preventing the formation of colorless forms, through the □ complex displacement of the anthocyanin hydration equilibrium toward the pigmented forms and color enhancement [7]. Anthocyanins – polysaccharides interaction is likewise a very important topic to be considered on anthocyanin's stabilization, as these pigments are bio-synthetized in a polysaccharide rich environment [9]. In fact, anthocyanins are located within the vacuole of plant cells, enclosed by the plant cell wall. With the disruption of plant tissues, anthocyanins and plant cell walls become into contact with the potential for binding interaction to take place [10]. The association between macromolecules resulting from disrupted cell walls (*e.g.* pectins) and anthocyanins may affect pigments chemical stability and color properties thus playing an important role in the final color of food products. The anthocyanins-polysaccharide association could also be important for anthocyanin's copigmentation (Figure 1). Bering this, the main goal of this work is to evaluate the impact of pectin on anthocyanin's copigmentation mechanisms.

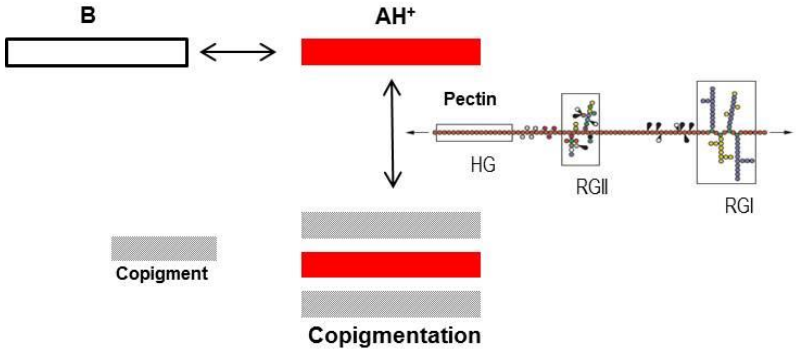

Figure 1. Copigmentation mechanism. Adapted from Fulcrand *et al*., 2004 [8].

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A UNIFIED BIOINSPIRED "APLYSINOPSIN CASCADE": TOTAL SYNTHESIS OF (±)-TUBASTRINDOLE B

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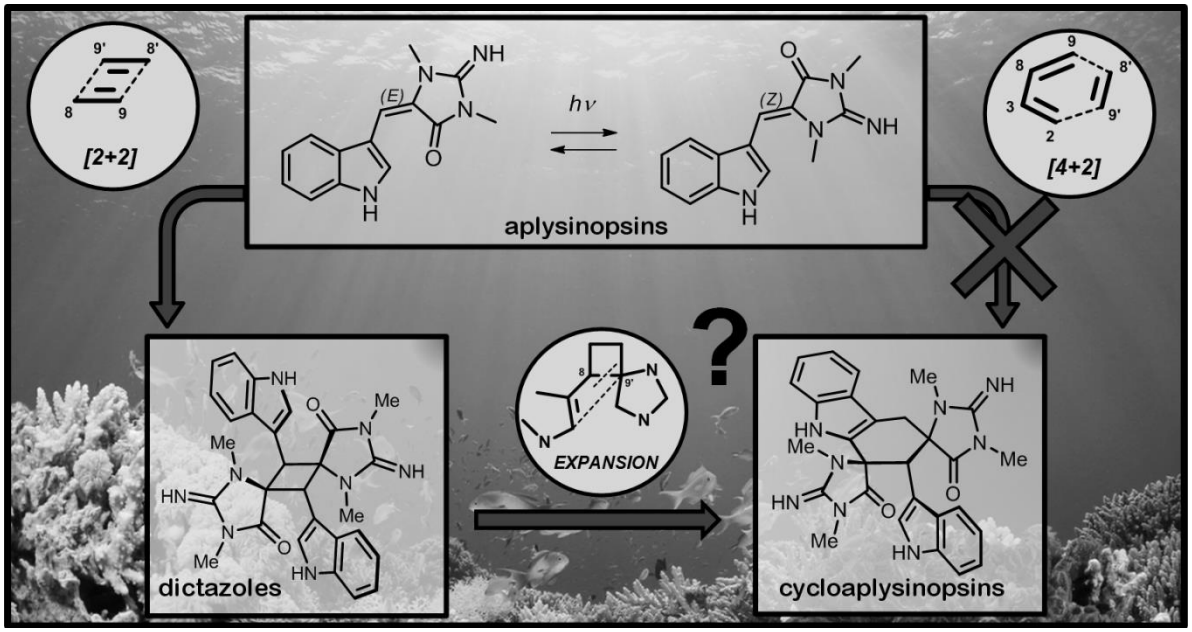
Applying a biomimetic approach, we report the first total syntheses of (±)-dictazole B and (±)-tubastrindole B. This work features [2+2] photocycloadditions of aplysinopsin monomers into dictazole-type intermediates. The following ring-expansion of the dictazole-type intermediate affords (±)-tubastrindole B. Moreover, the isolation of a transient biogenetic intermediate represents a milestone in the biosynthetic understanding of this family of marine alkaloids as we will discuss.



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THE INFLUENCE OF ENVIRONMENTAL SALINITY, IN THE MARRUBIIN PRODUCTION AND ANTIOXIDANT ACTIVITY OF *MARRUBIUM VULGARE*

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Marrubium vulgare is a medicinal plant included in the Lamiaceae family considered as one of the popular and traditional remedies in the regulation of diabetes in Tunisia. Plant growth and development are negatively affected by some environmental factors being salinity one of the major environmental constraints worldwide. In the Maghreb and the Middle East about 15 million hectares are damaged by salinity. One of the countries whose lands are affected by salinity stress is Tunisia where the semi-arid Mediterranean bio-climatic territories are frequently irrigated with brackish water.

Plants were watered with water containing NaCl at several concentrations, 0, 25, 50 and 100 mM, under controlled conditions. The increase of salt stress influenced the fresh biomass and caused a severe damage to plants. The plants exposed to a high level of salinity were significantly affected and presented clear symptoms of damage such as leaves chlorosis and necrosis.

In general the synthesis of bioactive compounds is usually stimulated in response to biotic/abiotic stresses such as salinity. Marrubiin, a furane labdane diterpene, is the main bioactive compound present in *Marrubium vulgare* and it has potent cardioprotective, vasorelaxant, gastroprotective and antispasmodic proprieties [1]. In this work marrubiin was isolated, identified by FTIR and NMR, and quantified by ^{1}H NMR. Results showed that salinity enhanced its production as a response to salt stress.

In addition nothing had yet been described about how *Marrubium vulgare* reacts to salt stress regarding its antioxidant protection. Hence the total phenolic content (TPC), and the antioxidant activity of methanolic extract were evaluated, using four different tests (ferric reducing power ability, the DPPH test, the β-carotene bleaching assay and the ability to scavenge hydrogen peroxide). Salt stress resulted in a decrease of total phenolic compounds of methanolic extracts, in contrast the ferric reducing power ability increased with increasing salinity. The highest diphenylpicrylhydrazyl radical (DPPH) scavenging activity was found in plant treated with 100 mM NaCl (IC_{50}=199.86 μg·mL^{-1}) which was also quite potent in the β-carotene bleaching assay (40%). Among the tested extracts, only the plants treated with NaCl 25 mM (IC_{50}=626.68 μg·mL^{-1}) and 100 mM (IC_{50}=653.03 μg·mL^{-1}) presented the ability to scavenge hydrogen peroxide.

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TOTAL SYNTHESIS OF LYCORINE-TYPE ALKALOIDS

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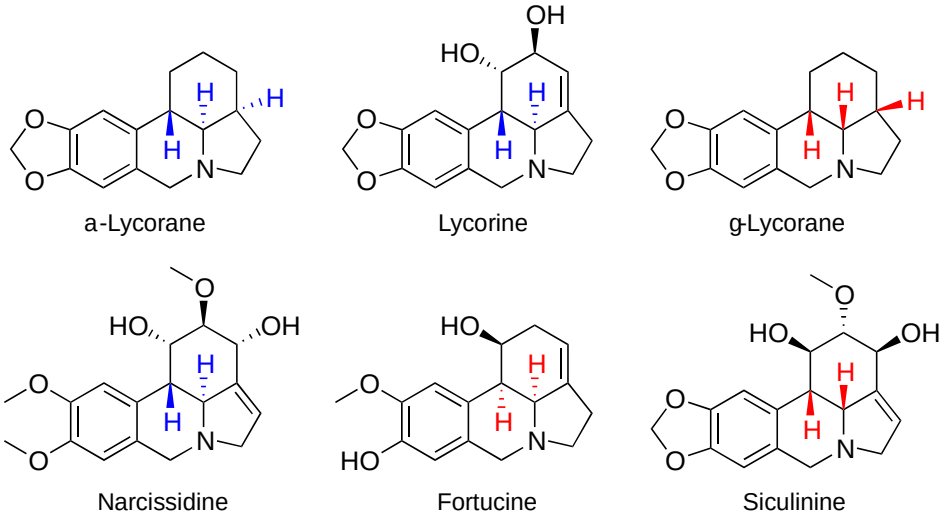
Lycorine-type alkaloids, extracted from the Amaryllidaceae family of plants, are structurally and biologically stimulating. Their biological activites,[1] low natural abundance, few available asymmetric syntheses,[2] and redundant mis-assignment of structure of congeners[3] prompt synthetic chemists to investigate new synthetic approaches to this challenging class of natural product. We have developed an original and flexible synthetic strategy allowing the synthesis to *several* congeners of the Lycorine family bearing either a *trans* or a *cis* B,C-ring junction. The synthetic key steps rely on tandem metathesis (RCM) and chiral sulfinylimidates to forge the asymmetric contiguous stereocentres. The total syntheses of Lycoranes and advances toward more functionalized members of the family will be presented.[4]



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ANTIOXIDANT ACTIVITY OF SUNSCREENS CONTAINING TEA AS EXTERNAL FASE: *IN VIVO/IN VITRO* CORRELATION

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Tea has been widely studied, since it represents a source of bioactive compounds that provide antioxidant activity, particularly polyphenols. It has been demonstrated that topical application or oral intake of green tea polyphenols prevents the development of cancer and also that galloyl catechins confer an effective protection against oxidative stress caused by UVB [1]. Black tea has a lower content in polyphenols, but it has a considerable amount of tannins in its composition.

The aim of this study was to assess and compare the *in vitro* and *in vivo* antioxidant activities of emulsions containing green tea or black tea as external phase, as well avobenzone (UVA filter) and octyl methoxycinnamate (UVB filter). The *in vivo* safety and biocompatibility of the studied emulsions was also evaluated.

Formulations were prepared, containing either green or black tea and with or without the UV filters. A blank formulation (without tea) was also tested. The *in vitro* antioxidant activity was assessed using the radical scavenging assay with DPPH radical (DPPH assay). For the *in vivo* measurements, twelve volunteers participated in this study. Six 9 cm^2 sites were marked on the volar surface of both subjects' forearms. Basal measurements of skin hydration, TEWL and colour were attained at day 1. Five of the sites were topically treated with the different formulations, twice daily during seven days. The sixth site remained untreated. The measurements of the referred skin properties were repeated after this seven days period. Subsequently, an ethyl nicotinate (EN) solution was applied for 60 seconds on each site to induce an inflammatory response and skin perfusion was measured for 20 minutes with LDF (PF 5010 system, Perimed, Sweden). Onset time, area under the curve (AUC) and the slope of the curve on the hyperemic phase were chosen as comparison parameters between sites.

Both formulations containing tea showed good skin biocompatibility. After one week of application, no significant changes were observed in hydration and skin barrier, and no erythema was detected in the treated sites. For both *in vivo* and *in vitro* studies the formulation containing green tea showed a higher antioxidant activity. However these differences were more apparent with the *in vitro* study and so it would be interesting to increase the sample size (*n*) of the *in vivo* tests to confirm these results. The formulation with black tea showed no differences when compared to the blank formulation.

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CHEMICAL CHARACTERIZATION OF THE ESSENTIAL OILS FROM *ERICA AUSTRALIS* L.

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The chemical composition of the essential oils isolated from the flowering aerial parts of *Erica australis* L. (Ericaceae), collected in Portugal, were studied by gas–chromatography (GC) and by gas-chromatography/mass spectrometry (GC/MS). In order to evaluate if the flower colour was related to different volatiles composition, the dried flowering aerials parts of *E. australis*, were separated into flowers showing light pink-, medium pink- and dark pink colour, and assessed separately. Forty-three components were identified in each sample showing the predominance of 1-octen-3-ol (33-38%), the aldehyde *n*-nonanal (8-11%), and the alcohol *n*-octanol (6-7%). Other alcohols were also present, although in minor amounts, like *n*-heptanol (4%), *cis*-3-hexen-1-ol (2-5%), and 2-octen-1-ol (2-3 %). The aldehydes 2-*trans*, 4-*trans*-decadienal (2-4%), and 2-*trans*-decenal (2%), and nonanoic acid (2 %) were also identified in the analysed samples. No remarkable differences were observed on their chemical composition, suggesting that colour polymorphism does not influence *E. australis* essential oil yield or composition.

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F – BIOMOLECULAR CHEMISTRY

PROMISCUOUS ENZYMES AS EFFICIENT TOOLS IN ORGANIC SYNTHESIS

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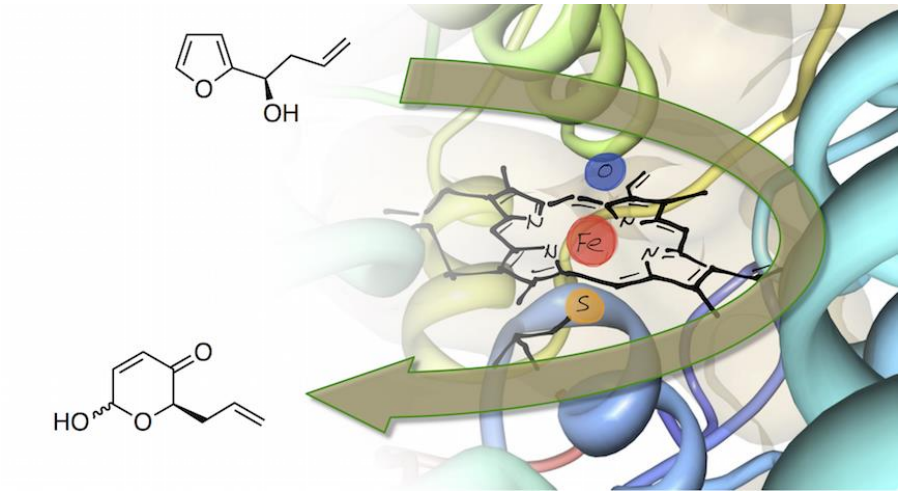
Thanks to unrivalled selectivities and good availability of stable and optimized enzyme preparations, biocatalysis is increasingly gaining ground as module in the organic chemist's toolbox for the synthesis of well-defined building blocks. However, with regard to an even broader application of enzyme catalysts in classical synthetic chemistry, the lack of biosynthetic precedence for numerous synthetically relevant reactions and the consequent lack of biocatalysts to promote those reactions needs to be considered a major drawback. Since many years, catalytic promiscuity, the enzymes' capability to catalyze fundamentally different chemical interconversions, has been in the scientific focus,[1,2] however, just recently entirely abiotic transformations came within reach by means of specialized, evolved proteins.[3,4,5]

In our search of biological catalysts with abilities to address synthetically important reactions beyond the biosynthetic repertoire, a first breakthrough was achieved in form of non-natural ring-closing and ring-expanding transformations, respectively.[6] Here, heme-based wild-type enzymes are not only qualifying as exquisite alternatives to chemical reagents or catalysts, but moreover, allow for the construction of short in vitro metabolisms and thus for the stereoselective preparation of highly functionalized building blocks on basis of a biological synthetic-organic machinery.



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SYNTHETIC ROUTES TO NEW PYRIMIDYL PORPHYRINS AND CORROLES

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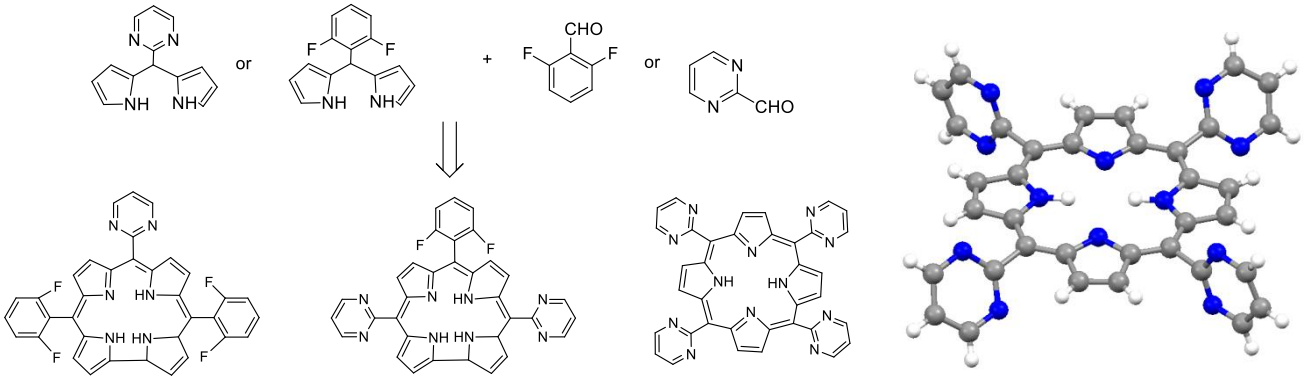
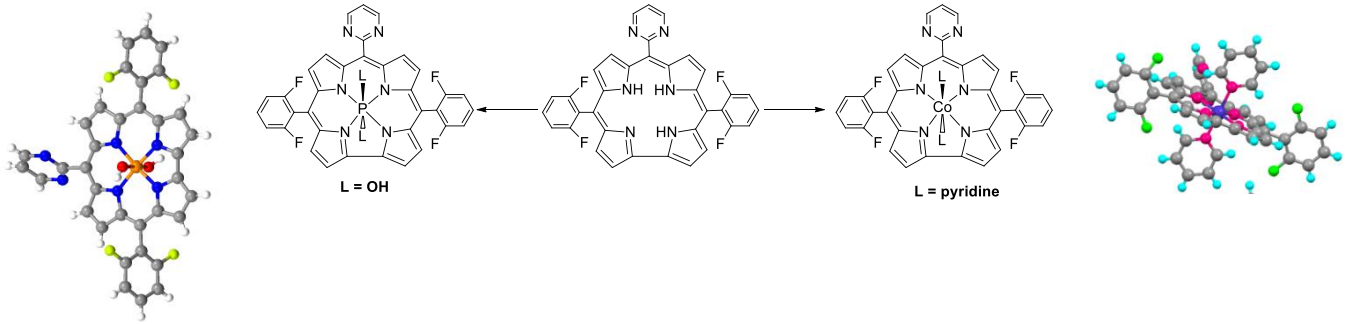
The importance of porphyrins and corroles that are decorated by basic nitrogen atoms close to their respective N4 coordination core is well appreciated.[1] The discovery of stable corroles and their metal-complexes has initiated extensive research on their fundamental physical and chemical properties, which was rapidly followed by advantageous utilization on these molecules in many fields.[2] Within the course of our investigations on corroles as catalysts for medicine-relevant and many other applications we became interested in *non-charged* derivatives that would not suffer from the atropoisomer problem, have nitrogen atoms in the vicinity of the N4 coordination core, and could also be of sufficient solubility in water.



We have developed the synthesis of corroles with one and two 2,6-pyrimidyl substituents, including the crystal structures of the corresponding phosphorous and cobalt chelates of the former, as well as of tetra(2,6-pyrimidyl)porphyrin. The latter compound was characterized by X-ray crystallography and it also displays high solubility in water.



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HELICAL AMINOISOBUTYRIC ACID FOLDAMERS: MEMBRANE ACTIVITY AND INTER-HELICAL COMMUNICATION OF CHIRALITY

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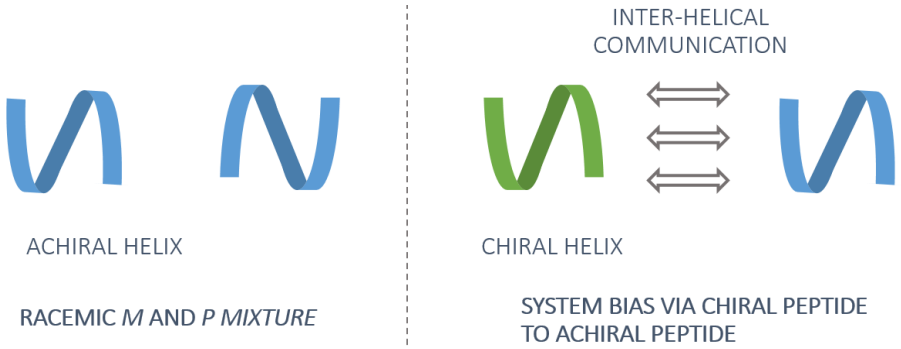
Synthetic foldamers built from the achiral amino acid α-aminoisobutyric acid (Aib) adopt racemic mixtures of left (*M*) and right (*P*) handed 3_{10} helices in solution.[1] Previous work has shown that screw-sense preference can be diverted toward one chirality using covalently-bound chiral residues[2] and non-covalently interacting chiral ligands.[3]



Recently it has emerged that inter-helical communication of stereochemical information is also possible and Aib peptides furnished with a single chiral residue can influence the screw-sense preference of exclusively achiral oligomers. Even peptides with N and C-terminal protecting groups are able to interact to bias the system and, in this poster, work will be presented towards understanding the influence of different terminal groups on these interactions.

Aib foldamers are of particular interest, as high proportions of Aib residues are found in the natural class of antimicrobial peptides, peptaibols. These peptides possess C-terminal alcohols, commonly adopt helical structures and are known to disrupt lipid bilayers, which is implicated in their antibacterial activity.[4] For instance, the extensively-studied peptaibol, alamethicin is able to form ion channels across membranes.[5]

Rigid-rod, helical Aib foldamers have also been shown to form ion channels across lipid membranes. This ability to conduct ions across lipid membranes has been investigated with respect to the physical properties of oligomers, such as length and N and C-terminal functionality, which will also be addressed here.

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TOWARDS FOLDAMER-UREA SYSTEMS FOR INTERMOLECULAR COMMUNICATION OF STEREOCHEMICAL INFORMATION

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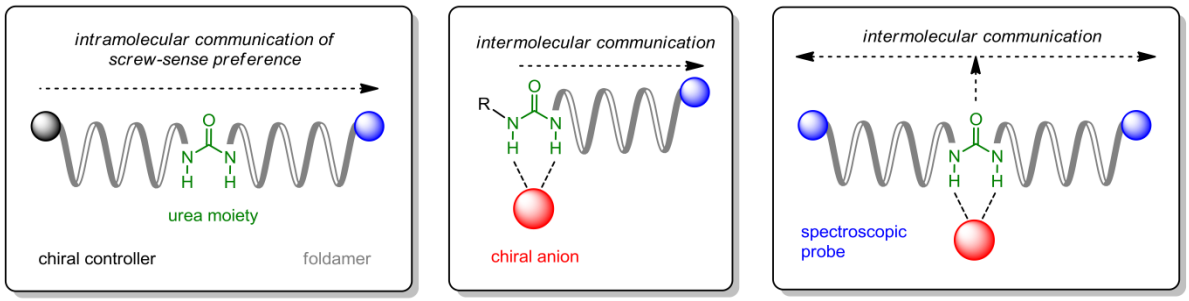
When stereochemistry is seen as information, the concept of communicating information between molecules becomes clearer. Transduction of signals in synthetic structures can be achieved by foldamers, extended molecules with well-defined conformational properties.[1]

Oligomers of the achiral aminoisobutyric acid (Aib) form stable, well-defined 3_{10}-helical foldamer structures. Work done by our group has shown that a stereochemical influence at one end of an otherwise achiral helix is capable of inducing a screw-sense preference extending over numerous helical turns.[2-4] By using switchable structures, we demonstrated for the first time that information in an otherwise achiral can be communicated over multi-nanometer distances[5] and that reversible covalent interactions can be used to mimic the binding of a ligand at a binding site.[6]

The next key breakthrough is the development and investigation of methods for direct intermolecular communication between helical molecules. Ureas possess unique structural features including their ability to function as hydrogen-bond donors. Therefore, by introducing them into Aib-oligomers, potential binding sites for chiral anion recognition involving hydrogen bonding are obtained. The following figure shows general structures of the targeted molecules and potential ways for transfer of stereochemical information.



