Book of Abstracts

UNIVERSIDADE DE ÉVORA

SOCIEDADE PORTUGUESA DE QUÍMICA

Contents

Welcome

On behalf of the Organizing Committee I am very pleased to welcome you to the fifth edition of the International Symposium on Synthesis and Catalysis (ISySyCat2023) once again at the historic University of Évora. The inaugural edition of this conference that took place in September 2015 (ISySyCat2015) was a great success and from that moment we have been building on this success, making this a regular biannual event, which we can be proud of, and can put our country on the map. The conference focuses on various aspects of organic, organometallic and inorganic synthesis, as well as all areas of catalysis, including metal-based catalysis, organocatalysis and biocatalysis as well as polymer, soft material and inorganic synthesis. Issues of current major interest will be discussed, which include the sustainable production of important bulk, high-added value, continuous flow chemistry, photo-redox processes, electrosynthesis, enantiomerically pure compounds and biologically active compounds, from both academic and industrial perspectives.

To vindicate the resilience of this conference, ISySyCat21 successfully took place in September 2021, despite the COVID-19 pandemic. It was successfully organized as a hybrid conference, with both in person and on-line speakers and participants. It was a very memorable and rewarding event for us.

We are proud to have a delightful mixture of both academic and industrial chemists from all corners of the globe, making this yet again a very international event. This is also reflected in the fine line-up of speakers, which includes well-known experts and up-and-coming “rising” stars. There is also a very extensive line-up of oral and short oral presentations who in the main are junior researchers, post-docs or PhD students with some tantalizing research to discuss. Besides, there will be a smorgasbord of poster presentations, covering all aspects of these pivotal areas. Prizes will be awarded (to be announced during the Gala Dinner) for the best oral and poster presentations.

This conference should be the ideal venue for updating you on current developments and advances in these areas, for net-working, making new acquaintances, and at the same time allowing you to relax, soak up and enjoy the special surroundings, along with the unique food, drink and hospitality provided by this special region of Portugal.

We are very grateful to the Portuguese Chemical Society (Sociedade Portuguesa de Química), the University of Évora, and all our generous sponsors and supporters, without their valuable support this special event would not be possible.

We thank Wiley, Thieme and the RSC for making available prizes for the best oral and poster presentations.

We also thank Beilstein Organic Chemistry for running a special edition of this conference.

Last, but not least, we would like to thank all the participants at ISySyCat2023 for attending this conference and travelling from various parts of the world.

We hope that your participation will be rewarding, fulfilling, and of course, very pleasurable.

So, make the most of it and enjoy!

Anthony J. Burke
(Conference Chair)

Organization

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Artur Silva, University of Aveiro, Portugal

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Acknowledgments and Sponsors

The Organizing Committee is very grateful to the following companies and organizations for their kind sponsorship and support of ISySyCat_2023.

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Prize Sponsors

WILEY-VCH

Wiley-VCH has very kindly agreed to sponsor a prize for the best oral communication. The winner will be announced during the gala dinner on the night of the 7th of September at the Hotel M'AR De AR Muralhas.

Thieme

Thieme has very kindly agreed to sponsor two poster prizes. The winner will be announced during the gala dinner on the night of the 7th of September at the Hotel M'AR De AR Muralhas.

ROYAL SOCIETY OF CHEMISTRY

We are very grateful to the Royal Society of Chemistry (RSC) for sponsoring four best poster prizes, through their journals; Organic & Biomolecular Chemistry, Catalysis Science and Technology, RSC Sustainability and RSC Sustainability. Each winner will receive a prize worth of £100.

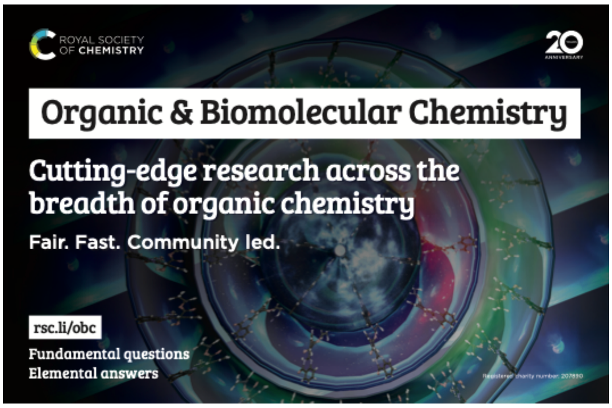
Catalysis Science & Technology

Organic & Biomolecular Chemistry

Reaction Chemistry & Engineering

RSC Sustainability


ROYAL SOCIETY OF CHEMISTRY
NEW JOURNAL
RSC Sustainability
GOLD OPEN ACCESS
Dedicated to sustainable chemistry and new solutions
For an open, green and inclusive future
rsc.li/RSCSus
Fundamental questions
Elemental answers
Registered charity number: 207890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20
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Fair. Fast. Community led.
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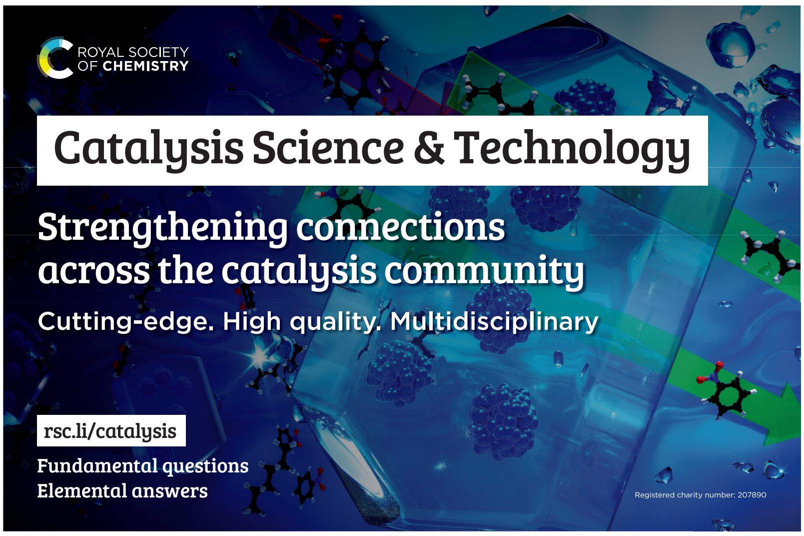
Reaction Chemistry & Engineering
Bridging the gap between chemistry and chemical engineering
Multiple communities advancing reaction science together
rsc.li/reaction-engineering
Fundamental questions
Elemental answers


ROYAL SOCIETY OF CHEMISTRY
Catalysis Science & Technology
Strengthening connections across the catalysis community
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Media Partner

Chimica Oggi – Chemistry Today is a peer reviewed, bimonthly journal, of the TKS TeknoScienze Publisher.
It deals with Fine Chemicals, Applied Chemistry and Biotechnology.
Founded in 1983 Chimica Oggi – Chemistry Today soon became a leading journal in linking industry and academia and gained an immediate appreciation worldwide.

Open Chemistry is a peer-reviewed, open access journal that publishes original research, reviews, and communications in the fields of chemistry in an ongoing way. The central goal is to provide a hub for researchers working across all subjects to present their discoveries, and to be a forum for the discussion of the important issues in the field.

Advanced Synthesis & Catalysis (ASC) is the leading primary journal in organic, organometallic, and applied chemistry.
The high impact of ASC can be attributed to the unique focus of the journal, which publishes exciting new results from academic and industrial labs on efficient, practical, and environmentally friendly organic synthesis. While homogeneous, heterogeneous, organic, and enzyme catalysis are key technologies to achieve green synthesis, significant contributions to the same goal by synthesis design, reaction techniques, flow chemistry, and continuous processing, multiphase catalysis, green solvents, catalyst immobilization, and recycling, separation science, and process development are also featured in ASC.

The **Beilstein Journal of Organic Chemistry** is an international, peer-reviewed, Open Access journal. It provides a unique platform for rapid publication without any charges (free for author and reader) – diamond open access. The content is freely accessible 365 days a year to any user worldwide. Articles are available online immediately upon publication and are publicly archived in all major repositories. In addition, it provides a platform for publishing thematic issues (theme-based collections of articles) on topical issues in organic chemistry.

We are thrilled to announce that Beilstein Journal of Organic Chemistry will be running a thematic issue of ISySyCat23, which will be open to all contributors at ISySyCat23

INVITATION TO PUBLISH IN THE SPECIAL EDITION OF ISYSYCAT23 PUBLISHED BY BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Dear Participant of ISySyCat 2023,

We cordially invite you to submit your most exciting, original research to be published in the Thematic Issue "5th International Symposium on Synthesis and Catalysis (ISySyCat 2023)" in the nonprofit, peer-reviewed *Beilstein Journal of Organic Chemistry* (*BJOC*).

This thematic issue is dedicated to the 5th International Symposium on Synthesis and Catalysis (ISySyCat 2023). Submission is open to all participants of the meeting and their co-authors.

The focus is on current themes of chemical synthesis and catalysis, for example, total synthesis and synthesis in medicinal chemistry, chemical biology, and materials science. Topics covered are new reagents, catalysts, strategies and concepts for organic synthesis, biocatalysis, organocatalysis, flow chemistry, process development towards the synthesis of key pharmaceutical targets, applications of organometallic compounds in synthesis and catalysis, stereoselective synthesis, synthesis and properties of functional molecules and organic materials, sustainable and green synthetic and catalytic methods, computational tools for synthesis and catalysis, and polymer synthesis.

Why choose *BJOC*?

The *Beilstein Journal of Organic Chemistry* is a true open access journal (no cost for authors and readers) and fully Plan S-compliant. We are funded entirely by the Beilstein-Institut, a charitable non-profit foundation that supports the communication of high-quality science without barriers. Benefits of publishing in *BJOC* include:

- Important specialist journal in the field of organic chemistry
- Diamond open access (no cost for authors or readers)
- Rapid publication
- Peer review to high standards (2–3 referees per paper)
- High production and online presentation standards
- Authors retain copyright and can reuse their work
- Article indexing and archiving
- Focus on quality, not profit

Thematic Issues

A thematic issue is a collection of articles dedicated to a focused topic. These issues are edited by guest editors who are experts in the respective field and aim to stand out as valuable and unique reference works.

How to Submit

The submission deadline for this thematic issue is **December 15, 2023**. We would greatly appreciate if you could let us know via email by **September 14th, 2023** (this date was extended from the 15th of August) whether you intend to submit a paper, and if so, in which format (review, research article, letter, or perspective). Please contact Dr. Marc Kielmann of the editorial office (mkielmann@beilstein-institut.de)

To submit your article, please upload it directly to the Beilstein Publishing System at https://www.beilstein-journals.org/bps/ and ensure that the submitting author includes the following information in the cover letter:

Thematic Issue: 5th International Symposium on Synthesis and Catalysis (ISySyCat 2023)
Corresponding Editor: Anthony J. Burke

Please find further information on the submission process at www.beilstein-journals.org/bjoc/submissionOverview and feel free to consult the *Beilstein Journal of Organic Chemistry* Editorial Team (bjoc-editorial-office@beilstein-institut.de) in case you have questions regarding the submission and processing of your article.

Given your expertise in the field, we would be very pleased to receive a manuscript submission from you, and we look forward to hearing from you on your acceptance to this invitation.

Best wishes,

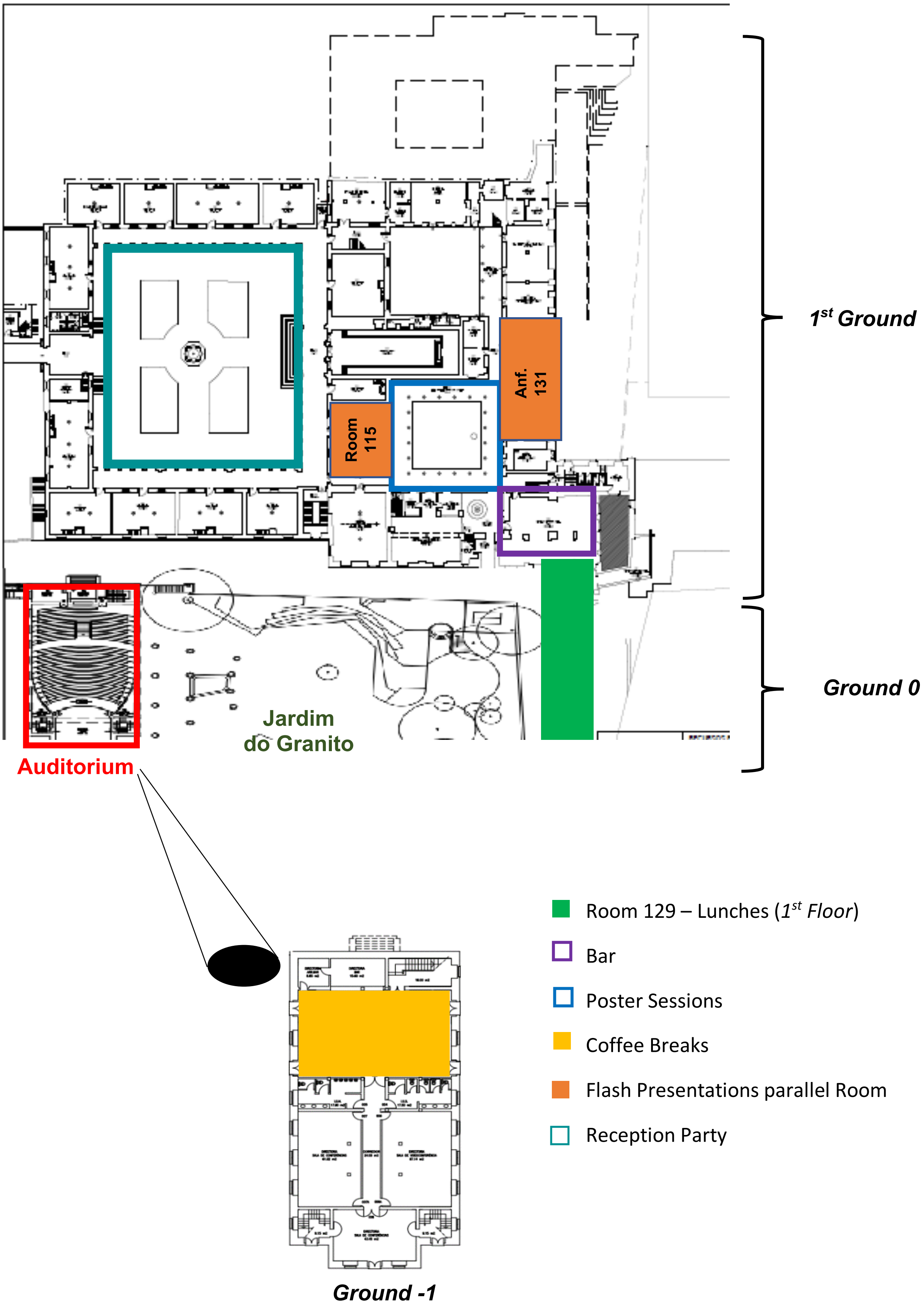
Anthony J. Burke (Guest Editor) and Marc Kielmann (Managing Editor)

General Information

Meeting Venue

The meeting will take place at the auditory of Colégio Espírito Santo (CES) located in University of Évora, Largo dos Colegiais, number 2, 7004-516 Évora, Portugal.

Inside the CES building, the main conference room (the Auditorium), the speaker's preview rooms, poster session venue, exhibition and coffee break areas will be appropriately signposted, as illustrated in the map below.



- Room 129 – Lunches (*1st Floor*)
- Bar
- Poster Sessions
- Coffee Breaks
- Flash Presentations parallel Room
- Reception Party

Important and useful information

Access and stay at the Venue

Suitable identification (corresponding name badge) should be used by all the attendants, during the meeting.

Lunches

Lunches on Tuesday 5, Wednesday 6 and Thursday 7 of September will be served at the room 129 of CES and are included in the registration fee. We kindly ask all participants to use their ID badge to access lunch area.

Internet Access

A temporary login for the wireless Academic Network (eduroam) for the University of Évora has been created (valid from 30th of August to 11th of September). Please use the following credentials:

Username: isysycat2023

Password: Uevora9775

Scientific Information

Presentation Preview Room

To ensure that sessions run on time, speakers are kindly asked to provide the oral communication files in advance, preferably 24 h before their presentation. Please use the following email address to send your communication: isysycat2023.pres@gmail.com.

Oral presentations will be in PowerPoint on a Windows OS. Therefore, Mac users should verify that their presentations work well in a Windows environment. If you intend to use your computer, please inform us by e-mail (isysycat2023.pres@gmail.com) in advance.

Flash Sessions

On the 5th, 6th and 7th of September three parallel Flash session presentations will take place in the main Auditorium, in Room 131 and in Room 115. The talks will have a maximum time of 10 minutes each.

Poster Sessions

Posters will be displayed in the selected halls of CES. Authors are requested to display their posters on the post panels during the first coffee break (or lunchtime) on the 5th of September. Material to attach posters will be made available by the organizing committee at the front desks. Posters should be on display from Tuesday morning and left for the entire Conference (remove them by the coffee break on the last day (8th of September)). Authors are requested to stay near their posters during the assigned session so they will be available to answer any questions from the participants and by the evaluation panel, who will select the posters for the Poster Prize awards.

Awards and Prizes

In ISySyCat 2023, a number of exciting Awards will be given, for both the best Oral and Poster communications.

Oral Talks

Wiley-VCH Verlag GmbH & Co. KGaA – A company of John Wiley & Sons, Inc, has very kindly agreed to sponsor a textbook for the best oral communication.

Poster Prizes

Thieme Group Stuttgart have very kindly agreed to sponsor two poster prizes, consisting of a one-year subscription to SYNFACTS and the corresponding certificate.

Royal Society of Chemistry, through its affiliated journals (RSC Sustainability, Reaction Chemistry & Engineering, Organic & Biomolecular Chemistry and Catalysis Science & Technology) have very kindly agreed to sponsor four poster prizes, that includes a certificate and a cheque for £100.

Language

English is the official language of ISySyCat 2023.

Other information

Time Zone: The time zone in Portugal is GMT.

Water: Tap water in Portugal is drinking water.

Electricity: In Portugal, the line voltage is 220 V and the connection is made by a two-pin plug. Travelers from the USA will require a voltage converter. Travelers from the UK will require a plug adapter, and this is best bought in the UK as they are hard to find in Lisbon (can try at the Lisbon airport).

Currency, Banks and Post Offices: 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.

Going out in Évora: With your conference material, you will find a city map and a brochure of Évora with lots of necessary information.

Climate: In early September, the temperature in Évora is on average 30ºC (the nights are hot). Rain is very unlikely.

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Establishment according to Health Measures Portugal
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Social Programme

Reception Party *(included in the registration fee):*

The reception party will be in the CES cloisters on Tuesday the 5th of September at 19:40h. It will include appetizers, drinks and a live DJ.

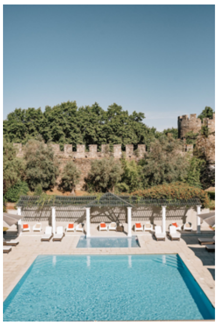
Banquet Dinner *(included in the registration fee):*

On Thursday the 7th of September at 20:00h, the conference Gala Dinner will take place at the Hotel M'AR De AR Muralhas, a 4-star hotel just within the main city walls. The buffet dinner will consist of a fine selection of local and regional dishes and wines, and other beverages, that will be preceded by a pleasant outdoor (garden) cocktail reception. We greatly look forward to sharing your company.

M'AR De AR Muralhas is a timeless charm Hotel in the historic center of the city of Évora, right in the heart of the area classified by UNESCO as World Heritage. Quality is here a synonym of a warm and friendly welcome.

Located on the ground floor, facing the garden and the swimming pool, the Restaurant *Sabores do Alentejo* has the signature of Chef António Nobre. Menu's privilege local innovative cuisine, based on regional flavors and delicious, surprising combinations. The atmosphere is cozy and comfortable. Natural light makes it very attractive for lunch, and the outside porch, facing the pool, is the ideal place for dinner in a warm summer night.

M'AR De AR Muralhas offers beautiful gardens, where you can enjoy the beauty of the historic surrounding city wall, relaxing on the porch or by the swimming pool while drinking a delicious cocktail.



Excursion on the 8th of September *(not included in the registration fee with limited seats):*

On the afternoon of the 8th of September, conference participants are invited to part-take in a delightful social program to the famous **Quinta da Plansel** (https://www.plansel.com) in Montemor-o-Novo (a typical Alentejo town, 30 km outside of Évora). After a welcoming cocktail, it will be served a beautiful three course set lunch, accompanied by a selection of excellent wines, including wine tasting from the Quinta da Plansel wine cellar, and a guided visit to the winery. As the visit will coincide with the peak of the active and busy vine harvesting season, it should be an interesting experience. Full details can be seen below and will be given during the conference.

Important Note: Persons with dietary restrictions should indicate this on the registration form (preferentially) or in the registration desk during the conference so that an alternative can be arranged.

Quinta da Plansel was born out of a misunderstanding by its founder, Jörg Böhm, when in 1961 his sailing boat sank in the port of Cascais. Forced to stay here for some time, he ended up getting to know and surrendering to different Portuguese landscapes. And that's how he saw the huge winegrowing potential of the Alentejo grape varieties, and in 1975 he bought the first land for vineyards and set up Viveiros Plansel.

This family has always been connected to wine. The first records date back to the 11th century, but from the 18th century onward the Böhm family's mission to the industry became more evident, being one of Germany's leading wine importers and distributors. The passion for wine and for Portugal would eventually infect the whole family. In the early 1990s, daughter Dorina Lindemann, an oenologist with a degree from the University of Geisenheim (Hessen), came from Germany to Portugal with her husband Thomas Lindemann and, taking advantage of the existing vineyards linked to her father's technical improvement program, dedicated herself to wine production.

With the young engineer Paulo Laureano, Dorina Lindemann produced her first wine at the Adega Experimental da Mitra (**University of Évora**), in 1993. The first brand was Plansel (which means from Selected Plants). Over the next five years, Dorina and her husband, Thomas, built their own winery, Quinta da Plansel.

Dorina's goal was to transfer all of her father's basic knowledge to oenology. The revival of old varieties was the secret of the differentiation of these wines, both in quality and quantity. Currently, daughters Júlia and Luísa are also part of the wine business, from marketing to oenology, ensuring the future of the project.

Today, the winery reaches an annual production of 400,000 liters, having diversified its products into five different ranges, with wines of very unique profiles. Quinta da Plansel is mainly known for its work with the Touriga Nacional, Touriga Franca, and Tinta Barroca grape varieties, its favorites.

The very specific microclimate of Montemor-o-Novo, with a maritime influence and sheltered from the hot southerly winds by the small mountains, turned out to be beneficial to the vines, making them more resistant to the drier year.
Despite the challenges, we believe that the references signed by the year 2022 will be very rich, both in the nose and in the mouth. Now we just have to wait a few years to taste them.

- Walking Guide tour to Évora (included in the registration fee):

The participants who are interested in this tour should contact the staff on the first day of the conference to book their place (limited to 100 participants). It will be on the 8th of September at 15h. The meeting point will be in the Tourist Office in Giraldo's square and will end in the bone chapel around 16:30h. The participants should present the corresponding badge of the conference.

Évora was considered a world heritage place by UNESCO in 1986. According to this organization, Évora is a museum-city with roots dating back to roman times. The golden age happened in the 16th century, when the Portuguese kings lived here. Among many others, the old wall, the aqueduct, medieval buildings like the cathedral, convents, palaces, churches and squares are convincing reasons for a walking tour. Some of the highlights in Évora are the architecture of the white houses, the tiles and the balconies. Come and see these places with your own eyes.

The light that illuminates you,
Land the color of the eyes of those who look!