Our approach to synthesise and investigate urea-Aib oligomers as well as oligomer-urea-oligomer systems to observe the interactions between foldamers as well as ongoing structure modifications will be presented.

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DYNAMIC EXPRESSION OF DNA COMPLEXATION WITH SELF-ASSEMBLED BIOMOLECULAR CLUSTERS

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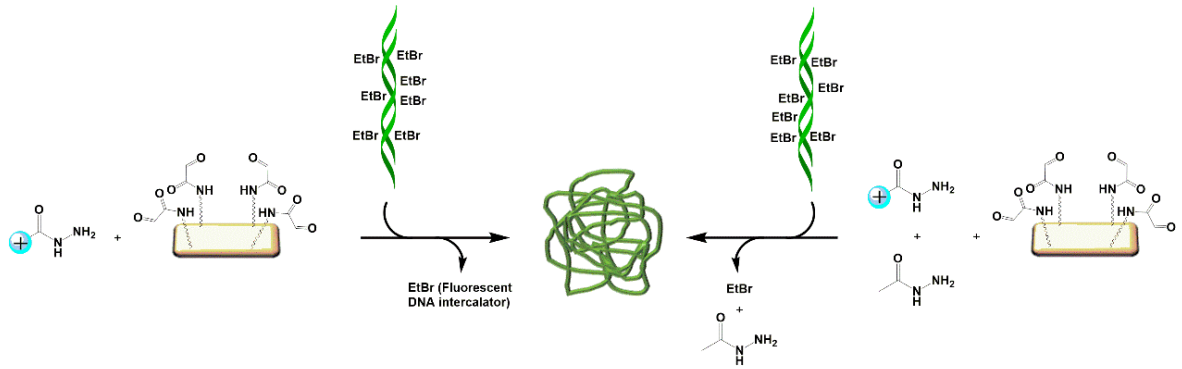
Multivalency[1] is of great importance for the non-covalent recognition of biomolecules in aqueous media. In the context of dsDNA recognition, cationic clusters have recently emerged as a novel class of compounds that may be used in gene delivery applications.[2]
While the traditional approach involves the design, preparation and evaluation of a large number of clusters, self-assembly processes may be considered to generate multivalent nanoconstructs[3] In particular, the use of reversible chemoselective ligation should enable the *in situ* expression of multivalent clusters through dynamic covalent chemistry.

We prepared several hydrazide building blocks and selected a pre-organized cyclodecapeptide scaffold appended with four aldehydes oriented on the same face. The reaction progress of the hydrazone ligation was monitored by RP-HPLC and indicated the formation of the tetra-functionalized cluster in a variety of aqueous media. Then, we tested DNA interaction by using a fluorescent displacement assay. While the hydrazide building blocks and the cyclodecapeptide scaffold were found to be ineffective for dsDNA complexation the resulting mixture of both components displayed a high activity that emerge from the *in situ* generation of a cationic cluster. The self-assembly approach allows the study of dynamic combinatorial libraries consisting of a mixture of various hydrazide building blocks and a single peptide scaffold for the *in situ* generation of biomolecular clusters that effectively complex dsDNA through multivalent interactions. HPLC analysis revealed the preparation of libraries which tended to the formation of the neutral cluster. By adding dsDNA, the fluorescent emission signal decrease was explained by template effects of the target which imposed the formation of the active cluster.



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B-N DATIVE BOND: A USEFUL TOOL TO MODIFY PROTEINS AND TO ASSEMBLE TUMOR TARGETING CONJUGATES

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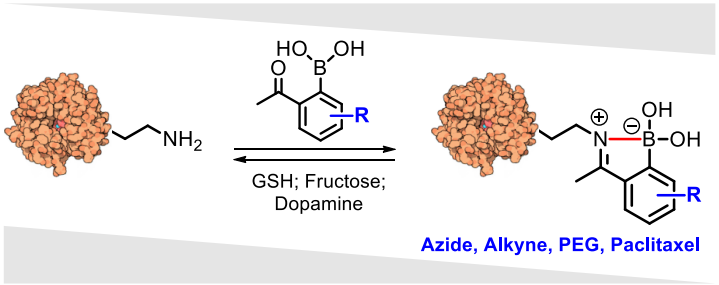
Recent appreciation for the unique Boron-Nitrogen bond properties triggered a burgeoning interest for this motif. B-N bonds have been extensively exploited to construct self-assembled molecularly defined nanostructures, polymeric materials and sensors. Recently, the isosterism between B-N and C-C bonds was also recognized as a powerful tool to tune the properties of organic molecules. In this context, we have used the B-N bond to prepare natural product-like structures and heterocycles with activity against HNE.[1,2] In this communication, we will present the use of this bonding motif to efficiently modify proteins and to promote the assemblage of constructs that selectively internalize into tumor cells.[3-5]



This protocol relies on the formation of alkylic iminoboronates in aqueous media. Despite their stability, these modifications were shown reversible in the presence of fructose, dopamine and glutathione, as they presumably induce hydrolysis by disruption of the B-N bond. Fluorescent 2-acetylbenzeneboronic acids derivatives were successfully prepared and conjugated via a B N linkage with lysozyme and N-(2-aminoethyl) folic acid, generating conjugates that were selectively recognized and internalized by NCI-H460 cancer cells, which over-express folic acid receptors. The ability of these iminoboronates to undergo a receptor mediated internalization and their efficiency to promote the selective and reversible functionalization of proteins, highlights these constructs to have a promising future in the design of conjugates that selectively target and deliver cargo to cancer cells.

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SYNTHETIC TOOLS FOR SELECTIVE PROTEIN ISOTOPE LABELING

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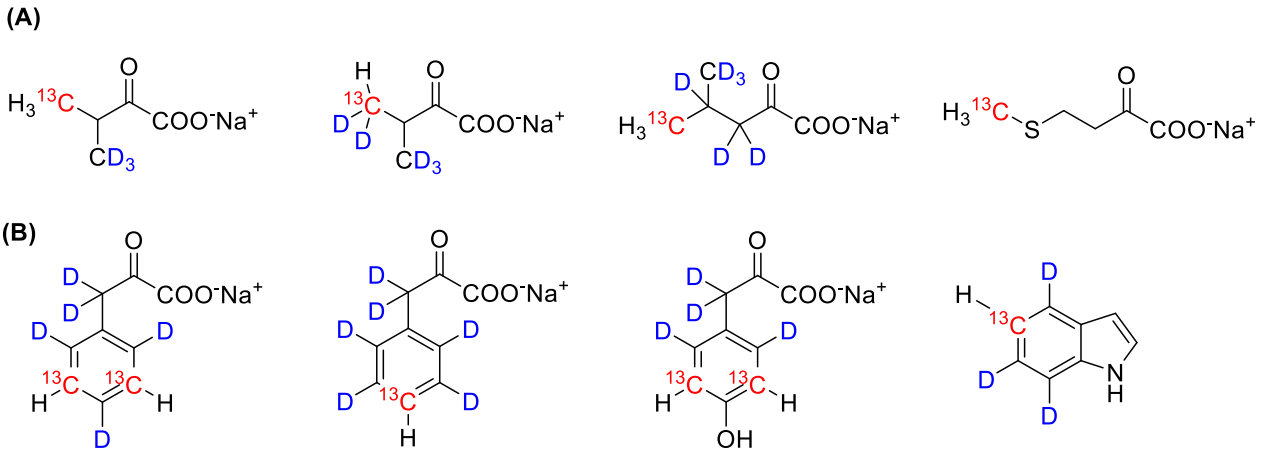
Protein NMR spectroscopy is the most important method to probe both the structure and the conformational dynamics of protein complexes at an atomic resolution. Monitoring enzyme catalysis, ligand binding or molecular recognition using sophisticated NMR experiments requires selective patterns of ^{13}C, ^{15}N and ^{2}H in the target proteins to reduce signal overlap and/or optimize magnetization transfer pathways. The isotope distribution aimed for must be tailored to the requirements of the corresponding NMR application, whereas the appropriate labeling techniques have to be optimized for selectivity, general applicability and economic considerations.

We develop synthetic routes to access isotope labeled amino acid precursors, which serve as additional nutrients in the growth media of overexpressing microorganisms. Our synthetic approaches feature robust reaction sequences in combination with low-cost isotope sources (e.g. ^{13}C-acetone, $^{13}CH_3I$, $^{2}H_2O$, ^{13}C-glycine). By now, our precursor toolbox features compounds for selective labeling of Ile-, Val-, Leu-, Met-, Phe-, Tyr-, and Trp- residues[1-7] (a selection of aliphatic (A) and aromatic precursor compounds (B) is given below). The synthesis of these molecules, as well as their use in protein overexpression and examples of protein NMR applications are reported.



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CHEMICAL SYNTHESIS OF PEPTIDE-NUCLEOTIDE CONJUGATES AND BIOPHYSICAL STUDIES ON THEIR ABILITY TO TRANSLOCATE ACROSS LIPID MEMBRANE USING CONFOCAL FLUORESCENCE MICROSCOPY

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It has been shown that various nucleosides, nucleotides, and oligonucleotides exhibit significant potential as therapeutic agents. Among these compounds are analogues of the 5' end of mRNA, the cap, that in its basic form consists of a 7-methylguanosine connected via a 5',5'-triphosphate bridge with the second nucleotide (usually G). Chemically-modified cap analogues are being studied extensively and show very promising anti-cancer properties. Unfortunately despite a great potential of such analogs difficulties associated with membrane permeability, caused mainly by the ionizable phosphate groups present within the cap structure, strictly limit their usage. To overcome problems with intracellular delivery of therapeutic molecules through a cell membrane, the use of diverse methods has been developed. Among them, cell-penetrating peptides are very promising and powerful tools for cellular uptake of biologically active compounds. Here we report the chemical synthesis of a peptide–nucleotide conjugate consisting of a MPS cell-penetrating peptide (membrane permeable sequence) and model: a) dinucleotide, b) mononucleotide and c) mononucleoside cap analogue and comprehensive biophysical studies on the ability of such conjugates to translocate across lipid membrane using confocal fluorescence microscopy.

Acknowledgements: This work was supported by grants 2012/07/D/NZ1/04255 and DEC-2013/11/B/ST5/02226 from the National Science Centre and 0055/IP3/2013/72 from Polish Ministry of Science and Higher Education

TOOLS FOR LABELING LIVING BACTERIA

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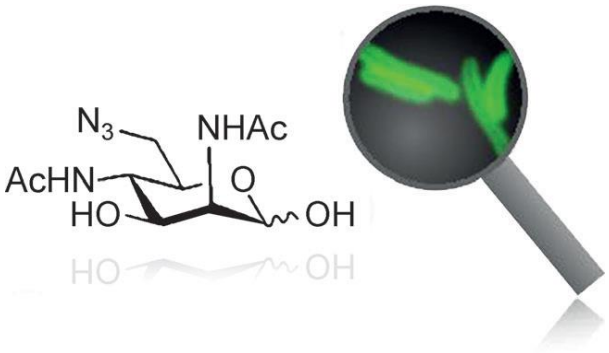
Sudden outbreaks of new epidemics regularly warn us against the severe sanitary and economical impact resistant bacterial infections could have on our industrialized and globalized societies. The rapid identification of viable bacteria is therefore a fundamental challenge.

The outer membrane of Gram-negative bacteria is covered by a dense layer of Lipopolysaccharides (LPS), which are considered to participate into cell integrity, as well as to the level of pathogenicity of a given strain.

In this communication, we will show that, when they are metabolically active, Gram-negative bacteria can specifically incorporate into their Lipopolysaccharides a monosaccharide, which has been modified by the introduction of an *azido* anchor.[1]

This bioorthogonal chemical reporter can then be further exploited in the *click-chemistry* mediated labeling of these bacteria. This overall procedure offers an efficient and rapid strategy to identify living, or metabolically active, bacteria. This communication will present our latest results in this field including the specific identification of *Legionnella pneumophila*.[2]



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SYNTHESIS OF LIPO-CHITOOLIGOSACCHARIDE ANALOGS FOR AGROCHEMICAL APPLICATIONS

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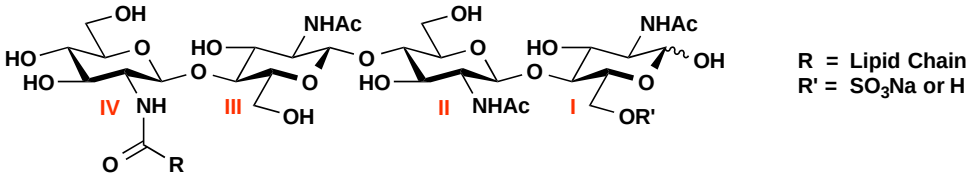
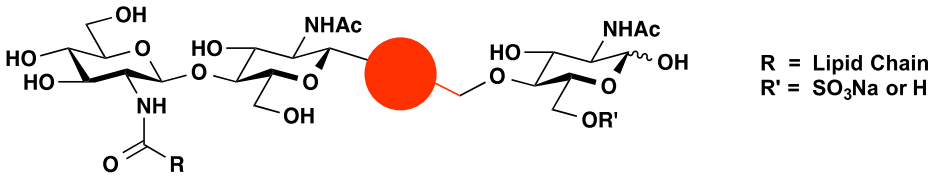
The arbuscular mycorrhizal symbiosis is an association between fungi and plant roots, regulated by a molecular dialogue.[1] This symbiosis plays a crucial role in plants nutrition, allowing them to grow on arid and unfertile soil, as well as in plant protection from pathogens. Recently, the symbiotic signals emitted by fungi (« Myc factors ») were identified as a mixture of lipo-chitooligosaccharides (LCOs), similar to those discovered in rhizobia symbiosis.[2]



The chemical synthesis[3] of these molecules is difficult, time consuming and the chemoenzymatic synthesis[4] does not allow easy introduction of molecular diversity for structure-activity relationship studies. Modelisation studies[5] of protein-ligand interactions, showed that the monosaccharidic unit II would have a less important role in the interaction with the receptor. In order to obtain LCO analogs, we are exploring the replacement of the GlcNAc unit II by simpler structure.



The targeted analogues permit an easier synthesis avoiding tricky glycosylation steps and the proposal of interesting molecules to understanding which structural elements are important for LCOs bioactivities.

This communication will present our latest results in this field.

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SINGLET OXYGEN INDUCED FURAN OXIDATION FOR PEPTIDE DERIVATISATION

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Site-specific chemical modification of proteins is crucial for understanding protein structure and interactions as well as providing insights into cellular events.[1] In continuation of previous work conducted in our lab, where an efficient solid phase-based peptide labeling method was developed,[2] in this study, we investigated the singlet oxygen ($^1O_2$) mediated furan-modified peptide labeling in physiological aqueous solutions. Furan-containing peptides were subjected to the standard oxidative conditions (air, light, photosensitiser) so that the reactive electrophilic species were generated. These reactive intermediates were intercepted by good nucleophiles to form stable conjugates. Incorporation of nucleophilic fluorophores through a cascade reaction sequence, led to the efficient construction of site-selectively labeled fluorescent peptides.[3]

Furan-peptides bearing sensitive residues such as tryptophan, methionine and histidine as well as a cell-penetrating peptide were subjected to the newly developed oxidation and labeling protocol. Desired products were efficiently obtained in relatively high yields, without the use of any quencher, considering the oxidative damage of ROS species. Additionally, fluorophores of different properties regarding their water solubility, pH sensitivity and fluororescence intensity were tested for their capacity to efficiently label our model peptide. Labeling with Alexa dye proclaims that our methodology could be suitable for biological applications. In summary, a novel methodology has been developed which transforms furan-modified peptides to fluorescent probes and tags in a single operation in solution, thus enlarging the toolbox of bioorthogonal conjugations.

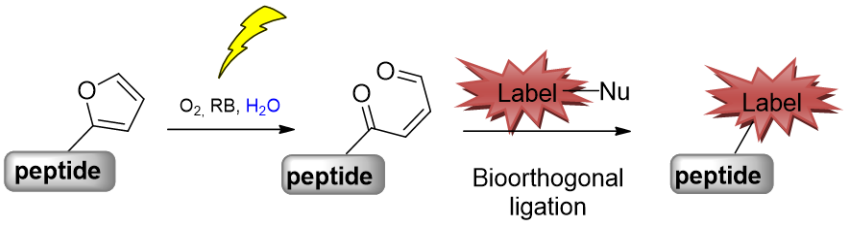

Figure 1. Proposed labeling strategy initiated by singlet oxygen.

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CONFORMATIONAL ANALYSIS OF α,β-PEPTIDES WITH VARIOUS SEQUENCE PATTERNS

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Constrained β-amino acid residues incorporated in the peptide sequence can considerably alter its propensity for folding. Even short sequences of that type can adopt well-defined conformation in solution. 2-Aminocyclohexanecarboxylic acid and 2-aminocyclopentanecarboxylic acid are the most widely studied molecular building blocks with such properties. In particular, sequences combining both α- and β-amino acid residues are of a high interest, due to the simultaneous possibility of incorporation of various functional groups in side chains (by α-residues) and effective control of conformational preferences in solution (by β-residues).[1] Such approach gives the possibility to construct molecules with rationally designed function, e.g. antimicrobial, protein-protein interaction inhibition, GPCR receptor antagonism/agonism.[2] Several sequence patterns of α,β-peptides containing *trans*-2-aminocyclopentanecarboxylic acid were studied by Gellman.[3] We have previously shown that the use of *cis*-2-aminocyclopentanecarboxylic acid in αβ and ααββ sequence pattern yields a stable helical structures.[4]

Here we present an extensive screening of various sequence patterns of α,β-peptides containing *cis*-2-aminocyclopentanecarboxylic acid residues. The conformational stability and the preferred three-dimensional arrangements in water and methanol solutions were studied using circular dichroism and NMR spectroscopy.

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SYNTHESIS AND MOLECULAR DYNAMICS STUDY OF NEW MEMBRANE-ACTIVE ANTIBACTERIAL GLYCOSIDES

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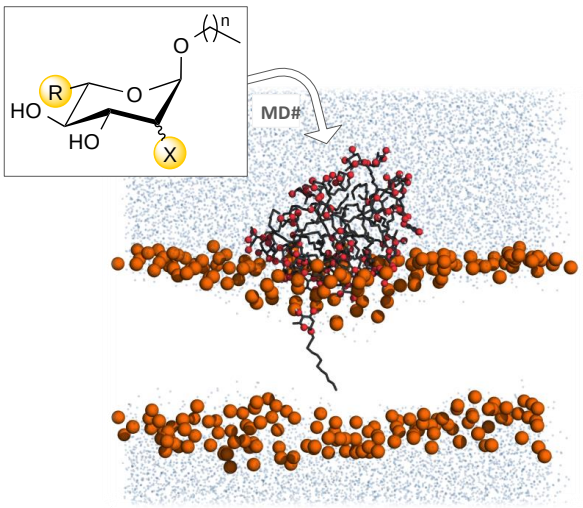
The search for new antibiotics with innovative mechanisms of action represents a foremost challenge to the scientific community owing to the increasing spread of bacterial resistance to the available therapeutics. In this context, our research group is particularly interested in exploiting the potential usefulness of sugar-based surfactants as antibacterial agents. These molecules are known for their biocompatibility properties and feature low toxicity, making them suitable for several industrial and medicinal applications. In previous work [1], we have reported a series of alkyl 2-deoxy/2,6-dideoxy-*arabino*-hexopyranosides exhibiting antimicrobial activity against several pathogens including *Bacillus anthracis*, which is considered a bioterrorism agent. Their synthesis has been efficiently accomplished by reaction of a variety of alcohols with protected glycals in the presence of triphenylphosphane hydrobromide, a procedure that stereoselectively delivers the bioactive α-anomers in high yields. The antimicrobial activity is modulated by the deoxygenation pattern of the sugar moiety, and preliminary studies indicate that these glycosides act through destabilization of bacterial cell membranes.

In this communication we present the synthesis and biological screening of a small library of alkyl glycosides structurally related to the most active compound, including 2-deoxyglycosides derived from pentoses, 2-fluorinated analogues and glycosides deoxygenated at 6-position of the sugar, which were accessed by distinct methodologies starting from either glycals or glycosyl trichloroacetimidates. This study led to several promising molecular entities, providing important insights into the key structural features required for tuning their antimicrobial properties. Aiming at further contributing to the elucidation of the mechanism of action for this family of compounds, molecular dynamics (MD) simulations were performed in order to study their effect on model membranes. In particular, we studied the partitioning of glycosides from micelles in solution at the interface of a phospholipid bilayer and subsequently analyzed the structural properties of the bilayer and the molecular interactions involved in lipid phase reorganization. These results will also be highlighted and discussed.



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G – GREEN CHEMISTRY

ORGANOCATALYZED ALDOL REACTION IN DEEP EUTECTIC SOLVENTS

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Organic Chemistry Department and Instituto de Síntesis Orgánica, University of Alicante, Spain;
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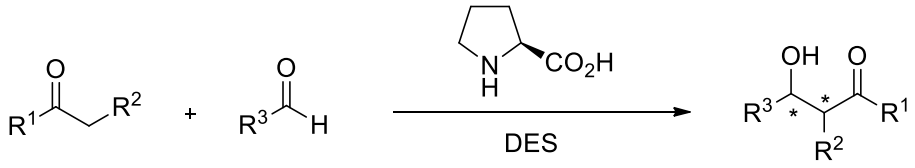
Deep eutectic solvents are considered “green solvents” to carry out chemical transformations, due to their low costs, biodegradability and possible recovery and reuse.[1] However, these type of solvents have been rarely used in organic synthesis, with only a few examples of their application involving the use of a transition metal catalysts.[2] The combination of these media with organocatalyzed processes, where the catalysis involves a simple organic molecule, is even scarcer.[3] This type of reactions would be highly interesting for industrial segments such as pharmaceuticals and agrochemicals because the achieved products would be free of metallic traces and obtained through simple, clean, safe and efficient processes. In this work, the use of different deep eutectic solvents to carry out the proline organocatalyzed aldol reaction will be described (Scheme 1).



1 **2** **3**

Scheme 1

References:

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LEACHING FREE GOLD NANOPARTICLES AS GREEN CATALYST FOR CYCLOISOMERIZATION REACTIONS

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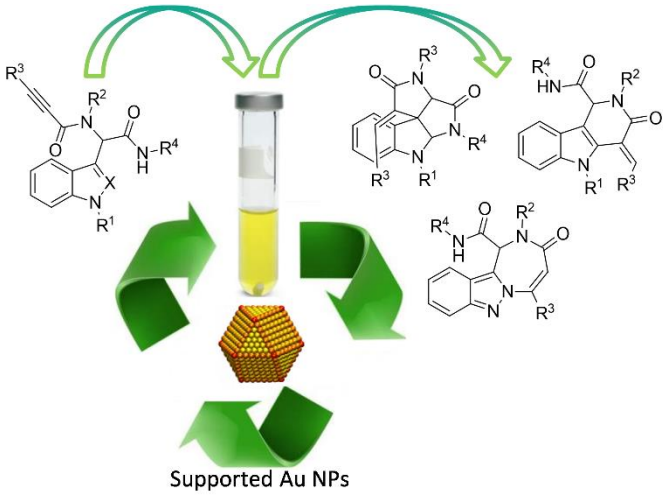
We report the utilization of a novel catalyst for cycloisomerizations. The novel catalyst system contains gold nanoparticles supported on Al-SBA15, which was prepared by the ball-milling process.[1] We developed a greener methodology for synthesizing spiroindolines under heterogeneous conditions, using this novel class of supported gold nanoparticles in combination with microwave irradiation.[2] The catalyst is highly reusable and selective. Cycloisomerization reaction yields ranged from good to excellent leading to the formation of two novel classes of six- and seven-membered heterocycles, which are unprecedented so far. The selectivity of the catalyst towards the desired products is high and the reaction can be performed in ethanol as solvent. A one-pot cascade reaction could be established commencing with the Ugi-reaction to ensure diversity. The application of micro-flow technology extended the scope to sterically hindered substrates.[3]



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[3] Manuscript in preparation

AZO DYES BIOSYNTHESIS MEDIATED BY CotA-LACCASE

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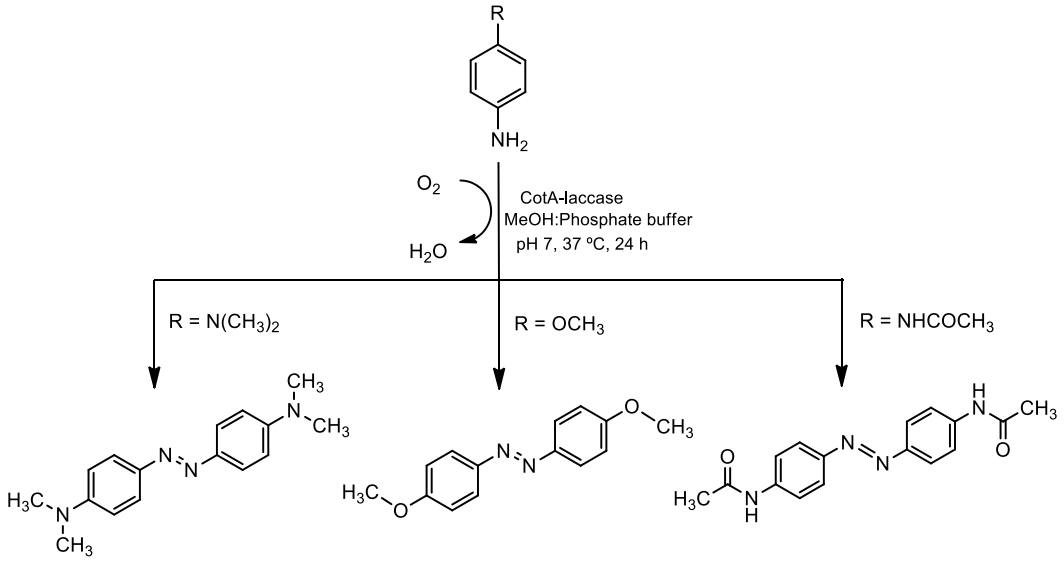
Azo dyes constitute the largest group of dyes used in industry. They are usually synthetized under aggressive chemical conditions, with chemical oxidizing agents such as lead tetraacetate, potassium ferrocyanate and sodium hypochlorite at stoichiometric conditions. [1, 2] The demands for more sustainable methods encourage the study of alternative synthetic routes. [3,4]The application of enzymes as biocatalysts, to substitute the classical stoichiometric chemical oxidants, represent a promising alternative in the friendly synthesis of "*new green*" compounds, with both economic and environmental benefits. Herein we report the oxidative laccase-mediated formation of azo dyes. Different *para*-substituted aromatic amines were oxidised by CotA-laccase, a multi-copper oxidase, under mild conditions of pH and temperature, in aqueous systems, to give the corresponding azo compound isolated with good to moderated yields (Scheme 1).



Scheme 1. Formation of azo dyes catalysed by CotA-lacase

Acknowledgements: The authors thank the FCT-Fundação para a Ciência e a Tecnologia (Projecto Estratégico UID/QUI/00100/2013 and REM2013) and the IST-UTL NMR Network for facilities.

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OXIDATION WITH AIR BY ASCORBATE-DRIVEN QUINONE REDOX CYCLING

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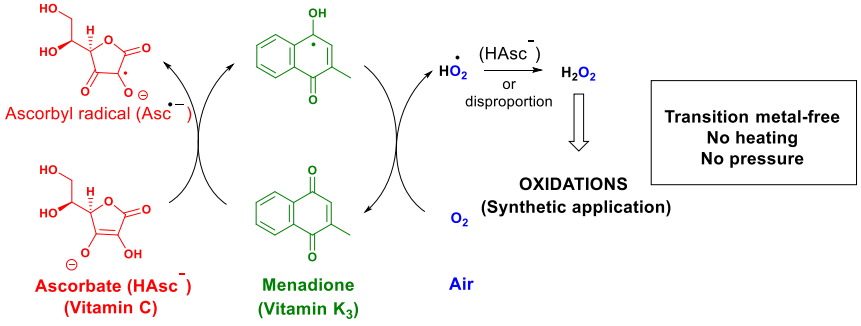
Oxidation is one of the most fundamental processes in chemistry. Conventional chemical oxidants, however, are usually toxic and there is an increasing academic and societal demand for environment-friendly oxidation methods. In this regard, molecular oxygen seems to be an ideal oxidant and an oxygen-atom source for organic synthesis: it is abundant, environmentally benign and inexpensive, particularly if used directly from air.

However, the direct reaction of triplet dioxygen with singlet organic molecules is a spin-forbidden process. As a consequence, oxidation with atmospheric oxygen displays an extremely slow kinetics and it is usually accomplished only under transition metal catalysis, very high temperatures, and in some cases, the reagents employed are toxic and/or too expensive.

Our group has been lately involved in the development of greener synthetic methodologies.[1] In this communication, a novel and green method for oxidation with air is described.[2] This procedure requires no transition metals but combines just two vitamins (ascorbate and menadione) at room temperature and atmospheric pressure. Hydrogen peroxide generated in situ by this method has been proven to act efficiently as an oxidant of arylboronic acids and a few other organic moieties. These results can find several applications in many fields besides synthesis, such as water decontamination, cosmetics, or powering nanomotors.



Acknowledgements: This project has been financed by the European Commission (FP7-REGPOT-2012-CT2012-31637-IMBRAIN), the Spanish MINECO (CTQ2011-28417-C02-01) and co-financed with European Regional Development Fund (FEDER). D. M. Monzón thanks the EU Social Fund (FSE) and the Canary Islands ACIISI for the funding granted to Universidad de la Laguna. G.S.-D. thanks the EU Social Fund (FSE) and the Canary Islands ACIISI for a predoctoral grant.

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DESIGN OF VERSATILE SYNTHETIC PROBES FOR EFFICIENT SCREENING AND EVALUATION OF FERULOYL ESTERASE ACTIVITY

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The growth of industrial biotechnology field is driving enzyme discovery and engineering. Consequently, the need for high-throughput screening (HTS) methods, as those employed in functional metagenomics, [1] is also increasing. Ideally, such methods should provide efficient and reliable detection of a wide range of enzymes. In many cases, HTS employs chromogenic substrates for their easy utilization, but also because they provide fast detection of activity in liquid and/or solid culture media.

In the field of biomass degradation, considerable attention was given to the development of detection methods for cellulose-degrading enzymes. Detection of other enzymes (e.g. carbohydrate esterases), [2] received less attention, despite the fact that hydroxycinnamoyl esters (e.g. *trans*-ferulic acid and *p*-coumaric acid) in plant cell walls can reach up to 3% (w/w, dry weight) and play vital roles in cell-wall polysaccharide crosslinking.

During our work, aiming to expand the number of chromogenic substrates available for the detection of hemicellulases, we interested in the design of substrates for hydroxycinnamoyl esterases, particularly feruloyl esterases (FAEs - E.C. 3.1.1.73). [3] These serine esterases belong mainly to the carbohydrate esterase family CE1 of the CAZy classification. FAEs cleave ester linkages between ferulic acid and hemicellulosic sugars. The chromogenic molecules that we have designed in this work are indolyl and 4-nitrocatechol (4NTC) derivatives that were synthesized in good overall yields (56 and 61% in 4 steps). Thus, we will describe the synthetic pathway used to obtain these molecules and we will show their usefulness in various experimental contexts that require either qualitative (solid), semi- or totally-quantitative (liquid) detection of FAE activities.

Acknowledgments: This research was supported by the European Union's Seventh Programme for Research, Technological Development and Demonstration under Grant Agreement No 613868 and the Région Midi-Pyrénées grants DAER-Recherche 07009817.

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VARIOUS FUNCTIONALIZATION OF IMIDAZO[1,2-*a*]PYRIDINES IN PEG$_{400}$ MEDIUM

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Imidazo[1,2-a]pyridines are recognized to exhibit a broad range of biological activities.[1] They are often used as building blocks in pharmaceutical compounds, and several commercially available drugs such as the sedative Zolpidem, the anxiolytic Alpidem or Saripidem, or the heart failure drug Olprinone (Figure 1).

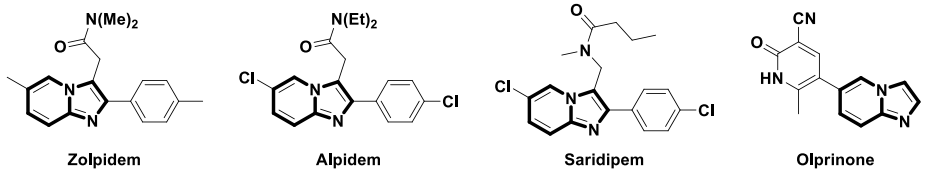
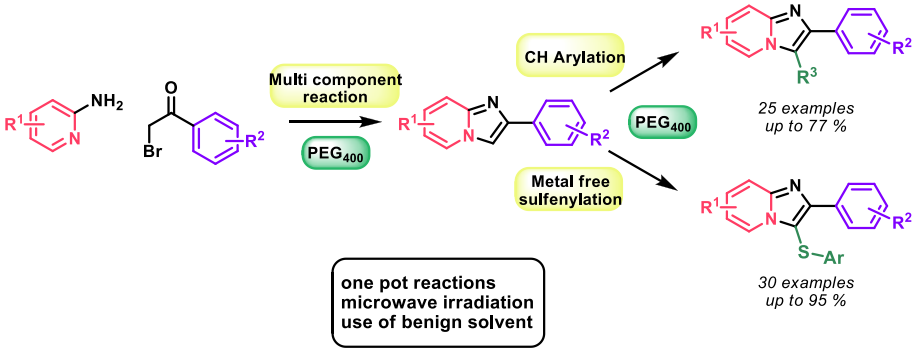


Figure 1. Examples of imidazoheterocyclic-containing therapeutics

In our effort to develop environmentally sound tools, we focus our attention to promote the use of PEG$_{400}$. PEG$_{400}$ is a viscous sustainable liquid soluble in water and many organic solvents. This medium has the advantage of being non-toxic, odorless, neutral, nonvolatile, and non-irritating and is used in a variety of pharmaceuticals and medications. Herein we report the possible use of PEG$_{400}$ as an efficient medium to first synthesize and functionalize the imidazo[1,2-*a*]pyridine moiety in a one-pot condensation and C–H-activation process and to introduce sulfenyl groups under transition metal free conditions (Scheme 1).



Scheme 1

Our method enabled the efficient formation of 3-aryl- and arylthioimidazoheterocycles in moderate to excellent yields under a reduced amount of palladium catalyst without ligand for the C–H arylation and without any metal for the sulfenylation step.

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ULTRASOUND ACCELERATED CHALCONE SYNTHESIS USING AMBERLYST-26

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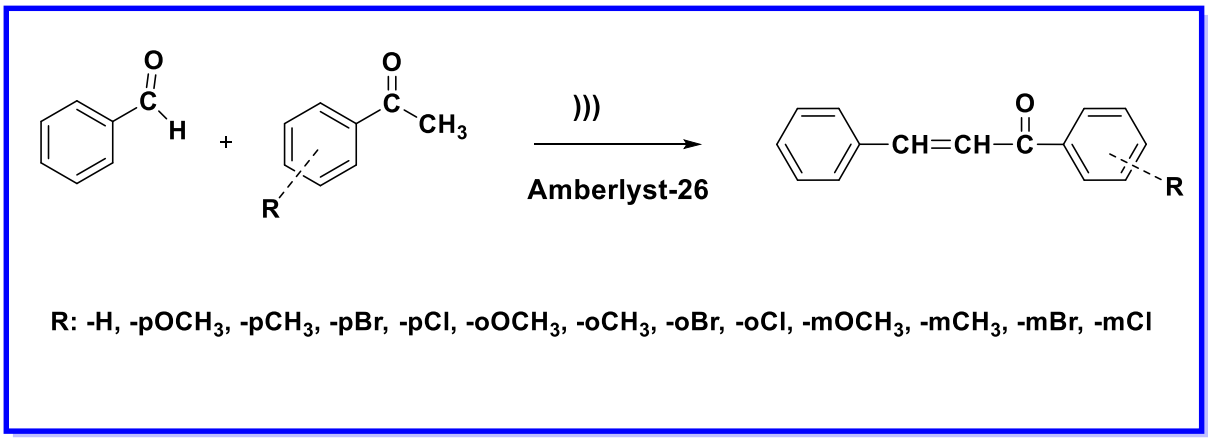
Chalcone compounds, chemically consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system. They are also called as open-chained pyran flavonoid. On the other side, chalcones, one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices, tea and soy-based foodstuff, have been recently the subject of extensive investigations due to their interesting pharmacological activities such as antibacterial[1], anti-malarial[2], antiulcer, anti-virial, insecticidal[3], anticancer[4], anti-inflammatory[5], and anti-HIV[6]. It is a unique template molecule that is associated with several biological activities. Ultrasound mediated reactions have gained attention increasingly and had broad applications in organic synthesis due to be faster, convenient, and high yielding process compared to the traditional methods[7]. Herein, we propose a new, efficient method to synthesize chalcone derivatives from good to excellent yields (80-90 %) using Amberlyst-26 which is an inexpensive and commercially available solid base catalyst under ultrasound sonication.



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A CATALYTIC GREEN CHEMISTRY ROUTE TOWARDS HANTZSCH THREE COMPONENTS CONDENSATION

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A green and reusable ionic liquid and catalyst, of imidazolium family was designed and fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry. The catalytic application of the presented catalyst was successfully tested on the Hantzsch four-component reaction of various aromatic aldehydes, enaminone and aromatic amines under microwave irradiation to give the pyridine derivatives in good to excellent yields. In the presented work, all products have been reported for the first time, and characterized with ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry.

MAGNETIC IONIC LIQUIDS BASED ON CHOLINE – SYNTHESIS AND BIOLOGICAL EVALUATION

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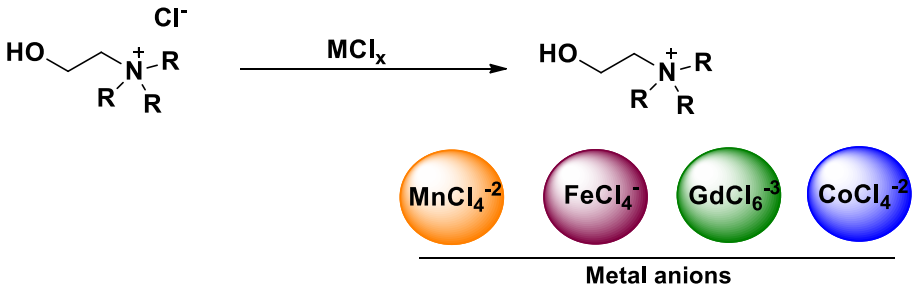
In 2004 was described a new type of magnetic materials based on paramagnetic metal salts - Magnetic Ionic Liquids (MILs).[1] Several MILs have been reported to use combinations of different organic cations with anionic metal complexes possessing magnetic properties.[2] All present similar magnetic moments and show a strong response to external magnetic fields. Most of these MILs can be obtained by mixing the halide salts ([cation][X]) with neutral metal complexes (MX_n). For example [BMIM][$FeCl_4$] was prepared by mixing crystalline [BMIM][Cl] and a slight excess of FeCl3 under inert atmosphere.[1,3] Although, when the cation is a strong hydrogen bond donor, the formation of an organized network of hydrogen bonding is enhanced resulting in a more organized structure. Consequently the crystallization of the salt is enhanced. On the other hand cations that don't have this hydrogen bonding network, such as the bulky tetraalkylphosphonium or tetralkylguanidinium, have a low tendency to crystalize, even when paired with metal anions (iron, cobalt, manganese and gadolinium). In this work, were synthetized more than fifteen different MILs based on the paramagnetic anions $FeCl_4^-$$CoCl_4^{2-}$, $MnCl_4^{2-}$ and $GdCl_6^{3-}$ with the aim of producing low viscous MILs, and also less toxic as possible. The MILs were synthetized by combination of different cations based on the choline unit followed by the addition of the respective metal chloride (**Scheme 1**).



Scheme 1. Synthesis of the Magnetic Ionic Liquids based on choline derivatives cations

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia for financial support (SFRH/BPD/75045/2010, SFRH/BPD/73822/2010, SFRH/BPD/88666/2012,PTDC/QEQ-PRS/2824/2012).

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MECHANOCHEMISTRY: A GREENER APPROACH TO PAAL KNORR SYNTHESIS?

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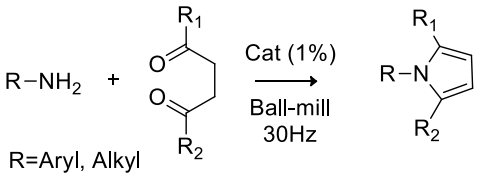
The development of advanced, non-expensive and cleaner protocols for chemical industry became the biggest challenge. According to twelve green chemistry principles, the avoiding of harmful organic solvents motives the chemists to revise all existing synthesis methods and/or envisage a new possibilities. Among the numerous environmentally friendly processes, the use of solvent-free conditions offerings one of most economical attractive alternatives for industrials.

The ball-milling of solids is a scalable mechanical technique that has been largely used for preparation of inorganics. Similar to ultrasound energy, presently this mechanochemical reaction activation method lives a veritable renaissance. Almost unanimously, ball-mills applications in the field of organics allows a process intensification and/or possibility to provide the synthesis on solids in solvent-free without supplementary thermal activation.[1]

Pyrrole is one of the most valuable heterocyclic, which is found in broad structures of many bioactive natural products as porphyrins, alkaloids, vitamins and synthetic molecules of pharmacological interest but also as building blocks for optical materials.[2] Pyrrole synthesis is largely described in the literature usually by the classical methods including multistep approach such as reductive couplings, aza-Wittig reactions or transition-metal intermediates as well as some multicomponent reactions.[3] Among all of these techniques, the classic Paal Knorr cyclization reaction between one 1,4-dicarbonyl compound and one primary amines under slightly acidic conditions offerings a very attractive. According to bibliographic data, the different attempts to optimize this methodology leading to environmentally friendly processes as the use of water, ionic liquid or solvent-free media, with Lewis acid or heterogenous catalysis, activation by microwave heating or ultrasound energy as well as microreactor in continuous flow, were realized.[4] But to our knowledge to date, no mechanical ball milling conditions was described yet. Subsequently, we focused on the use of ball shaker for Paal Knorr pyrrole synthesis in solvent-less conditions assisted by a green organic acid.[4]



R=Aryl, Alkyl

R_1=R_2=Me or R_1=Me & R_2=Ph

Different amines and ketones were tested and for all of them the desired pyrroles were obtained with a yield from acceptable to good (49-84%). For this approach to Paal-Knorr pyrrole synthesis, actually we have demonstrated the real improvement of time, solvent and energy savings through the mechanochemical activation.

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H – POLYMER CHEMISTRY

SYNTHESIS AND PROPERTIES OF FLAME RETARDANT POLYURETHANE ACRYLATE MATERIAL BY SOL-GEL METHOD

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Polyurethanes (PUs) materials have been commonly used as coating because of their excellent abrasion resistance, low temperature flexibility, mechanical and chemical properties. Acrylate modification for PUs is one of the best process to obtaining UV curable resins. Polyurethane Acrylates (PUAs) have reactive parts which able to cure UV irradiation that means highly performance and shorter curing time. PUAs have been also environmentally friendly because of needn't have include VOCs (Volatile Organic Compound). [1] [5]

The sol–gel process is the most commonly used method for the preparation of organic inorganic hybrid materials at macro- or micro-scale, even at molecular level in mild conditions. It involves a series of hydrolysis and condensation reactions starting from a hydrolysable multi-functional alkoxysilane as precursor for the inorganic domain formation. Properties of the resulting hybrids heavily rely on the distribution of inorganic nanoparticles within the organic matrix. The use of suitable coupling agent provides bonding between the organic and the inorganic phases, which are linked by chemical covalent bonds, hydrogen bonds or physical interaction, therefore, well-dispersed nanostructured phases may result [2,3]

Avoid the oxygen contact one of the most know situation for flame retardancy. P-O-C bonds have been disintegrated lower temperature than C-O-C bonds. Material and oxygen contact have been hindered by phosphorus and it gives excellent flammability properties. [4]

In this study, hybrid UV curable PUA oligomers based phosphine oxide were prepared aromatic phosphine oxide diols, IPDI and fluorinated sol-gel agent. Phosphine oxide diol, silica and fluorinated content effects on physical, mechanical, thermal and hydrophilic properties of UC cured hybrid coatings were systematically investigated. Furthermore, the nanostructure of hybrid materials were examined.

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SELF-ASSEMBLED ORGANIC FRAMEWORK: WHOLLY ORGANIC ANHYDROUS PROTON CONDUCTOR

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Molecular self-assembly is an important subject for the practical applications of supramolecular chemistry [1]. Recently, extensive research on accumulation of functional guest molecules has focused on metal organic frameworks (MOFs) [2] and covalent organic frameworks (COFs)[3]. These frameworks enabled a wide variety of applications such as gas storage, separation, catalysis and conductors [4]. In contrast, the construction of self-assembled organic frameworks (SAOF), unemployed by the coordination or covalent bonds, is typically hard to achieve due to the delicate balance and competition between directional and nondirectional noncovalent interactions and often results in self-interpenetration to fill the voids in the host structure. This adversity hampers possible applications that utilise the advantage of self-assembled organic molecules. Under such conditions, we recently found that an organic compound **1** (Figure 1a) comprising a twisted geometry and hydrogen bonding units can discretely self-assemble into a high-density nanostructure homogeneously including several functional guest molecules. Being motivated by this unique behaviour, we have constructed an imidazole-based wholly organic anhydrous proton conductor (**1⊂Im**), as one of the potential applications, using the self-assembling process of compound **1** (Figure 1b).