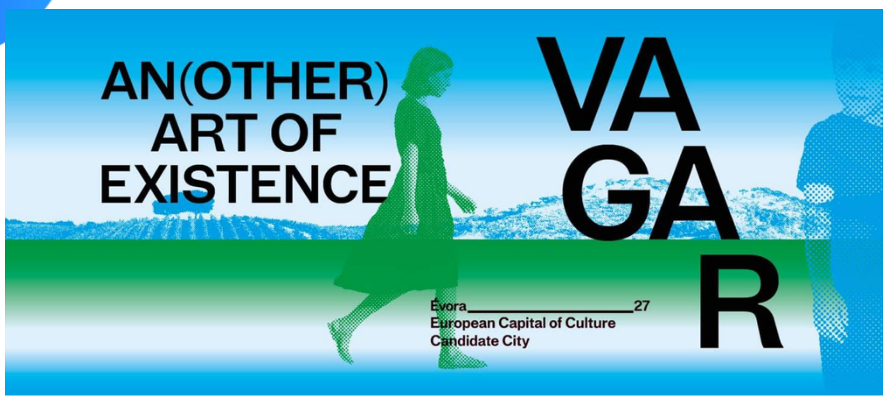
Miguel Torga (Portuguese writer)

The tour itinerary is:

- ⇒ Praça de Giraldo (Giraldo's square)
- ⇒ Rua 5 de Outubro (5th October street)
- ⇒ Catedral (Cathedral, to visit inside a fee must be paid per person, or you can enjoy only outside)
- ⇒ Templo Romano (Roman Temple, Diana's Temple)
- ⇒ Jardim Diana (Diana's Garden; viewpoint)
- ⇒ Igreja da Graça (Graça's churche, only outside)
- ⇒ Igreja de S. Francisco (S. Francisco church)
- ⇒ Capela dos Ossos (Bone chapel, to visit inside a fee must be paid per person)

Language: English

Évora 2027, European Capital of Culture is a call for everyone to be an agent of change, taking our vagar to the world: young and old, cultural agents and civil society. Doers and thinkers. Dreamers and the down-to-earth. That's why we say - Take Évora!



Scientific Programme (Conference Time Schedule)

Time	5th Sept	6th Sept	7th Sept	8th Sept	Time 5th Sept (afternoon)
9.00-9.45	Registration and Opening Ceremony	**(PL5)** Ben L. Feringa	**(PL9)** Robert M. Waymouth	**(PL13)** Jonathan T. Reeves	
9.45-10.30	**(PL1)** Karl Anker Jørgensen	**(PL6)** Joanna Wencel-Delord	**(PL10)** Teresa M. V. D. Pinho e Melo	**(PL14)** Yoshiaki Nakao	
	Coffee Break				
11.15-12.00	**(PL2)** Francesca Paradisi	**(PL7)** Tanja Weil	**(PL11)** L.-C. Campeau	**(PL15)** Kendall N. Houk	
12.00-12:15	**(OC1)** Arlene G. Corrêa	**(OC7)** José Ferraz-Caetano	**(OC15)** Alex M. Szpilman	Awards and Closing Ceremony	
12:15-12:30	**(OC2)** Dylan Rigby	**(OC8)** Paul W. Davies	**(OC16)** Māris Turks		
	Lunch			Social Program	
14.00-14:45	**(PL3)** Richmond Sarpong	**(PL8)** Martin A. Hayes	**(PL12)** Michael Rack		
14:45-15:00	**(OC3)** João P. M. António	**(OC9)** Nieves P. Ramirez	**(OC17)** Ricardo Mendonça		
15:00-15:15	**(OC4)** Alexander Ahrens	**(OC10)** Lukas Enders	**(OC18)** Klara Bangert		
15:15-15:30	**(OC5)** Ana L. Cardoso	**(OC11)** Roberto del Río-Rodríguez	**(OC19)** Asunción Barbero		
	Coffee Break				**5th Sept**
16:30-16:45	**(OC6)** Juliette Martin	**(OC12)** Alan R. Healy	**(OC20)** Liam T. Ball		
16:45-17:00	**(PL4)** Lionel Saudan	**(OC13)** Laura Cunningham	**(OC21)** Jens Frackenpohl		**16:45-17:30**
17:00-17:15		**(OC14)** Carlos Roque Correia	**(OC22)** Hannah K. Adams		
17:15-18:25	Flash Talks	Flash Talks	Flash Talks **(17:15-18:15)**		**17:30-18:30**
18:25-19:25	Poster Session 1	Poster session 2	Poster session 3 **(18:15-19:15)**		**18:30-19:30**
19:30-23:00	Reception party with live Dj		Banquet (20:00-23:30)		

Detailed Scientific Programme:

Tuesday, the 5th of September of 2023

9:00	**Registration**	
9:30	**Opening Ceremony,** which includes the Rector of the University of Évora, Professor Hermínia Vasconcelos Vilar (or representative), the president of the Portuguese Chemical Society (SPQ), Professor Joaquim Luís Bernardes Martins de Faria, the director of the Institute for Advanced Studies and Research, University of Évora, Professor Rui Paulo Vasco Salgado (or representative), the director of the School of Science and Technology, University of Évora, Professor Maria Clara Canotilho Grácio (or representative) and the conference chairman, Professor Anthony Burke, University of Coimbra.	
Chairman: Hans-Jürgen Federsel (RISE Research Institutes of Sweden, Sweden)		
9:45	**PL 1**	**Expanding the Borders of Chemical Reactivity** Karl Anker Jørgensen
10:30	**Coffee Break**	
Chairman: Artur Silva (University of Aveiro, Portugal)		
11:15	**PL 2**	**Biocatalysis in flow: when it works and when it doesn't** Francesca Paradisi
12:00	**OC 1**	**Synthesis of γ-lactams and Δ1-pyrroline from chalcones using aziridines and 2H-azirines** Arlene G. Corrêa
12:15	**OC 2**	**Towards the Total Synthesis of Mycapolyol E** Dylan Rigby
12:30	**Lunch**	
Chairman: Jorge Salvador (University of Coimbra, Portugal)		
14:00	**PL 3**	**Break-it-to-Make-it Strategies for Chemical Synthesis Inspired by Complex Natural Products** Richmond Sarpong
14:45	**OC 3**	**Diazaborines as stable and ROS-responsive linkers: Uncovering a new class of responsive Antibody-Drug Conjugates** João P. M. António
15:00	**OC 4**	**Catalytic Disconnection of C–O Bonds in Epoxy Resins and Composites** Alexander Ahrens

15:15	**OC 5**	**Sustainability meets structural diversity: exploring the furan-based chemical space** Ana L. Cardoso
15:30	**Coffee Break**	

Chairman: Pedro Cintas (University of Extremadura, Spain)

16:30	**OC 6**	**Biocatalysis: a Necessary Tool for Synthetic Chemist – a Focus on Industrial Applications"** Juliette Martin
16:45	**PL 4**	**Catalysis for the Synthesis of Perfumery Ingredients** Lionel Saudan
17:30	**Flash Talks – 1st session**	

	Main Auditorium *Synthetic Methodology I* *Chairman: Artur Silva* *(University of Aveiro, Portugal)*	***Room 131*** *PhotoRedox Processes* *Chairman: Narciso Garrido* *(University of Salamanca, Spain)*	***Room 115*** *Green Processes I* *Chairman: Jorge Salvador* *(University of Coimbra, Portugal)*
17:30	**F 1** Maria João Ferreira	**F 7** Pablo Garrido García	**F 13** Juliana G. Pereira
17:40	**F 2** Sean McCarthy	**F 8** Francisco Juliá-Hernández	**F 14** Zsuzsanna Fehér
17:50	**F 3** Angela Milinkovic	**F 9** Adrián Pastor	**F 15** Ana C. Fernandes
18:00	**F 4** Bogdan R. Brutiu	**F 10** Késsia Andrade	**F 16** Gyula Dargó
18:10	**F 5** Aline Makhloutah	**F 11** Lukas-Maximilian Entgelmeier	**F 17** Giulia Coffetti
18:20	**F 6** David Ryan	**F 12** Tomasz Wdowik	**F 18** Raquel Viveiros

18:30	**Poster Session 1**
19:30	**Reception Party**

Wednesday, the 6th of September of 2023

Chairman: Martin Ernst (BASF, Germany)

9:00	**PL 5**	**Exploring Chemical Activation** Ben L. Feringa

9:45	**PL6**	**Towards sustainable synthesis of complex molecules via metal-catalyzed or metal-free C-H functionalization** Joanna Wencel-Delord
10:30	**Coffee Break**	

Chairman: Chris Willis (University of Bristol, UK)

11:15	**PL 7**	**Polymer Synthesis in Living Systems** Tanja Weil
12:00	**OC 7**	**Explainable Catalytic Epoxide Synthesis Prediction through Machine Learning Models and Descriptive Features** José Ferraz-Caetano
12:15	**OC 8**	**A Nitrenoid Strategy for Efficient N-Heterocycle Synthesis** Paul W. Davies
12:30	**Lunch**	

Chairman: Alex Martin Szpilman (Ariel University, Israel)

14:00	**PL 8**	**Biocatalysis in early drug discovery** Martin A. Hayes
14:45	**OC 9**	**Asymmetric Synthesis of Trifluoromethylated Propargylic Ethers and Anilines through Multi-Component Reactions** Nieves P. Ramirez
15:00	**OC 10**	**Novel Chiral Imidazopyridine Au(I)-NHC Complexes for Enantioselective Enyne Cycloisomerizations** Lukas Enders
15:15	**OC 11**	**Electrochemical Reactions towards the Synthesis of Distinctive Organic Structures** Roberto del Río-Rodríguez
15:30	**Coffee Break**	

Chairman: Maria João Queiroz (University of Minho, Portugal)

16:30	**OC 12**	**A catalytic enantioselective stereodivergent aldol reaction** Alan R. Healy
16:45	**OC 13**	**Scale-up of an Asymmetric sp3-sp2 Suzuki-Miyaura Type Reaction** Laura Cunningham

17:00	**OC 14**	**Enantioselective One-pot Cascade Heck-Matsuda Reactions for the Construction of Complex Scaffolds** Carlos Roque D. Correia
17:15	**Flash Talks – 2nd session**	

	Main Auditorium *Synthetic Methodology II* *Chairman: Gesine Hermann* *(ChiraTecnics, Portugal)*	***Room 131*** *Synthetic Methodology III* *Chairman: Martin Ernst* *(BASF, Germany)*	***Room 115*** *Flow Chemistry/ ElectroSynthesis* *Chairman: Chris Willis* *(University of Bristol, UK)*
17:15	**F 19** Sergey Ryabukhin	**F 25** Rūdolfs Beļaunieks	**F 30** Américo Alves
17:25	**F 20** Ross Jansen-van Vuuren	**F 26** Olimpia M. Steiner	**F 31** Inês S. Martins
17:35	**F 21** Tymoteusz Basak	**F 27** Rachel Lynch	**F 32** Dmitry Pirgach
17:45	**F 22** Enol López	**F 28** Erin C. Boddie	**F 33** Raquel M. Durão
17:55	**F 23** Miguel Mateus	**F 29** Nallappan Sundaravelu	**F 34** Mariana Monteiro
18:05	**F 24** Nieves Ledesma		**F 35** Miguel A. Bárbara
18:15			**F 36** Milene Fortunato

18:25	**Poster Session 2**	

Thursday, the 7th of September of 2023

Chairman: Narciso Garrido (University of Salamanca, Spain)

9:00	**PL 9**	**Dynamic Nanomaterials for Gene Delivery: From Chemistry to Biology** Robert M. Waymouth
9:45	**PL 10**	**Innovative Chemistry Toward Novel Tetrapyrrolic Macrocycles: Therapy and Imaging of Cancer** Teresa M. V. D. Pinho e Melo
10:30	**Coffee Break**	

Chairman: Carlos Afonso (Faculty of Pharmacy, University of Lisbon, Portugal)

11:15	**PL 11**	**Changing the World, One Reaction at a Time: The Discovery and Development of Orally Bioavailable Macrocyclic Peptide That Inhibits Binding of PCSK9 to the LDL Receptor** L.-C. Campeau
12:00	**OC 15**	**New Concept: Umpolung Morita-Baylis-Hillman Reactions** Alex M. Szpilman
12:15	**OC 16**	**Synthesis of allylic systems and heterocycles with highly functionalized olefin side chain from propargyl silanes via 1,2-silyl shift** Māris Turks
12:30	**Lunch**	

Chairman: Gesine Hermann (ChiraTecnics, Portugal)

14:00	**PL 12**	**Fluorine Chemistry for Agrochemicals** Michael Rack
14:45	**OC 17**	**Towards Greener Synthesis: Developing an Environmentally Friendly Process for the Synthesis of an Amide-Containing Drug** Ricardo Mendonça
15:00	**OC 18**	**Preparative scale synthesis of α-hydroxylated fatty acids with P450 peroxygenases** Klara Bangert
15:15	**OC 19**	**Recent Approaches Towards the Synthesis of Polysubstituted Heterocyclic Structures** Asunción Barbero
15:30	**Coffee Break**	

Chairman: Maria Manuel Marques (FCT-UNL, Portugal)

16:30	**OC 20**	**Design and Applications of Bi(V) Reagents for Electrophilic Arylation** Liam T. Ball
16:45	**OC 21**	**Transition metal-mediated transformations in Plant Hormone Chemistry: Valuable tools to create new lead structures against abiotic stress in crops** Jens Frackenpohl
17:00	**OC 22**	**The Design and Synthesis of Anionic Porphyrins Bearing Chiral Cations and Their Exploration in Catalysis** Hannah K. Adams

17:15 **Flash Talks – 3rd session**

	Main Auditorium *Synthetic Methodology IV Chairman: Hans-Jürgen Federsel (RISE Research Institutes of Sweden, Sweden)*	***Room 131*** *Target Oriented Synthesis Chairman: Matthieu Dorbec (Janssen Pharmaceutica)*	***Room 115*** *Green (and some other) Processes II Chairman: Maria João Queiroz (University of Minho, Portugal)*
17:15	**F 37** Dmitriy Volochnyuk	**F 43** Soussana Azar	**F 49** Luís C. Branco
17:25	**F 38** Paula González-Andrés	**F 44** Carlos Nieto	**F 50** Rafael Gomes
17:35	**F 39** Laura F. Peña	**F 45** João R. Vale	**F 51** Maria Manuel Marques
17:45	**F 40** Rocío Bautista	**F 46** Vida Malinauskienė	**F 52** Yichao Jin
17:55	**F 41** Dara Curran	**F 47** Daniel Hoffmann	**F 53** Alberto Esteban
18:05	**F 42** Jasmine Catlow	**F 48** Vilija Kederienė	

18:15 **Poster Session 3**

20:00 **Banquet Dinner**

Friday, the 8th of September of 2023

Chairman: Matthieu Dorbec (Janssen Pharmaceutica)

9:00	**PL 13**	**Practical Organofluorine Chemistry for Large Scale API Synthesis** Jonathan T. Reeves
9:45	**PL 14**	**Catalytic Denitrative Transformations** Yoshiaki Nakao

10:30 **Coffee Break**

Chairman: Luís Branco (FCT-UNL, Portugal)

11:15	**PL 15**	**Computations and Collaborations on Synthetically Important Catalytic Reactions** Kendall N. Houk

12:00 **Closing Ceremony**, which includes the conference chairman, Professor Anthony Burke, University of Coimbra.

Social Program

Plenary Lectures

Oral Communications

OC 15 **New Concept: Umpolung Morita-Baylis-Hillman Reactions**
Alex M. Szpilman

OC 16 **Synthesis of allylic systems and heterocycles with highly functionalized olefin side chain from propargyl silanes via 1,2-silyl shift**
Māris Turks

OC 17 **Towards Greener Synthesis: Developing an Environmentally Friendly Process for the Synthesis of an Amide-Containing Drug**
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Liam T. Ball

OC 21 **Transition metal-mediated transformations in Plant Hormone Chemistry: Valuable tools to create new lead structures against abiotic stress in crops**
Jens Frackenpohl

OC 22 **The Design and Synthesis of Anionic Porphyrins Bearing Chiral Cations and Their Exploration in Catalysis**
Hannah K. Adams

Flash Communications

1st Session

Synthetic Methodology I - Main Auditorium

F 1 **P-C bond Cleavage + H2 addition in Ruthenium hydride complexes supported by di-tert-butylpyridylphosphine**
Maria João Ferreira

F 2 **Suzuki-Miyaura coupling using a recycled and reusable homogeneous palladium catalyst**
Sean McCarthy

F 3 **Mo(VI)=NR/Borane based Frustrated Lewis Pairs: H2 Activation and Catalytic Reduction of Aldehydes**
Angela Milinkovic

F 4 **Stereodivergent 1,3-difunctionalisation of unactivated alkenes by charge relocation**
Bogdan R. Brutiu

F 5 **The quest towards novel synthetic methodologies from nitroarenes for applications in organic electronics**
Aline Makhloutah

F 6 **H(O)P(OPh)2-Promoted Deoxygenative Halogenation of Alcohols**
David Ryan

PhotoRedox Processes - Room 131

F 7 **Enantioselective Photocatalytic Synthesis of Saturated Bicyclic Scaffolds as Phenyl Bioisosteres**
Pablo Garrido García

F 8 **Repurposing fluorinated carboxylic acids as fluoroalkylating reagents with Earth-abundant photocatalysts**
Francisco Juliá-Hernández

F 9 **Improved NOx removal by visible light photocatalysis trough ZnAlEu layered double hydroxides**
Adrián Pastor

F 10 **Photocatalytic oxidation of biomass-derived heterocycles**
Késsia Andrade

F 11 **Zwitterionic Acridinium Amidate: A Nitrogen-Centered Photoactive Catalyst Enabling Efficient Hydrogen-Atom Transfer**
Lukas-Maximilian Entgelmeier

F 12 **Red-Light-Induced Functionalizations of Biomolecules**
Tomasz Wdowik

Green Processes I - Room 115

F 13 **Diels Alder reaction of chitin derived furan**
Juliana G. Pereira

F 14 **Depolymerisation of polycarbonate applying silica gel-supported organocatalysts**
Zsuzsanna Fehér

F 15 **Plastic recycling using commercially available catalysts**
Ana C. Fernandes

F 16 **MeSesamol, a new, bio-based polar aprotic solvent with versatile applications**
Gyula Dargó

F 17 **Combined chemical and biocatalytic approach for asymmetric one-pot reactions**
Giulia Coffetti

F 18 **Green design of enzyme-inspired dry-powder polymeric catalyst for fast separation processes**
Raquel Viveiros

2nd Session:

Synthetic Methodology II - Main Auditorium

F 19 **Efficient Pd-catalyzed carbonylation of ‘benzyl chloride’ type compounds – a rare avenue to underrepresented (het)arylacetate platform**
Sergey V. Ryabukhin

F 20 **Directed ortho and Remote Metalation Chemistry for the Formation of Substituted Naphthalenes and Azafluorenol Core Liquid Crystals**
Ross D. Jansen-van Vuuren

F 21 **Cyclic Triel Carbenoids as Auxiliary Ligands for Ruthenium-Based Olefin Metathesis Catalysts**
Tymoteusz Basak

F 22 **C(sp3)-C(sp3) bond formation reactions through organozinc agents**
Enol López

F 23 **Unusual silver complexes bearing N-heterocyclic carbene ligands: synthesis and their application**
Miguel Mateus

F 24 **Diastereoselective synthesis of highly functionalized indolizidine and pyrrolo[1,2-a]azepine derivatives**
Nieves G. Ledesma

Synthetic Methodology III - Room 131

F 25 **Synthesis of Allyl Functionalized Vinyl Silanes from Propargyl Silanes via 1,2-Silyl Migration**
Rūdolfs Beļaunieks

F 26 **Stereoisomerism in the synthesis of chiral, bioactive Re(I) tricarbonyl complexes with enantiopure ligands: a drawback or an opportunity?**
Olimpia Mamula Steiner

F 27 **Phosphonium Ylide-Mediated CO2 Utilization for the of Synthesis of α,β-Unsaturated Carboxylic Acids**
Rachel Lynch

F 28 **Ir-Catalysed (Hetero)aryl C−H Functionalisation via N to C Alkyl Transfer**
Erin C. Boddie

F 29 **Rhodium-Catalyzed Intermolecular Cross-Cyclotrimerization To Access Selaginpulvilins Derivatives and Investigation of Their Medicinal Activity**
Nallappan Sundaravelu

Flow Chemistry/ElectroSynthesis - Room 115

F 30 **Batch and Continuous Flow Synthesis of Novel Spiro-β-Lactams with Antiviral Activity**
Américo J. S. Alves

F 31 **Continuous-Flow Electrochemical Oxidation of Abietanes**
Inês S. Martins

F 32 **Electrochemically Recoverable Homogeneous Catalyst: Genesis, Application and Capture**
Dmitry Pirgach

F 33 **Easy access to functionalized sparteine via electrochemical cyanation of quinolizidine alkaloids**
Raquel M. Durão

F 34 **Synthesis of Imidazolidinones via Palladium-catalysis**
Mariana Crespo Monteiro

F 35 **Photocatalytic modifications of quinic acid derivatives**
Miguel A. Bárbara

F 36 **Accessing Asymmetric Synthesis: Flow Enzymatic Kinetic Resolution of Bicyclic-Aziridines**
Milene A. G. Fortunato

3rd Session:

Synthetic Methodology IV - Main Auditorium

F 37 **Semi-Industrial Synthesis of Diverse Pyrazolines and Cyclopropanes via [3+2]-Cycloaddition between Flow-Generated Diazomethane and Alkenes**
Dmitriy M. Volochnyuk

F 38 **Stereoselective synthesis of an antinociceptive compound by silyl-Prins cyclization**
Paula González-Andrés

F 39 **Looking for the best selective pathway to obtain cis-2,6-dihydropyran derivatives**
Laura F. Peña

F 40 **New multitarget neuroprotective drugs with 1,3-cyclohexadien-1-als scaffold**
Rocío Bautista

F 41 **Phosphine-mediated Reductive Functionalisation of Aldehydes**
Dara Curran

F 42 **A computational investigation into the Cu-catalysed borylation of α,β-unsaturated compounds**
Jasmine Catlow

Target Oriented Synthesis - Room 131

F 43 **Thermo-responsive foldamers: Switching from supramolecular polymer to heteroduplex through kinetically trapped foldamers**
Soussana Azar

F 44 **Virtual Screening of New 2-Phenethylamine Hits Targeting μ-Opioid Receptor**
Carlos Nieto

F 45 **Total synthesis: From pyridine to (-)-agelastatin A**
João R. Vale

F 46 **2,5-Substituted-1,3,4-oxadiazoles: Synthesis and Protective Activity Against Oxidative Stress**
Vida Malinauskienė

F 47 **Development of Readily Accessible Organometallic Capping Reagents for Carbon Labeling of Drugs**
Daniel Vrønning Hoffmann

F 48 **Synthesis and Biological Studies of Functionalized Bipyrazole Compounds**
Vilija Kederienė

Green (and some other) Processes II - Room 115

F 49 **Natural Ionic Systems for Homogeneous and Heterogeneous Catalysis**
Luís C. Branco

F 50 **A New Bio-Based Nitrogen-Rich Furanic Platform Alternative for Lignocellulosic Derived Furfurals**
Rafael F. A. Gomes

F 51 **Bimetallic Catalysed Synthesis N-heterocycles**
M. Manuel B. Marques

F 52 **Engineering the surface configuration of AgPd alloy catalysts for highly selective oxidation of 5-hydroxymethyl-furfural at room temperature**
Yichao Jin

F 53 **Design of Cocaine Analogues to Treat Psychostimulant use Disorders**
Alberto Esteban

Poster Communications

P 100 **Synthesis of Zinc Oxide Nanoflowers and Nanoneedles and Application in Photocatalytic Antibiotic Ofloxacin Degradation by UV Irradiation**
Oksana Makota

P 101 **Reductive Amination as a Powerful Tool in the Stereoselective Synthesis of Selected Medicinal Drugs and their Analogues**
Kirill K. Popov

P 102 **Hypervalent Iodine(III) Reagents with Transferable Primary Amines for Electrophilic α-amination of Stabilized Enolates**
Ana Cláudia R. Negrão

P 103 **Oxidative Transformations with Photoactivated Phenanthrenequinone and Its Electron-Deficient Derivative**
Juulia Talvitie

P 104 **Distal meta-alkenylation of formal amines enabled by catalytic use of hydrogen-bonding anionic ligands**
Nupur Goswami

P 105 **Homogeneous versus Heterogeneous Catalysts in CO2 Addition Reactions to Epoxides**
Andreia C. S. Gonzalez

P 106 **ELPIS: Engaging Libraries of Promising Oxindoles as Tyrosine-Kinase InhibitorS in Cancer Target Therapy**
Carolina Marques

P 107 **Synthesis of new superhydrophobic and environmentally friendly coatings for stone protection**
Pedro Barrulas

P 108 **Mechanochemistry for the Transformation of Furanes through Multicomponent Reaction Catalysed by Zn**
Pedro Brandão

P 109 **Flavonoid-Triazole Hybrids as Potential Anti-Alzheimer's Agents: Synthesis and Biological Assays**
Elisabete P. Carreiro

P 110 **Synthesis and structural and photophysical characterizations of Diketopyrrolopyrroles for technical and biological applications**
Vítor A. S. Almodôvar

P 111 **Synthesis of Ultra-High Molecular Weight Polyethylenes Catalyzed by Vanadium(V) Aroylhydrazine-Arylolates**
Ana. M. Faisca Phillips

P 112 **Design and Synthesis of a Covalent Organic Polymer Towards the Environmental Remediation**
Argha Chakraborty

Plenary Lectures

Expanding the Borders of Chemical Reactivity

Karl Anker Jørgensen

Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Email: kaj@chem.au.dk

The lecture will demonstrate how to control cycloadditions for systems involving >6π-electrons – termed higher-order cycloadditions. This novel reaction concept, based on organocatalysis, makes it possible to not only control diastereo- and enantioselectivity, but also periselectivity, allowing for new classes of cycloadditions. The development, based on both experimental and computational investigations, will be shown, as well as the application of the products in bioactivity studies.