In this presentation, we report the molecular design and synthesis of a novel class of organic framework that can spontaneously include several guest molecules with selectivity. Based on comparison with a reference compound **2**, we demonstrate that the constructed nanostructure (**1⊂Im**) is attributed to the strong hydrogen bonding of **1** at termini. In addition, we also reveal that this organic framework **1** significantly improves the water durability, thermal stability and proton conductivity of imidazole molecules accompanied by the formation of a well-ordered nanostructure (**1⊂Im**), where the proton transfer take place with very low activation energy. This is likely due to both the homogeneously and locally increased concentration of proton carriers and the absence of metal species that are considered to act as trap sites for mobile protons. This study suggests that the use of discrete self-assembly could allow development of new design concepts for functional materials such as the high-temperature anhydrous proton conductors considered here. The detailed investigations on the structures, incluson profiles and proton conducting behaviour for **1** with gest molecules will be presented.

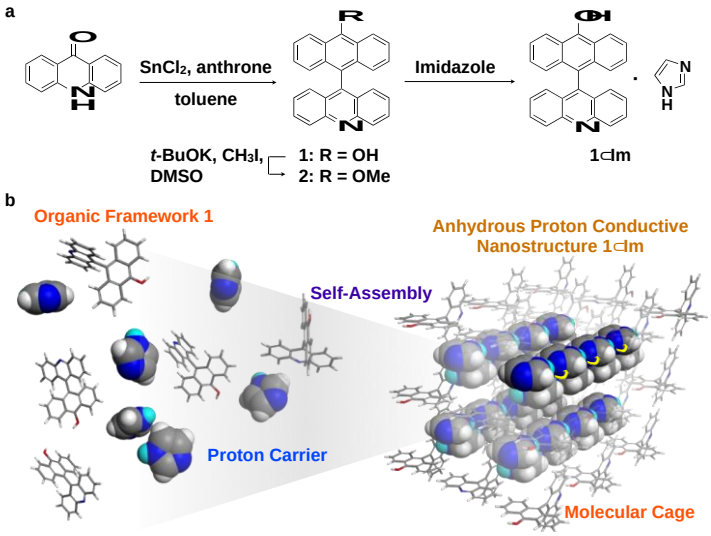

Figure 1. (a) Synthesis of the self-assembling organic framework **1**, its reference **2** and nanostructure **1⊂Im**. (b) Schematic illustration of discretely and one-dimensionally arraigned anhydrous proton-conductive channel **1⊂Im**.

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ENZYME-RESPONSIVE POLYMERIC HYBRIDS AS PLATFORM FOR SMART MATERIALS

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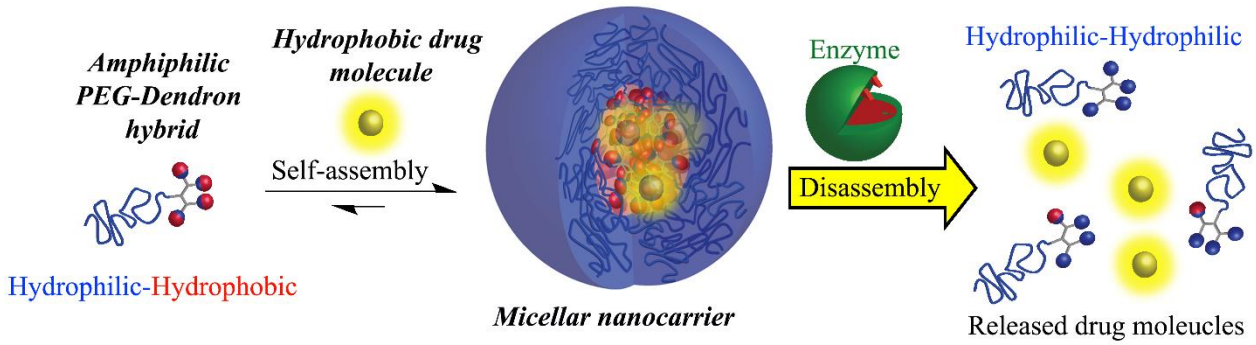
The increasing demand for smart delivery vehicles, which are capable of releasing their molecular cargo only at the target tissue, has motivated the development of stimuli-responsive micellar nanocarriers. Among the different types of stimuli, which can trigger the disassembly of such smart assemblies, enzymes could offer great advantages due to their catalytic nature, and selectivity. Furthermore, the often observed over expression of specific enzymes in various diseases could potentially be utilized to trigger the release at the target site. Here we report a highly modular molecular design of amphiphilic block copolymers based on a linear hydrophilic polyethyleneglycol (PEG) and an enzyme-responsive hydrophobic dendron [1,2]. The PEG-Dendron hybrids were synthesized in high yields through an accelerated divergent synthetic methodology [3] using a combination of amidation and thiol-yne reactions. We demonstrate that these amphiphilic hybrids self-assemble in water into smart micelles, which can disassemble and release their encapsulated molecular cargo upon enzymatic activation. The simple synthesis and high modularity of these PEG-dendron hybrids offers great control over the disassembly rates of the formed micelles by simply tuning of the length of the PEG [1]. Such enzyme-responsive amphiphilic hybrids could potentially be applied in the future as nanocarriers with adjustable release rates for biomedical delivery applications.



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I – MATERIALS

COMPOSITE MATERIALS FROM VEGETABLE OIL-BASED POLYESTERAMIDE AND LAYERED DOUBLE HYDROXIDES

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Renewable resources such as agricultural products can provide an interesting sustainable platform to substitute petroleum-based polymers through the design of bio-based polymers. Vegetable oil-based polymer composites have considerable importance in the development of advanced polymeric materials, offering significant improvement in performance characteristics without a large cost increase [1].

We report here the synthesis and characterization of new composite materials from vegetable oils (linseed and soybean oils – LO and SO, respectively) and layered double hydroxides (LDH). The macromolecular matrix was obtained from two monomers (anhydride type and diol type, respectively) both synthesized from vegetable oils: one of them (MA-LOME) was obtained from linseed oil methyl esters (LOME) by grafting reactive anhydride units from maleic anhydride (MA); the diol monomer is *N*, *N*-bis-(2 hydroxyethyl) soybean oil fatty amide (HESA), an amide synthesized through aminolysis of triglycerides from SO with diethanolamine in the presence of sodium methoxide as catalyst [2]. The fatty acids composition of the starting vegetable oils (LO and SO) was determined by GC. The obtained monomers were characterized by ^{1}H-NMR and FT-IR spectroscopy. The polycondensation reaction of MA-LOME and HESA was monitored through FT-IR spectroscopy (Figure 1). The obtained polyesteramide was characterized by ^{1}H-NMR and FT-IR spectra. The composite materials were synthesized from the polyesteramide and different amounts of LDH (1, 5 and 10%). The final materials were characterized by FT-IR, XRD, DMA and TGA.

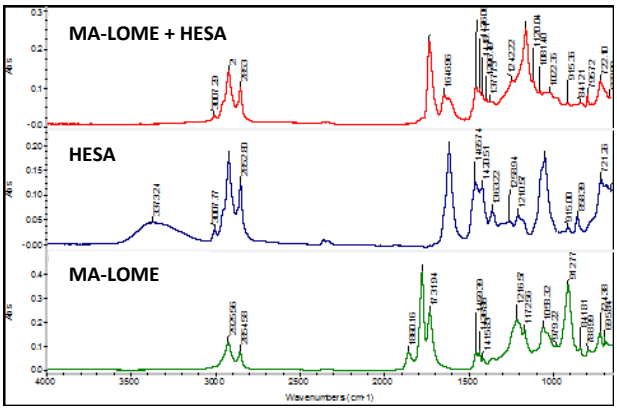

Figure 1. FT-IR spectra of monomers (MA-LOME and HESA) and of the polycondensation product

Acknowledgements: The work has been funded by the Sectoral Operational Programme Human Resources Development 2007-2013 of the Ministry of European Funds through the Financial Agreement POSDRU/159/1.5/S/132397

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ELECTROGRAFTING VIA ARYL DIAZONIUM CHEMISTRY: A VERSATILE METHOD FOR REDUCING INTERFERENCE IN GLUCOSE BIOSENSORS

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One of the key points in developing biosensors for glucose monitoring is the efficient elimination of the electrode response due to interferents commonly encountered in biological samples [1]. We report here a novel method for obtaining interference-free glucose biosensors using thin organic films deposited by electrografting aryl diazonium salts. The functionalization of conductive surfaces by electrochemical reduction of diazonium salts is a versatile and efficient method for obtaining modified electrodes [2].

Modified platinum electrodes were obtained by potential cycling in acetonitrile solutions of benzenediazonium salts having different substituents in the *para* position. We have studied the electrochemical oxidation of ascorbate, urate, paracetamol and cysteine on the modified electrodes and found that the oxidation of these species is suppressed to varying degrees, depending on the substituents attached to the phenyl rings. At the same time, the electrochemical oxidation of H_2O_2 is only affected to a minor extent by the surface layers.

Glucose biosensors were constructed by depositing on the modified platinum surfaces a sensing layer consisting of cross-linked glucose oxidase-chitosan composite, following a protocol developed by Tan et al. [3]. The biosensors had a fast response, an average sensitivity of 20÷25 mA mM^{-1} cm^{-2} and excellent selectivity.

Acknowledgements: The work has been funded by the Sectoral Operational Programme Human Resources Development 2007-2013 of the Ministry of European Funds through the Financial Agreement POSDRU/159/1.5/S/134398. The authors gratefully acknowledge the financial support of UEFISCDI, under grant ID PN-II-PT-PCCA-2013-4-2151, nr. 236/2014.

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REACTIVE DYES FOR SUPERHYDROPHOBIC COTTON

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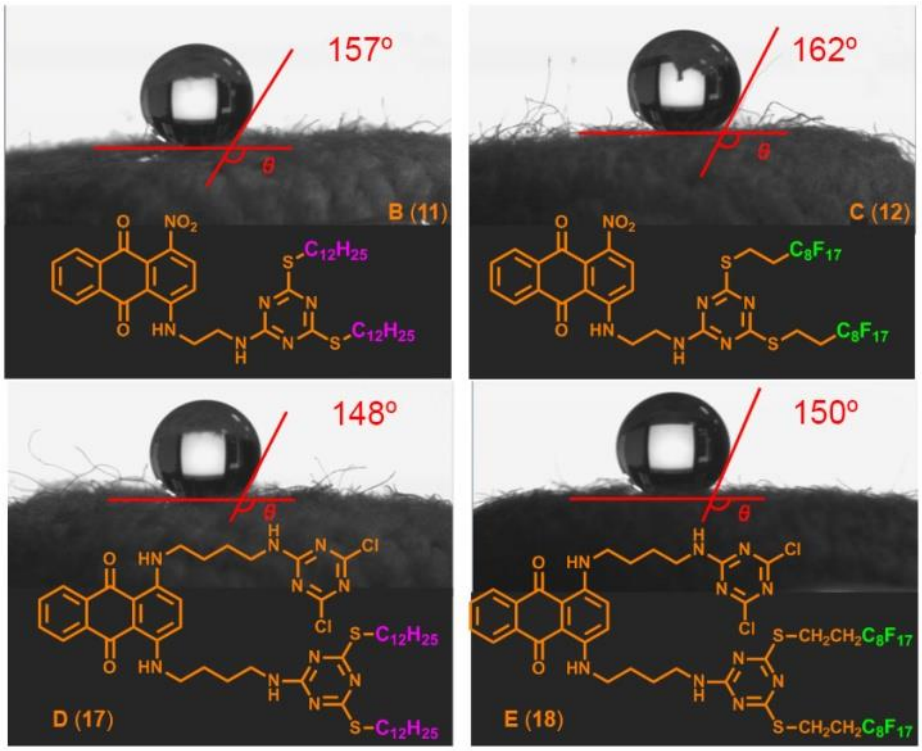
Control of the wettability of a surface is crucial for applications such as self-cleaning, antisticking, anti-corrosion and anti-contamination.[1] The equipment of fibers and textiles with hydrophobic properties is of high interest for textiles with water, oil or soil repellent properties, *e.g.* for special sportive clothes, home textiles like carpets or upholstered furniture and some out-door textiles like umbrellas. To obtain superhydrophobic surfaces, coating with low-surface-energy materials, such as polymers or fluorinated compounds is often necessary. Furthermore, the economic importance of reactive dyes for cotton has increased over the last twenty years. Azo,[2] anthraquinone and triphenylmethane dyes were decorated with fluorous or long hydrocarbonated ponytails and covalently anchored in different surfaces such as cellulose, obtaining new coloured hydrophobic textiles. In the figure, as an example, we can see the measurements of the contact angle of a drop of water on the surface of stained fabrics using different anthraquinone based dyes.



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DEBONDING ON DEMAND MATERIALS AS COMPONENTS IN DENTAL MATERIALS

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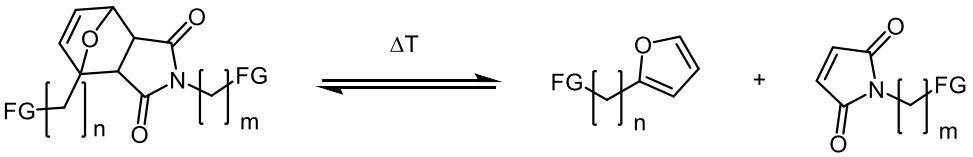
In restorative dentistry, temporary restorations play an essential role in treatment planning. However, to date, the provisional cementation of temporary materials (*e.g.* crowns, bridges, inlays, onlays or veneers) is performed with conventional luting composites (adhesives or cements) intended for the permanent fixation of prosthetic materials. In consequence, the removal of these provisional materials has to be made by the use of mechanical force. This is a time consuming procedure, which is not only destructive to the subjacent tooth structure but also uncomfortable for both, the patient and the dentist. Moreover, the complete removal of the cement from the tooth structure is a difficult and tedious operation.

These challenges can be overcome by the implementation of adhesives or cements, which on the one hand ensure a strong and permanent fixation of the prosthetic material over a desired period of time, but on the other hand allow the controlled release and complete removal of the provisional material when desired. This “debonding on demand” (DoD) may be induced by external stimuli, *e.g.* heat, light, or pH change. The corresponding adhesive or composite cements are comprised of crosslinking or functionalized monomers featuring stimuli-responsive linking units, which upon curing form a covalent polymer network. Controlled exposure to the external stimulus will induce the breakdown of the polymer network and the consequential deterioration of mechanical rigidity will result in the desired debonding.

The thermal reversibility of the Diels-Alder [4+2] cycloaddition reaction is well established. Therefore, crosslinking monomers, phosphate ester based adhesive monomers, or methacrylate silanes featuring a furan-maleimide Diels-Alder cycloadduct represent ideal candidates as components of thermally degradable DoD-adhesive or fixation composites. The synthesis of a thermo-responsive Diels-Alder crosslinker as well as various other tailor-made stimuli-responsively degradable monomers will be reported.

FG: functional group (polymerizable, acidic, or silyl group)



FROM 4-HYDROXYBENZOIC ACID TO LIGHT ACTIVATED MICROROBOTS

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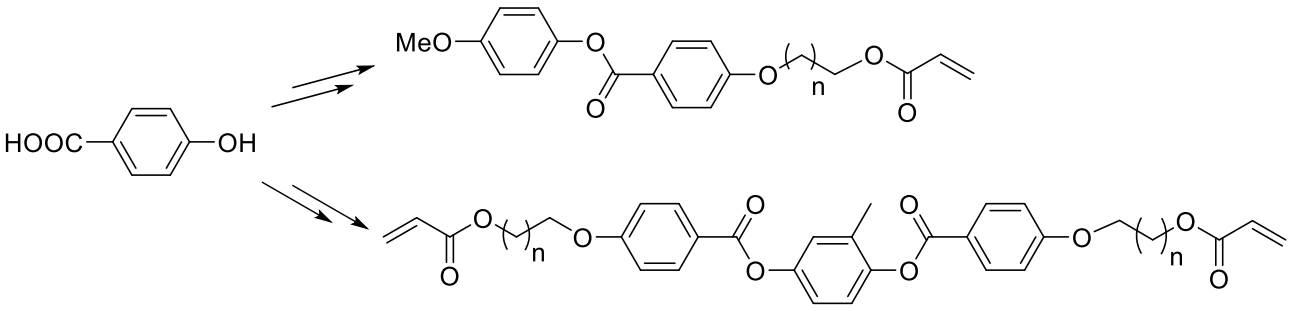
How can a commercial and simple starting material as 4-hydroxybenzoic acid become a micro-robot fueled by light? Obviously by the use of smart materials! Liquid-crystalline elastomers (LCEs) are materials combining the properties of polymeric elastomers with liquid crystalline orientations and are able to perform dramatic and reversible shape change (20-400%) in response to external stimuli.[1] Their use as artificial muscles allows for realization of remotely controlled robots. Combining such properties with light sensitive molecules consents to prepare LCEs with optical response. To obtain such polymers is important to start from liquid-crystalline molecules containing a rigid core functionalized by one or more flexible spacers. Often, the rigid part is composed by two or more consecutive aromatic rings and 4-hydroxybenzoic acid represent a very useful starting material to prepare these structures. Starting from this versatile molecule, and exploring different synthetic routes, we have synthesized different LC mesogens and cross-linkers.



Exploiting the free radical polymerization and including azobenzene units inside the polymer, we are able to prepare light activated LCEs.[2] Moreover, thanks to Direct Laser Writing (DLW) we can fabricate LCE structures with sub-micron resolution, exhibiting deformation under light excitation, [3],[4] bearing the realization of polymeric microstructures in which both, shape and molecular alignment, can be locally controlled with nanometer precision. This allows us to create free-form polymeric elements which can support multiple functionalities, and which cannot be fabricated with existing techniques.

Acknowledgements: The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ ERC grant agreement n° [291349] on photonic micro robotics.

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SYNTHESIS AND CHARACTERIZATION OF METALLODENDRIMERS AS ORGANIC SEMICONDUCTORS

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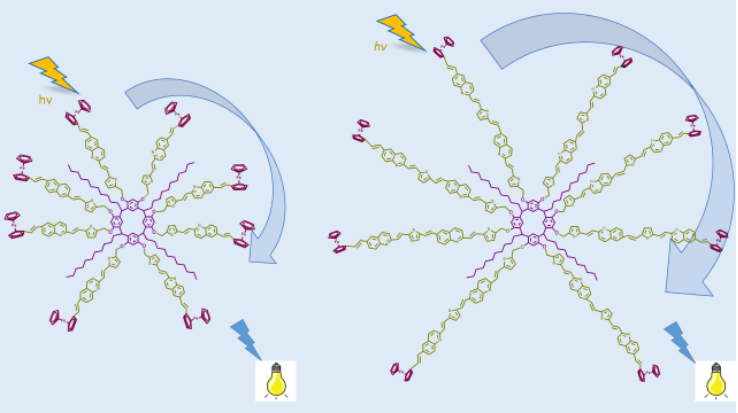
The search for clean, inexpensive and renewable energy sources is one of the most important challenges that mankind is currently confronting. The reduction of fossil combustible reservoirs shows this urgent need of having other energy alternatives. The direct transformation of sunlight into electricity through the photovoltaic (PV) effect has advantages with respect to other technologies. However, the actual used PV technology based on inorganic semiconductors, particularly use of silicon, requires very specialized fabrication conditions with a cost that restricts a wide implementation. In the last 15 years, there has been a notable interest of the scientific community to develop organic photovoltaic (OPV) technology as new alternative for photovoltaic devices. This technology combines low-cost and less specialized manufacturing conditions compared to its inorganic counterparts[1–3]. Metallodendrimers are branched spherically symmetric or asymmetric polymeric macromolecules with a strictly controlled structure, exactly molecular weight, monodispersity, these supramolecular compounds possess a series of novel physical, optical, electrochemical, photochemical, biological and catalytic properties [4]. Metallodendrimers containing ferrocene have been developed because their redox properties and their extremely rich chemistry, which provides great possibilities in terms of molecular engineering and functionalization [5-8]. Here, we focused on convergent design, synthesis and characterization of resorcinaren-ferrocene dendrimers, the ferrocene moieties are located in the periphery and π-electron system of thiophene and quinoline as dendrimeric branches. This π -conjugated system showed efficient energy transfer and good photovoltaic response and will be used as OPV devices. All the obtained compounds were characterized by ^{1}H, ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.



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INVESTIGATION ON THE REACTIVITIES OF BIFUNCTIONAL ORGANOSILANES FOR APPLICATIONS IN THE SYNTHESIS OF BIOMATERIALS USED IN REGENERATIVE MEDICINE

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Extra Cellular Matrix (ECM) is the intercellular substance of a tissue, consisting in collagen fibers embedded in an amorphous ground substance. In regenerative medicine, biomaterials can be used as a scaffold in combination with stem cells after trauma or diseases to induce cell proliferation, differentiation and the growth of new ECM to regenerate a functional new tissue. The most widely biomaterials used as scaffold are hydrogels of polymer.[1] Among those, biocompatible polysaccharides are excellent candidates to prepare injectable hydrogels. After chemical functionalization with a bifunctional organosilane, a pH-controlled change triggers the gelation.[2] Our research area is focused on the functionalization of these polysaccharides.

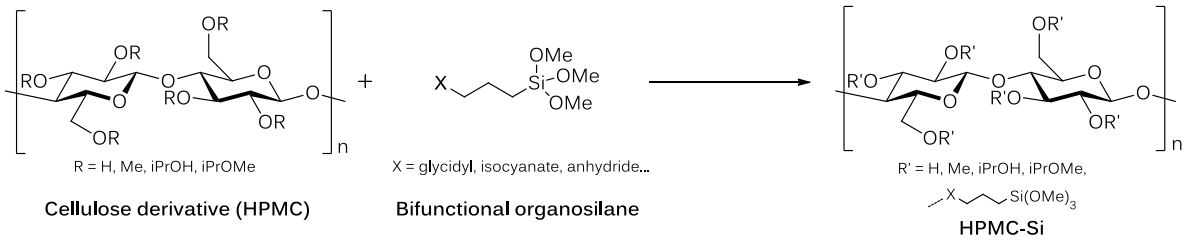

Figure 1. Example of functionalization on a biocompatible polysaccharide

The importance of this process for the elaboration of new biomaterials led us to carry out a fundamental study on various substrates, from simple nucleophiles to sugars to oligosaccharides, in order to establish the chemical behavior of major bifunctional organosilanes reported in the literature.[3,4]

With a focus on the structural elucidation of all isolated products, new and unexpected results that call into question some structures previously described have arisen from this study and will be discussed.