Furthermore, the application of organocatalysis for oxidative coupling reactions will be outlined.

Karl Anker Jørgensen received his Ph.D. from Aarhus University in 1984. He was a post-doc with Prof. Roald Hoffmann, Cornell University, 1985. In 1985, he became an Assistant Professor at Aarhus University and in 1992 he was appointed as Professor. His research interests are the development, understanding and application of asymmetric catalysis mainly in the field of asymmetric organocatalysis.

Biocatalysis in flow: when it works and when it doesn't

Francesca Paradisi*

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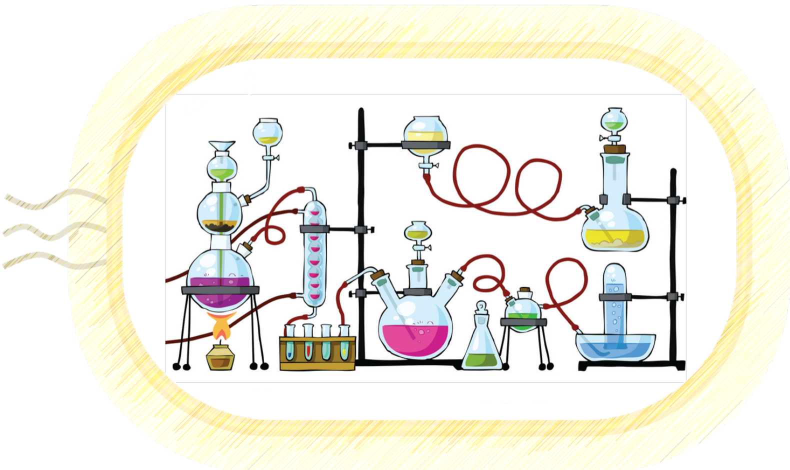
Flow chemistry has allowed many industrial processes to be carried out in continuous mode, with higher efficiency and automation. Biocatalysis has caught up with this technique and several examples have been reported in the literature in the last decade. However, the complexity of multi-enzymatic processes in the absence of cellular regulation, has limited their applications to some chemo-enzymatic synthesis, and just a few fully enzymatic processes have been implemented. Among others, the cofactor requirements of redox enzymes, the stability of the biocatalyst, and efficiency of the biotransformations, must be thoroughly optimised. Here an overview of the progress in our lab will be presented, including insights and hurdles which are sometimes unexpected when a reaction is moved from batch to flow.



Francesca Paradisi graduated with a BSc in Chemistry and then a PhD in synthetic organic chemistry from the University of Bologna. In 2002 she joined the group of Prof. Engel at University College Dublin for her post doc and started working in the area of Biocatalysis. After a brief stint in Enzolve Technologies, a spinoff company, she got her first academic position in the School of Chemistry in UCD in 2006 where she remained till 2016. She was recruited then by the University of Nottingham as Associate Professor in Biocatalysis and promoted to Full Professor in 2019. In the same year however, she was offered the Chair of Sustainable Pharmaceutical Chemistry at the University of Bern and relocated to Switzerland. She is the recipient of the Green and Sustainable Chemistry Award 2021 jointly sponsored by the Swiss Chemical Society and Syngenta for her ground-breaking work in developing eco-friendly and ultra-efficient biotransformations for the synthesis of high-value chemicals, dramatically increasing the applicability of biocatalysis.

Break-it-to-Make-it Strategies for Chemical Synthesis Inspired by Complex Natural Products

Sarpong R[a]

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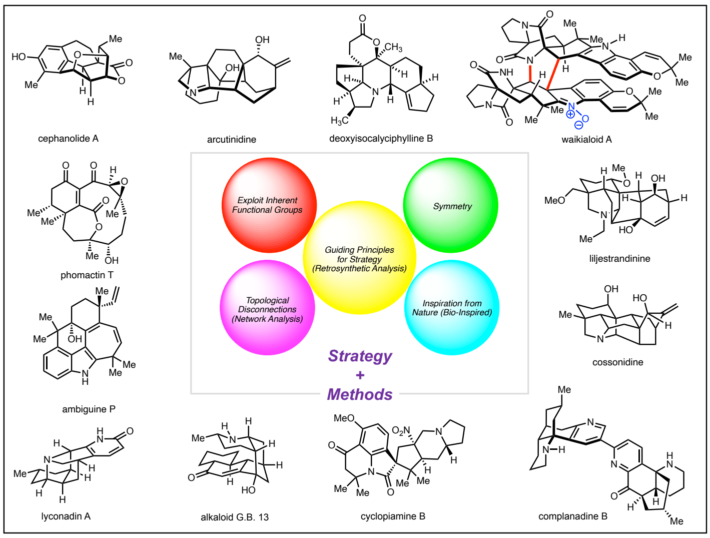
Natural products continue to inspire and serve as the basis of new medicines. They also provide intricate problems that expose limitations in the strategies and methods employed in chemical synthesis. Several strategies and methods that have been developed in our laboratory and applied to the syntheses of architecturally complex natural products will be discussed. In particular, new ways to employ the cleavage of core bonds such as C–C and C–N bonds (i.e., break-it-to-make-it strategies) to achieve skeletal editing will be presented.



Acknowledgements: We thank the USA National Institutes of General Medical Sciences and the US National Science Foundation for financial support.

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[1] Marth, C.J.; Gallego, G.M.; Lee, J.C.; Lebold, T.P.; Kulyk, S.; Kou, K.G.M.; Qin, J.; Lilien, R.; Sarpong, R.; *Nature* **2015**, *528*, 493.
[2] Mercado-Marin, E.V.; Garcia-Reynaga, P.; Romminger, S.; Pimenta, E.F.; Romney, D.K.; Lodewyk, M.W.; Williams, D.E.; Andersen, R.J.; Miller, S.J.; Tantillo, D.J.; Berlinck, R.G.S.; Sarpong, R.; *Nature* **2014**, *509,* 318.
[3] Roque, J. B.; Kuroda, Y.; Göttemann, L. T.; Sarpong, R. *Science*, **2018**, *361*, 171.
[4] Roque, J. B.; Kuroda, Y.; Göttemann, L. T.; Sarpong, R. *Nature*, **2018**, *564*, 244.
[5] Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S.F.; Lam, Y.; Yeung, C. S.; Sarpong, R. *Science* **2021**, *373*, 1004.

Richmond Sarpong is a Professor of Chemistry at the University of California Berkeley where he and his group specialize in synthetic organic chemistry. Richmond became interested in chemistry after seeing, firsthand, the effectiveness of the drug ivermectin in combating river blindness during his childhood in Ghana, West Africa. Richmond described his influences and inspirations in a TEDxBerkeley talk in 2015 (Face of Disease in Sub-Saharan Africa – https://www.youtube.com/watch?v=nIsY87-zkXA). Richmond completed his undergraduate studies at Macalester College in St. Paul, MN and his graduate work was carried out with Prof. Martin Semmelhack at Princeton. He conducted postdoctoral studies at Caltech with Prof. Brian Stoltz. At Berkeley, Richmond's laboratory focuses on the synthesis of bioactive complex organic molecules.

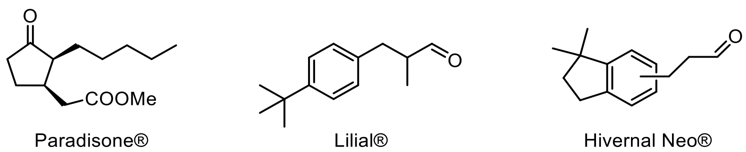
Catalysis for the Synthesis of Perfumery Ingredients

Lionel Saudan[a]

[a] Department of New Ingredient Process, Firmenich SA, Satigny, CH-1242, Switzerland

Email: lionel.saudan@firmenich.com

The research into new industrial catalytic processes is at the forefront of Firmenich's R&D and constitutes one of the main strategic pillars towards realizing its sustainability targets.[1] The development of industrial homogeneous catalytic hydrogenation processes was pioneered almost 25 year ago with the launch of the iconic Paradisone®[2] and has since expanded into a well-established domain of research at Firmenich.[3] During this presentation, several examples of catalytic processes used for the efficient synthesis of important perfumery ingredients will be presented. First, focus will be on the new catalytic processes[4] developed for the efficient preparation of Muguet type aldehydes,[5] key ingredients of the Perfumery palette with examples such as Lilial® and more recently Hivernal Neo® (**Scheme 1**) We will describe the development of new rhodium complexes for the chemo- and regioselective hydrogenation of conjugated dienals into the corresponding gamma-delta unsaturated aldehydes,[4] as an alternative to the Claisen-rearrangement, all while avoiding the formation of over-hydrogenated alcohol side products.



Scheme 1: Key perfumery ingredients.

Next, as alcohols are another class of important ingredients and building blocks in the synthesis of perfumery ingredients. The reduction of carboxylic esters to alcohols by hydrogenation with heterogeneous catalysts is currently the most common industrial alternative to the hazardous use of stoichiometric metal hydride (*e.g.* $LiAlH_4$). Despite the harsh conditions (T>100°C), this process is used for the large scale synthesis of fatty alcohols, important components of fabric softeners. The development of milder conditions and selective catalysts is highly desirable as it will provide a more atom economical and environmentally benign process for the reduction of a wider class of carboxylic esters to alcohols. Unlike the homogeneous catalyzed hydrogenation of olefins, the homogeneous catalyzed hydrogenation of esters has been quite overlooked until recently where, under the need of more environmentally-friendly processes, the field has gained an impressive development with the discovery of new catalysts based on ruthenium, iron, cobalt, and manganese.[6] We will present our own results concerning the use of readily prepared, and robust ruthenium complexes that allows the clean and selective hydrogenation of esters under mild conditions.[7] This catalytic process was successfully applied to lactones especially in the context of the synthesis of Cetalox®/ Ambrox®, important perfumery ingredients with Amber notes. Moreover, this process was successfully extended to esters containing C=C double bonds and heteroaromatics esters based on furane with the clean and selective formation of the corresponding unsaturated and heteroaromatic alcohols in high yield.

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2. Chapuis C. *Helv. Chim. Acta* **2012**, *95*, 1479-1511.
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4. Saudan C. M.; Berrocosa A.; Quintaine J.; Spoehrle S.; Maggi L.; Mosimann H.; Saudan L. *ChemCatChem* **2022**, *14*, e202200671.
5. a) Coulomb J. *Perfumer & Flavorist* **2018**, *43*, 2-6. b) Moretti, R. *Firmenich SA* (**2010**), WO 2010/052635.
6. a) Pandey M. K.; Choudhury J. *ACS Omega* **2020**, *5*, 30775-30786. b) Zhou Y.; Khan R.; Fan B.; Xu L. *Synthesis*, **2019**, *51*, 2491-2505. c) Garbe, M.; Junge K.; Beller M. *Eur. J. Org. Chem.* **2017**, 4344-4362.
7. Saudan, L.; Saudan, C. M.; Debieux, C.; Wyss, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7473−7476.

Dr. Lionel Saudan is a Principal Scientist at the corporate R&D Division of Firmenich S.A. in Geneva (Switzerland). He joined the company in 2000, after a two-year post-doctoral stay in the group of Professor J. M. Tour, working on the synthesis of a new 'nanocar' at the University of South Carolina and at Rice University (Texas). He obtained his BSc and PhD (1998) from the University of Geneva under the supervision of Professor E. P. Kündig working on the asymmetric synthesis of new chiral amines. His current research topics are in the field of homogeneous catalyzed hydrogenation, hydroformylation and photo-redox reactions in the context of the development of new perfumery ingredients.

Exploring Chemical Activation

Ben L. Feringa

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Abstract. Facing the future of chemistry, being the creating science par excellence, chemical synthesis is confronted with major challenges regarding catalysis, precision chemical transformations and adopting the principles of green chemistry. In this lecture we will explore chemical activation discussing recent advances in our program on asymmetric catalysis and adaptive catalysts using both metal- based and organo-catalytic approaches. Furthermore, novel organolithium- based cross coupling methodology illustrates fast high precision C-C bond formation. Towards sustainable chemical transformations the waste-free synthesis of alkylamines, using hydrogen borrowing catalysis, is discussed. Finally, a bio-based route to polymers and coatings using photocatalytic oxidation as a key transformation and ultrafast photoclick reactions and a brief outlook is presented.

Information on http://www.benferinga.com

Acknowledgements: We thank the ARC CBBC centre for sustainable chemistry for financial support.

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Ben L. Feringa obtained his PhD degree at the University of Groningen in the Netherlands under the guidance of Professor Hans Wynberg. After working as a research scientist at Shell in the Netherlands and the UK, he was appointed lecturer and in 1988 full professor at the University of Groningen and named the Jacobus H. van 't Hoff Distinguished Professor of Molecular Sciences in 2004. He was elected Foreign Honorary member of the American Academy of Arts and Sciences. He is a member of the Royal Netherlands Academy of Sciences. In 2008 he was appointed Academy Professor and he was knighted by Her Majesty the Queen of the Netherlands. Feringa's research has been recognized with numerous awards including the Körber European Science Award (2003), the Spinoza Award (2004), the Prelog gold medal (2005), the Norrish Award of the ACS (2007), the Paracelsus medal (2008), the Chirality medal (2009), the RSC Organic Stereochemistry Award (2011), the Humboldt award (2012), the Nagoya gold medal (2013), the ACS Cope Scholar Award (2015), the Chemistry for the Future Solvay Prize (2015), the August-Wilhelm-von-Hoffman Medal (2016), The 2016 Nobel prize in Chemistry, the Tetrahedron Prize (2017) and the European Chemistry Gold Medal (2018). In 2019 he was elected as a member of the European Research Council. Feringa's research interest includes stereochemistry, organic synthesis, asymmetric catalysis, molecular switches and motors, self-assembly, molecular nanosystems and photopharmacology.

Towards sustainable synthesis of complex molecules via metal-catalyzed or metal-free C-H functionalization

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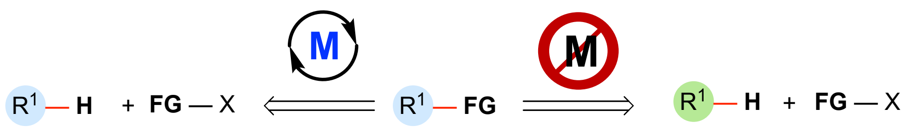
Sustainable, rapid, and efficient synthesis of complex organic molecules is one of the key challenges of modern organic chemistry. Aiming for this goal, the design of original transformations converting simple substrates into the desired, more complex products via C-H bond functionalization has been attracting the expanding attention of the scientific community.[1] Accordingly, a diversity of transformations, requiring either metal-based catalysts or alternative activation modes have been proposed. Herein, we would like to discuss our contribution to this field. We have developed various asymmetric C-H activation reactions to rapidly access complex atropisomeric molecules in high yields, using either atropodiastereoselective[2] or enantioselective protocols.[3] Use of water and micellar conditions turned out to be an additional handle to promote challenging Pd- or Ru-catalyzed C-H activation reactions while not only limiting the environmental impact of the transformations but also rendering them much milder.[4]

In parallel, we have also discovered that rare, hypervalent bromine and chlorine reagents provide an alternative, metal-free solution to expand the molecular complexity via direct functionalization of a C-H bond, followed by C-C, C-O, C-N, and C-X bond formation event.[5]



C-H activation-based strategy
- key step: insertion of a M into C-H bond

- possibility of affording chiral product

- use of micellar conditions for more sustainable transformations???

C-H functionalization-based strategy
- metal-free

- design of innovative activation modes

- use of hypervalent bromines and chlorines as original substrates

Figure 1: Metal- or metal-free approaches toward molecular complexity

Acknowledgements: J.W.-D. thanks the CNRS (Centre National de la Recherche Scientifique), the "Ministere de l'Education Nationale et de la Recherche", France, for financial support. J.W.-D. acknowledges the European Commission for the ERC-Starting Grant "AlCHIMIE" no. 949804 and for the MSCA-ITN Grant "CHAIR" Grant Agreement no. 860762 and ANR PRCI/DFG grant no. ANR-17-CE07-0049-01.

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Joanna Wencel-Delord was educated in chemistry at the Ecole Nationale Supérieure de Chimie de Rennes, France and she received her PhD in 2010 from the University of Rennes 1, France (Dr C. Crévisy and Dr M. Mauduit). After postdoctoral studies with Prof. F. Glorius at the Westfälische Wilhelms-Universität Münster (Germany) and a temporary assistant professor position (ATER) at the University of Strasbourg (Prof. P. Compain), she joined CNRS in 2013 as an associate researcher and in 2021 she has been promoted to Research Director. Her research focuses on the transition metal-catalyzed asymmetric C–H activation, synthesis of axially chiral compounds, and chemistry of hypervalent compounds, including original hypervalent bromines. Her recent awards and distinctions include Bronze Medal of CNRS 2020, ERC-SG (2020), Guy Ourisson 2020 award attributed by Cercle Gutenberg, and Prize M. Julia for Emerging Talents, French Society of Chemistry, Organic Chemistry Division, (2018). She has published 63 articles and is the author of 2 patents.

Polymer Synthesis in Living Systems

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Wouldn't it be amazing if we could design soft biomaterials that actively integrate into cells or tissues and stimulate cellular responses? Can we imagine nanostructures that instruct cells to grow, proliferate or induce apoptosis? Could we "learn the language of cells and integrate reaction networks to achieve communicating biomaterials?

In my presentation, I will present chemical reactions that take place in the dynamic and complex environment of living cells[1a,b]. Cascade reactions of peptide monomers proceed in defined nanoenvironments of the cell so that peptide nanostructures are formed by supramolecular polymerization[2a,b]. Depending of the synthetic reaction pathway, nanostructures with different morphologies can be formed[3]. Some characterisation techniques to analyse the nanostructures inside cells as well as their impact on cell viability and metabolism are discussed.

Our overall goal is to synthesize functional nanostructures that exhibit many of the properties of living matter so that they can integrate and communicate with living systems to provide new avenues for medical challenges (**Figure 1**).

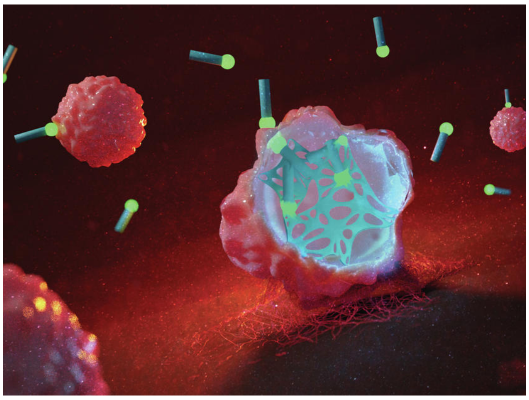

Figure 1: Uptake of monomers and supramolecular polymerization in the cytoplasm of living cells

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Tanja Weil joined the Max Planck Society in 2017 as one of the directors of the Max Planck Institute for Polymer Research (MPIP), heading the division “Synthesis of Macromolecules”. She studied chemistry (1993–1998) at the TU Braunschweig (Germany) and the University of Bordeaux I (France) and completed her PhD at the MPIP working with K. Müllen in 2002. From 2002 to 2008 she managed different leading positions at Merz Pharmaceuticals GmbH (Frankfurt) from Section Head Medicinal Chemistry to Director of Chemical Research and Development. In 2008 she accepted an Associate Professor position at the National University of Singapore. Tanja Weil joined Ulm University as Director of the Institute of Organic Chemistry III / Macromolecular Chemistry in 2010. She has received competitive funding and awards at both national and international level including the Otto Hahn Medal of the Max Planck Society, a Synergy Grant of the European Research Council (ERC), the Science Award of the City of Ulm and the Netherlands Supramolecular Chemistry Scholar Award. She is a member of the senate of the German Research Foundation, a member of the senate of the Leibniz Association and an associate editor of the Journal of the American Chemical Society. Her scientific interests focus on polymer synthesis to control material-cell-interactions to solve current challenges in biomedicine and material science.

Biocatalysis in early drug discovery

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There are myriad opportunities for using biocatalytic transformations in the early phases of drug discovery. Many, some would say the majority, of widely used transformations in medicinal chemistry now has a biocatalytic equivalent. Access to 'non-natural' chemistries via enzyme and reaction engineering has further expanded the toolkit of available transformations. Metagenomics has enable access to enormous genetic diversity and this combined with inexpensive gene synthesis has expanded available biocatalytic chemistries still further.

It is estimated that using current miniaturised HTS technologies ca. 0.5 mg of a typical small molecule hit or lead (130 µL of 10 mM stock solution) is sufficient for evaluation in hundreds of HTS campaigns or for early phase compound profiling (physchem and *in vitro* DMPK). In a typical early drug discovery project biocatalysis is often used to probe SAR, to introduce 'functionalisable' handles, to confirm metabolite ID data and occasionally to perform magic.

This talk will give examples of the use of N-methyltransferases, Diels-Alderases and RedAms in the drug discovery space and highlight a workflow which uses acoustic dispensing for both enzyme screening and reaction optimisation combined with desorption electrospray mass spectrometry for qualitiative analysis. We will highlight the value of open innovation and collaboration to biocatalysis efforts in the early phases of discovery at AstraZeneca.

Acknowledgements: We thank the AstraZeneca Postdoctoral programme and the BBSRC (UK) for financial support.

Martin is an industry scientist with over 25 years' experience working in the pharma and biotech sectors. He is currently Biocatalysis Leader in the iLAB, part of Discovery Sciences at AstraZeneca in Gothenburg, Sweden. His work focusses on developing enzyme catalyzed Late Stage Functionalisation approaches to hit and lead molecules to support early Drug Discovery Projects.

Previously he was a DMPK Design Leader working in the Cardiovascular and Metabolic Research area using combined DMPK and Medicinal Chemistry knowledge to influence the design of new chemical entities in lead generation and optimization projects. Martin led DMPK Design efforts for the FLAP inhibitor AZD5718 currently in Phase 2 trials for atherosclerosis. He worked on the development DMPK for the blockbuster platelet aggregation inhibitor Brilinta/Brilique.

Research interests include biotransformation in all its guises, from novel drug metabolism to preparative enzyme synthesis, directed evolution of human drug metabolizing enzymes, HTE and analytical methodologies for small molecule purification and structure elucidation. A recent highlight has been the discovery that human microsomal epoxide hydrolase catalyses the ring opening of oxetanes. He sits on the management team for the Prosperity Partnership UKRI funded Centre for the Biocatalytic Manufacture of New Modalities with University of Manchester, UK. Martin became a Fellow of the Royal Society of Chemistry in 2000. He was awarded an Hon. Professorship from the University of Manchester in 2021. He is a co-author on over 60 peer reviewed papers and patents.

Dynamic Nanomaterials for Gene Delivery: From Chemistry to Biology

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We have developed a family of verstatile organic catalysts for the living polymerization of lactone and carbonate monomers that have been integrated into efficient flow reactors for the programmed synthesis of block copolymer libraries.[1] These synthetic methods spawned the development of a new concept for gene delivery based on a class of dynamic oligomeric cationic materials that are designed to self-assemble with messenger RNA (mRNA) to form coascervate nanoparticles. These Charge-Altering Releasable Transporters (CARTs)[2] are structurally unique oligomers that operate through an unprecedented mechanism, serving initially as oligo(α- amino ester) cations that complex, protect and deliver mRNA, and then change physical properties through a degradative, charge-neutralizing intramolecular rearrangement, leading to intracellular release of functional mRNA and highly efficient protein expression, both in cell culture and in live mice. The key roles of the catalytic process, synthetic conditions and

structure of the materials on the biological performance will be described.

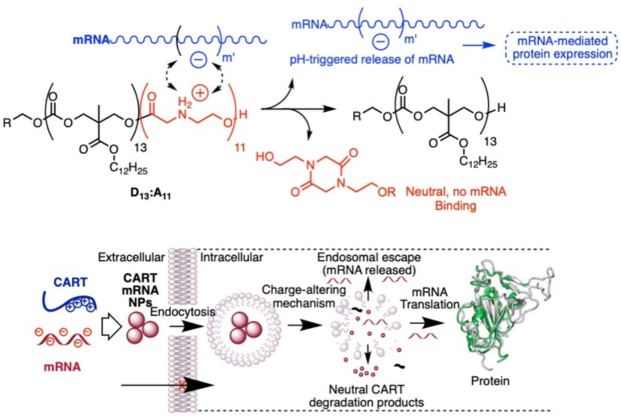

Figure 1: Amphiphilic CART oligomers assemble with RNA and degrade to facilitate intracellular release

Acknowledgements: We thank the National Science Foundation and National Institute of Health for financial support....

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Robert Waymouth is the Robert Eckles Swain Professor of Chemistry at Stanford University. He received B.S. in Mathematics and B.A. in Chemistry from Washington and Lee University and his Ph.D. in Chemistry at the Caltech in 1987 with Professor R.H. Grubbs. He was a postdoctoral fellow with the late Professor Piero Pino at the ETH in Zurich in 1987 and joined the faculty at Stanford as an Assistant Professor in 1988. He received the Alan T. Waterman Award from the NSF in 1996, the Cooperative Research Award in Polymer Science in 2009, and EPA's Presidential Green Chemistry Challenge Award in 2012 with Dr. James Hedrick. He has won several university teaching awards, including the Walter J. Gores Award, the Phi Beta Kappa Teaching Award, and is currently a Bass Fellow in Undergraduate Education. His research interests are at the interface of Inorganic, Organic and Polymer Chemistry, in particular the development of new concepts in catalysis for the selective synthesis of both macromolecules and fine chemicals. Particular areas of interest include catalytic polymerization reactions, selective oxidation catalysis, the development of organocatalytic polymerization strategies, and the design of functional macromolecules for applications in biology and medicine.

Innovative Chemistry Toward Novel Tetrapyrrolic Macrocycles: Therapy and Imaging of Cancer

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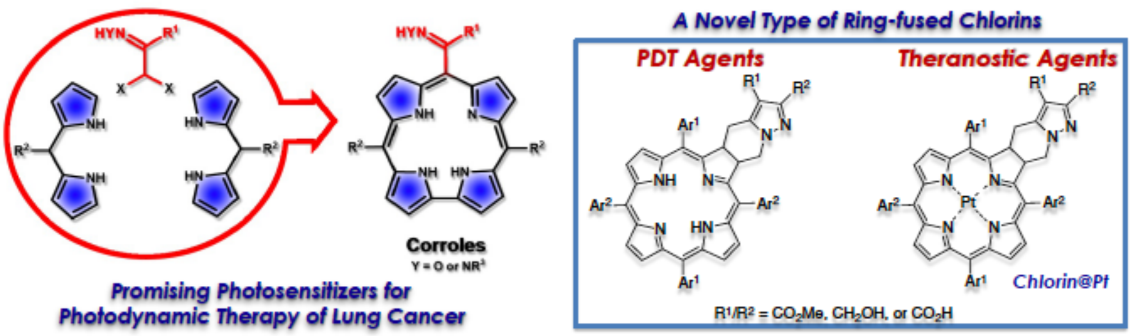
Photodynamic therapy (PDT) depends on the combined action of oxygen, light, and a suitable photosensitizing chromophore to selectively destroy abnormal cells in cancer. The development of more efficient photosensitizers and diagnostic tools are crucial to improve the therapeutic outcome and expand PDT applications. Therefore, the focus of our research has been on the development of innovative chemistry for the synthesis of novel tetrapyrrolic macrocycles (ring-fused chlorins and corroles) for PDT and theranostics of cancer.

New stable 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused chlorins, obtained via an unprecedented [8π+2π] cycloaddition of porphyrins with diazafulvenium methides, proved to be very active photodynamic agents against several types of cancer.[1] Moreover, *in vitro* and *in vivo* studies have demonstrated that the incorporation of platinum (II) into the structure of these ring-fused chlorins leads to molecules with theranostics features, acting as near-infrared luminescence probes as well as PDT photosensitizers.[2]

One of our research interests is to explore the chemistry of nitrosoalkenes and azoalkenes for the synthesis of heterocycles.[3] In this context, a novel synthetic strategy towards *trans*-A_2B-corroles, *meso*-substituted with an oxime moiety, from nitrosoalkenes and dipyrromethanes was developed.[3b] Recently, this synthetic methodology was extended to the reactivity of azoalkenes leading to corroles bearing a hydrazone functionality. These contracted porphyrins with a novel substitution pattern proved to be very efficient photosensitizers for PDT of lung cancer. Further details of this study regarding photophysical and photodynamic activity properties, as well as theranostics features of the studied tetrapyrrolic macrocycles will be disclosed.



Acknowledgements: The work was supported by Project PTDC/QUI-QOR/0103/2021, financed by Fundação para a Ciência e a Tecnologia (FCT), I.P./MCTES, by national funds (PIDDAC). Coimbra Chemistry Center (CQC) is supported by FCT through project UIDB/00313/2020 and UIDP/00313/2020.

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Teresa M.V.D. Pinho e Melo studied Chemistry at the University of Coimbra, where she graduated, got her MSc and her PhD in Organic Chemistry. She was Research Fellow at the University of Liverpool (1992-1993). She received her Habilitation in Organic Chemistry in 2003. Teresa Pinho e Melo is currently Associate Professor at the University of Coimbra, Group Leader of the Organic Chemistry Group of the Coimbra Chemistry Centre (CQC) and collaborator of iMed.ULisboa and CFisUC. She was President of the Division of Organic Chemistry, Portuguese Chemical Society (2016-2017) and Director of the Department of Chemistry, University of Coimbra (2015-2019). Her research interests are mainly in the area of synthetic and mechanistic heterocyclic chemistry and medicinal chemistry. Her research encompasses the development of new synthetic methodologies by exploring the chemistry of reactive intermediates (aza- and diazafulvenium methides; azo- and nitrosoalkenes; azadienes), allenes and small ring heterocycles. She is particularly concerned with the development of synthetic routes to new bioactive molecules namely spiro-penicillanates with antimicrobial activity, tetrapyrrolic macrocycles for photodynamic therapy and theranostics of cancer and chiral 6,7-bis(hydroxymethyl)-1H,3H-pyrrolo[1,2-c]thiazoles as new P53 activators.

Changing the World, One Reaction at a Time: The Discovery and Development of Orally Bioavailable Macrocyclic Peptide That Inhibits Binding of PCSK9 to the LDL Receptor

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Orally bioavailable macrocyclic peptides have the potential to unlock a new paradigm in drug discovery, enabling monoclonal antibody-like potency and selectivity despite 1000X smaller molecular weight. mRNA display screening technology has enabled identification of lead chemical matter that can inhibit binding of PCSK9 to the LDL receptor. This lead needed to be optimized via extensive structure-activity relationship studies to deliver exquisite potency and selectivity for PCSK9 resulting in MK-0616. To achieve this, extensive advances in synthetic methods and strategy were developed in order to enable discovery of a clinical candidate. Further process chemistry optimization was used to scale-up this lead-molecule, including novel biocatalytic methods to access key non-canonical amino acids. We believe this successful application of these synthetic chemistry advances pave the way for application to other important protein-protein interaction targets.[1]

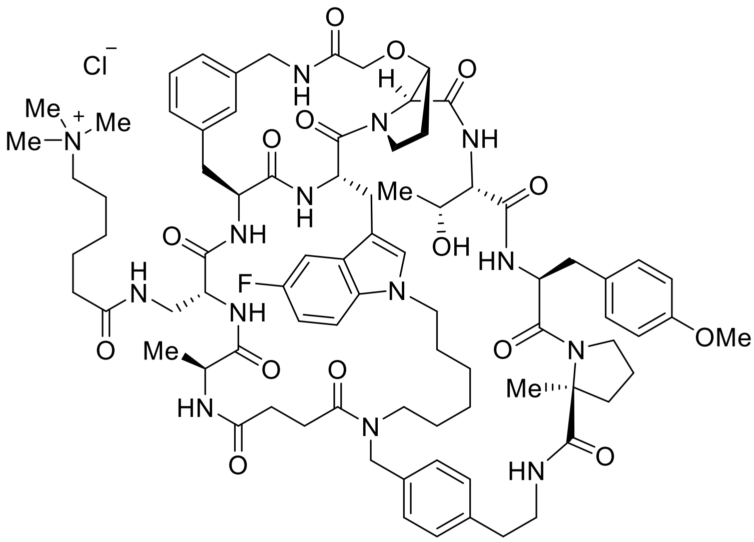

Figure 1: MK-0616

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L.-C. Campeau is the Head of Small Molecule Process Research and Development at Merck & Co., Inc. He is originally from Canada and received his Ph.D. from the University of Ottawa under the supervision of the late Keith Fagnou. He first joined Merck in 2007 in Montreal, Canada and relocated to New Jersey in 2010. During his career, he's led teams from Discovery to Commercialization, including enabling technologies investments, and was recently co-lead of Merck's PCSK9 development team. He's passionate about improving human health and believes that chemistry can change the world, one reaction at a time.

Fluorine Chemistry for Agrochemicals

M. Rack, M. Dochnahl, T. Frassetto, U. Vogelbacher, V. Maywald, B. Wolf

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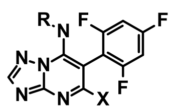
Inventing, developing, and commercializing new chemistry and products rapidly is a key for sustained profitability in the agrochemical, fine and specialty chemical, and pharmaceutical markets. New products require the development of efficient synthetic routes and robust manufacturing processes.

The presentation will give an overview of latest fluorinated agrochemical active ingredients (figure 1) developed at the BASF Agricultural Solutions division during the last years. Methods for their synthesis, an insight into the route scouting efforts, process development and different ways for the synthesis of certain fluorine containing key intermediates will be presented.



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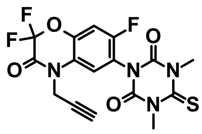

Tirexor^{R} (H)

Figure 1: Examples for highly fluorinated active ingredients

References: WO2014012811 A1; WO2015003858 A1; WO2013092850 A1; WO2014026893 A1; WO2006111583 A1; WO2006097510 A1

Michael Rack, has a master’s degree from the University of Leipzig (1990), and a Ph.D. from Eberhard-Karls-University Tuebingen (1990). He joined BASF in March 1995 as lab team leader for intermediates research process development agrochemicals research and was appointed to the role of Principal Scientist in 2003, followed by being appointed Senior Principal Scientist for Fluorine Chemistry in 2013. He is a leader of kilo- and fluorine labs, early phase process development, route scouting, upscaling of chemical processes in pilot plants, as well as cost of goods estimates for new active ingredients. He received the Agroscience Award in 2017.

Practical Organofluorine Chemistry for Large Scale API Synthesis

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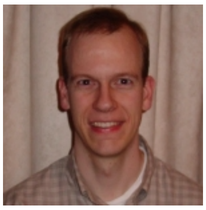
The introduction of fluorine into organic molecules often involves the use of hazardous reagents. While some fluorinating reagents and reaction conditions may be acceptable for laboratory scale, their use on large (multi-kg) scale presents major safety and environmental concerns. In this talk, examples will be given of the large scale preparation of organofluorine moieties found in APIs. The safety and environmental challenges associated with the original methods will be discussed, and the development of new methodologies to address these issues will be presented.



Jonathan Reeves received a B.S. in chemistry from Hope College in Holland, MI in 1997. He then obtained his Ph.D. in 2002 from the University of Pittsburgh under the guidance of Professor Peter Wipf. After two years as an NIH postdoctoral fellow at Indiana University with Professor David R. Williams he joined the Chemical Development department at Boehringer Ingelheim Pharmaceuticals in Ridgefield, CT in 2004, where he is currently a Distinguished Research Fellow.

Catalytic Denitrative Transformations

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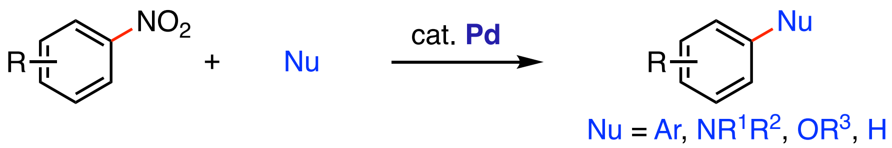
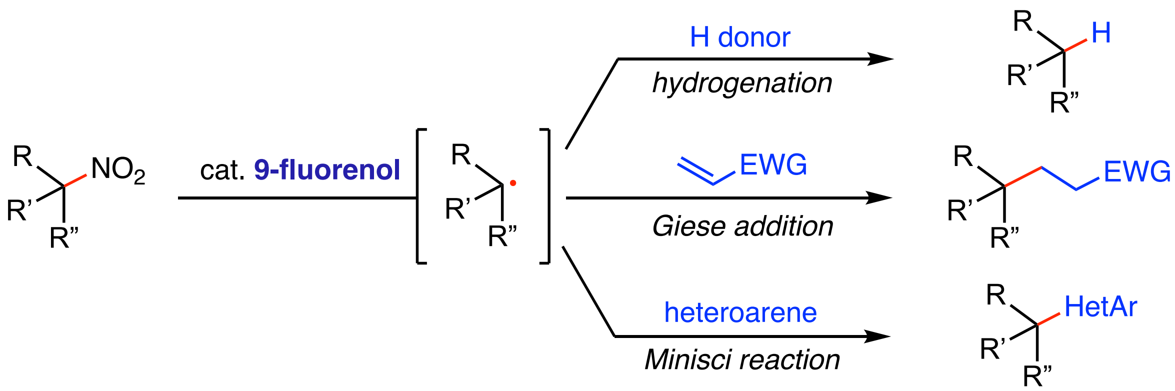
Nitroarenes are readily accessible chemical feed stock, but less used in cross-coupling reactions before being converted to aryl halides. We have demonstrated a series of Pd-catalyzed cross-coupling reactions using nitroarenes directly as electrophiles for the Suzuki–Miyaura coupling reaction, Buchwald–Hartwig amination/etherification, and reductive denitration reaction (Scheme 1).[1] Nitroalkanes are also useful synthetic intermediates to construct complex molecules. Despite obvious benefits of their denitrative transformations, reductive removal of a NO_2 group from nitroalkanes is challenging because of competitive reduction of the NO_2 group itself to give nitroso compounds, hydroxylamines, and amines. We have recently found that denitrative radical reactions of nitroalkane can efficiently be catalyzed by 9-fluorenol, possibly through single-electron transfer from a non-oxophilic reductant to avoid abstraction of oxygen from radical anions of nitroalkanes (Scheme 2).[2]



Scheme 1: Pd-catalyzed cross-coupling reactions of nitroarenes.



Scheme 2: 9-Fluorenol-catalyzed denitrative transformations of nitroalkanes.

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Yoshiaki Nakao studied chemistry at Kyoto University (PhD in 2005 under the tutelage of Profs. Tamejiro Hiyama and Eiji Shirakawa), Yale University (Prof. John F. Hartwig), and the Max-Planck-Institut fuumlr Kohlenforschung (Prof. Manfred T. Reetz). He has been a faculty member at Kyoto University since 2002 and is currently a full professor. He is interested in developing new reactions, reagents, and catalysts to streamline organic synthesis.

Computations and Collaborations on Synthetically Important Catalytic Reactions

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Nina Strassner, Cooper Jamieson, and Qianzhen Shao

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I will describe collaborations between my group and experimental groups, designed to determine mechanisms and origins of selectivities of synthetically valuable reactions. We used quantum mechanical methods to develop detailed understanding of reactions studied experimentally by the Glorius, Trauner, and Tang groups.

The Frank Glorius group at Muenster, Germany, has studied the photochemical reactions of a variety of arenes with alkenes, alkynes, and bicyclopentanes to give dearomatized complex cycloaddition adducts.[1] We have used quantum mechanical methods to establish mechanisms and origins of selectivities. Recent collaborations will be discussed.

We have had fruitful collaborations with the Dirk Trauner group, now at the University of Pennsylvania in the U.S. His synthesis of PF-1018 stimulated our calculations on the competition between various electrocyclizations and cycloadditions, understanding how substituents influence this competition, as well as the roles that enzymes must play in biosynthetic reactions to form PF-1018.[2]

In a related collaboration with the Yi Tang group at UCLA, we carried out computational studies of reactions occurring under catalysis by new pericyclase enzymes that Tang's group has identified and isolated. These enzymes are involved in the PF-1018 biosynthesis and in the related reactions of a vinylogous substrate to form new natural products.[3]

Acknowledgements: We are grateful to the National Science Foundation, the National Institutes of Health, and the Saul Winstein Chair for support of our research.

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K. N. Houk received his A.B. and Ph.D. degrees at Harvard, working with R. B. Woodward. on experimental tests of orbital symmetry selection rules. In 1968, he joined the faculty at Louisiana State University, moved to the University of Pittsburgh in 1980, and to UCLA in 1986. From 1988-1990, he was Director of the Chemistry Division of the National Science Foundation. He was Chairman of the UCLA Department of Chemistry and Biochemistry from 1991-1994, the Saul Winstein Chair in Organic Chemistry from 2009-2021, and now a Distinguished Research Professor. He is a member of the US National Academy of Sciences and recently was awarded the Roger Adams Award of the American Chemical Society and election to the Chinese Academy of Sciences. Professor Houk is an authority on theoretical and computational organic chemistry, and has published more than 1400 research papers and a textbook with Pierre Vogel.

Oral Communications

Synthesis of γ-lactams and Δ^1-pyrroline from chalcones using aziridines and 2*H*-azirines

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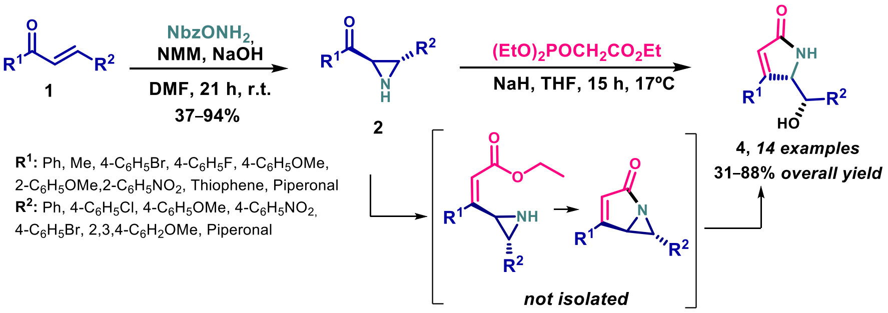
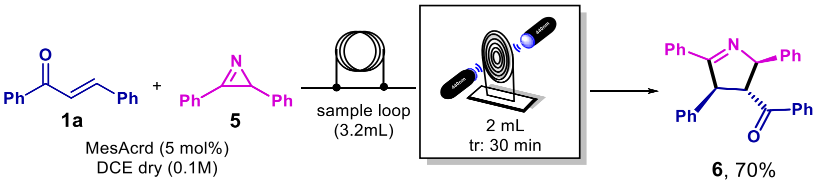
A plethora of biological activities of 5-membered ring *N*-heterocyclic compounds, such as γ-lactams and Δ^1-pyrrolines, have been described in literature, stimulating the search for efficient synthetic methods to achieve these scaffolds.[1] Based on our previous work on the synthesis of γ-lactones,[2] in this work we have developed a simple and efficient diastereoselective synthesis of new γ-lactams from chalcones **1** and aziridines **2** (Scheme 1). This two-step protocol allowed to prepare 14 examples of γ-lactams in 31-88% yield. The intermediate azabicyclo[3.1.0]hexenone was isolated and characterized by x-ray crystallography. The asymmetric version of this method is under investigation.



Scheme 1. Synthesis of γ-lactams **4**.

Guo *et al*. have reported the diastereoselective synthesis of polysubstituted Δ^1-pyrroline derivatives from *in situ* generated nitrile ylides.[3] Based on this work, and looking for greener conditions, we have evaluated this reaction using photocatalysis under continuous flow regime. After evaluation of different catalysts and solvents, *N*-heterocycle **6** could be obtained from chalcone **1** and 2*H*-azirine **5** in the presence of 9-mesityl-10-methylacridinium tetrafluoroborate as photocatalyst and two blue LED lamps in continuous flow with 70% yield as a 1:1 mixture of diastereoisomers (Scheme 2). The optimization of the method is still undergoing, as well as the evaluation of scope and mechanism studies.



Scheme 2. Continuous flow synthesis of compound **6** using blue LEDs.

Acknowledgements: We thank FAPESP (2018/23761-0), CNPq, CAPES (001) and GSK for financial support and fellowships.

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Towards the Total Synthesis of Mycapolyol E

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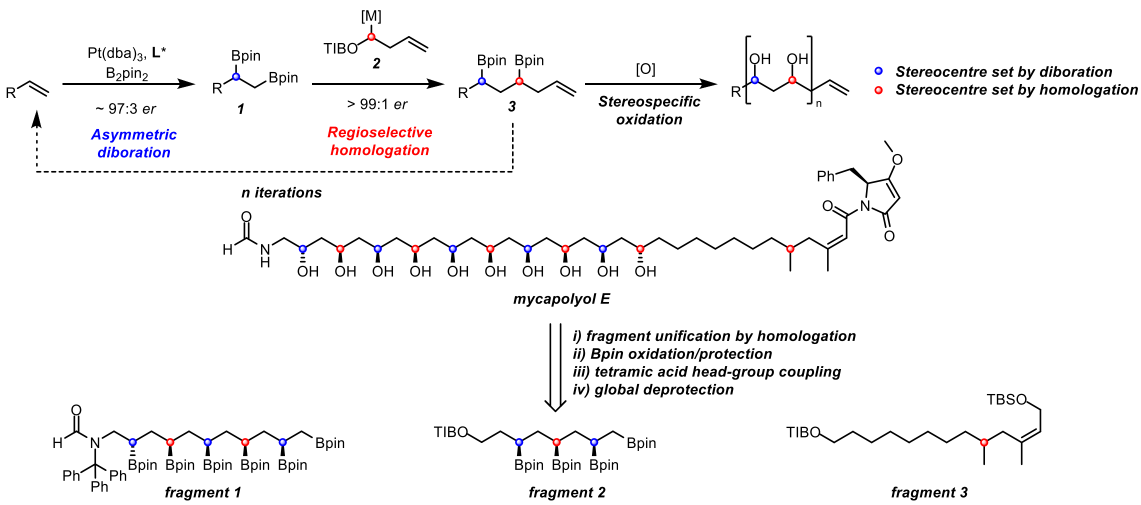

Polyketides are arguably the most important class of natural products, given their extensive application as small-molecule drugs. Due to their assembly-line like biosynthesis from small repeating building blocks, these compounds often possess repeating motifs. This is true for polyacetates, a sub-class of polyketides, which display repeating 1,3-hydroxyl stereocentres.

Our research group recently reported a two-step iterative strategy for the rapid synthesis of stereodefined 1,3-polyol motifs. This strategy harnesses asymmetric diboration of terminal alkenes, furnishing an enantioenriched 1,2-bis boronic ester **1**. This is then followed by a regioselective homologation of the primary boronic ester with enantiopure metal carbenoid **2**, yielding an enantioenriched 1,3-bis boronic ester **3**, which bears a terminal alkene primed for subsequent iterations. Finally, stereospecific oxidation of the enantioenriched polyboronic ester provides the desired 1,3-polyol motif.