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1,3,4-OXADIAZOLE BASED MONOMERS AND H-SHAPED DIMERS: SYNTHESIS, LIQUID CRYSTALLINE AND PHOTOLUMINESCENT PROPERTIES

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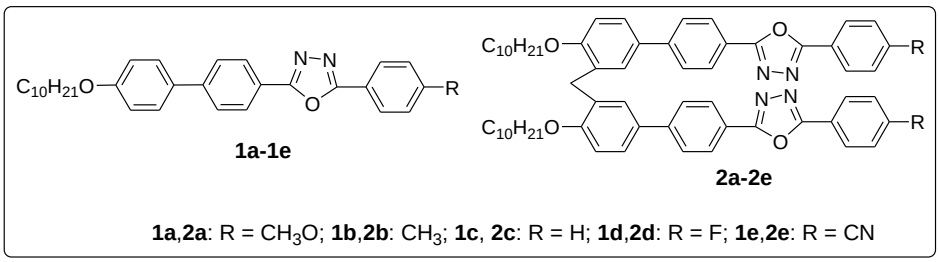
In recent years, 1,3,4-oxadiazole derivatives have drawn continuous interest in liquid crystals [1,2] and fluorescent materials [3] in organic light-emitting devices owing to their electron deficiency, high photoluminescence quantum yield, and excellent chemical and thermal stability. The 1,3,4-oxadiazole moiety can also be used as a signaling component in fluorescent chemosensors because of the potential coordination sites (N and O atoms) with metal ions. [4] In this work, a new class of 1,3,4-oxadiazole based monomers **1a**-**1e** and H-shaped dimers **2a**-**2e** (Scheme 1) have been synthesized, the liquid crystalline properties and photoluminescent behaviors have been investigated systematically. For **1a**-**1e**, they all display stable liquid crystalline properties with smectic and/or nematic mesophases (Figure 1a), which are determined by the nature of the terminal groups. In contrast, all the corresponding H-shaped dimers **2a**-**2e** are not mesogenic, while they show specific selectivity for Cu^{2+} through the fluorescent emission intensity quenching (Figure 1b).



Scheme 1. The molecular structures of **1a**-**1e** and **2a**-**2e**

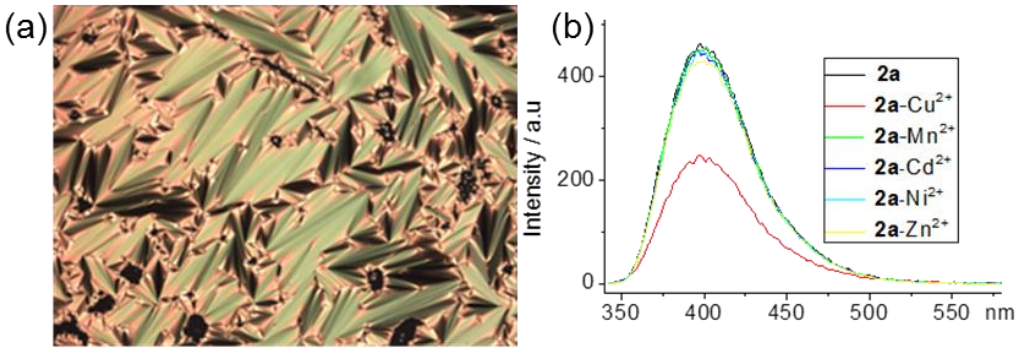


Figure 1. (a) Photomicrographs (× 200) of **1c** on cooling cycle: fan-shaped texture of SmA phase at 164.3 ºC; (b) Fluorescence spectra of compound **2a** (5×10^{-6} M) upon addition of different metal ions (90 equiv) in CH_3CN/CH_2Cl_2 (4:1) (λ_{ex} = 315nm)

Acknowledgements: This work was financially supported by the National Natural Science Foundation of China (No. 21272130), which is gratefully acknowledged.

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SUPRAMOLECULAR ASSEMBLIES OF PERYLENE CHROMOPHORES ON A SOLID SUBSTRATE

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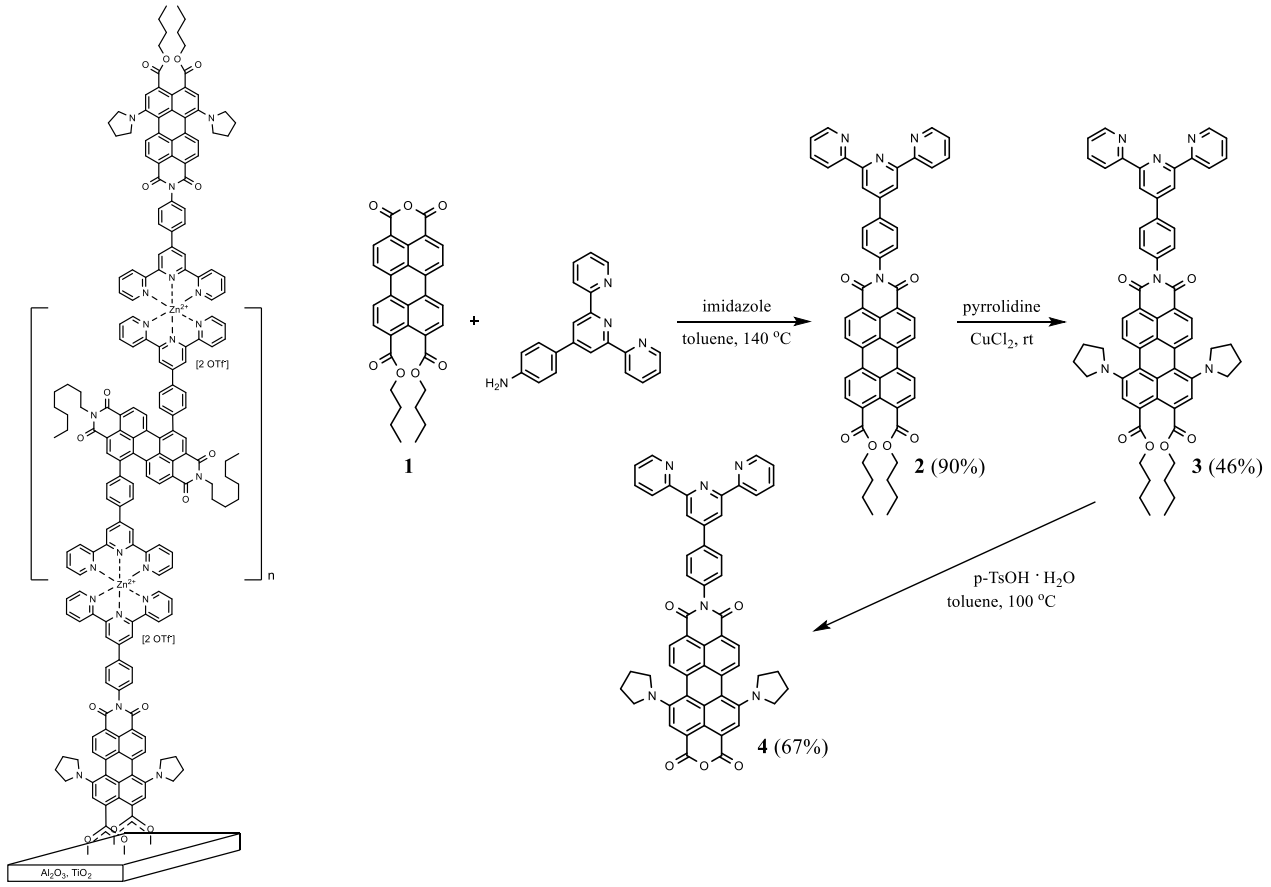
Perylene dyes are a unique class of chromophores, which exhibit outstanding optical, electronic and physical properties.[1] Their functionalization at the imide and *bay*-region gives opportunity to modify and fine tune their properties.[2] Terpyridine ligands are highly attractive terminal groups to be incorporated into perylene moiety. Terpyridines can coordinate to a broad range of metals and thus are powerful building blocks for supramolecular assemblies.[3]



We have synthesized various perylenes containing terpyridine moieties along with other functionalities. Compound **4** has the anhydride group in *peri*-position on perylene core which does the anchoring role *via* ring opening and the resultant dicarboxylates bind to the substrate surface.[4] We have assembled target chromophore as monomolecular layer on metal oxides. Coordination to Zn^{2+} ions provides the means for layer-by-layer formation of supramolecular assemblies of photoactive compounds. With this specifically rigid anchor it was possible to build even multilayer structures.

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MICROSTRUCTURED POLYMER/HYDROXYAPATITE COMPOSITE MATERIALS

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Materials based on combination of bioactive inorganic materials and biodegradable polymers are widely used for prosthetics and implants [1]. Amongst many inorganic materials, calcium phosphates are noteworthy because of their abundance in the hard tissues of living organisms. One of them, the hydroxyapatite (HAP), is well-known for its osteoconductive effect and is used for bone tissue engineering [2]. It is used as the main material or as a coating for parts of the implants with both applications providing basis for growth of bone and dental tissues. However, HAP mechanical properties are not ideal: like many ceramic materials it is brittle and have low fracture toughness [3]. To overcome these problems, polymers are added to the composition of the implant materials. Addition of biodegradable polymer improves toughness and provides necessary osteointegration of the implant after the degradation. Moreover, polymers open possibility for addition of antimicrobial drugs that prevent inflammation processes in the surrounding tissues and prevent rejection of the implant [4]. Depending on the bonding of the drug to the materials (covalent or electrostatic), the antibiotic can be released in a controlled manner, depending on the pH and the presence of lipases [5].

We have prepared composites containing different amounts of hydroxyapatite and biodegradable polymers, both non-modified and chemically modified. We have chosen ε-polylysine, polyvinyl alcohol, and polyvinyl alcohol modified with succinate moieties [6]. Blends were prepared using different approaches: suspension of pre-synthesized HAP [7] in polymer solution or *in situ* syntheses of HAP in the presence of polymers, and studied to determine their physical and chemical properties. Spray-drying of the suspension gives agglomerates with non-uniform particle size while the composites obtained by *in situ* syntheses upon spray-drying gave microparticles with nanocrystalline HAP embedded in the polymer matrix. The size distribution and forms of particles depend on the used polymer. In the case of succinate-modified polyvinyl alcohol, all obtained materials were probed for the content of free succinic acid/calcium succinate that can be formed due to alkaline hydrolysis during the *in situ* formation of HAP in polymer solution. The results of XRD studies of the obtained materials before and after pyrolysis indicate that no free calcium succinate is formed.

Acknowledgments: This work has been supported by the European Social Fund within the project “Involvement of new scientist group for synergistic investigation to development of nanostructured composite materials for bone tissue regeneration“, No. 2013/0007/1DP/1.1.1.2.0/13/APIA/VIAA/024.

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SYNTHESIS OF PHOTOCHROMIC DIARYLETHENES FOR PHASE AND AMPLITUDE OPTICAL ELEMENTS

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Materials showing a light-induced modification of properties are attractive to develop active optical elements. Among optical switches, photochromic diarylethenes have received increasing attention [1]. Their ability to reversibly change color upon irradiation with photons of suitable wavelength is the peculiar feature, but many other physical-chemical properties like refractive index or fluorescence also change along with the photochromic reaction [2].

We synthesized diarylethene derivatives with different lateral aromatic and heteroaromatic rings to finely tune their conjugation. Specifically, thiophene and thiazole moieties have been considered as aryls, the latter providing high fatigue resistance materials.

Introduction of hydroxyl as lateral units of a series of diarylethenes allowed polymerization to occur, thus providing Photochromic Polyurethanes, which were characterized by high content of photochromic units in the main chain, namely high contrast between the two states of the switch. Moreover, these amorphous polymer materials afforded good optical quality films, which is a fundamental requirement for applications in optics. Specifically, the photochromic monomer dialcohol-substituted reacted with an aliphatic diisocianate (H12MDI) to *in-situ* afford the photochromic coating onto a glass substrate. The bicomponent polymerization turned out to be highly versatile and allowed the optimization of the mechanical properties, whereas the nature and content of the photochromic monomeric units determined the optical properties of the layer.

By exploiting change in transmittance, photochromic Computer Generated Holograms (CGHs) [3] have been developed as amplitude optical element for the quality test of aspheric and free-form optical elements [4].The main advantage for the photochromic CGHs with respect to the traditional elements is the writing procedure simply consisting in a light exposure without any chemical post-processing, making the process fast and reliable. Moreover, as the light-triggered modulation is reversible, the written pattern can be erased and photochromic layers can be reused. Finally, two different photochromic diarylethenes can be copolymerized to develop multiplexed CGHs for simultaneous multi-wavelength interferometry.

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REACTION OF PERYLENE WITH ARYNES

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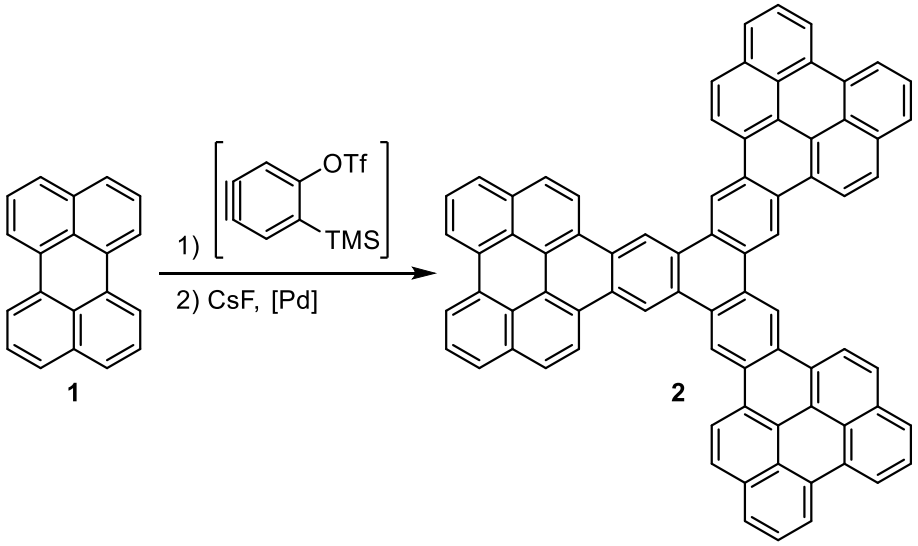
In recent years, the chemistry of polycyclic aromatic compounds (PACs) has sparked renewed interest in the scientific community. In particular, extended PACs with nano-sized planar geometries can be considered as “nanographenes” or substructures of graphene with a defined geometry. [1,2]

Arynes are privileged building blocks for the preparation of PACs.[3] In 2011, Fort and Scott reported the Diels-Alder cycloaddition of benzyne to the bay region of perylene (**1**). [4] In this contribution, we describe the use of this reaction to prepare large PACs and nanographenes such as compound **2**. [5]



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SYNTHESIS OF NEW ORGANIC-INORGANIC HYBRID MATERIALS BY CATALYTIC FUNCTIONALIZATION OF DOUBLE-DECKER SILSESQUIOXANES DDSQ-R_2

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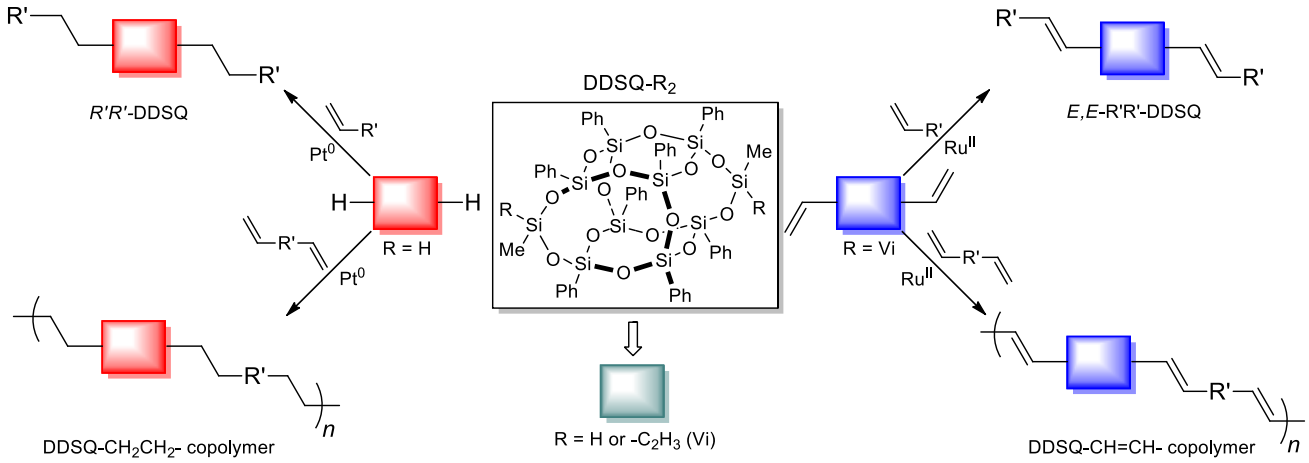
POSS-based polymers are a technologically important class of materials.[1] The broad classes of monomeric reagents based on well-defined polyhedral oligomeric silsesquioxanes have been established recently. Together with the development of bulk-scale preparative methods of these monomers they allow a new chemical technology for the modification of properties in nearly all thermoset and thermoplastic materials.

In this communication we would like to present control catalytic transformations of double-decker silsequioxanes (DDSQ-R_2) containing silicon-vinylene[2a] or silicon-hydrogen[2b] groups for the synthesis of new organic-inorganic hybrid materials. To achieve this we have used known silylative coupling[3] and hydrosilylation[4] reactions catalyzed by well-defined transition metal complexes as useful synthetic tools.



R' = highly conjugated aromatic part

Acknowledgments: The authors gratefully acknowledge the financial support from National Science Centre - Projects: SONATA 3 No. 2012/05/D/ST5/03348 and MAESTRO No. Project UMO-2011/02/A/ST5/00472.

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NOVEL CONJUGATED PHENOQUINONES WITH INTRIGUING ELECTRONIC FEATURES FOR ORGANIC PHOTOVOLTAICS

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A strategy which has been proposed to improve the power conversion efficiency (PCE) of the P3HT:PCBM organic photovoltaic (OPV) composites is the addition of a third component. Conjugated phenoquinones with photon harvesting complementary to the binary blend are presented in this framework.

These conjugated phenoquinones show peculiar electronic features: by a combined experimental (NMR, UV-vis, Raman and Resonant Raman) and theoretical study, an unexpected turning of the quinoidal into a biradicaloid character occurs by increasing the length of a homologous series of thiophene-based quinoidal species [1]. The possible contribution of a diradical electronic structure to the ground state is discussed in new phenoquinones depending on the structure of the central core and/or the nature and position of electroactive substituents [2].

Among this homologous series of conjugated phenoquinones, the role of 5,5'-bis- (3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadiene-1-ylidene)-2,2'-dihydroxy bithiophene (QBT) in influencing the PCE of the P3HT:PCBM heterojunction is shown [3]. Keeping fixed the relative content of P3HT:PCBM:Quinones at the value which gives the best efficiency enhancement in the case of QBT as third component, the effect of some other quinoidal materials is highlighted and shown to be dependent on their electronic structure.

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POLYMER AND IONIC LIQUIDS: A SUCCESSFUL COMBINATION

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Innovation in the materials field, particularly for polymer materials undoubtedly requires the control of their structure at the nanoscale. In fact, the way for significantly improving the functional properties lies at this scale: mechanical performances but also optical, electrical, fire retardant capabilities. To achieve this objective, several approaches have been considered and investigated such as the use of block copolymers, chemical species or nanoparticles. More recently, due to their excellent properties such as their high ionic conductivity, their high thermal and electrochemical stability, their non-volatility and their inflammability, ionic liquids are increasingly used in the polymers as surfactant agent in the field of nanocomposites[1-6], as plasticizer agent of polymers for medical grade, as building blocks[7-8] in fluoropolymers where one structuration to the nanometer scale, modulated by the chemical nature of the cation/anion combination, could be generated channels for lithium ion batteries. Moreover, they are also known as compatibilizing agents of polymer blends but also as new additive agent for the preparation of polymer electrolytes[9-11]. For these reasons, our laboratory has multiplied these activities on ionic liquids/polymer research and a research group at the national level with the support of the CNRS was created (GDR LIPS- http://www.gdr-lips.fr). Thus, in this study, an overview of the true potential of ionic liquids in the world of polymers will be presented.

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CHALLENGE: DESIGN A COLORLESS DYE THAT ABSORBS INTENSLY IN THE NEAR-INFRARED REGION

Synthesis and Properties of Croconaine Dyes and Their Application in Laser Welding of Plastic

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Laser welding of plastic is an important emerging technology with an array of applications ranging from electronic devices, medicinal equipment and automotive compartments. [1] In the laser welding process a laser transparent plastic is placed on top of a laser absorbing plastic and laser light is transmitted through the laser transparent plastic. The laser light excites the absorbing dye and heat is generated, thus causing the welding of the two items of plastic to occur (Figure 1).

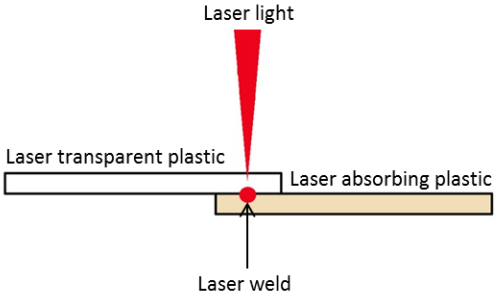

Figure 1. Laser welding of plastic

To obtain a colorless product two colorless items of plastic must be welded together. The laser absorbing dye must therefore itself be colorless, while still absorbing the near-infrared laser. This leaves an interesting molecular design challenge: how to design and prepare a near-infrared dye that does not absorb in the visible region?

We have addressed this challenge by preparing a range of croconaine dyes. The specific croconaine dyes have a donor-acceptor-donor type structure and their absorption can be adjusted by modifying the donor component (Figure 2). [2-3] Most croconic acid dyes show a strong absorption in the near infrared region. Due to these favorable properties croconic acid dyes can be used as the absorbing component in plastic.

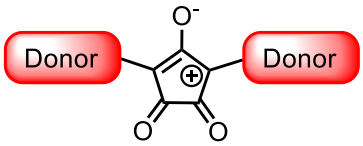

Figure 2. Example of croconic acid dye

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J – PHYSICAL ORGANIC CHEMISTRY

SUPERCONDUCTING METAL-INTERCALATED POLYAROMATIC HYDROCARBONS (MI-PAH)

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Superconductivity is the ultimate energy-saving technology because this state of matter exhibits zero resistance (when the material is cooled below a certain temperature T_C), enabling electrical transport without dissipation. In a society where we aim for green energy provision, it can be considered as a great opportunity. Many applications based on superconductivity have already been developed but we need to achieve real technological breakthroughs in order to make superconductors with better characteristics (high T_C, easy to synthetize, reduced impact on the environment).[1]

In 2010, a new breakthrough came with the discovery of superconductivity at relatively high temperature (18 K) in alkaline-doped picene.[2] Following this work, other MI-PAH molecules have shown a superconducting behavior with T_C ranging from 5 to 33K.[3] These studies suggest that longer molecules have higher T_C's. In this context, we were interested in studying the occurrence of superconductivity within a group of PAH molecules and comparing the electronic properties between different families.

Indeed, polycyclic aromatic hydrocarbons are a class of compounds that have stimulated a lot of interest since the beginning of the 20th century. But most of knowledge about their synthesis and their properties has only been gained during the past 20 years as the main difficulties in their formation lies in their high insolubility and their chemical fragility.[4] Here, we aim to develop new and innovative strategies to synthetize entire families of long PAH.