We now aim to apply this methodology towards the first total synthesis of Mycapolyol E, a member of a family of polyketide metabolites which display cytotoxicity towards HeLa cell. These compounds bear 9-14 contiguous, stereodefined, skipped hydroxyl groups and are flanked by a tetramic acid derived and formamide head groups.

Our retrosynthetic analysis of Mycapolyol E disconnects to three fragments of equal complexity, of which two would utilise our iterative strategy to set the 1,3-polyol stereocentres. The synthesis of these fragments, and their unification by regioselective homologation of primary boronic esters, has now been optimised. All that remains to complete the first synthesis of any member of the Mycapolyol family is downstream manipulations to install the tetramic acid derived head-group, where our efforts are currently focused.

Acknowledgements: DR thanks VKA for his continued support and guidance and to the EPSRC sponsored TECS CDT and Vertex Pharmaceuticals for a PhD studentship.

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Synthesis and Evaluation of ROS-responsive Diazaborines

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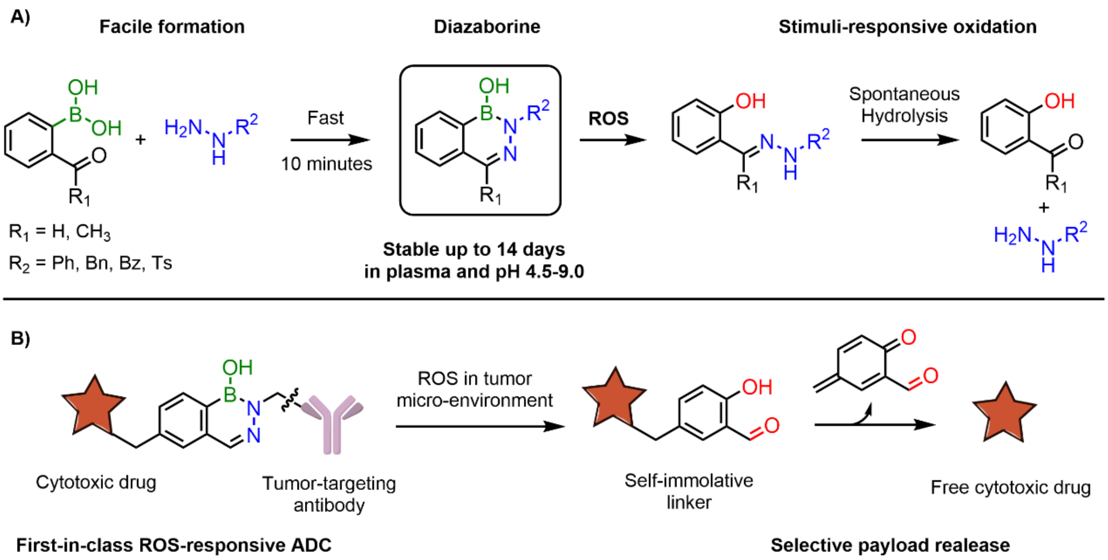
Antibody-drug conjugates (ADCs) are one of the most promising class of therapeutics in the battle against cancer. The linker, in particular, must be stable in solution and capable of releasing the payload upon a predetermined stimulus.[1] Current ADCs explore the distinctive microenvironment of cancer cells to ensure a selective deliver of the drug, including its acidic pH, high glutathione levels and overexpressed proteolytic enzymes. In this work, we demonstrate for the first time that the high reactive oxygen species (ROS) concentrations present in tumor cells can be exploited to generate a first-in-class ROS-responsive ADC.[2] The synthesis of this ADC was possible due to the discovery that diazaborines (DABs) are a very efficient ROS-responsive unit while being stable in buffer and in plasma. DABs can be generated with click-like kinetics (bioorthogonal, 10 min aqueous pH 7.4) and displayed remarkable stability in pH 4.5-9.0 and plasma. However, in the presence of 100 equiv. H_2O_2 they were swiftly oxidized ($t_{1/2}$= 15 min). Mechanistic and DFT experiments were performed on the system to further understand the details behind their stability and selectivity. To showcase their potential, a DAB-based self-immolative linker was designed and used in the construction of a homogenous ADC. The ADC, featuring a SN-38 cytotoxic drug and a B-cell lymphoma targeting antibody, showed remarkable activity (IC_{50} = 54.1 nM) and selectivity (>100 μM in T-cell lymphoma). Due to their modularity and fast kinetics, we envision that DABs will play an important role in the development of a new generation of targeted therapies and responsive materials.[2]



Acknowledgements: We thank the Fundação para a Ciência e Tecnolgia for financial support (SFRH/BD/90514/2012 PD/BD/128239/2016, PD/BD/143124/2019, SFRH/BPD/102296/2014, iMed.ULisboa UIDB/04138/2020; SAICTPAC/0019/2015, PTDC/QUI-QOR/29967/2017, PTDC/BTM-SAL/32085/2017); LISBOA-01-0145-FEDER-029967. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996

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Catalytic Disconnection of C–O Bonds in Epoxy Resins and Composites

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Fiber-reinforced epoxy composites are well established for load bearing applications in the aerospace, automotive and wind power industries, due to their light weight and high durability. These composites are based on thermoset resins, consisting of s bond linkages and aromatic backbones, embedding glass or carbon fibers. *In lieu* of viable recycling strategies, end-of-use composite-based structures such as wind turbine blades are commonly landfilled. Due to the negative environmental impact of plastic waste, the need for circular economies of plastics has become pressing. However, recycling thermoset plastics is not trivial. Here, we present a transition metal catalysed protocol for recovering the base chemical bisphenol A and fibers from thermoset epoxy resins. Our approach is based on disconnecting C(alkyl)–O bonds of the most common linkages of the polymer, using a ruthenium-catalysed dehydrogenation/bond cleavage/reduction cascade. We showcase the application of this methodology to relevant unmodified amine-cured epoxy resins as well as commercial composites (Figure 1), including the shell of a wind turbine blade. The high quality of the recovered fibers was confirmed using X-ray micro-computed tomography, X-ray photoelectron spectroscopy and scanning electron microscopy. Our results demonstrate that chemical recycling approaches for thermoset epoxy resins and composites are achievable.[1]

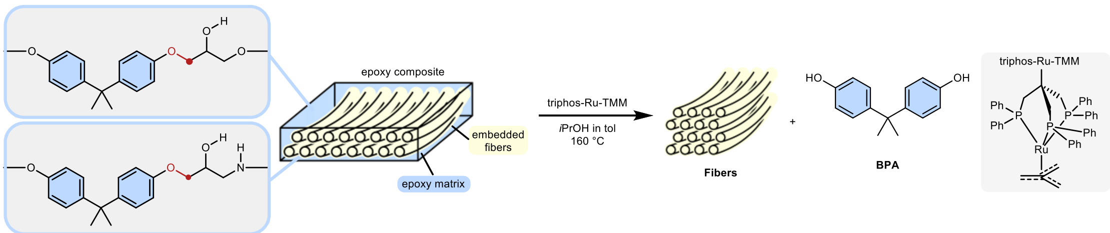

Figure 1: Disconnection of C–O bonds in epoxy composites using ruthenium catalysis.

Acknowledgements: We thank the Innovation Fund Denmark, Carlsberg Foundation, Danish National Research Foundation, Novo Nordisk Foundation for financial support.

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Sustainability meets structural diversity: exploring the furan-based chemical space

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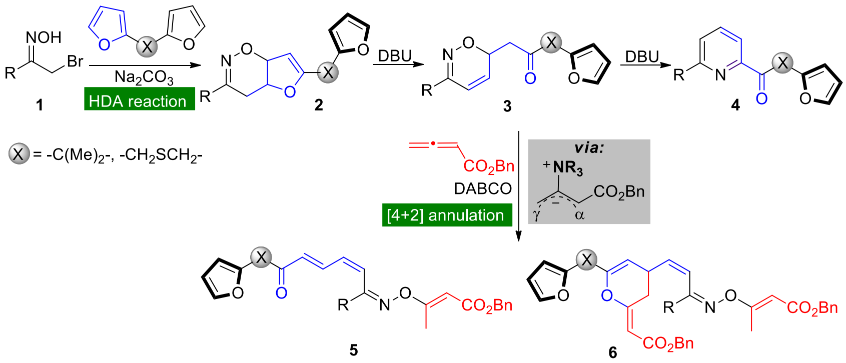
Carbohydrate-derived furanic platforms have become increasingly important over the last decades by giving access to an array of value-added chemicals and fuels through greener and more sustainable processes.[1] Furan derivatives can be easily accessed from lignocellulosic biomass, the most abundant and available renewable resource in nature. Their quite rich chemistry has made them valuable building blocks in the construction of a wide range of heterocyclic and acyclic structures, some of which finding applications in natural product synthesis and medicinal chemistry.[1c]

The hetero-Diels-Alder (HDA) reaction between conjugated nitroso- and azoalkenes and electron-rich heterocycles has been one of our topics of research.[3] In this context, we have described the dienophilic behavior of furan derivatives towards nitroso- and azoalkenes, generated *in situ* by base-mediated dehydrohalogenation of α-halo oximes (*e.g.* **1**) and α-halo hydrazones, respectively, giving access to dihydrofurooxazines (*e.g* **2**) and tetrahydropyridazines.[4] This work was now extended to other bis-furan derivatives and led to a great variety of dihydrofurooxazines **2**. Additionally, studies on the reactivity of **2** originated multiple novel furan-hybrids such as furan-6*H*-oxazines **3**, furan-pyridines **4**, furan-polyenes **5**, and furan-dihydropyranes **6,** under classical reaction conditions (**Scheme**). To further increase the sustainability of these new synthetic methodologies, the selective hetero-Diels-Alder reaction under mechanochemistry to transform bis-furan into furan-hybrids has also been explored, in compliance with the principles of Green Chemistry. Details of these studies and the mechanisms underlying these transformations will be disclosed in this communication.



Scheme: Novel synthetic routes towards furan-hybrids.

Acknowledgements: Thanks are due to Coimbra Chemistry Centre – Institute of Molecular Sciences (CQC-IMS), supported by the Portuguese Agency for Scientific Research "Fundação para a Ciência e a Tecnologia" (FCT), through projects UIDB/00313/2020 and UIDP/00313/2020, co-funded by COMPETE2020-UE, and the IMS special complementary funds provided by FCT. This work was also supported by Project PTDC/QUI-QOR/0103/2021, funded by national funds (PIDDAC). The authors also acknowledge the UC-NMR facility for obtaining the NMR data (www.nmrccc.uc.pt).

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"Biocatalysis : a Necessary Tool for Synthetic Chemist – a Focus on Industrial Applications"

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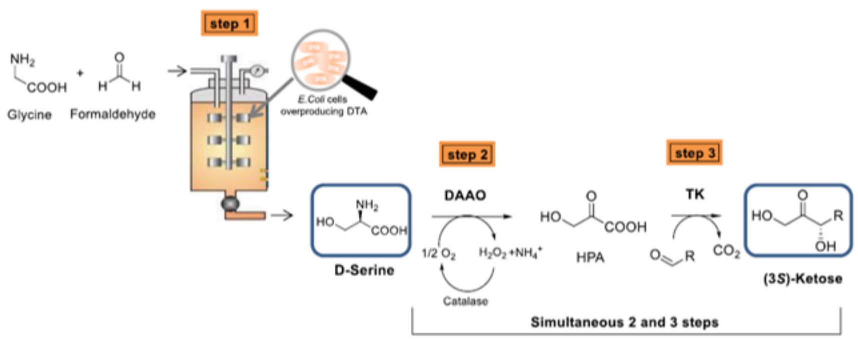
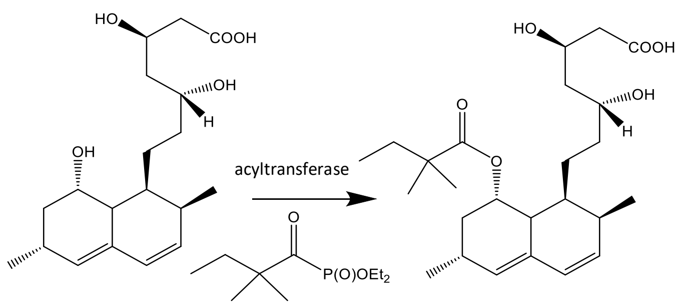
Protéus by SEQENS is a pioneer in biotechnology field, specialized in the discovery, engineering and production of enzymes for industrial applications, as well as in the development of innovative bioprocesses involving these enzymes. Protéus by SEQENS is part of the SEQENS Group, an integrated global leader in pharmaceutical solutions and specialty ingredients producing high-value complex molecules.

Enzymes enable unique and specific functionalization difficult to achieve by conventional chemical processes within competitiveness. Taking advantage of this attribute, we will demonstrate their potential through several examples showing the high selectivity and specificity of these enzymes as well as their potential industrial applications. For instance, non-natural aminoacids synthesis[1] without protection/deprotection steps, we will also present an example of regioselective acylation within high specificity[2]. Finally, biocatalysis can be a true alternative for precious metal replacement.





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[2] WO2012013765

Explainable Catalytic Epoxide Synthesis Prediction through Machine Learning Models and Descriptive Features

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The catalytic epoxidation of allylic alcohols and alkenes is a highly employed synthetic route in industrial chemistry[1]. This reaction produces epoxides used to manufacture valuable chemical commodities in everyday plastics, detergents and pharmaceuticals. Most industrial catalytic sources are fossil-fuel based olefins, making epoxides one of the chemicals with the highest CO_2 footprint. As small epoxides represent over a $20 billion industry, it is pivotal to provide alternative sources, overcoming its environmental costs with sustainable production routes. Optimizing organic catalytic reactions normally use trial-and-error empirical approaches, but these strategies are often time-consuming which only work for a handful of reactions. To overcome this accuracy-speed trade-off, data science methods have been developed to design new efficient catalysts using chemical descriptors as numerical representations of molecular properties[2]. Fast and accurate Machine Learning (ML) models can estimate the suitability of novel catalysts with a trained model on experimental data by predicting reaction outcomes. But to grasp relevant chemical features for novel catalysts, ML models need to calculate the best descriptors associated with higher reaction yields through seldom available *in silico* libraries with extensive reaction parameters.

In this communication, we report an explainable computational model for predicting catalytic epoxidation yield of allylic alcohols and alkenes using vanadium-based catalysts. Using a data science framework, we developed a model capable of forecasting key catalyst and substrate features associated with higher epoxidation yields, allowing to describe ideal reaction conditions and molecular properties (**Figure 1**). We built a dataset of 273 epoxidation reactions with a comprehensive library of documented experimental conditions and molecular open-source descriptors. Our supervised ensemble algorithms successfully predicted catalytic epoxidation yields with 91% accuracy, further certified with a validation set for reporting the out-of-sample errors with a maximum error of 4.1%. Our model revealed significant descriptor contributions from substrate and catalyst's structural and electronic features, providing chemical explanation for ML predictions. Key descriptor analysis was able to interpret model accuracy with major contributions from substrate and catalyst volume surface area, increasing overall prediction accuracy by 70%. We thus present our findings as a framework model, able to identify relevant features for catalyst design and ideal substrate selection.

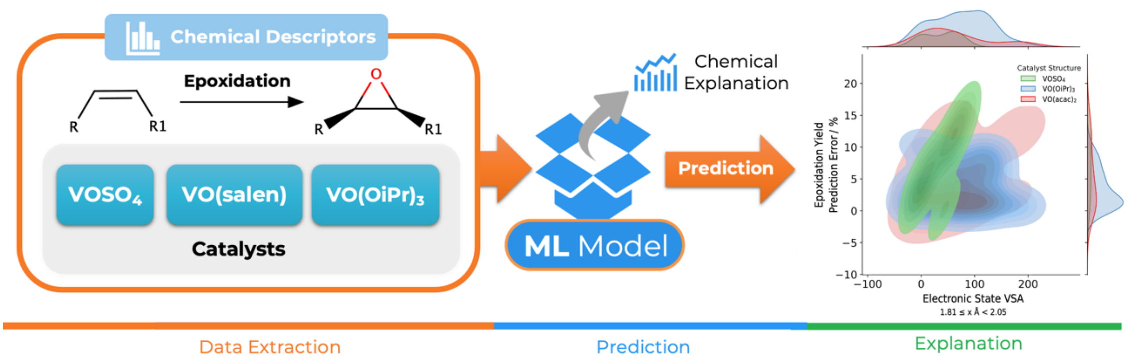

Figure 1: Workflow for catalytic epoxidation yield model prediction using an explainable ML-based model.

Acknowledgements: The authors thank the Fundação para a Ciência e Tecnologia (FCT/MCTES) support to LAQV-REQUIMTE (UIDP/50006/2020). JFC's PhD Fellowship is supported by the doctoral Grant (SFRH/BD/151159/2021) financed by FCT, with funds from the State and EU Budget through the Social European Fund and Programa Por_Centro, under the MIT Portugal Program.

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A Nitrenoid Strategy for Efficient *N*-Heterocycle Synthesis

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Five and six-membered nitrogen-containing rings are ubiquitous structures in pharmaceuticals and agrochemicals, as well as bioactive natural products and other functional molecules. Their preparation can be highly challenging, often requiring bespoke and lengthy route development when even relatively limited structural changes are required. New advances in functional molecules will be made possible if such core motifs can be prepared more easily, and with new substitution patterns to access novel properties. A unifying strategy that allows access to different types of sp^2- and sp^3-rich azacyclic motifs from a common approach would offer a significant enabling tool in molecular synthesis. In addition to providing more efficient routes for sustainable chemical synthesis, the ability to access more diverse azacyclic substitution patterns would allow the exploration of novel volumes of chemical space to facilitate early-stage drug discovery and other applications that depend on azacyclic motifs.

The combination of an alkyne and newly introduced nitrenoid reagents under gold catalysis provides access to α-imino gold carbene reactivity patterns that can be used to access a diverse array of transformations (Figure 1).[1] This presentation will outline the development and application of a nucleophilic nitrenoid-based annulation strategy for convergent access into different types of azacyclic motifs. The resulting reactions are efficient, functional group tolerant, and gram scalable processes.[2-4] The role of the alkyne substituents is critical in the developed transformations and the talk will show how nitrogen[2] and sulfur[3] substituents enable reactivty and can be used to access complementary and regiodivergent outcomes under gold catalysis (Figure 1, box). The talk will show how the nitrenoid strategy allows fast entry into sp^3-rich azacyclic motifs[4] and provides an enabling tool to assess uncharted volumes of drug-like chemical space.

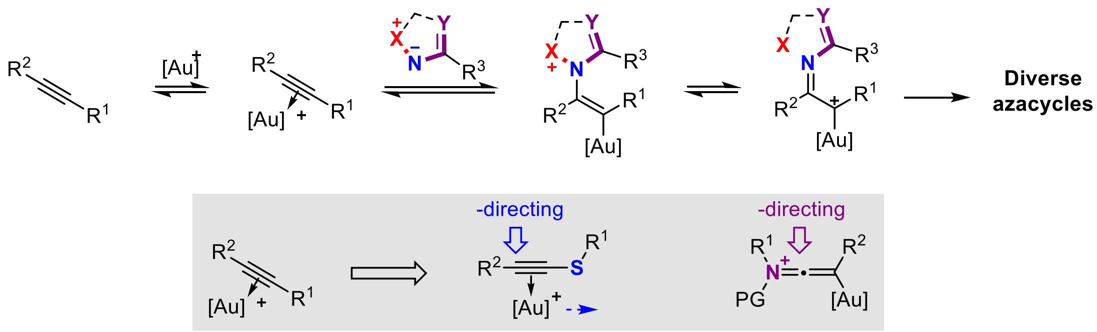

Figure 1: The nucleophilic nitrenoid strategy to access *N*-heterocycles via α-imino gold carbene reactivity patterns

Acknowledgements: The EPSRC (EP/V061690/1, EP/R512436/1), The EU Horizon 2020 programme (MSC 839037, ITN 765116), the Royal Society and Leverhulme Trust (SRF\R1\191033), Eli Lilly, AstraZeneca and the University of Birmingham are thanked for financial support. Support from the Centre for Chemical and Materials Analysis (UoB) is gratefully acknowledged.

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Asymmetric Synthesis of Trifluoromethylated Propargylic Ethers and Anilines through Multi-Component Reactions

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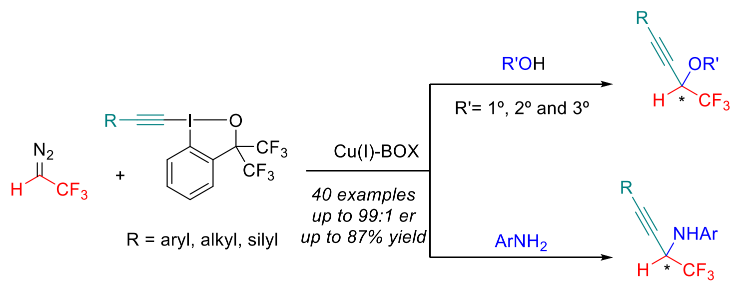
Chiral trifluoromethylated (CF_3) compounds have excellent physical and pharmacological properties, making them very important in organic and medicinal chemistry. Despite of their importance, traditional methods often rely on the use of strongly basic reaction conditions, presenting a narrow scope. For this reason, it is worth to find alternatives that allow the preparation of enantioenriched CF_3-compounds in a more efficient manner.[1] Propargylic ethers and anilines represent a versatile class of organic compounds in synthetically and medicinal chemistry due to the rigidity, electronic properties and easy post-functionalization of the alkyne group.

Multi-Component Reactions (MCRs) represent an easily way to synthesize libraries of compounds from simple and accessible starting materials, being often employed in medicinal chemistry. Diazo compounds represent an important example of precursors in MCRs since they can react with both nucleophiles and electrophiles on the same reactive center, allowing the formation of multiple bonds in a single step.

In this context, Hypervalent Iodine Reagents (HIR) have been widely used in organic chemistry for the Umpolung of the reactivity of nucleophiles [2], but barely in MCRs with diazo compounds. In the last years, our group has reported different multi-component reactions with HIR and diazo compounds as starting materials. [3,4] Here, we report the first enantioselective 3-CR reaction between fluorinated diazo compounds, nucleophiles and HIRs allowing the asymmetric synthesis of trifluoromethylated propargylic ethers or anilines (**Scheme I**) catalyzed by a simple Cu(I)-BOX catalytic system. The reaction proceeds with a broad functional group tolerance, since primary, secondary and tertiary alcohols as well as both electron-rich and electron-poor anilines can be used as a nucleophiles. Regarding the electrophilic partner, aryl-, alkyl- and silyl-substituted alkynes can be successfully introduced. In the case of chiral natural alcohols, the reaction proceeds with high catalyst control, achieving the synthesis of the trifluorinated propargylic ethers with very high diastereoselectivity [5]



Scheme I. Enantioselective 3-Component Reaction.

Acknowledgements: This publication was created as a part of NCCR Catalysis, a National Center of Competence in Research funded by the Swiss National Science Foundation (Grant No. 180544).

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Novel Chiral Imidazopyridine Au(I)-NHC Complexes for Enantioselective Enyne Cycloisomerizations

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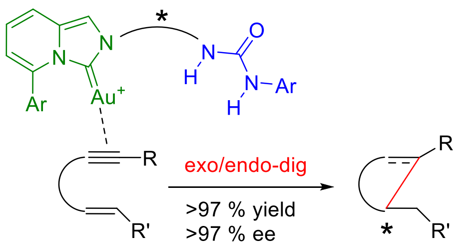
Enyne cycloisomerizations are a powerful tool to create complexity within a molecule from easily accessible starting materials. Metallic Lewis acids such as gold, palladium and platinum have been utilized for this type of reactions in recent years, activating unsaturated hydrocarbon bonds for intramolecular cyclization reactions.[1] Establishing Au(I) complexes as enantioselective catalysts presents a special challenge, which is due to the linear coordination sphere and therefore large distances between a chiral ligand and the reactive center.

Pathfinding works by Echavarren and Toste utilize axial chirality to tackle this issue.[2,3] In their case, binaphthyl-based counterions result in high enantioselectivities. Other approaches employ direct phosphine or N-heterocyclic carbene (NHC)-tethered axial chirality as well as cyclodextrin-based ligands, while examples of ligands featuring a single stereocenter are very rare.[4,5]

In our study we show the first example of a chiral, non-symmetric Au(I)-NHC, which is able to perform various enyne cycloisomerization reactions in up to excellent yields and enantioselectivities. The studied complexes utilize an imidazopyridine-based NHC core in combination with a chiral, urea-containing side-arm. We observe tunable selectivity dependent on the urea-moiety as well as unique reactivity due to urea-substrate interactions.



Scheme 1: Cycloisomerization reactions catalyzed by chiral Au(I) NHC.

Acknowledgements: We thank the Magnus Ernrooth foundation and the Maupertuis program for financial support.

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Electrochemical Reactions towards the Synthesis of Distinctive Organic Structures

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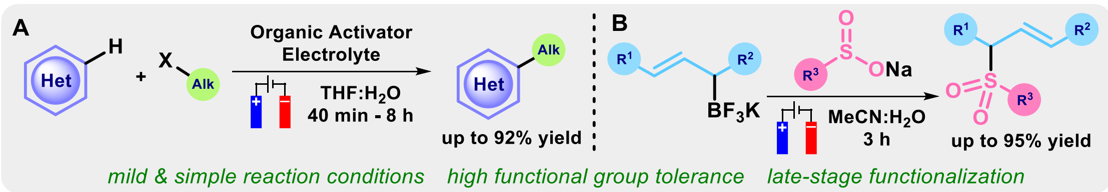
During the last years, our group has maintained a sustainable chemistry research line mainly based on organocatalysis, photocatalysis and catalytic materials. In the pursuit for new research avenues and greener methodologies, electrochemistry is quickly becoming one of the most popular paths to access radical intermediates among the multiple strategies based on the single-electron activation of organic substrates.[1] The venerable Minisci reaction stands as a powerful and appealing synthetic tool for the direct and rapid modification of *N*-heterocycles. Thus, electrochemical Minisci-type processes have recently begun to attract considerable attention employing different alkyl radical precursors.[2] In this context, we have described a general, facile and environmentally friendly Minisci-type alkylation of *N*-heteroarenes under simple electrochemical conditions using widely available alkyl halides as radical precursors (**Scheme 1A**).[3]



Scheme 1. **A**: Electrochemical Minisci-type alkylation. **B**: Electrochemical synthesis of allyl sulfones.

On the other hand, allyl sulfones are common scaffolds present in several biologically active molecules and serve as a popular building block in organic synthesis. Since the generation of sulfonyl radicals takes place under mild electrochemical conditions through anodic oxidation,[4] we have described the sulfonylation of allyl trifluoroborates (**Scheme 1B**). The radical addition to the alkene is followed by the elimination of the trifluoroborate moiety, giving rise to various substituted allyl sulfones. This methodology take advantage of low-cost, bench stable and easy-to-handle starting materials, providing a general, appealing and environmentally friendly alternative to conventional strategies for the synthesis of this valuable building blocks.[5]

Acknowledgements

Financial support was provided by the Spanish Government (PID2021-122299NB-100, TED2021-130470B-I00 and TED2021-129999B-C32) and "Comunidad Autónoma de Madrid" (S2018/NMT-4367 and Y2020/NMT-6469). J. A. F.-S. thanks the Spanish Government for a Ramón y Cajal contract (RYC2018-026178-I).

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A catalytic enantioselective stereodivergent aldol reaction

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The aldol reaction is among the most powerful and strategically important carbon–carbon bond–forming transformations in organic chemistry. The importance of the aldol reaction in constructing chiral building blocks for complex small-molecule synthesis has spurred continuous efforts toward the development of direct catalytic variants. The realization of a general catalytic aldol reaction with control over both the relative and absolute configurations of the newly formed stereogenic centers has been a longstanding goal in the field. Here, we report a decarboxylative aldol reaction that provides access to all four possible stereoisomers of the aldol product in one step from identical reactants. The mild reaction can be carried out on a large scale in an open flask, and generates CO_2 as the only by-product. The method tolerates a broad substrate scope and generates chiral β-hydroxy thioester products with substantial downstream utility. We will also discuss continuing efforts to tune the catalyst system for the development of a suite of stereodivergent enantioselective carbon–carbon bond forming reactions.

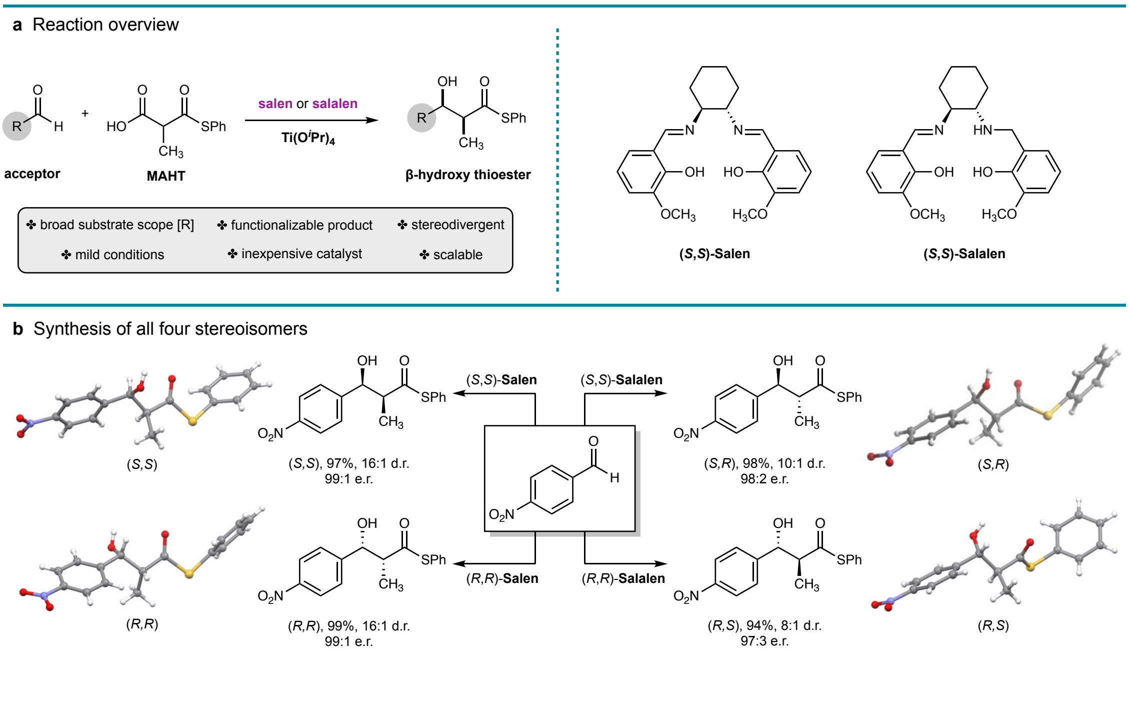

Figure 1: The development of a stereodivergent direct aldol reaction. (a) A stereodivergent catalytic aldol reaction using MAHT as a latent pronucleophile. (b) Synthesis of all four stereoisomers of the aldol product from identical substrates.

Acknowledgements: We thank New York University Abu Dhabi (NYUAD) and the Core Technology Platform for its generous support of this research program

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Scale-up of an Asymmetric sp^3-sp^2 Suzuki-Miyaura Type Reaction

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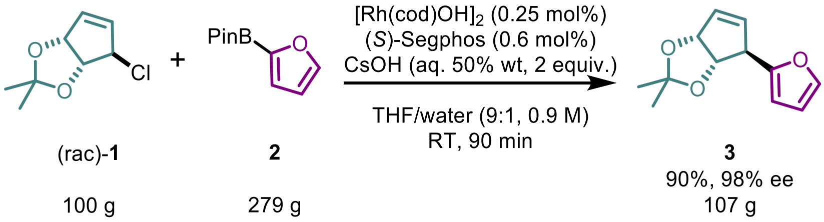
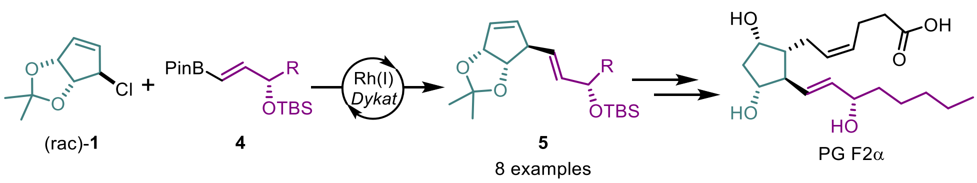
Csp^2-Csp^2 Suzuki-Miyaura couplings (SMCs) are ubiquitous in the synthesis of small molecules, but analogous Csp^2-Csp^3 bond forming reactions are rare, especially asymmetric variants. The simplicity by which Csp^2-Csp^2 SMCs has been directly correlated to significant issues in medicinal chemistry programs, which are oversaturated with achiral planar molecules.[1] This is despite the understanding that 3-dimensional and chiral compounds have repeatedly been shown to have higher success rates in discovery programs.[1,2] The synthesis of axially chiral molecules through Csp^2-Csp^2 SMCs is possible, but these find limited application in medicinal compounds.[3] As such, the development of a methodology which exploits the tremendous advantages of standard SMCs, while accessing 3D compounds.



Scheme 1. 100g scale SMC of sp^3 hybridized electrophile to yield 3-dimensional product.

We developed a series of Rh-catalysed couplings between racemic sp^3-hybridized allyl chlorides and heteroaryl boronic acids.[4] Here, we demonstrate that these catalytic asymmetric reactions can be scaled-up to give over 100 g of product, coupling a challenging heteroaromatic boronic acid and racemic bicyclic allyl chloride (Scheme 1).[5] The SMC product possesses three contiguous stereocentres, and is obtained as a single diastereomer in 90% yield and 98% ee. Thorough kinetic analysis of the reaction reveals two exothermic steps in the reaction set up and revealed the means by which to prevent the deleterious effects of heat spikes on the health of the catalyst.

To further demonstrate the potential utility of this methodology in industrially relevant settings, we have been able to demonstrate the application of allyl chloride (rac)-**1** in the synthesis of prostaglandin PG F2$_{\alpha}$ and a series of other intermediates which serve as precursors to several commercial prostaglandin drugs.[6]



Scheme 2. Application of asymmetric sp^3-sp^2 SMC in natural product synthesis

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Enantioselective One-pot Cascade Heck-Matsuda Reactions for the Construction of Complex Scaffolds

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The enantioselective Heck reactions stand among the most effective synthetic methods to create strategic C-C bonds and stereogenic centers. We recently reported the enantioselective Heck-Matsuda directly from anilines in a sequential manner thus circumventing the need for the synthesis and handling of unstable or challenging-to-synthesize aryldiazonium salts. The method relies on synchronized processes involving the progressive *in situ* diazotization of the starting anilines followed by a palladium-catalyzed Heck arylation using chiral *N*,*N*-ligands. Recent reports from our group showcased the intermolecular enantioselective HM arylation strategy applied to the desymmetrization of several unactivated olefins in good to excellent er (up to 99:1), dr > 20:1 and good overall yields of up to 82% over 2 or 3 steps.[1] The challenging intramolecular version was instrumental in the synthesis of enantioenriched bridged benzoxacines, unsaturated spirobenzofurans, 2,3-dihydrobenzofuran and 2,3-indoline acetate scaffolds in yields up to 91%, and er up to 97:3, including quaternary stereocenters.[2] Moreover, these HM protocols have been demonstrated to be amenable to several gram-scale reactions, and are equally effective with some heteroaromatic anilines. These cascade processes are now being extended to include easily accessible nitroarenes involving sequential reduction/diazotization/Heck reactions. This oral presentation will describe our recent results in these one-pot cascade reactions and applications in the enantioselective synthesis of interesting scaffolds and bioactive compounds.

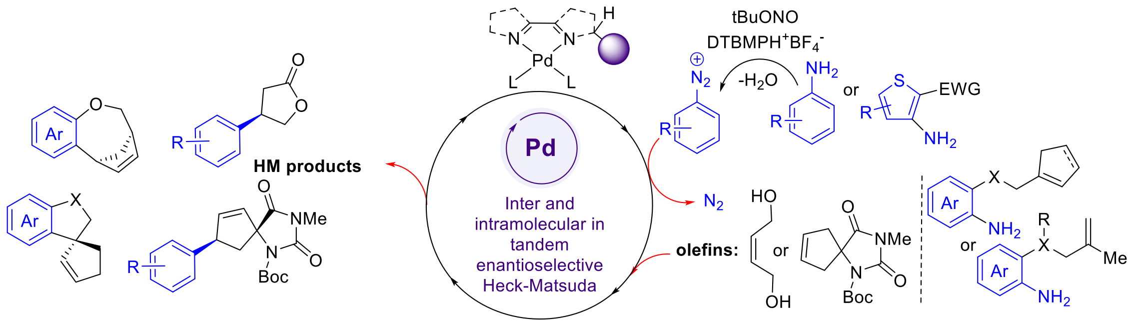

Figure 1. Some representative examples of the tandem enantioselective HM transformations

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New Concept: Umpolung Morita-Baylis-Hillman Reactions

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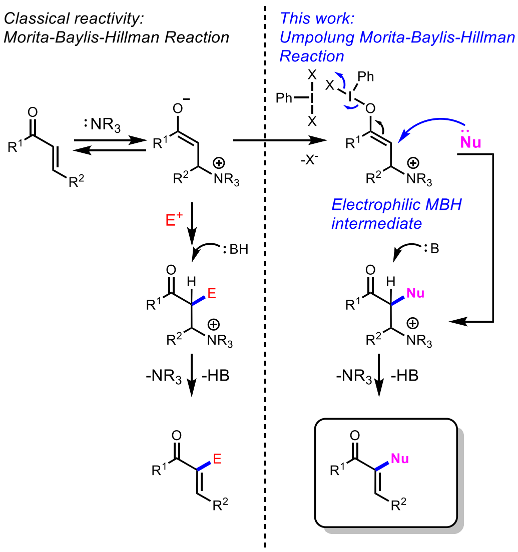
Our group has developed a uniqe synthetic strategy involving the umpolung of enolates, from nucleophiles to electrophiles, by the action of hypervalent iodine to form enolonium species.[1] We have applied this strategy to a plethora of new ketone α-functionalization reactions including allylation[1a] arylation,[1b] azidation,[1c] N-heteroarylation,[1c] and cross-coupling with TMS enolethers to give 1,4- dicarbonyl compounds.[1d] We have now expanded this chemistry to new reactive species such as azido-enolonium species.[1e] In this talk we will cover the development of a new concept in which the key nucleophilic enolate intermediate in the classical Morita-Baylis-Hillman reaction is inverted into an electrophilic enolonium species that may react with nucelophiles (**Scheme 1**).[2] This new concept was initally applied to two new reactions namely, formal α-hydroxylation and α-tosylation of enones.[2] Recently, the concept has been applied to α-fluorination as well.[3] As an aside this chemistry also led us to the serendisious discovery of the nitro-cyclopropanation of enones.[4] The mechanistic underpinnings of this new concept will be discussed.



Scheme1: The Classical and the Novel Umpolung Morita-Baylis-Hillman Concept.

Acknowledgements: This research was supported by the Israel Science Foundation (Grant No. 870/19)

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Synthesis of allylic systems and heterocycles with highly functionalized olefin side chain from propargyl silanes via 1,2-silyl shift

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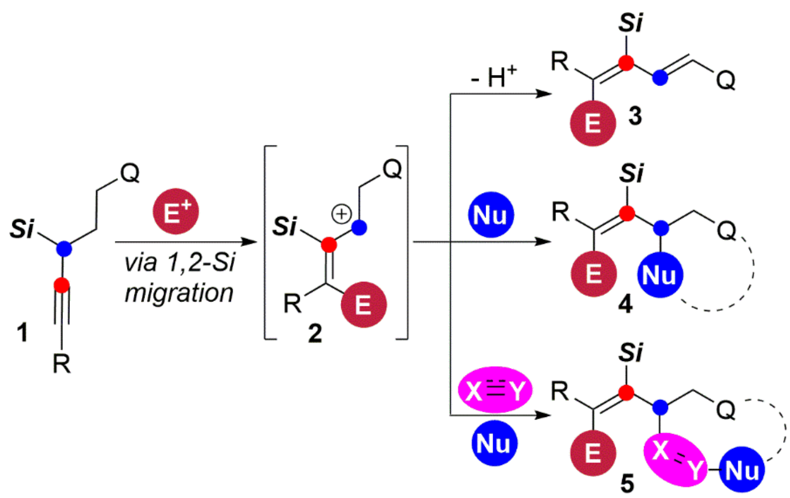
A non-vertical stabilization of β-silyl carbocations (formation of cyclic silonium ion) can lead to 1,2-silyl migration.[1] Recently, we have applied this phenomenon in the Brønsted acid catalyzed synthesis of silyldienes **3** from propargylsilanes **1** ($E^+ = H^+$).[2]

Herein, we report a further development of this methodology, which profits from the vinyl cation - allyl cation rearrangement via 1,2-silyl shift. Electrophiles like H^+, Br^+, I^+, $PhSe^+$ and *in situ* generated organocopper(III) species can be used for the transformation **1** + E^+ → **2**. The latter is prone to accept various nucleophiles in either intramolecular or intermolecular manner. These include alcohols, carboxylic acids, oximes, acyl and sulfonyl amides, carbamates and thioacetates. In this way highly functionalized allylic systems or heterocycles with substituted olefin side chain are obtained. The latter are shown to undergo further transformations by reactions like C-C cross-coupling reactions of vinyl halide or vinyl silane moieties, and allylic substitution. We have also extended this methodology to multicomponent approach by combining propargyl silane, incoming electrophile and nitrile for the Ritter type process, which is terminated by nucleophilic attack. Preliminary studies suggest that the transformation **1** → **4** can be performed in the enantioselective fashion in the presence of chiral Brønsted acids.



Acknowledgements: This work has been supported by the Latvian Council of Science Grant LZP-2023/1-0576. R.B and R.K thank the European Social Fund within the project 8.2.2.0/20/I/008 and Riga Technical University Doctoral Student Grant.

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Towards Greener Synthesis: Developing an Environmentally Friendly Process for the Synthesis of an Amide-Containing Drug

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In the process development of a new API (Active Pharmaceutical Ingredient), the synthesis and isolation of intermediates and the final product are critical steps. Amide bond formation plays a vital role in industrial processes for manufacturing pharmaceutical drugs due to the prevalence of amide functional groups in bioactive molecules. However, finding the optimal amide coupling methodology can be a challenging task, especially when there is a simultaneous need to reduce costs, enhance product quality, and ensure ease of operation.

In the pursuit of developing a scalable process for amide formation, the initial approach involved the *in-situ* use of thionyl chloride, a hazardous reagent, to convert the parent acid into the desired amide. However, during the scale-up phase, several challenges were encountered, prompting the need to explore alternative and safer conditions.

To address the issues associated with the hazardous nature of thionyl chloride, a scouting process was initiated. The aim was to identify alternative reagents and reaction conditions that would facilitate smoother and safer amide formation.

By exploring alternative conditions, the development team aimed to find a more practical and environmentally friendly approach while ensuring the desired conversion and yield. This scouting process not only focused on improving safety during the synthesis but also aimed to streamline the scale-up process and ultimately enhance the overall efficiency of the API manufacturing process.

This presentation covers the exploration of reagents, process development, and enhanced amide coupling techniques, as well as the subsequent isolation of the final API with the desired polymorphic purity.

Preparative scale synthesis of α-hydroxylated fatty acids with P450 peroxygenases

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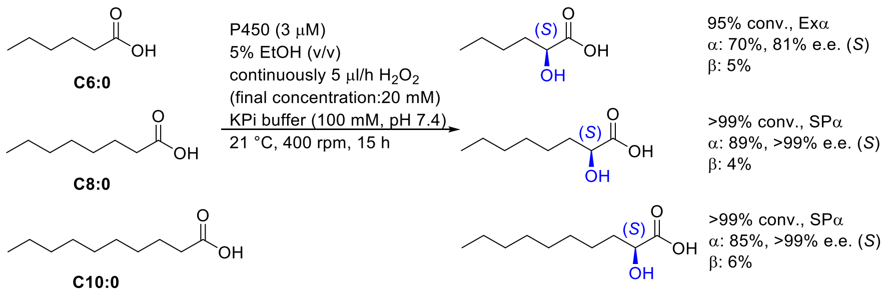
α-Hydroxylated fatty acids are of industrial interest as they can be used as building blocks for high value fine chemicals, in cosmetics and for biobased/ biodegradable polymers.[1] Six candidates of the bacterial cytochrome P450 peroxygenase family, $P450_{Sp\alpha}$[2], $P450_{CLA}$[3], $P450_{Bs\beta\ F79L/G290F}$[4], $P450_{Ex\alpha}$[5], CYP152K6[6] and $P450_{J\alpha}$[7] were tested for the biocatalytic α-functionalization of medium-chain fatty acids. These enzymes belong to a subgroup of the cytochrome P450 enzyme family and use hydrogen peroxide as the only electron and oxygen source to drive hydroxylation and decarboxylation of fatty acids.[8] $P450_{Ex\alpha}$ was the perfect candidate for the conversion of C6:0, (95% conv.) and showed high regioselectivity (70% α-hydroxylation). $P450_{Sp\alpha}$ showed excellent conversion (>99% conv.) and formation of α-hydroxylated fatty acids [for C8:0 (89%) and C10:0 (85%)] **Scheme 1**. Despite their high regioselectivity, all enzyme candidates are also highly stereoselective enzymes as they are all (*S*)-selective. A suitable process for larger scale production of α-hydroxylated fatty acids was established. C8:0 (up to 150 mM), C10:0 (10 mM) and sebacic acid (10 mM) were successfully converted into the corresponding α-hydroxylated acid. P450 enzymes showed good catalytic performance and TONs of 3333 to 50000 for the conversion of C8:0 and C10:0 by $P450_{Sp\alpha}$ and TONs of 3333 to 16667 for the conversion of sebacic acid with $P450_{Ex\alpha}$ were reached.



Scheme 1: Conversion of medium chain fatty acids with P450 enzymes

Acknowledgements: This project received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement BioBased ValueCircle No 956621.

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RECENT APPROACHES TOWARDS THE SYNTHESIS OF POLYSUBSTITUTED HETEROCYCLIC STRUCTURES

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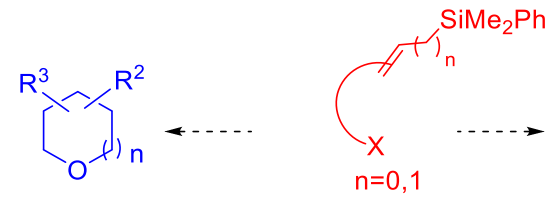
Heterocycles are scaffolds present in a wide variety of natural products with important medicinal properties. Among them, 6, 7 and 8-membered heterocycles have attracted special attention due to their occurrence in bioactive compounds of great pharmacological interest. Consequently, a great number of scientifics have reported a variety of synthetic protocols to afford these substrates.

Within the known strategies, Prins cyclization has emerged as a very efficient tool to obtain heterocycles in a very stereoselective manner.[1,2]

Following our interest in the development of new approaches to the synthesis of heterocyclic structures, promoted by silicon-mediated cyclizations, we now present our recent results in the application of the silyl-Prins cyclization to the synthesis of different sized heterocycles (Scheme 1), including 6, 7 and 8-membered derivatives.[3-5]



Scheme or Figure 1: Towards de synthesis of polysubstituted heterocycles.

Acknowledgements: We thank the Spanish Ministry of Science and Innovation for financial support.