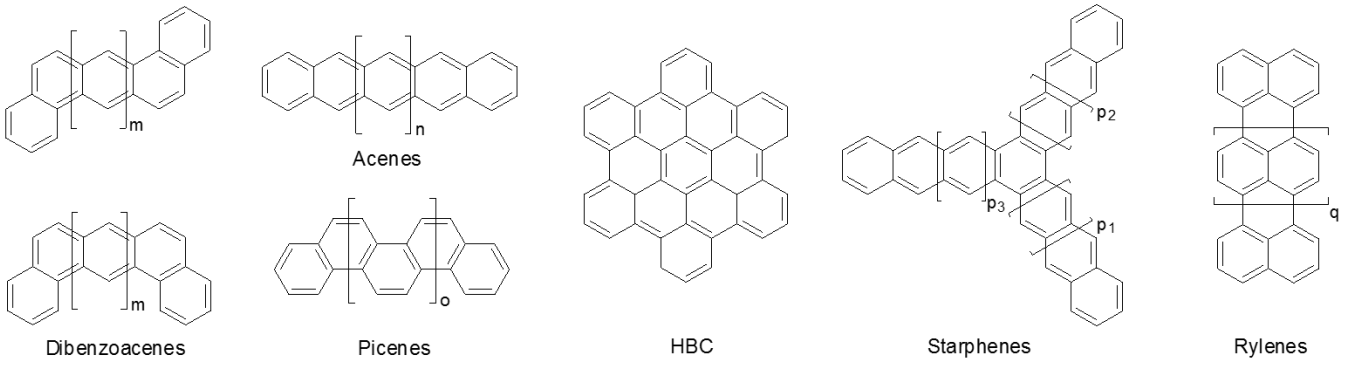

Figure 2. Target molecules

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STRUCTURE AND REACTIVITY OF SULPHUR-LINKED SACCHARINATE-TETRAZOLE

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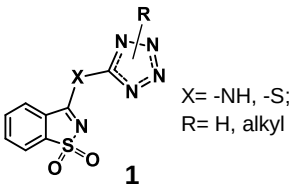
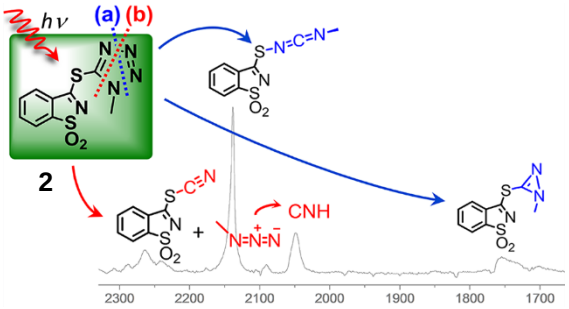
The design of multidentate ligands remains a challenge due to potential applications in a multitude of fields, such as catalysis, supramolecular chemistry, molecular magnetism environmental chemistry and medicine. We have devised synthetic routes to a representative library of saccharyl-tetrazoles **1** with the aim of exploring their applications as multidentate nitrogen ligands. Understanding the relevance of different tautomeric forms and preferred conformations of these systems appears of fundamental importance to this purpose. We found that the preferred tautomeric species of the N-linked conjugates (**1**, X=NH) are very much determined by the chemical environment.[1–3] On the contrary, for an S-linked saccharyl-tetrazole (**1,** X=S), the structure simplifies because no tautomerism involving the saccharyl system is observed. When considering applications of saccharyl−tetrazole conjugates, the assessment of their thermal and photochemical stability may also be of relevance.





The structure of saccharyl-tetrazole **2** was studied,[4] in the crystalline state, by X-ray crystallography, and as an isolated molecule, using matrix isolation coupled to infrared spectroscopy. Interpretation of experimental results was assisted by quantum chemical calculations [DFT(O3LYP)/6-311++G(3df,3pd)]. The UV-induced photodegradation pathways of **2**, isolated in solid argon, were also investigated. Recent results concerning the structure, photochemistry and chelating properties of conjugate **2** will be presented and discussed.

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THEORETICAL AND EXPERIMENTAL STUDY OF PALLADIUM-CATALYSED CROSS-COUPLING REACTIONS INVOLVING TRIARYLBISMUTHS

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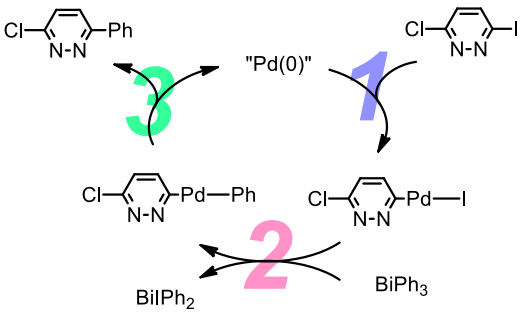
Triarylbismuths are organometallic reagents of growing interest in organic synthesis, for their ability to transfer the three aryl moieties in C-C coupling reactions[1]. These essentially non-toxic, atom efficient reactants are attractive in the context of environment-friendly chemistry and have applications in pharmaceutical chemistry and in material science.

Even if their synthesis dates before the 60s for the most common, their extensive use in metal-catalyzed coupling reactions is more recent, about ten years. These compounds have an intriguing geometry because they are characterized by three bulky aromatic rings with C-Bi-C bond angles of around 90°. Geometry optimizations of various Ar_3Bi with the DFT method and the hybrid B3LYP functional show that a lone pair on Bi atom is responsible for the basicity of these compounds.

After explaining the intrinsic properties, the study of coupling reactions was started. In particular we considered the cross-coupling reaction between the 3-chloro-6-iodopyridazine and the triphenylbismuth under palladium catalysis[2], using the DFT approach. We examined the three major steps of the full catalytic cycle, *i.e.* the oxidative addition, transmetallation and reductive elimination, and validated that by characterizing the different intermediates and transition states[3].



This kind of study will be helpful in explaining the differences in yields and selectivities observed in the coupling reactions involving substituted triarylbismuths.

In addition, we will investigate the transferability or non-transferability of the second and third aryl units in different triarylbismuths and we will compare our results to existing experimental data.

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BALDWIN-TYPE RULES FOR METAL-CATALYZED CYCLIZATIONS

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The basic framework of many complex and biologically interesting molecules includes cyclic moieties.[1] Therefore, to predict the outcome (*e.g.* exo or endo) of cyclizations is crucial in the design of synthetic procedures. Baldwin's rules [2,3] for ring closure are empirical descriptions of the relative easiness of ring formations (ring closure/cyclization). These rules were applied very effeciently in the last decades, but they have some limitations as well (*e.g.* do not apply to second row elements). An important question is the presence/absence of metals in the system. Are there any Baldwin's type rules for cyclization in the case of metal containing systems? To explore these possibilites, metal catalysed ring-closure reactions were studied computationally (Figure 1). Every combination of four main factors were investigated:

1) transition metals (9 late Transition Metals)
2) size of the formed rings (3-7)
3) geometry of the atom being attacked (dig and trig)
4) type of the ring closure (exo and endo).

A total of 144 different possible model reactions were designed and finally 136 transition states were located. There is a clear preference favoring the exo process over the endo based on the results.

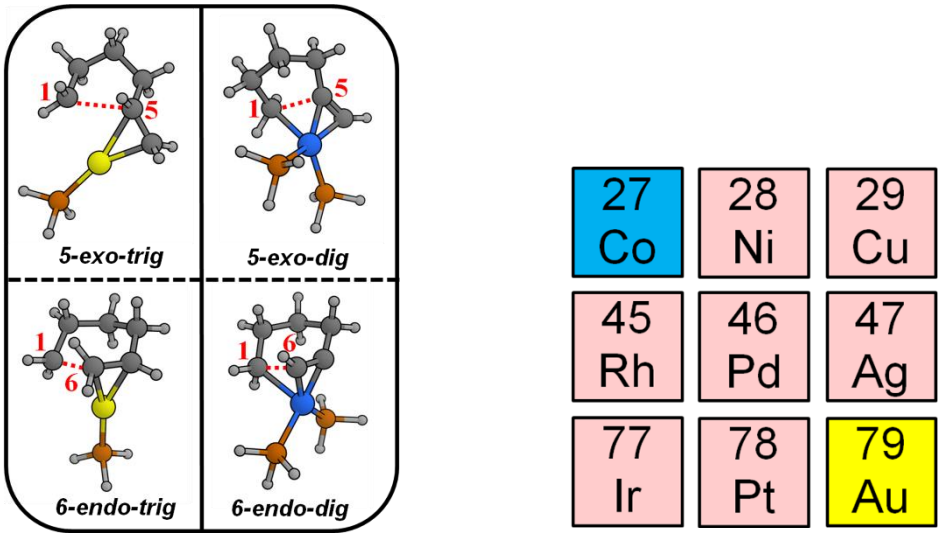

Figure 1. Calculated transition states: 5-exo- & 6-endo-trig with Au(I) and 5-exo- & 6-endo-dig with Co(I). Investigated transition metals.

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ALL-CARBON VICINAL QUATERNARY CENTERS – AN EXCITING STORY

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The carbon-carbon (C-C) bond formation is a fundamental aspect in organic synthesis. There is an ever-growing number of methods available to accomplish C-C bond formation, and making it more efficiently is an ongoing challenge in organic chemistry. The synthesis of carbon atoms bonded to four carbon substituents (all-carbon quaternary centers) is one of the most difficult standard carbon architectures to achieve [1,2]. Such centers are found in many biologically active natural products (*e.g.* cortisone, morphine). The synthesis of this kind of centers is rather complicated due to the steric hindrance that develops during transition state [3].

Three different reaction types (Claisen rearrangement, Nazarov cyclization, Michael addition) - which result in C-C bond formation - were studied computationally using Density Functional Theory. The C-C bond forming abilities of the different reactions were compared. The electronic, steric and solvent effects were analyzed besides the “degree of substitution: 0, 1 or 2 – number of methyl groups attached to the bond forming carbons” (Figure 1) on the nucleophile and electrophile part of the reactants.

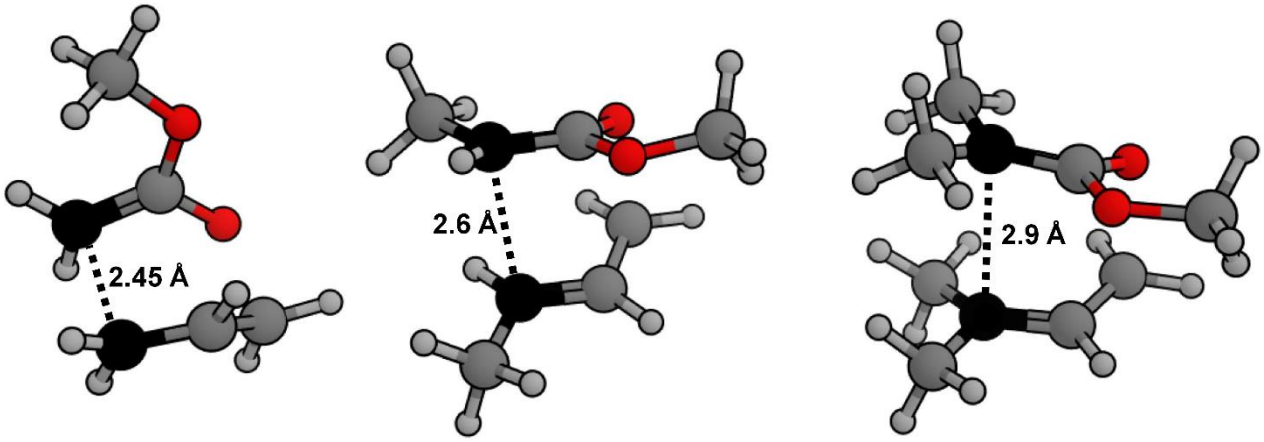

Figure 1. C-C bond formation: Claisen rearrangement. The “degree of substitution” is 0, 1 and 2 from left to right, respectively. The bond forming carbons are indicated with black.

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LUMINESCENT BORANILS AND BORON-DIKETONATES

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Luminescent organic compounds have a wide range of applications, from cellular imaging to light emitting devices, and much attention has been devoted to the development of dyes adapted to specific purposes. Boron complexes based on *N*- and *O*- donor ligands present excellent photo-physical properties, such as high quantum yields in dilute solution, good thermal and photo stability, and a wide range of emission wavelengths. Although BODIPY dyes are well-known examples,[1] recently boranils[2] and boron-diketonates[3] have emerged as efficient fluorophores in both solution and solid state.

In the course of our investigations, we have developed new boranils[4] with extended cores and dimeric units, in order to enhance their emission properties in the blue region of the spectrum (Figure 1.a). We found that the quantum yield increases when two boranils are linked together, even if they are not conjugated. Furthermore, decorating their periphery with bulky aromatic groups also improves the emission properties. We concluded that the electron donating nature of these groups, rather than their steric hindrance, is responsible for the increased quantum yield.

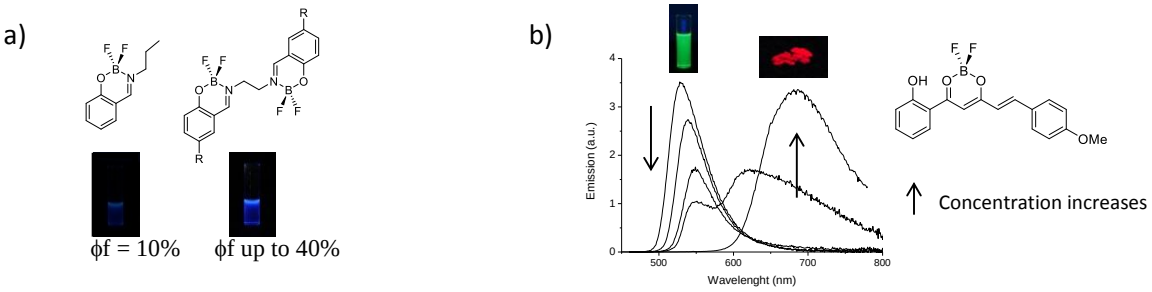

Figure 1. a) Enhanced luminescence of extended boranils.[4] b) Excimer formation upon aggregation of a boron-diketonate chromophore.[5]

We have also developed new boron-diketonates complexes[5] emitting efficiently in dilute solution (Figure 1.b). Interestingly, in concentrated solution, a new emission band appeared at a red-shifted wavelength, due to the formation of excimers. The study of the crystal structures showed that, in the solid state, the boron-diketonates complexes arrange into isolated dimers reminiscent of *J*-aggregates. By changing the nature of the peripheral substituents, it is possible to tune the emission color of these solid dyes from yellow to red. This presentation will report on these different approaches towards fluorophores with enhanced emission properties: covalent dimers in solution and supramolecular dimers in the solid state.

Acknowledgements: Thanks are due to the University of Aveiro. This work was developed within the scope of the projects CICECO-Aveiro Institute of Materials (Ref. FCT UID /CTM /50011/2013) and UI QOPNA (Ref. FCT UID/QUI/00062/2013), financed by national funds through the FCT/MEC and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement.

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DIHOMOOXACALIX[4]ARENE BASED HETERODITOPIC RECEPTORS FOR RECOGNITION OF BIOGENIC AMINE HYDROCHLORIDES

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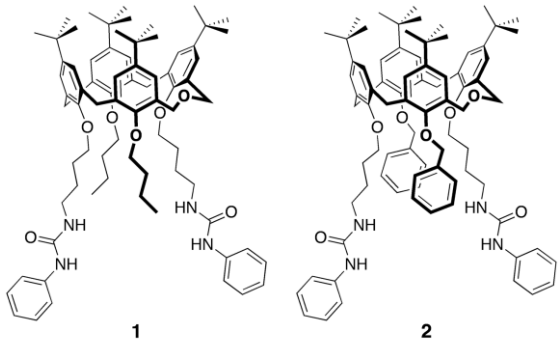
Calixarenes represent an extremely versatile class of macrocyclic receptors, able to bind and selectively transport ions and neutral molecules. Over the past three decades, a large interest has been devoted to the design of host systems for metal cations based on calixarenes. More recently, anion receptors based on these macrocycles have also been more investigated, mainly due to the recognized importance of anions in biological, medicinal and environmental areas.[1] To obtain anion recognition, many neutral receptors take advantage of hydrogen bond donor groups, such as amides, ureas and thioureas. These monotopic receptors described so far are focused on the selective recognition of a cation or an anion only.

Recently, heteroditopic receptors, molecules containing recognition sites for both ions of a given ion pair, have been synthesised and are an emerging area in supramolecular chemistry.[2] These systems have important applications for example as membrane transport agents, sensors and in salt extraction and solubilisation.

In the course of our studies on cation binding properties of dihomooxacalix[4]arenes, we have recently extended our research into the study of anion complexation.[3,4] In the present work, we report our results on the ion-binding properties and selectivities of new heteroditopic ureido-dihomooxacalix[4]arenes **1** and **2** towards *n*-butylammonium halides and a number of biogenic amine hydrochlorides (such as phenylethylamine, tyramine, dopamine, serotonin, histamine and norepinephrine).[5] These properties were assessed by proton NMR titrations in $CDCl_3/CD_3OD$ (10:1) at room and low temperatures.



1 **2**

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STUDY OF ISOMERIZATION OF A SYNTHETIC FLAVYLIUM: 6-, 8-BROMO-4',5,7-TRIHYDROXYFLAVYLIUM

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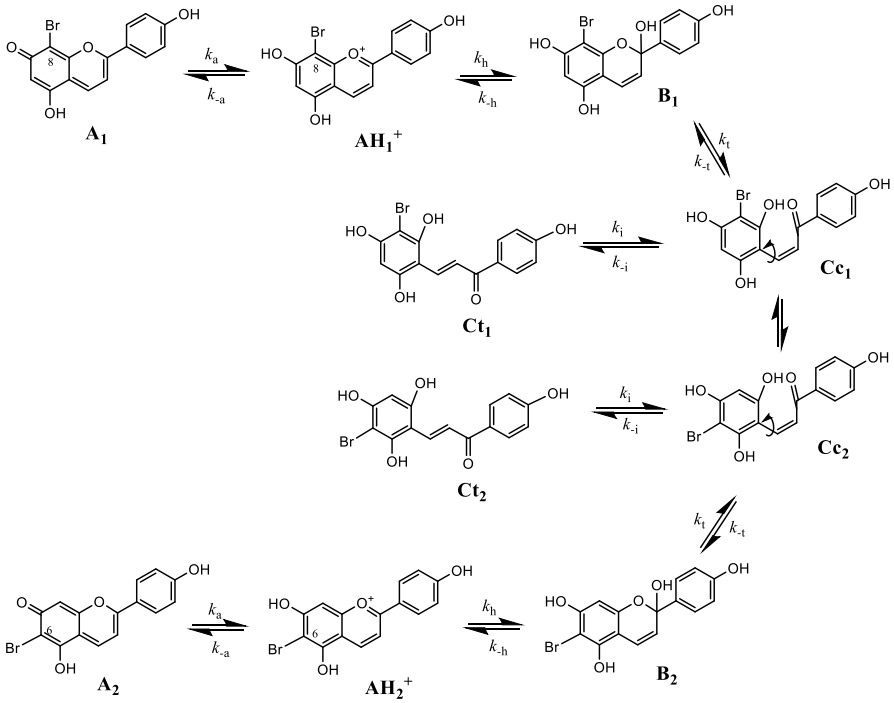
Flavylium compounds represent a family of synthetic and natural pigments present in plant kingdom which included anthocyanins, anthocyanidins and 3-deoxyanthocyanins. 3-deoxyanthocyanins are known to be more stable in aqueous solutions than anthocyanins[1], and therefore, they have been demonstrated a wide range of potential applications namely as food colorants, hair dyes, laser dyes, dye-sensitized solar cells and molecular-level memory systems[2,3].

This work aims to synthesize the 3-deoxyanthocyanidin 8-bromo-4',5,7-trihydroxyflavylium and further to study its isomerization to 6-bromo-4',5,7-trihydroxyflavylium (Scheme 1). Its kinetic and thermodynamic constants will be determined by means of by UV-Vis and stopped-flow techniques. After HPLC semi-preparative separation of each isomer, their kinetics were followed over the time. After 400 minutes the equilibrium was reached and the proportion of isomers is 72% of 8-bromo-4',5,7-trihydroxyflavylium and 28% of 6-bromo-4',5,7-trihydroxyflavylium.



Scheme 1. Isomerization reaction to obtain of 6-, 8-bromo-4',5,7-trihydroxyflavylium isomers through hemiketal and *cis*-chalcone species.

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AQUEOUS PHOTOCHEMISTRY OF BISPHENOL F

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Bisphenol F (4,4'-dihydroxydiphenylmethane, BPF) is widely used in industry (polycarbonate plastics, epoxy resins, adhesives, drink packages and food cans) and agriculture. Huge amounts of production and consumption of goods manufactured on the basis of BPF result in its presence in environment, farm products and drinking water [1]. As well as its structural analog bisphenol A, BPF refers to endocrine-disrupting chemicals (EDCs), substances that mimic hormones and produce number of disorders in endocrine functions and reproduction of living organisms [2-3]. Conventional treatment techniques are not enough effective for the removal of majority of EDCs, while photochemical and photocatalytic processes have proved themselves as perspective methods for water purification and disinfection from such compounds. In order to improve and develop these methods it is necessary to obtain information about mechanistic aspects regarding photochemistry of EDCs.

This work is devoted to study of BPF photochemistry in aqueous solutions by means of optical spectroscopy, steady-state (λ_{ex} = 282 nm, exilamp XeBr) and laser flash (λ_{ex} = 266 nm, 6 ns, Nd:YAG laser) photolysis.

Transient absorption spectra obtained during the flash photolysis of air-free and air-saturated solutions of BPF exhibit characteristic bands with maxima at 720 nm (hydrated electron [4]) and 400 nm (phenoxyl radical [5]). Also formation of triplet state of BPF was detected with maximum at 450 nm. Thus, UV excitation of BPF result in photoionization with formation hydrated electron – phenoxyl radical pair. Quantum yield of photoionization $\varphi_{ion} = 2.3 \times 10^{-2}$ and absorption coefficient of phenoxyl radical ε^{400} = 3200 $M^{-1}cm^{-1}$ were determined using known value of absorption coefficient of hydrated electron (e_{aq}^-, $\varepsilon^{720} = 2.27\times10^4$ $M^{-1}cm^{-1}$ [4]). In air-saturated solutions hydrated electron decays more rapidly than phenoxyl radical due to reaction with dissolved oxygen. The set of kinetics curves obtained in this conditions were processed by formula $\Delta A = A_1\exp^{(-t/t1)} + A_2/(1+t/t_2) + A_3$, where A_1, t_1 (≈1 μs) fits to decay of excited triplet state BPF, A_2, t_2 describe disappearance of phenoxyl radical due to second order processes, A_3 belongs to long-lived absorption (t > 400 μs) of intermediate/final photoproducts.

The second order decay of phenoxyl radical is caused by reactions with another phenoxyl radical and/or with super-oxide anion radical formed in the reaction between hydrated electron and oxygen. The rate constant was determined as equal to 5.1×10^9 $M^{-1}s^{-1}$. Further investigations will be aimed to study of influence of different factors (e.g. presence of Fe(III) ions and cyclodextrins) on this process in order to increase its efficiency. Preliminary experiments have shown that β-cyclodextrin complexation leads to 3-times increase of photoionization quantum yield.

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COMBINATION OF SPIN TRAPPING, EPR AND MASS SPECTOMETRY: AN EFFICIENT TOOL TO STUDY RADICAL REACTION MECHANISMS

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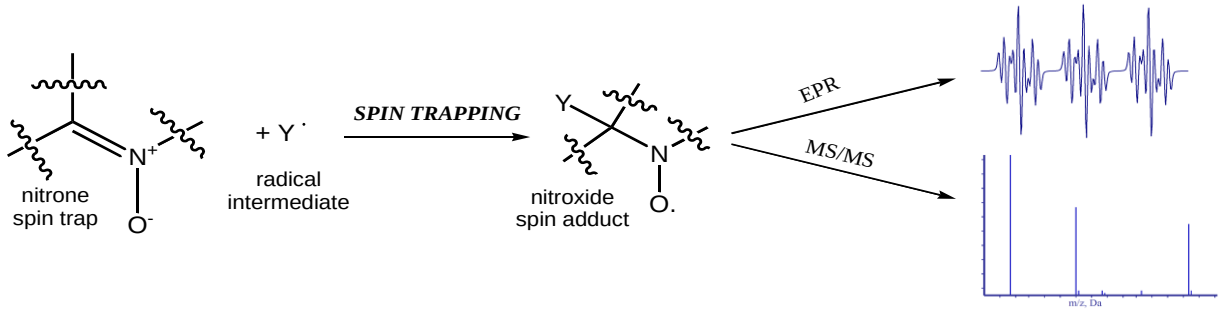
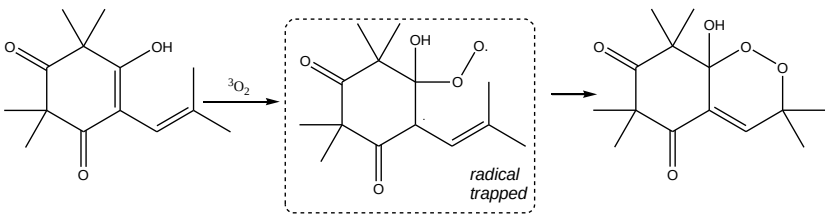
Spin trapping (ST) in conjunction with EPR spectroscopy is a valuable tool for the detection of low amounts of radical intermediates. This technique involves the addition reaction of a transient radical to a diamagnetic spin trap, commonly a nitrone or a nitroso compound, to yield a relative long-lived paramagnetic adduct, a nitroxide, which accumulates to a concentration high enough to be studied by EPR. In favorable cases, the resulting EPR spectrum allows the identification of the radical trapped. However, unique assignment is not always feasible, and nitroxides with analogous structures generally lead to identical EPR spectra. Note also that changes in the environment, such as in the solvent polarity, can greatly modify the observed EPR spectrum. Moreover, the nitroxide spin adducts can be transformed into EPR-silent species, notably by redox processes. Mass spectrometry (MS) has been shown to successfully overcome these limitations, using the MS mode to detect low quantities of both paramagnetic nitroxides and their reduced or oxidised forms, even in complex matrices, and performing MS/MS experiments for structural characterisation.



Several examples will be presented to illustrate the efficiency of this approach,[1-3] In particular, the spontaneous addition of air oxygen to a dienolic compound, yielding a cyclic peroxide, was followed by ST combined with EPR spectroscopy and MS. Using two different nitrones, the ST/EPR study allowed the detection of a radical intermediate, and the radical centre in the addend was identified after similar experiments performed with ^{13}C-labelled analogues of the substrate. The media were also submitted to electrospray ionisation for structural characterization of the spin adducts by MS/MS, which allowed the structure of the hydroxylamine derivatives of the nitroxides formed to be identified.



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A WATER-SOLUBLE GOLD NANOPARTICLE CAPPED [2]ROTAXANE

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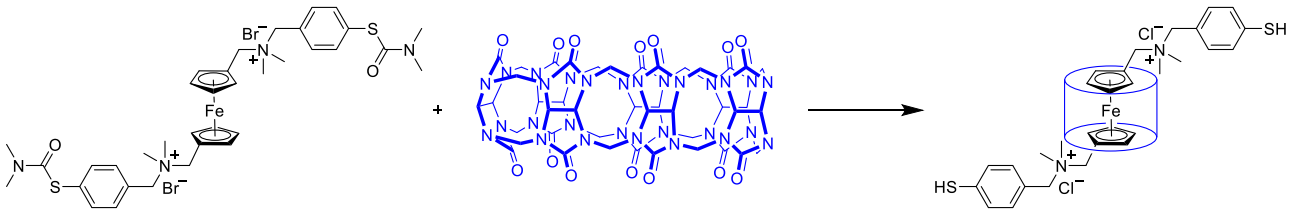
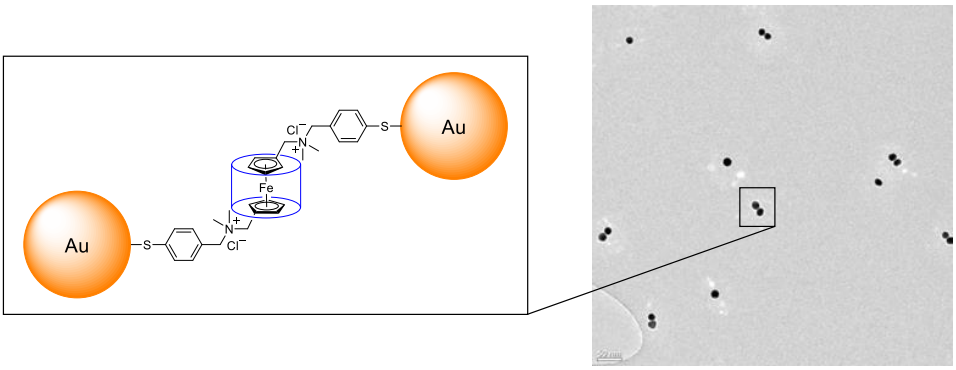
Here we describe the formation of a gold nanoparticle capped [2]rotaxane that is soluble in water. The centre of the compound is a [2]pseudorotaxane formed between cucurbit[7]uril (CB[7]) and a novel ferrocene based bis-ammonium cation. The design of the ferrocene guest molecule is inspired by the work of Rekharsky *et al.*,[1] however the compound has been expanded with two thiol functionalities. We have found that the ferrocene guest is capable of binding inside CB[7] and the complex show an equilibrium constant as high as 10^{15} M^{-1} in water. This is caused by (*i*) favourable hydrophobic interactions between the ferrocene derivative and the inner surface of the CB[7] cavity and (*ii*) ion-dipole interactions between the ammonium cations on the ferrocene guest molecule and the carbonyl oxygen atoms covering both CB[7] cavity openings.



The gold nanoparticle capped [2]rotaxane is synthesised via the “threading followed by stoppering” procedure where the [2]pseudorotaxane is used as a linker to connect the two stopper groups, the gold nanoparticles. This is done by introducing each of the thiol functionalities on the ferrocene guest molecule on the surface of gold nanoparticles. The resulting [2]rotaxane can be studied by transmission electron microscopy (TEM) as shown below.



Preliminary studies show how the [2]pseudorotaxane is capable of forming self-assembled monolayers (SAMs) on gold surfaces that can be examined by electrochemistry and scanning tunnelling microscopy (STM).

References:

[1] M. V. Rekharsky, T. Mori, C. Yang, Y. H. Ko, N. Selvapalam, H. Kim, D. Sobransingh, A. E. Kaifer, S. Liu, L. Isaacs, W. Chen, S. Moghaddam, M. K. Gilson, K. Kim, Y. Inoue, *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 20737-20742.

TWO-DIMENSIONAL BRICKLAYER ARRANGEMENTS IN CONJUGATED SYSTEMS USING HALOGEN BONDING INTERACTION

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The packing of conjugated materials in the solid state is directed by non-covalent interactions that govern their optoelectronic properties as semiconductors. Most systems exhibit typical herringbone packing motifs, driven by edge-face interactions. However, modified materials with 2-D bricklayer packing show improved device performance compared to their herringbone packing analogues.[1,2] Efforts to control packing of these materials have focused on aliphatic interactions[3], aromatic stacking[4], and hydrogen bonding.[5] In contrast, halogen bonding (XB), which provides consistent 180˚ angle interactions between the donor and acceptor, has not been examined systematically for organizing the solid state arrangement of conjugated materials until now. Using tolans (diphenylacetylenes) as a test model, halogen bonding has proven to be an effective in creating 2-D bricklayer packing motifs (Figure 1).

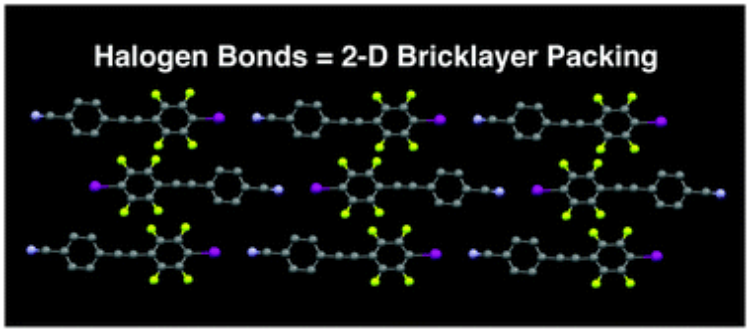

Figure 1. Halogen Bonding in the crystal structure of 4-(2-(4-iodotetrafluorophenyl) ethynyl)-benzonitrile.

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GLOBAL MIRROR-SYMMETRY BREAKING: CHEMICAL CONTROL OVER AN ENANTIOFACIAL ADSORPTION OF NON-CHIRAL MOLECULES ON A NON-CHIRAL METAL SURFACE

Irena G. Stará,[a],* Jaroslav Vacek,[a],* Pavel Jelínek,[b],* Oleksander Stetsovych,[b] Martin Švec,[b] Andrej Jančařík,[a] Jiří Rybáček,[a] Jana Vacek Chocholoušová,[a] Ivo Starý[a],*

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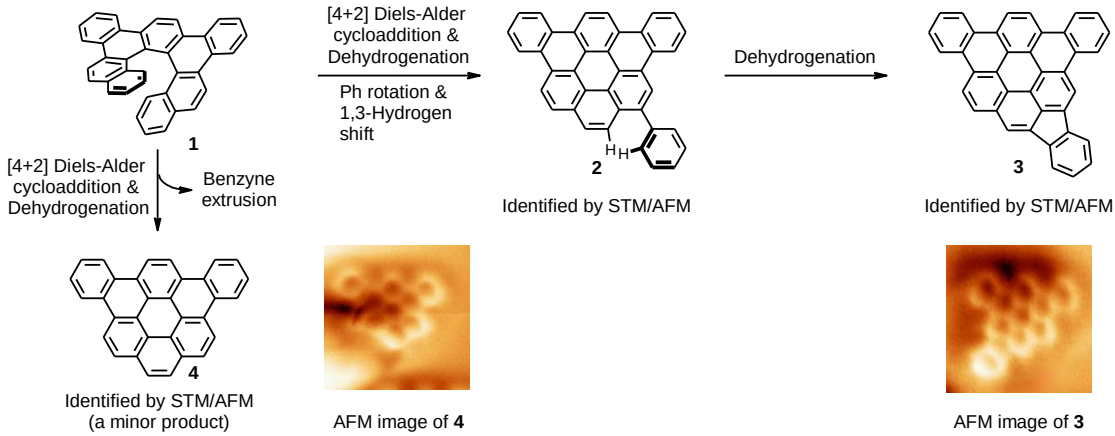
High-resolution AFM images of single molecules [1] provide completely new perspectives in investigation of chemical processes on surfaces [2]. Here, we report on on-surface chemistry of dibenzo[7]helicene **1** [3] deposited on Ag(111). Annealing above 100° C has induced a [4+2] Diels-Alder cycloaddition reaction, which has triggered a cascade of chemical processes on the surface (Scheme 1). We have been able to identify an intermediate step **2** and two final products **3** and **4** by means of simultaneous AFM/STM measurements. The sharp submolecular resolution of the flat molecules **3** and **4** has been obtained using the high-resolution AFM images with a functionalised Xe-tip.

To understand the origin of an enantiofacial selectivity of adsorption, we investigated both the racemic mixture and the pure (+)-(*P*) enantiomer of dibenzo[7]helicene **1** deposited on the Ag(111) surface. We have found that the chiral orientation of the individual molecules as well as their complexes is driven both by chirality of helicene initially deposited on the surface and annealing conditions. We have demonstrated for the first time the chemical control over the final enantiofacial adsorption of the planar non-chiral aromatic molecules of **3** formed from the enantiopure precursor **1** on the non-chiral metal surface that has resulted in a global mirror-symmetry breaking.



Scheme 1

Acknowledgements: Supported by the Czech Science Foundation (Reg. No. 14-29667S) and IOCB ASCR (RVO: 61388963).

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K – OTHER AREAS

SYNTHESIS, SPECTRAL AND THEORETICAL CHARACTERIZATIONS OF 2-(2´,3´/2´,4´/2´,5´/3´,4´/3´,5´-DIMETHOXYPHENYL)-5,6-DIMETHYL-1*H*-BENZIMIDAZOLES

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Various benzimidazole derivatives display a wide range of biological activity. For instance, vitamin B12 has 5,6-dimethylbenzimidazole moiety as coordinated to the Co(II) ion. On the other hand, various drugs and pharmaceutical compositions contain benzimidazole derivatives. Some of benzimidazole derivatives are used as drugs such as omeprazole, thiabendazole, albendazole, mebendazole, flubendazole, astemizole and fenbendazole [1-3].

In this study, 2-(2´,3´/2´,4´/2´,5´/3´,4´/3´,5´-dimethoxyphenyl)- 5,6-dimethyl-1*H*-benzimidazoles (**1** – **5**) were synthesized and characterized by using analytical data, FT-IR, FT-Raman, NMR, ESI-MS and fluorescence spectroscopy. Most of the compounds show dual fluorescence in ethanol whereas some of them present triple fluorescence. The optimized molecular geometry, zero point energy, dipole moment, ESE, band gap and charge distributions were calculated by Gaussian 09 using DFT method (B3LYP) with 6-31G(d,p) basis set. According to the calculations, the molecules have structures with various torsions between the benzimidazole and benzene rings from 10.6º to 47.8º.

2-(3´,4´-Dimethoxyphenyl)-5,6-dimethyl-1*H*-benzimidazole (**4**) has the highest dipole moment value of 4.79 D and 2-(2´,5´-dimethoxyphenyl)-5,6-dimethyl-1*H*-benzimidazole (**3**) has the lowest dipole moment (2.78 D). The calculated energy values based on ZPE and DFT show that the order of stability is **5** > **1** > **3** > **4** > **2**. The charge distribution shows that the most positive charge is concentrated on C2. In all the compounds, C6' atom is negatively charged and the partial positive charge resides at C8 and C9. The carbon atoms bonded to the methoxy groups are positively charged as expected. Atomic charge of the NH nitrogen (N1) is more negative than that of the C=N nitrogen atom (N3). The dimethoxy carbon atoms are partial negatively charged (dark red) and the methoxy oxygen atom negatively charged (red) in all of the compounds as shown in Figure 1.

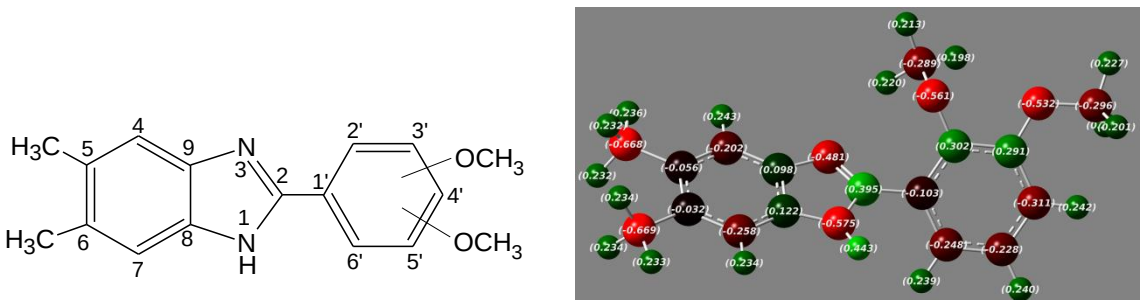

Figure 1. The general formula of the compounds in the study and atomic charges of the compound **1**.

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THE ROLE OF ORGANIC CHEMISTRY IN THE HYDROMETALLURGICAL RECYCLING OF VALUABLE METALS

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The European Union published a report in 2014 identifying a series of critical raw materials with potential supply risks in 2020: antimony, coking coal, gallium, indium, platinum-group metals (PGMs) and heavy rare-earth elements (HREEs) [1]. Within the six entries of this list, five are metals, and this situation is a reality that should not be ignored, as the day-to-day life of the developed countries is under threat if no responsible measures are taken to overcome this scarcity problem.

Recycling of metals from anthropogenic supplies at the end of their lives has been an increasing contribution to save the rarest primary raw metal sources. A few examples of those materials are catalysts, *e.g.*, of automobile and industrial origins (for which PGMs are the determinant components), and LEDs and computer screens (indium and gallium being the basis of the most widely used semi-conductor materials). Accordingly, a strong research effort is visible in recent years to find and establish efficient and selective processes to recycle these critical metals from secondary sources.

Liquid-liquid extraction (or solvent extraction) has been thoroughly used in industrial hydrometallurgy to concentrate and/or purify leaching solutions of different origin [2]. That cumulative knowledge has been the basis for the application of this technique to the recycling of anthropogenic supplies, but the increasingly complex compositions of the leaches have been requiring the design of adequate organic compounds with proven ability to selectively recover the desired metals.

After a brief introduction and historical perspective of hydrometallurgical solvent extraction, the aim of this work is to describe some case studies illustrating the role of organic chemistry in the development of specific compounds for the extraction of critical metals. Special emphasis will be devoted to amide compounds for PGMs recovery from chloride media, namely sulfide-containing monoamides [3], pyridine carboxamides [4], tertiary thioamide [5] and *N,N'*-tetrasubstituted thiodiglycolamide [6] derivatives, amongst many others. The two latter examples – whose general structures are depicted in Fig. 1 - will be further discussed, since the efficient and selective performance of thioamides and thiodiglycolamides to recover palladium from real leaching solutions of spent automobile and petrochemical catalysts is remarkable.

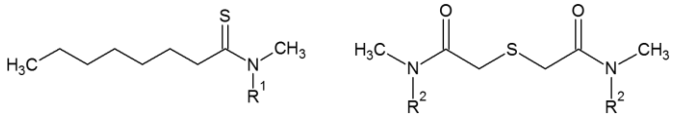

Figure 1. Structures of the thioamide and thiodiglycolamide derivatives for Pd(II) recovery (R^1, R^2 – alkyl groups)

Acknowledgements: The financial support for the experimental work reported in this communication has been kindly provided by "FCT - Fundação para a Ciência e a Tecnologia" (Portugal) under the projects PTDC/QUI-QUI/109970/2009 and PEst-OE/QUI/UI0612/2013. O. Ortet PhD grant offered by FCT (SFRH/BD/78289/2011) is gratefully acknowledged.

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SELF-ASSEMBLED GIANT VESICLES FORMED BY TYPE I [3:3]-HEXAKIS ADDUCTS OF C_{60} EQUIPPED WITH ENANTIOMERICALLY PURE *CYCLO*-MONOMALONATE ADDENDS

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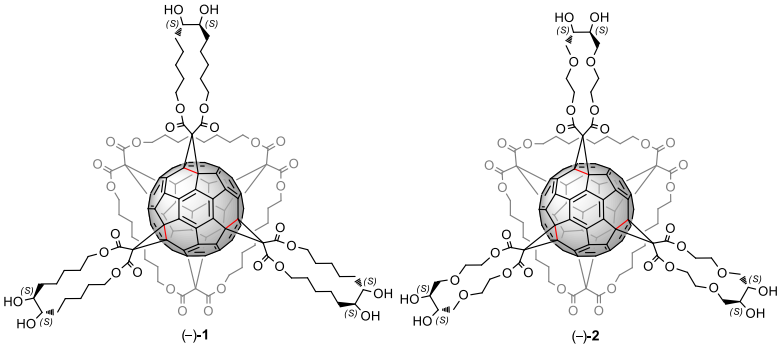
The emergence of giant shape amphiphiles [1] synthesized by the modification of single molecular nanoparticles (MNPs) [2] has set new perspectives in the area of supramolecular aggregation. C_{60} has been defined as a molecular nanoparticle due to the well-defined, rigid and highly symmetrical molecular structure. A common characteristic of small amphiphilic molecules and giant shape amphiphiles is the unusual sensitivity of solution self-assembly behaviour to primary chemical structures. The prediction of the self-assembled architectures in relation to the exact molecular shape has not been realized yet setting the design and synthesis of new C_{60} shape amphiphiles and the characterization of their nano-structures a primary target.

The family of type I [3:3]-hexakis adducts of C_{60} [3] offers an excellent platform for designing and synthesizing a diversity of giant shape amphiphiles by incorporating different hydrophobic and hydrophilic addends in their structures. As such, the investigation of shape-self-assembly behaviour relationship can be considerably extended by systematically varying the chemical structure of the polar and/or non-polar addends which are covalently connected on the six *equatorial* bonds of C_{60} located at the octahedral sites of the fullerene sphere. With this in mind, we designed and synthesized the giant shape amphiphilic adducts (–)-**1** and (–)-**2** equipped with three enantiomerically pure *cyclo*-monomalonate addends located on one hemisphere of C_{60} and a *cyclo*-[3]-octylmalonate addend on the other. Each *cyclo*-monomalonate addend bears a non-ionic 1,2-diol moiety which serves as the hydrophilic head. The structural difference between (–)-**1** and (–)-**2** originates from the different size and chemical nature (incorporation of oxygen heteroatoms) of the *cyclo*-monomalonate moieties. Studies on their self-assembling behaviour by TEM and SEM revealed that the minor modification in the size and chemical nature of their glycol-substituted monomalonate addends and consequently, in the shape of these giant molecules, significantly influences their corresponding self-assembling architectures. Specifically, the self-assembling behaviour of (–)-**1** in water revealed the remarkable ability of this giant shape amphiphile to form stable, giant vesicles with diameters varying from 500 nm up to 5 μm. Interestingly, the fullerene vesicles formed were found to be robust and retained their structural integrity in air or under vacuum, a behaviour inherent to giant molecules. However, the giant shape amphiphilic adduct (–)-**2** afforded mostly ill-defined, clustered, spherical aggregates with diameters ranging from 20 to 50 nm.