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OC 20

Design and Applications of Bi(V) Reagents for Electrophilic Arylation

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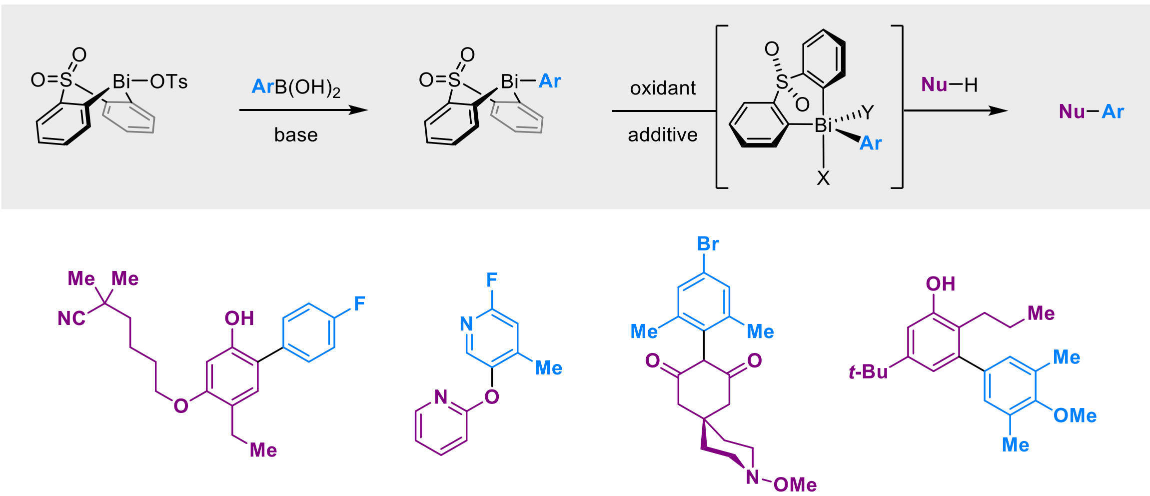
The catalytic cross-coupling of *C*-, *N*- and *O*-nucleophiles is an essential tool for the pharmaceutical and agrochemical industries. However, despite the highly sophisticated state of the art, the arylation of weak nucleophiles remains challenging due to the low rate of reductive elimination from highly polarized M−R bonds. We have developed a suite of methods for the electrophilic arylation of weak nucleophiles with non-toxic Bi(V) reagents (**Scheme 1**). This methodology relies on *in situ* generation of a reactive Bi(V) arylating agent from a bench-stable Bi(III) precursor *via* telescoped B-to-Bi transmetallation and oxidation. Insight from experimental and computational mechanistic studies has revealed the key role that the identity of the Bi(V) intermediate plays in controlling reactivity and selectivity, ultimately allowing extension of our methodology from the *ortho*-selective arylation of phenols[1] to O-H,[2] C(sp^3)-H[3] and *meta*-selective[4] arylation.



Scheme 1: Bismuth-mediated electrophilic arylation.

This talk will discuss the design, development and new applications of bismacyclic reagents in electrophilic arylation. Particular focus will be given to addressing challenges in the agrochemical discovery sector, and the development of scalable synthesis methodology.

Acknowledgements: This work was supported by the University of Nottingham (studentships to M.J. and L.M.), the EPSRC Centre for Doctoral Training in Sustainable Chemistry (grant no. EP/S022236/1, studentship to A.S.), Syngenta (studentship to K.R.), and the UKRI (grant no. MR/V022067/1, Future Leaders Fellowship to L.T.B.).

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Transition metal-mediated transformations in Plant Hormone Chemistry: Valuable tools to create new lead structures against abiotic stress in crops

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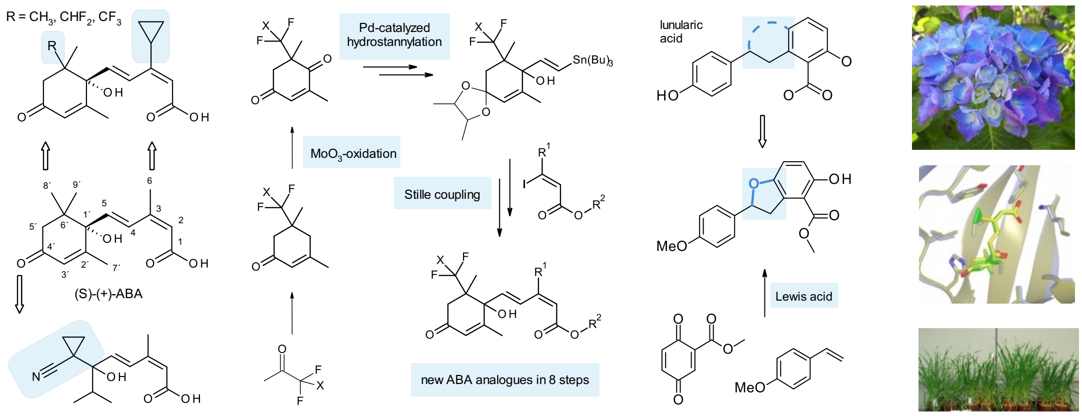
Abiotic stress adversely affects crop production in various parts of the world, decreasing average yields for most of the crops significantly. Several strategies have been investigated for reducing the impact of drought on crop yield, such as exploiting beneficial effects of crop protection agents, developing drought tolerant crops through transgenic approaches or breeding, but also exploring novel chemical entities inspired by naturally occurring plant hormones.

Herein, novel analogues of plant hormones abscisic acid (ABA) and lunularic acid (LA) bearing yet unexplored motifs have been prepared *via* transition-metal mediated key steps.[1] It could thus be explored how modifying key parts of ABA influenced receptor affinity and in vivo efficacy against drought stress. In line with X-ray crystallography studies and molecular modeling novel ABA-derivatives showed strong effects against drought stress in wheat, corn and barley. Furthermore, cyano-cycloalkyl groups and haloalkyl-substituted cyclohexenones proved to be suitable isosteric replacements of the cyclohexenone moiety.[2-3] The versatile synthesis of these target compounds proceeded *via* Stille or Sonogashira couplings as the key steps enabling us to carry out in-depth SAR studies. Haloalkyl-substituted cyclohexenedione precursors could be prepared via MoO_3-mediated allylic oxidation. Furthermore, we have identified and prepared several synthetic ABA-agonists based on tetrahydroquinolinone and dihydroindolone scaffolds.[4]

Lunularic acid, a dihydrostilbenoid carrying a salicylate moiety has been suspected to be substituting the role of ABA in some lower plants, but it can also be found in *Hydrangea macrophylla*. Whilst modifying structural features of ABA has attracted considerable interest in recent years,[1] a surprisingly limited number of studies has been carried out so far to investigate structural modifications of LA. Albeit the precise mode of action of LA and its analogues still remains unknown, we identified a set of 2,3-dihydro-1-benzofuran-4-carboxylates as potent lead structures against drought and cold stress in crops accessible *via* an attractively short Lewis-acid catalyzed cyclization approach.[5] Notably, some of the new 2,3-dihydro-1-benzofuran-4-carboxylates surpassed the efficacy of ABA in *in vivo* tests.



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The Design and Synthesis of Anionic Porphyrins Bearing Chiral Cations and Their Exploration in Catalysis

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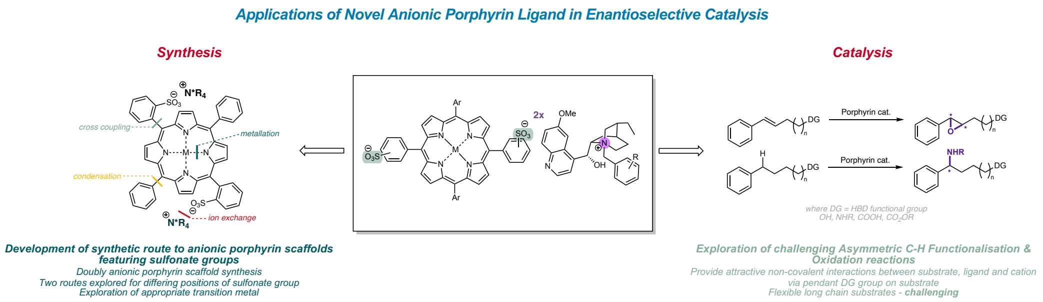
Asymmetric transition-metal catalysed reactions are commonly used to access highly enantioenriched compounds.[1] Classical approaches in this field involve the use of chiral ligands on the metal to induce asymmetry, favouring the major enantiomer through less steric repulsion at the transition state. Whilst a powerful and well-proven approach to enantiocontrol, it is not always universally applicable.

Our group has recently developed a new approach in which achiral anionic ligands are paired with chiral cations based on the readily available cinchona alkaloid scaffold. A network of attractive non-covalent interactions between the anionic ligand, cation and substrate can provide an organised transition state and have been shown to induce enantioselectivity into challenging reaction types; iridium catalysed C-H borylation and rhodium-catalysed C-H amination.[2,3]

One privileged class of ligands that is particularly challenging to render chiral is the porphyrin framework.[4] This could be due to the relative distance between the metal centre and the porphyrin backbone, making asymmetry hard to transfer based on steric repulsion from the ligand to the substrate. Porphyrin ligands are also flat molecules hence, incorporating 3D conformation onto the scaffold is challenging due to geometric constraints.

We have designed and executed the syntheses of novel classes of sulfonated, doubly anionic porphyrins, exploring two different routes to access a variety of catalyst systems. Once in hand, the anionic porphyrin scaffolds were ion-paired to a range of chiral, privileged cationic scaffolds based upon cinchona alkaloids. Since development of two reliable synthetic routes to these privileged chiral ligand scaffolds, we are currently progressing in the discovery of potential catalytic C-H functionalisation and oxidation reactions where inducing chirality is challenging.



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Flash Communications

P-C bond Cleavage + H_2 addition in Ruthenium hydride complexes supported by di-tert-butylpyridylphosphine

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Metal hydrides are an important class of compounds that catalyze industrially relevant processes like hydrogenation, hydrosilylation and hydroformylation. Transition metal hydrides are also intermediates in other important reactions like C-H activation and olefin isomerization. More recent applications can be found in emerging fields like Energy Conversion and Hydrogen Storage, where they provide H^- for generation of H_2, and materials that can reversibly and heterolytically cleave H_2, respectively.[1]

The reactivity of ruthenium hydride complexes that are supported by 2-((ditert-butylphosphino)methyl)pyridine, **L1**, and 2-[bis(2-methyl-2-propanyl)phosphino]pyridine, **L2**, was explored (Figure 1).[2] $\{Ru(COD)Cl_2\}_n$ reacts with **L1** at 80 °C in the presence of a base and 10 bar of H_2 to afford the expected [Ru(**L1**)$_2$(H)Cl], **1**, but the same reaction with **L2** gave unexpectedly [Ru(**L2**)(P(H)^{t}Bu$_2$)(H)Cl], **2**, that results from the cleavage+H_2 addition to a P-C bond. By combining NMR, carefully planned experiments and DFT we were able to propose a mechanism for this reaction, that has the protonation of the carbon as the highest energy step (38.9 kcal/mol), which is consistent with a slow reaction. Preliminary catalytic results for the hydrogenation of benzaldehyde are also reported.

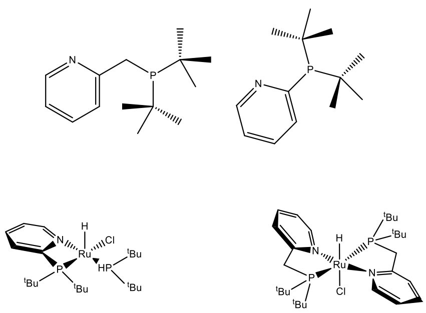

Figure 1: Ligands and complexes.

Acknowledgements: We thank the Fundação para a Ciência e Tecnolgia for financial support. Centro de Química Estrutural is a Research Unit funded by Fundação para a Ciência e Tecnologia through projects UIDB/00100/2020 and UIDP/00100/2020. Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020. V.R.G.C acknowledges FCT for the doctoral fellowship PD/BD/147841/2019 integrated in the PhD Program in NMR applied to chemistry, materials, and biosciences (PD/00065/2013). The NMR spectrometers are part of the National NMR Network (PTNMR) and are partially supported by Infrastructure Project No 022161 (co-financed by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC).

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Suzuki-Miyaura coupling using a recycled and reusable homogeneous palladium catalyst

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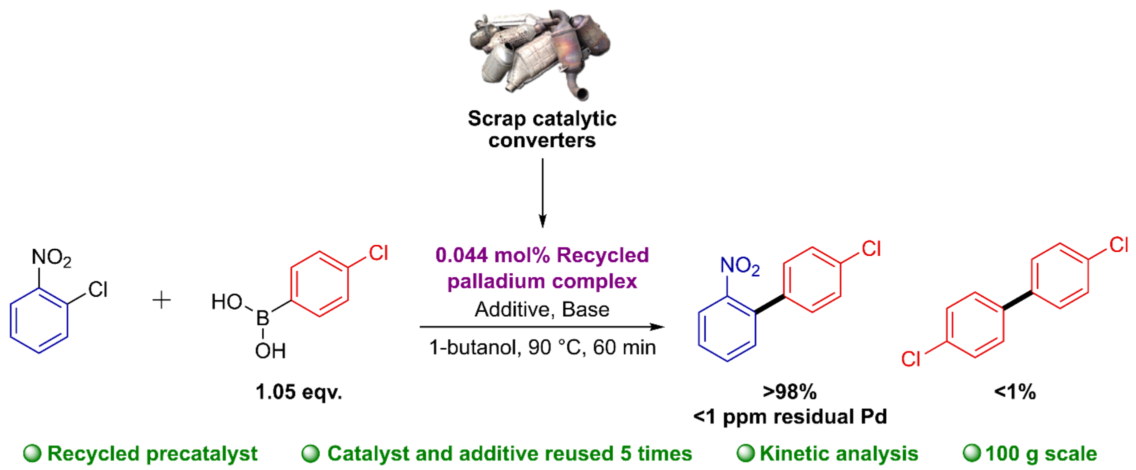
Unrelenting demand for the finite natural supply of palladium has resulted in supply deficits and record prices (~350% price increase since 2012).[1] Palladium production is also plagued with the environmental impact of mining and refining processes.[2] As a result, palladium consumption in its current form is unsustainable and improvements to the lifecycle of the metal are needed.[3] Owing to their short lifetime and rich palladium content (2000 ppm versus <10 ppm in ore), scrap catalytic converters (SCCs) offer a valuable 'urban mine' of palladium. Despite this, existing recovery technologies are limited by energy intensive pyrometallurgy (temperatures >1000 °C) and undesirable hydrometallurgical processes e.g. *aqua regia* and multi-step liquid-liquid extractions. This has led to our research on molecular palladium compounds recovered directly by solvometallurgy from solid SCCs for use as catalysts.[4-6] Herein, a molecular palladium complex recyclable from SCCs has been applied as a homogeneous Suzuki-Miyaura catalyst. A design of experiments (DoE) optimisation on a model reaction (**Scheme 1**, Boscalid intermediate, BASF) provided conditions for high conversions (>98%) and cross-coupling selectivity (99:1) on a 100 g scale. A novel strategy for both catalyst and additive recycling has been demonstrated over five reuse cycles by kinetic reaction profiles. ICP-MS, TEM and kinetic analysis revealed that palladium speciation and recycling was influenced by water leaching during work-up. Kinetic and mechanistic analysis also revealed the role of catalyst aggregates and an unusual catalyst deactivation pathway. Finally, kinetic profiles illustrate that the recycled and recyclable palladium catalyst perform comparably to traditional catalysts. Our results offer a unique strategy for achieving 'closed-loop' sustainable consumption of palladium in the chemical industry.



Scheme 1: Graphical abstract – Model Suzuki-Miyaura coupling.

Acknowledgements: We are grateful for a studentship to S.M. funded by the EPSRC Centre for Doctoral Training in Next Generation Synthesis and Reaction Technology (Imperial College London, EP/S023232/1).

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Mo(VI)=NR/Borane based Frustrated Lewis Pairs: H_2 Activation and Catalytic Reduction of Aldehydes

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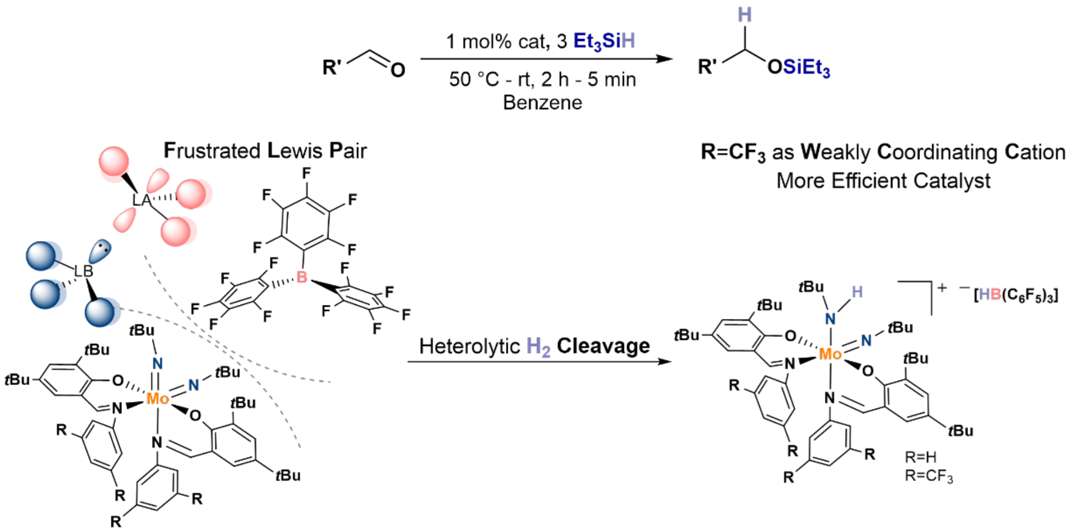
The term "Frustrated Lewis pair" (FLP) was introduced in 2007 describing a non-classical Lewis pair but rather an association of a Lewis acid and a Lewis base that are hindered by steric and/or electronic factors from forming a strong bond. As a result, the respective functionalities of the acid and the base are retained.[1] Herein, we present two bis-imido Mo(VI) complexes bearing Schiff-base ligands that exhibit, together with tris(pentafluorophenyl)borane Frustrated Lewis pair character. These bimolecular systems are able to activate molecular hydrogen and form stable ion pairs composed of a Mo(VI) amido imido cation and a hydridoborate anion. The obtained ion pairs are effective catalysts in the hydrosilylation of various aldehydes. Mechanistic elucidation of the catalytic cycle reveals the insertion of the aldehyde into the anion's B-H bond forming an isolable intermediate. The catalytic activity takes place at the anion while the cation seems to be an innocent by-stander. However, the investigated catalysts show significantly different activities despite the identical anionic active site. The fluorinated cation with higher steric bulk and charge distribution renders the hydride at boron more nucleophilic leading to higher reaction rates.[2] These results give evidence that the molybdenum cations influence the outcome pointing towards a behavior as weakly coordinating cation (WCC). While the concept of weakly coordinating anions (WCA)[3] is well described, the cations are yet rarely studied, particularly in combination with transition metal complexes.



Scheme 1: Synthesis of the catalysts via heterolytical H_2 cleavage with Frustrated Lewis pairs leading to ion pairs capable to convert aldehydes to corresponding hydrosilylated products. Depending on the catalyst's nature, behavior as WCC can be observed.

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Stereodivergent 1,3-difunctionalisation of unactivated alkenes by charge relocation

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Alkene difunctionalisation is a text-book paradigm in organic chemistry, with 1,2-addition across a double bond and allylic functionalisation being among the most widely employed reactions of alkenes.[1]
While difunctionalisation at distal positions has been reported, it typically relies on carefully crafted substrates featuring directing groups and/or stabilising features, all of which control the final site of bond formation.
Herein, we present our results of a study culminating in the development of a process that enables stereodivergent access to 1,3-difunctionalised products of either syn- or anti-configuration. Notably, our approach allows the use of unactivated alkenes, lacking any directing groups, as substrates – through a novel reactivity paradigm which we term "charge relocation" (**Figure 1**).[2]

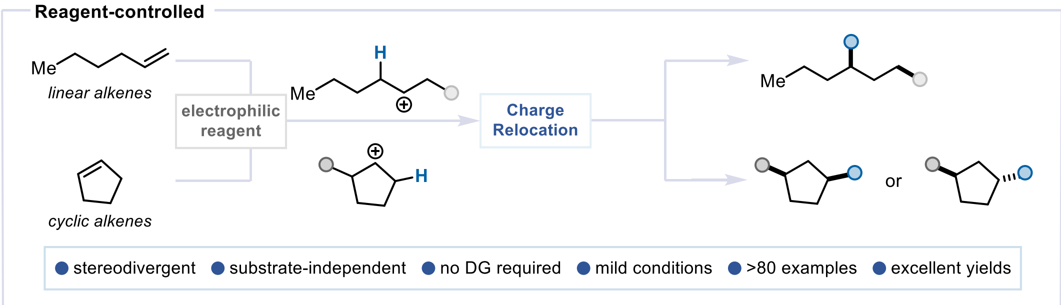

Figure 1: A stereodivergent reagent-controlled 1,3-functionalisation of alkenes *via* charge relocation.

Acknowledgements: This work has been supported by the Austrian Academy of Sciences (DOC Fellowship to B.R.B.) and the European Research Council (CoG VINCAT to N.M.). Generous support by the University of Vienna is acknowledged. We thank A. Roller (U. Vienna) for X-ray crystallographic structure determination.

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The quest towards novel synthetic methodologies from nitroarenes for applications in organic electronics

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Cross-coupling reactions are essential tools in the elaboration of functional organic materials[1]. As the trend in chemistry is directed towards greener answers to synthetic challenges, the use of the haloarenes, often involved in the construction of these materials, became problematic. Indeed, the synthesis of these haloarenes lacks in efficiency, selectivity and environmental conscientiousness. Established in the fact that the nitration reaction in arene series is common at the industrial scale, nitroarenes have recently attracted a great interest to replace haloarenes in nickel and pallado-catalysed cross-couplings[2]. Since our project is also geared towards applications in organic photovoltaics, our focus will be on the use of nitro-PDI (perylenediimide) derivatives as starting materials to prepare original architectures for such applications. Although they started off as industrial dyes, PDIs found their ways into the field of functional organic materials due to a low lying LUMO, electron mobility, and exceptional optical properties[3]. PDIs can be easily functionalized in the bay, ortho and imide positions thus tuning their properties for the desired application. In recent research conducted by our team, we have demonstrated that nitro-PDIs could be used as electrophilic substrates in both Stille[4] and Suzuki-Miyaura[5] couplings. Starting from the dinitro-PDI, the unprecedented bay-dessymetrization of the PDI skeleton was also demonstrated proving the selectivity of both reactions, knowing that the dessymetrization is not accessible from the dibromoPDI.

We will present an overview of these cross-coupling reactions carried out on mononitro- and dinitro-PDI. Moreover the application of the bay-dessymetrization will be discussed with the synthesis of new PDI based dyes for dye-sensitized solar cells (DSSCs) **(Figure 1)**. We will also present original structures constructed using original methodology developed through our research.

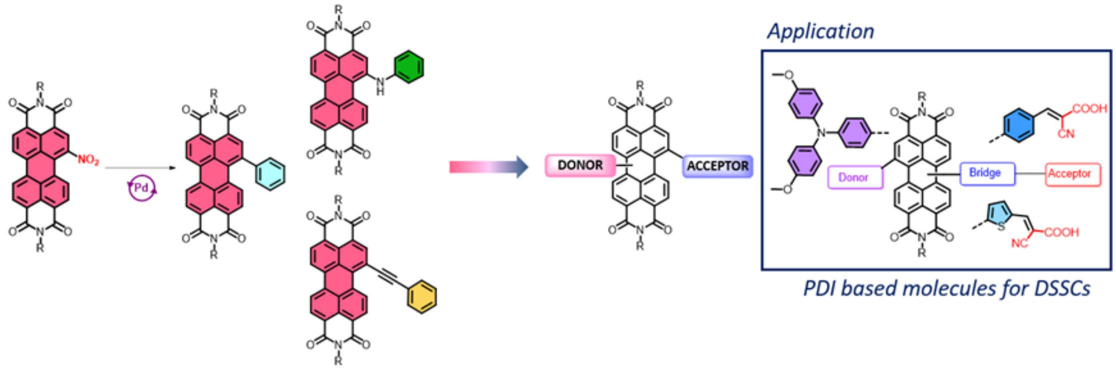

Figure 1: New cross-coupling methodology and suggested target molecules.