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DE NOVO DESIGN OF AN ARTIFICIAL HELICAL AROMATIC OLIGOAMIDE FRUCTOSE RECEPTOR

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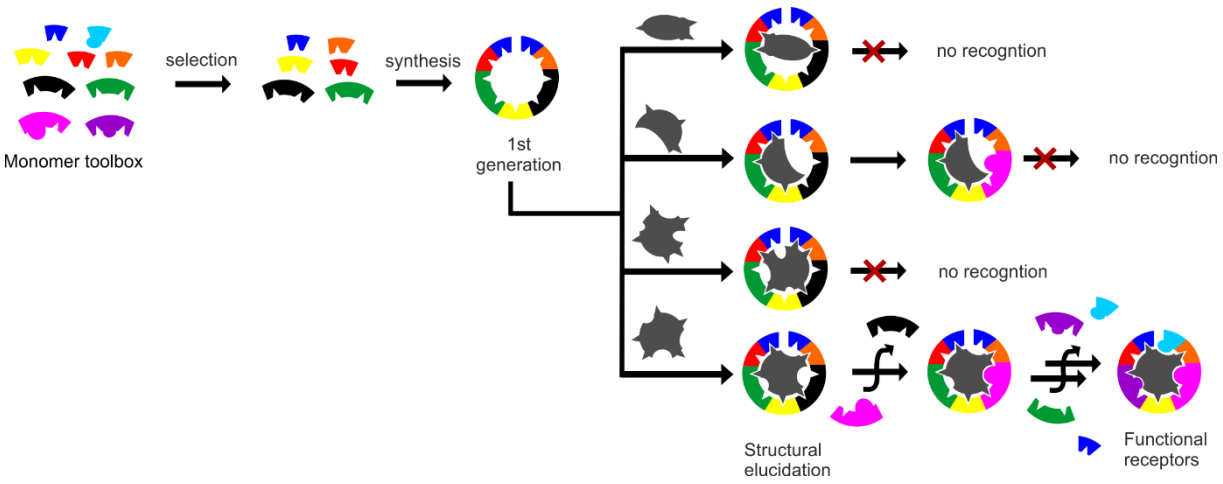
During the last decade major breakthroughs have been made in the recognition of carbohydrates by synthetic receptors both in organic solvents and water. However, practical applications (*e.g.* tools for glycobiology, sensors…) are still premature at this stage and there is still a need for new receptor architectures. In the recent years, our group has developed helical foldamers [1] – oligomers that adopt stable helical folded conformations – derived from a large toolbox of aromatic amino acids. Cavities can be designed within such synthetic molecules that enable them to act as artificial receptors for chiral polar guests. Inspired by Nature, we describe here a powerful and novel approach to produce receptors of exquisite selectivity in the challenging context of monosaccharide recognition by using an iterative evolution process that exploits the modular structure of folded synthetic oligomer sequences coupled with molecular modelling and structural characterizations. This scheme, which mimics the adaptable construction of biopolymers from a limited number of monomer units, provides a general protocol by which to create highly selective receptors towards an eventual wide range of monosaccharides as well as other biological or synthetic compounds (see Figure below). In this presentation we will show how we produced a fully functional receptor for β-D-fructopyranose in just a few iterations. [2]



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NEW PYRIDYL-OXAZOLE OLIGOMERS FOR TARGETING CANCER-RELEVANT G-QUADRUPLEXES

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Department of Chemistry, University of Cyprus

G-rich DNA sequences are abundant in the human genome. In recent years, the anticancer potential of G-rich sequences found in the human telomeres, within certain oncogene promoters and in other regulatory regions has unfolded, as their ability to fold into G-quadruplex helices under the influence of custom-designed small molecules was found to result in inhibition of specific tumour-promoting functions.

We report herein on the synthesis of a new family of pyridyl-oxazole oligomers of various lengths and architectures. These are intended to interact with G-quadruplexes of anticancer interest via modes different from those previously reported for planar quadruplex-binding molecules. Specifically, our compounds are designed to target different binding loci (grooves) rather than the terminally exposed G-quartets of a quadruplex. A critical Pd^{II}/Cu^{I}-mediated C-H activation, C-C cross-coupling method is employed to connect oxazole intermediates to 2-bromopyridine intermediates, en route to the compounds.

PHTHALOCYANINES AS CHROMOGENIC ANION SENSORS

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The field of supramolecular recognition of anions by different host molecules has been highly explored during the last few decades due to the important roles that anions play in chemical, biological, medical and environmental processes [1,2]. The design and development of artificial receptors that can recognize and sense efficiently and selectively anionic species, *via* changes in their optical signature, have assumed great importance due to their potential applications in the development of analytical devices [2,3]. Synthetic anion chemosensors should have the ability to selectively recognize and sense anionic analytes using naked eye (chromogenic chemosensors) or via an easy-to-monitor electrochemical or spectroscopic response [4,5].

In this communication, we report the synthesis and characterization of a phthalocyanine and two metallophthalocyanines (compounds **1-3**) and the evaluation of their anion binding properties as chromogenic (chemo)sensors (Figure 1). The anion binding studies were performed using typical anionic substrates, such as acetate, bromide, chloride, cyanide, fluoride, nitrate, nitrite, sulfate and dihydrogen phosphate, and were conducted by UV-Vis and ^{1}H NMR spectroscopic methods.

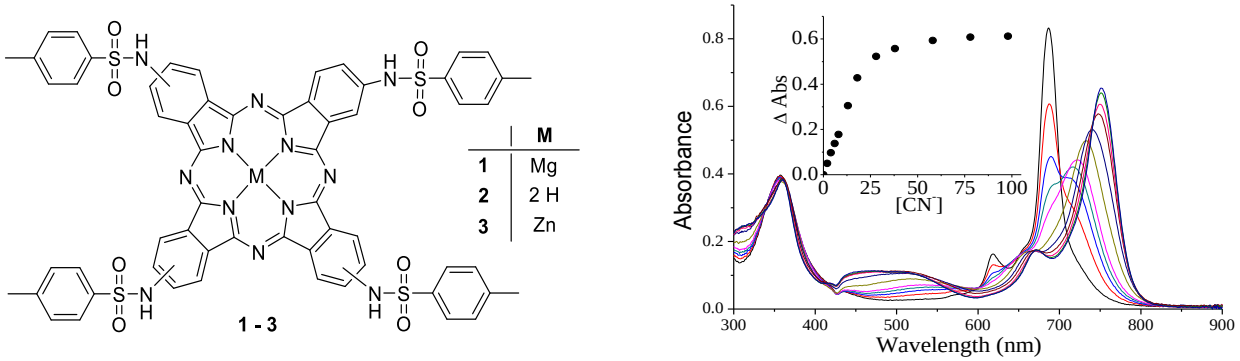

Figure 1. *Left*: structures of **Pc 1–3**; *Right*: UV-Vis titration of **Pc 3** with CN^- in DMSO.

Acknowledgments: Thanks are due to the Universidade de Aveiro, Fundação para a Ciência e a Tecnologia (FCT), European Union, QREN, FEDER and COMPETE for funding the QOPNA research unit (PEst-C/QUI/UI0062/2013; FCOMP-01-0124-FEDER-037296). J. M. M. Rodrigues and A. S. F. Farinha also thank FCT for their PhD (SFRH/BD/81014/2011) and post-doc (SFRH/BPD/73060/2010) grants, respectively.

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SYNTHESIS AND STUDY OF TRIPTYCENE−BASED ANION RECEPTORS

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Triptycene was first synthesised by Bartlett[1] in order to study its radical activity. Over the years, however, triptycene has found numerous applications in various fields of chemistry, including catalysis,[2] polymer chemistry,[3] and supramolecular chemistry.[4,5] Due to the unique structural properties of triptycene, such as rigid structure and C_3 symmetry, we have decided to synthesise an anion receptor **1** (**Fig. 1.**), in which pyrrole rings are fused to the triptycene skeleton. Using molecular modelling, we have determined that this receptor would have a well-defined binding pocket, which would allow it to bind anions effectively, even in highly demanding solvents.

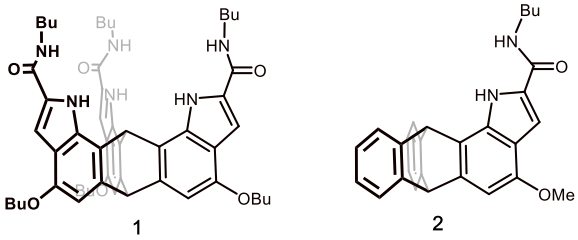

Figure 1. Structures of receptors **1** and **2**

We realised, however, that the synthetic path towards compound **1** would prove challenging, and therefore we obtained a simpler analogue of the target molecule. In a nine step synthesis we have constructed receptor **2** (**Fig. 1.**), in which one benzene ring is fused with pyrrole. We were able to obtain a monocrystal suitable for X-ray analysis, which showed formation of tetramers of receptor **2** in the solid state (**Fig. 2.**). Binding properties were studied by titration under ^{1}H NMR control in DMSO-d_6+0.5% H_2O.

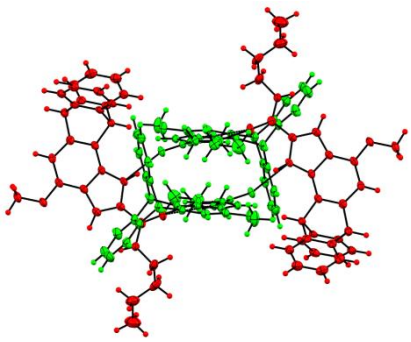

Figure 2. Tetramer of receptor **2** in the solid state

Acknowledgements: This work was financed by Polish National Science Center, grant Preludium 2012/07/N/ST5/02169.

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DEVELOPMENT OF HPLC METHOD FOR MONITORING ACID-CATALYZED CONVERSION OF 7-ETHYLTRYPTOPHOL TO METHYL ESTER OF ETODOLAC

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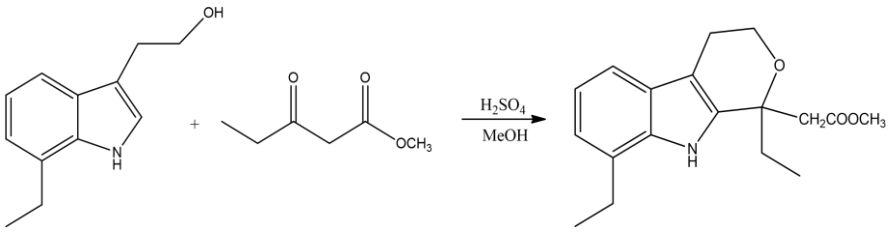
Etodolac methyl ester is a key intermediate in the synthesis of Etodolac, a non-steroidal anti-inflammatory drug. It can be obtained by oxa-Pictet-Spengler reaction, starting from 7-ethyltriptophol and using inorganic mineral acids as catalysts.[1] In order to get kinetic profiles of reactions catalyzed with different molar ratios of sulfuric and hydrochloric acid, a high performance liquid chromatography method with UV detection was developed for monitoring conversion of 7-ethyltryptophol to methyl ester of Etodolac.



7-Ethyltryptophol **Methyl 3-oxopentanoate** **Methyl ester of Etodolac**

For that purpose different stationary phases (C18, Phenyl and NH_2 column) were investigated for separation of 7-ethyltryptophol and Etodolac methyl ester. Elution was performed with three different solvent mixtures in isocratic and/or gradient mode. The best chromatographic separation was achieved isocratically using Waters Symmetry Shield RP 18 column with 55% acetonitrile and 45% water.

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NMR CHARACTERISATION OF SGT-25: A NEW PSYCHOACTIVE SUBSTANCE

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In the past few years, there has been an uprising of new psychoactive substances (NPS) available in Smartshops and over the Internet. These NPS have been separated in different categories, either according to their structure, like synthetic cathinones, or according to their biological activity, like synthetic cannabinoids. [1] Over the past years, more than 450 new NPS have been reported to the Early Warning System by EU Member States. In 2014 alone, more than 100 substances were reported. Up to that date, more than 130 of the reported substances were synthetic cannabinoids. These compounds are characterised by its affinity to the CB1 and CB2 receptor sites, similar to Δ9-THC, the compound present in cannabis. [1]

Two years ago, a Decree-Law was published in Portugal, [2] which forbids the production and commercialisation of about 159 NPS, 46 of which are synthetic cannabinoids, being liable to fast updates, in order to keep up with the everyday appearance of new substances.

In order to circumvent the new legislation, compounds that fall outside the list of prohibited substances may arise and their rapid identification is of the uttermost importance in forensic laboratories. However, the rapidly growing problem of NPS makes the time management for international control a real challenge, with the traditional detection methods becoming increasingly inadequate. Nuclear Magnetic Resonance (NMR) spectroscopy offers a rapid solution to this problem as it allows the identification of a compound, even in a mixture, without the need of the analyte standard. Using this methodology we have recently characterised a new synthetic cathinone, 4F-PBP and reported it for the first time to the European Union Early Warning System. [3]

This study describes the application of NMR in the characterisation of SGT-25 (1-(5-fluoropentyl)-N-(1-methyl-1-phenylethyl)-1H-indazole-3-carboxamide), a novel 'third generation' synthetic cannabinoid, from a sample seized in Portugal, which is not part of the list of controlled NPS from the new Decree-Law. This compound was firstly synthesised with the aim to be used as medication in animals and humans, due to high affinities for the cannabinoid CB1 and CB2 receptor sites. [4]

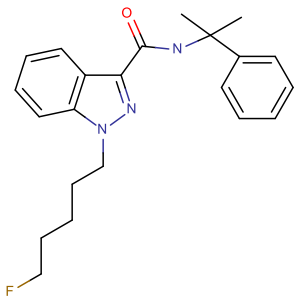

Figure 1. Chemical Structure of SGT-25

The structural characterisation of SGT-25 was elucidated in the seized sample and confirmed after isolation using a liquid chromatography system by 1D and 2D NMR techniques, in different solvents ($CDCl_3$, benzene (D_6), MeOD and DMSO) and also by GC-MS. This is a newly detected compound in Portugal and has only recently been detected in the EU (first report from November 2014).

Acknowledgements: The authors thank Fundação para a Ciência e a Tecnologia (FCT) for financial support through project UID/MULTI/00612/2013 and the toxicology sector at LPC/PJ.

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π- CONJUGATED OLIGOMERS AND POLYMERS FOR THE ELECTRICAL DETECTION OF ALKYLATING AGENTS

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Alkylating agents (like alkyl-halides) are materials which have severe affects on human health, owing to their ability to react with many nucleophilic species in the body, and are unfortunately used, amongst other purposes, as chemical warfare agents. Detecting the presence of an alkylating agent in the atmosphere is thus an important need in modern society environment for early-warning purposes. Currently available sensing systems are, however, high-cost, cumbersome, and handled only by professional personnel.

Here we demonstrate the fabrication of an Organic Field-Effect Transistor (OFET) as an electronic sensor (E-nose) for the detection of alkylating agents in the atmosphere. Original π-conjugated polymers were synthesized to serve as the active layer of the OFET sensor. Figure 1 presents a schematic view of an OFET device. The π-conjugated polymer serves as the active channel. Upon exposure to alkylating agents there is a change in the electronic characteristic of the device. The novel thiophene-pyridine-based polymers chemically react with various alkylating agents thus altering the transistor characteristics. The sensor is highly sensitive and is able to discriminate between alkylating agents and common volatile organic compounds like alcohols. The advantage of such an electronic-responsive device is the ability to easily fabricate a low-cost and small-size detector which could be used for wide spread deployment in public arenas and even as a disposable sensor for short term requirements.

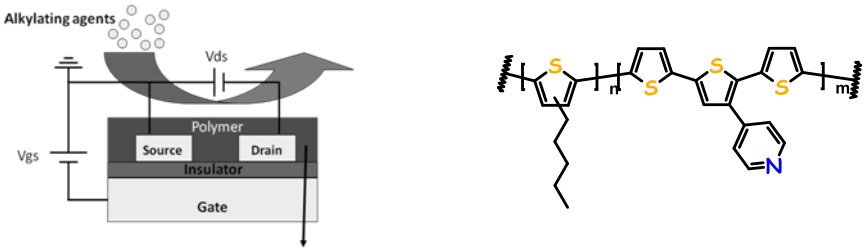

Figure 1. A schematic cross-section of the OFET structure

IONIC LIQUIDS AS SOLUBILITY/PERMEATION ENHANCERS IN TOPICAL DRUG DELIVERY SYSTEMS

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Topical drug delivery systems represent numerous advantages when compared to other delivery systems, namely the avoidance of significant systemic metabolism and thus lowering the required daily doses, better patient compliance and even economic benefits. Currently most of the actives are practically insoluble or sparingly soluble in water and in most pharmaceutical grade solvents. This represents a major problem for the development of new and efficient topical formulations. Hence, it is crucial to find/synthesize new excipients that facilitate drug solubility and/or skin permeation.

Ionic liquids (ILs) are salts with a melting temperature below 100 °C, which exhibit valuable properties arising from their specific structures. These assets allow ILs to be placed in water, oils, or hydroalcoholic solutions which convey them the prospect to be incorporated in emulsions and gels, offering many advantages as ingredients in topical drug delivery systems [1].

In this work, two model actives were studied, the hydrophilic drug caffeine and the more lipophilic salicylic acid. Five different ILs were synthesized, characterized and investigated as solubility/permeation enhancers - three imidazole-based ILs, namely [C2mim][Br], [C4mim][Br] and [C6mim][Br] and two choline based ILs, [Cho][Phe] and [Cho][Glu]. Caffeine and salicylic acid solubilities in water or in water:IL mixtures (95:5) were evaluated at room temperature (rt) and at 32 °C. All ILs promoted an enhancement in solubility for both the actives studied, although the choline based ILs proved to be the best solubility promoters.

To estimate the use of the studied ILs as permeation promoters, *in vitro* permeation studies from saturated solutions of each active in water and in the different water:IL mixtures (95:5) were performed, using pig ear skin. Generally, the ILs provided some improvement in the active's flux and the observed differences amongst the two actives may be due to the differences in the partition of each active into the membrane and/or in the diffusion, depending on the lipophilicity/hydrophilicity of the different ILs used.

Cytotoxicity of the ILs was characterized in human keratinocytes (HaCat cells) using the MTT assay. The three halogenated ILs showed a clear increase in cytotoxicity associated with the length of the alkyl chains, and the choline based ILs appear to be the less toxic.

Finally, stable oil-in-water (O/W) emulsions containing ILs and/or the active were also successfully prepared.

This study confirms the potential use of these materials as ingredients in topical emulsions to promote solubility/permeation of actives. Furthermore, since the ILs properties considerably depend upon the cation or anion present in these salts, further studies are needed towards the tailoring of more suited and less toxic ILs.

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SYNTHESIS OF SUGAR DERIVATIVES RECEPTORS AND THEIR APPLICATION IN CHIRAL RECOGNITION OF ANIONS

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Anions are ubiquitous in the natural world and play important roles in biological and chemical features.[1] Among them, chiral anions represent very interesting area of research, because the chemical and biological activity of any chiral substance depends on its stereochemistry. That is why design, synthesis and studies on binding properties of chiral receptors are supposed to open new possibilities, for example in enantioseparation of racemic chiral compounds and enantioselective catalysis.[2]

In this study we decided to pursue the idea of chiral recognition of anions by neutral receptors by synthesizing a hybrid, sugar-decorated receptor containing bis-chromenyl and bis-indolyl urea**.** Compounds **1** and **2** (**Fig.1**) can be easily functionalized by the formation of amide, readily available peracetylated glucosamine. Binding properties were studied by titration under ^{1}H NMR control in DMSO-d_6+5% H_2O. In all cases, binding affinities were measured by anion complexation-induced resonance shift change upon addition of anionic guests in the form of tetrabutylammonium salts.

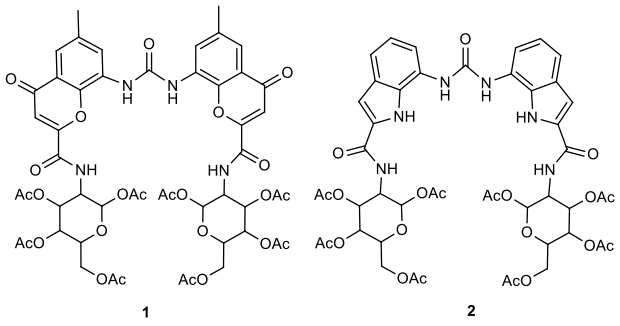

Figure 1. Synthesized receptors **1** and **2**

We were able to obtain a monocrystal suitable for X-ray analysis, which showed conformation of receptor **a** and formation complex of receptor **1** with 2-hydroxy-3-phenylpropanoate in the solid state (**Fig. 2**).

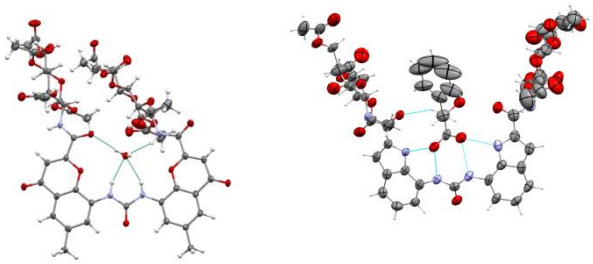

Figure 2. X-ray analysis. Monohydrate of receptor **1**(left) and complex of receptor **2** with 2-hydroxy-3-phenylpropanoate

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SYNTHETIC TETRAAMIDES ANION RECEPTORS WITH AZULENE MOIETIES

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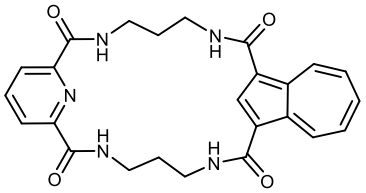
Anions play crucial role in many fields of chemistry, hence research on anion receptors is very important area of supramolecular chemistry.[1] Hydrogen bonds are the most common among interactions which can be used in anion binding process. Their accessibility and directionality enable assembly of binding sites adjusted for specific anionic species.[2,3] In this communication we would like to present our studies on new ligands **1**-**2** with four donors of hydrogen bonds in macrocyclic structure. In these compounds we use azulene moieties, which potentially offer optical anion sensor properties. Our research show strong affinity of receptors **1**-**2** towards model anions in very competitive media like DMSO/H_2O as well as in DMSO/MeOH mixture.



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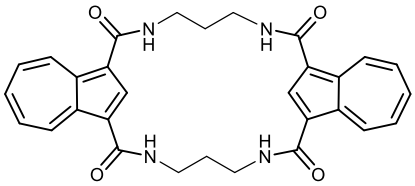

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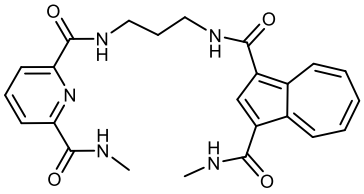

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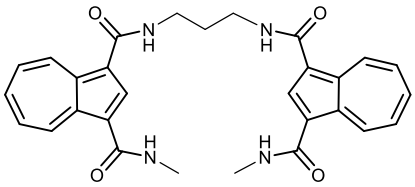

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To determine how important macrocyclic effect is we synthesized acyclic receptors **3**-**4** investigation of which shows weak interactions with model anions. Furthermore, we obtained diffraction grade crystals of receptor **1**-**2** and their complexes with anions. In our discussion we will include the results of their structural analysis.

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DIRECT PREPARATION OF PYRROLIZIDINES USING IMINES AND ISONITRILES

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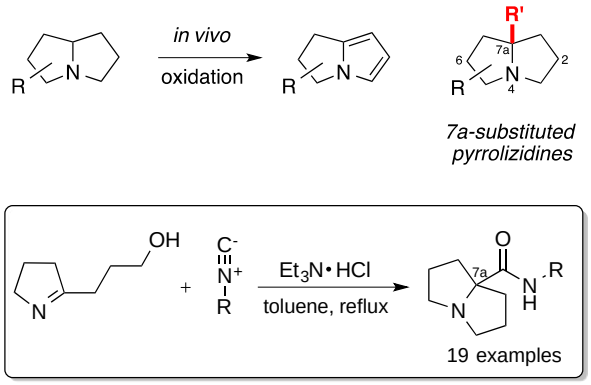
Pyrrolizidines constitute a privileged ring structure in alkaloids, with hundreds of natural products employing this motif.[1] The utilization of these bicyclic N–heterocycles in drug discovery has been hampered by their well-known *in vivo* oxidation to the corresponding pyrrole derivatives, which can undergo undesired off-target reactions.[2] One way of preventing this aromatization involves quaternization by the presence of an additional substituent on the 7a-position. Interestingly, among the many approaches to these heterocycles, there are only few methods reported in the literature to prepare these 7a-substituted pyrrolizidine carboxamides.[3] We describe an acid mediated annulation reaction for the direct preparation of 7a-substituted unnatural pyrrolizidines. A hydroxy-functionalized pyrroline is reacted with a large variety of isonitriles directly resulting in the target compounds. The reaction is operationally simple and tolerates air and water and the resulting pyrrolizidines can be further transformed to the corresponding oxidized and reduced derivatives. Preliminary mechanistic studies were performed to understand this unusual cyclization reaction.



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