Acknowledgements: We thank the University of Angers for the financial support

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H(O)P(OPh)2-PROMOTED DEOXYGENATIVE HALOGENATION OF ALCOHOLS

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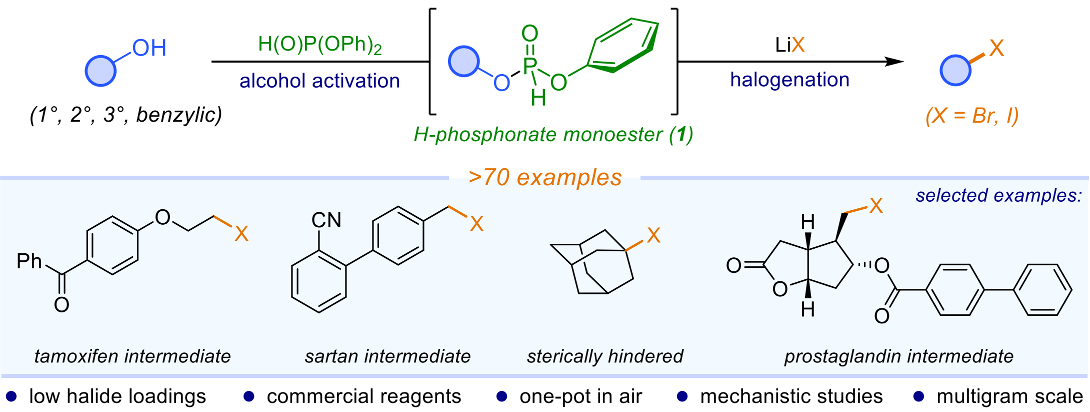
Organic halides are ubiquitous amongst target molecules such as pharmaceuticals, natural products and agrochemicals,[1–3] however, the use of this class of compounds is more often attributed to their inherent reactivity. C(sp^3)–halogenated compounds in particular are synthetically useful reagents as they enable molecular construction by nucleophilic substitution and can serve as precursors to organometallic reagents or carbon radicals. Traditional means of preparing organic halides from alcohols typically make use of hazardous, high-energy reagents and generate stoichiometric quantities of halogenated waste,[4] resulting in processes that are incongruent with the principles of green chemistry.



We report an operationally convenient protocol for the iodination and bromination of alcohols that exploits the inherent behaviour of a commercially available diaryl H-phosphonate promoter, H(O)P(OPh)$_2$.[5] Alcohol activation is achieved by a key transesterification event furnishing the reactive H-phosphonate monoester (1), thus transforming the parent alcohol into an electrophilic intermediate, under halogen-free conditions. Lithium halide salts employed at low loadings carry out the subsequent deoxygenative halogenation, circumventing the requirement for toxic molecular halogens or highly reactive, electrophilic halogenating agents. This strategy has been applied in the synthesis of a variety of primary, secondary, tertiary and benzylic organic halides, demonstrating its synthetic utility as a novel halogenation protocol.

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ENANTIOSELECTIVE PHOTOCATALYTIC SYNTHESIS OF SATURATED BICYCLIC SCAFFOLDS AS PHENYL BIOISOSTERES

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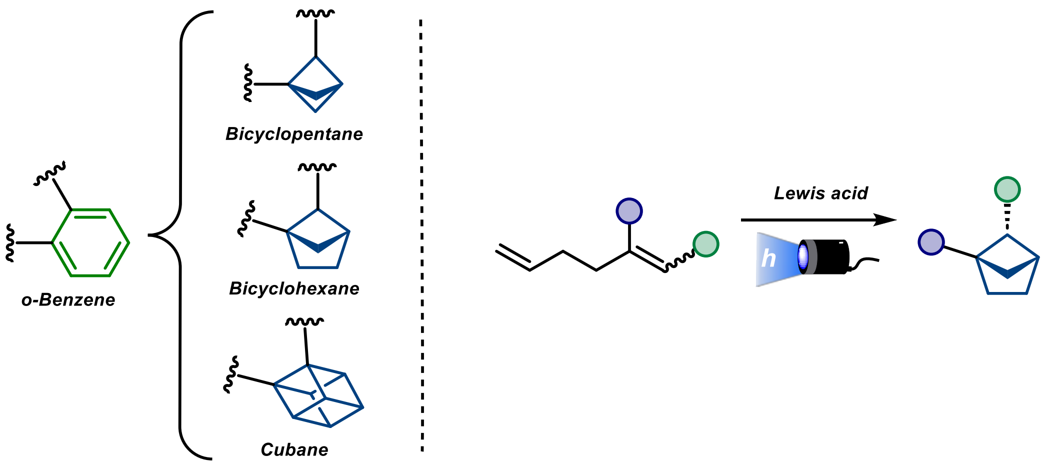
Benzene rings are one of the most abundant structural motifs present in drugs and bioactive molecules. The replacement of these scaffolds for sp^3-rich analogues as suitable bioisosteres represents an interesting approach when seeking diversity in medicinal chemistry.[1]

Over the last years, some saturated bicyclic structures have been described and validated as appropriate bioisosteres of disubstituted benzenes. The substitution of sp^2-hybridized scaffolds with rigid three-dimensional building blocks with well-defined exit vectors, open access to a novel and unexplored chemical space. Pharmaceutical properties of drugs, such as solubility and metabolic stability can be improved with the replacement of planar aromatic rings with their saturated bioisosteres. These compounds have also the advantage of avoiding conflict with patents concerning benzene and its various substitution.[2] Despite these facts and even though the enantioenriched drug analogues could potentially result in an improvement of their biological properties, the enantioselective catalytic synthesis of disubstituted benzene bioisosteres remains unexplored, and no methodology has been reported yet.

Herein we will describe a unique approach for the enantioselective catalytic synthesis of 1,5-disubstituted bicyclo[2.1.1]hexanes based on a Lewis acid-catalyzed [2+2] photocycloaddition. The pharmaceutical properties were evaluated for the individual enantiomers of biologically active compounds in which the bicyclic scaffold was implemented, indicating that the developed catalytic strategy has the potential to be employed for the construction of enantioenriched drug analogues with enhanced biological activity.



Scheme 1: Examples of ortho-disubstituted benzene bioisosteres, and proposed method for the synthesis of enantioenriched bicyclo[2.1.1]hexanes.

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Repurposing fluorinated carboxylic acids as fluoroalkylating reagents with Earth-abundant photocatalysts

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Fluorinated carboxylic acids are the most abundant and accessible sources of fluoroalkyl groups such as CF_3, CF_2H and CF_2R, which are some of the most significant fluorine-containing motifs in medicinal and agricultural chemistry.[1] However, its use in fluoroalkylation reactions requires the generation of C-centered radical species via decarboxylation, a process which is difficulted by their high oxidation potential and slow decarboxylation rates. This poses a significant barrier for redox-based techniques, because of the need to pair such high redox potentials.[2] As a result, the use of the most available, stable, and inexpensive fluoroalkylating sources hasn't had much impact in applied campaigns, which are dominated by expensive and tricky-to-handle tailored reagents. In this communication, I will present our group's efforts to enable the possibility of repurposing trifluoroacetic, difluoroacetic and halodifluoroacetic acid chemical feedstocks as fluoroalkylating reagents via direct decarboxylation with Earth-abundant photocatalysts (**Figure 1**). Unlike canonical photoredox catalysis, our catalytic design works via a complementary inner-sphere electron transfer pathway[3] which is not constrained by thermodynamic prerequisites. This has allowed us to promote radical C(sp^2)–H fluoroalkylation reactions of organic substrates with much lower oxidation potentials, including late-stage scenarios with the derivatization of molecules of interest for the pharmaceutical and agrochemical sectors.

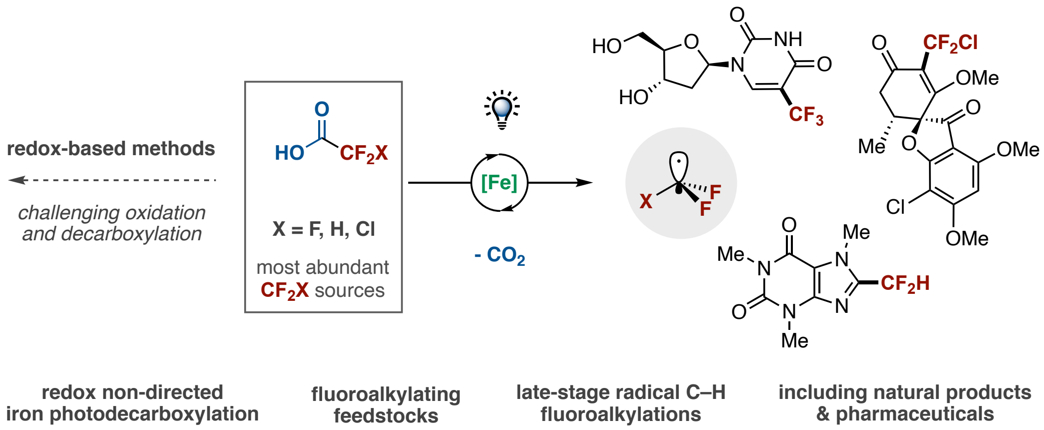

Figure 1: Fluoroalkylation of organic molecules via direct decarboxylation of fluorinated carboxylic acids with Earth-abundant metal photocatalysts.

Acknowledgements: We thank the Spanish Research Council MCIN/AEI/10.13039/501100011033, "ESF Investing in your future" (PID2020-115408GA-I00 and RYC2018-024643-I) and the University of Murcia (ATTRACT-RYC 2023) for financial support.

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Improved NO_x removal by visible light photocatalysis trough ZnAlEu layered double hydroxides

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Currently there is huge concern to address the NO_x gases pollution ($NO + NO_2$), due to their hazardous effects on citizen health and environment. The concentration of these gases can be reduced directly from the air at ppb levels in cities through photocatalytic technology (De-NO_x process), by using the sunlight irradiation and a photocatalyst at soft conditions. Nevertheless, this technology is not extended enough mainly because of commercial photocatalysts (TiO_2-based) are active only under UV light, not taking advantage of the visible light (about 43 % of the received solar energy), resulting in low NO_x removal efficiencies[1].

Layered Double Hydroxides (LDHs) are interesting materials due to its high photocatalytic De-NO_x selectivity[2], low cost and chemical tuneability[3]. Herein, ZnAl-LDHs were doped with small amounts of Eu^{3+}. In order to keep a "green" scope, the synthesis was carried out by a simple coprecipitation method, at room temperature, with water as a the only solvent and without using complex apparatuses. The substitution of Al^{3+} by Eu^{3+}, cations with quite different atomic radii, should induce some disorder in the LDH structure, which might improve its photocatalytic efficiency.

The samples were characterised to analyse their structure, porosity, morphology, optical and electronic properties. The results showed that Eu incorporation in LDH layers decreased its crystallinity, also producing a *110* plane reflection shifting, confirming the Eu doping. The optical band gap was decreased with the Eu^{3+} content, and the electronic bands of the compounds were modified, as observed by VB-XPS. The photocatalytic NO_x removal efficiency of the doped samples was improved. Additionally, the optimal Eu-doped LDH showed a De-NO_x efficiency under visible irradiation (420 nm) of ~ 47 %, overcoming the activity of the undoped LDH (~ 12 %). In addition, the optimal photocatalyst virtually maintained its high removal efficiency for long irradiation tests (up to 18 h), the photocatalyst being stable and reusable after those tests. The enhanced NO_x removal efficiency is related to a lessening of the electron/hole recombination (confirmed by PL) and an improved generation of ·OH radicals (confirmed by EPR spin-trapping experiments), resulting from the unusual position of Eu in the LDH framework and its electronic configuration. The positive results open the door to use these doped LDHs for other photocatalytic applications where the harvesting of visible light is a key.

Acknowledgements: We thank the support of Junta de Andalucía, Spain (PAI Groups FQM-214 and FQM-175, FQM-192) Agencia Estatal de Investigación and Spanish Government (PID2020-117516GB-I00, PID2020-117832RB-100). Chunping Chen acknowledges support from SCG Chemicals ublic Co Ltd. Adrián Pastor is grateful for a contract received by Universidad de Córdoba (Plan Propio de Investigación de la Universidad de Córdoba 2022).

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Photocatalytic oxidation of biomass-derived heterocycles

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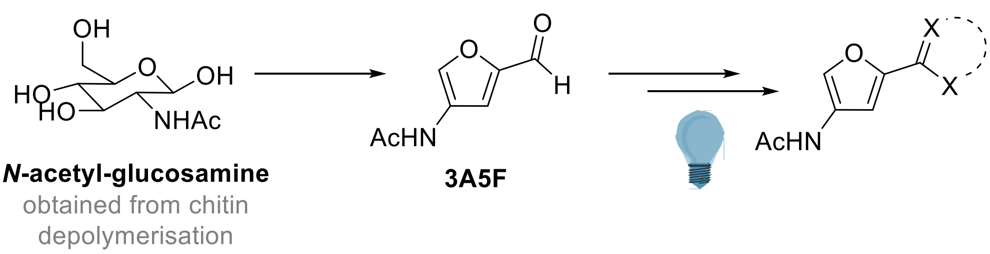
The demand for novel biomass-derived fine and commodity chemicals has driven the exploration of innovative methodologies and synthetic building blocks. *N*-heterocyclic compounds have proven to be highly versatile, finding applications in various fields such as natural compound production and coordination chemistry. In this context, the photochemical oxidation of heterocycles emerges as a versatile and valuable approach for accessing a wide range of oxidized derivatives. By utilizing light and a photocatalyst, this process selectively oxidizes heterocycles, in particular cycle rich in nitrogen. Notably, recent advances have introduced visible light-active, porous organic, and metal-free materials as photocatalysts in various photoredox applications.[1] These advancements enhance the versatility and efficiency of the photochemical oxidation process.

In our study, we have developed a novel photocatalytic oxidation route for heterocycles derived from 3-acetamido-5-furfuryl aldehyde (3A5F), a promising *N*-rich furan building block obtained from chitin biomass.[2] Chitin, an abundant waste byproduct, is a bio-polymer composed of *N*-acetyl-glucosamine (NAG) units, which serve as a valuable source of bio-renewable nitrogen. Through our photocatalytic approach, we have successfully harnessed the potential of 3A5F and its nitrogen-rich composition and prepared complex hetrocyclic structures that will undergo biological evaluation screening (**Scheme 1**).



Scheme 1: Photocatalytic oxidation route for heterocycles derived from chitin depolymerisation

Acknowledgements: The authors acknowledge Fundação para a Ciência e Tecnologia (FCT, Ref. SFRH/BD/148211/2019, UIDB/04138/2020, UIDP/04138/2020, PTDC/QUI-QOR/32008/2017) and CENTRO 2020 Ref. CENTRO-01-0247-FEDER-072630 (BioPINUS) for financial support. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

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Zwitterionic Acridinium Amidate: A Nitrogen-Centered Photoactive Catalyst Enabling Efficient Hydrogen-Atom Transfer

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Photocatalytic hydrogen atom transfer (HAT) reactions allow the direct functionalization of C-H bonds, leading to increased molecular complexity within minimal steps and without the use of functional groups.[1] To achieve these transformations, direct HAT (*d*-HAT) is a straightforward approach in which the photocatalyst directly abstracts an H-atom from the substrate.[2] To date, several classes of *d*-HAT catalysts have been investigated, including aromatic ketones, polyoxometallates such as the decatungstate anion, and the xanthene dye Eosin Y. All of these *d*-HAT photocatalysts have in common that when excited with light, an *O*-centered radical is formed which serves as the active HAT species and can abstract an H-atom from the substrate.[3] Although these photocatalysts are partially suitable for the activation of strong C-H bonds, for example in simple alkanes, there are some limitations and drawbacks, such as the use of transition metal-based photocatalysts, the use of high catalyst loadings, or the application of UV light. Our strategy to overcome these limitations was the development of a zwitterionic acridinium amidate as a new class of *d*-HAT photocatalysts. To the best of our knowledge, this is the first *d*-HAT photocatalyst based on the formation of a *N*-centered radical as the active species. The formation of an amidyl radical enables the activation of strong C-H bonds in simple alkanes and apply them in Giese-type reactions with low catalyst loading (1 mol%) and short reaction times (6 h). With its facile synthesis and high activity, we believe that the acridinium amidate provides inspiration for future catalyst designs.

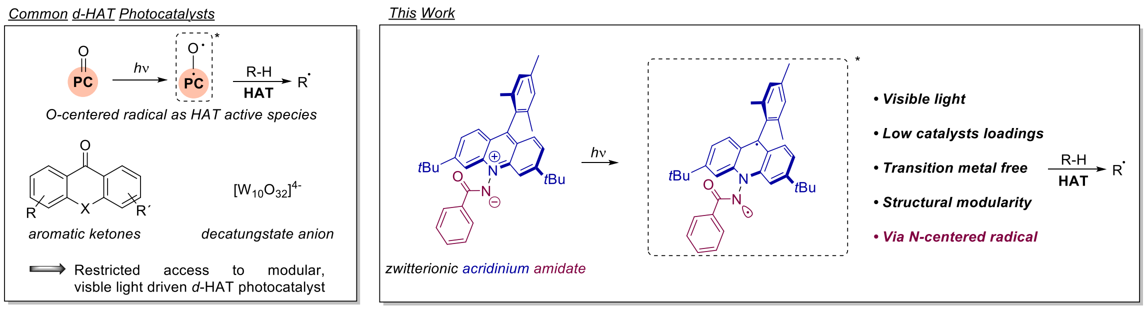

Figure 1: Common *d*-HAT photocatalyst with an *O*-centered radical as active HAT species (left). Zwitterionic acridinium amidate as new class of *d*-HAT photocatalysts, with a *N*-centered radical as active species (right).

Acknowledgements: We gratefully thank the International Research Training Group 2678 for the financial support of this collaborative research project.

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Red-Light-Induced Functionalizations of Biomolecules

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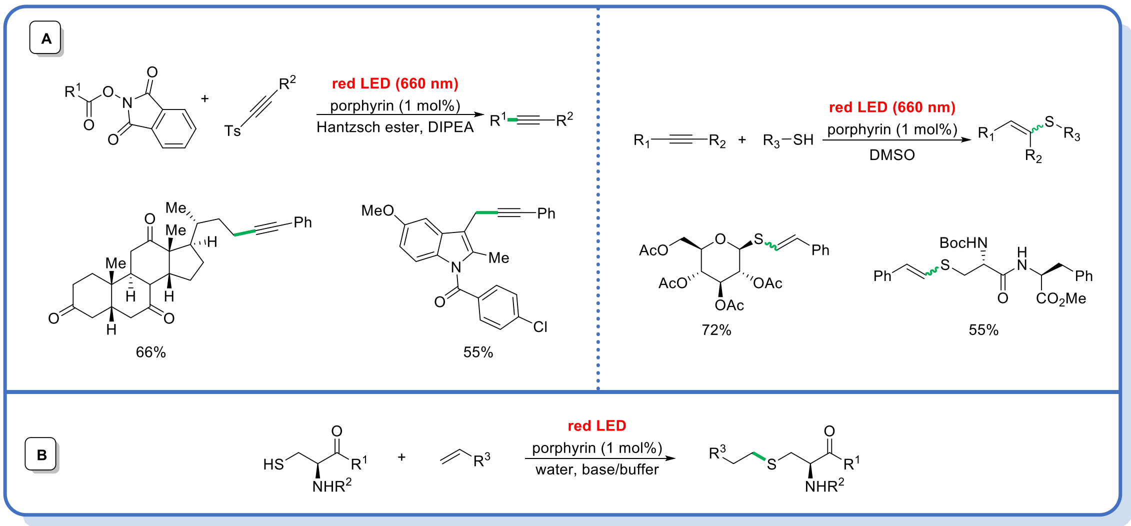
The last decade has witnessed a rapidly growing interest in the application of visible-light in catalysis.[1] Yet photocatalysis remains dominated by the use of blue light in combination with Ir or Ru complexes, which is not a sustainable approach and difficult to scale-up. Red-light, on the other hand, with its deeper material and medium penetration, emerges as a superior alternative for larger scale processes or reactions in biological environment.[2] While the latter aspect has been recognized in the development of photodynamic therapy, red-light-based photocatalysis prevails underdeveloped.

Recently, we have demonstrated that porphyrins can serve as photocatalysts for red-light-induced reactions, including both oxidative and reductive quenching.[3] We were able to apply this approach to the modification of biologically relevant molecules (**Scheme 1A**). To ensure compatibility of this methodology with biological/physiological conditions, we focused then on red-light induced modifications of the cysteine moiety via a thiol-ene type reaction in aqueous media under porphyrin-based photocatalysis (**Scheme 1B**).



Scheme 1: Red-Light-Induced Modifications of Biomolecules.

Our studies revealed the importance of a base/buffer solution for the reactivity of the system. Under optimal conditions we obtained several biomolecule derivatives, including biotin-peptide conjugates.[4]

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Diels Alder reaction of chitin derived furan

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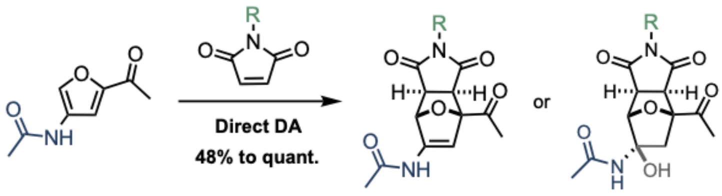
The Diels-Alder (DA) cycloaddition of furans as dienes and suitable dienophiles is an excellent example of a "green" process, with 100% atom economy and with a good E-factor.[1] Nevertheless, due to electronic incompatibility established by Frontier Molecular Orbital (FMO) theory, the approach of directly employing furfural and 5-hydroxymethylfurfural (HMF) as a diene in a DA reaction is not feasible. Several authors have reported HMF and furfural derivatizations in an attempt to bypass this barrier through the production of more electron-rich dienes.[2] However, when considering C5 or C6 carbohydrate feedstocks from lignocellulosic biomass, those methods result in routes with poor atom and redox economy.[3] As a result, we proposed the use of *N*-containing furan 3-acetamido-5-acetyl-furan (3A5AF) derived from chitin biopolymer, a widely available waste byproduct, as a diene in a direct DA reaction.

In this work we report for the first time the use of 3-acetamido-5-acetyl-furan (3A5AF) as a diene in a Diels-Alder reaction with *N*-substituted maleimides as dienophiles. Given the presence of the amido group in 3A5AF, direct DA cycloaddition was permitted, leading to the synthesis of 7-oxanorbornenes with high yields. Our mild method was capable of chemoselectively synthetizing enamides **1** and hemi-acylaminals **2** (hindering retro DA) through the Diels-Alder reaction of chitin derived furan with *N*-substituted maleimides (**Scheme 1**).[4] These novel molecular entities have the potential to be employed as precursors in the production of polymer materials, fine chemicals, and commodity aromatics with nitrogen atoms derived from renewable resources. It is noteworthy that the described methodology has the potential to serve as source of nitrogen-containing platform chemicals independent of the Haber Bosh process.



Scheme 1. Direct Diels-Alder reaction of 3A5AF and *N*-substituted maleimide yielding 7-oxanorbornenes **1** and 7-oxanorbornenes derivatives **2**.

Acknowledgements: The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996. We thank the Fundação para a Ciência e Tecnologia (UIDB/04138/2020, UIDP/04138/2020, PD/BD/143162/2019) for financial support.

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Depolymerisation of polycarbonate applying silica gel-supported organocatalysts

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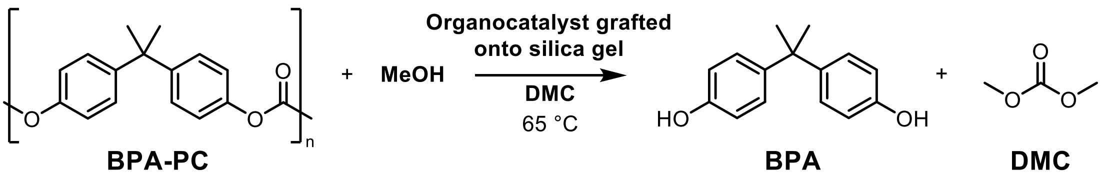
Poly(bisphenol A-carbonate) (BPA-PC) is a thermoplastic engineering polymer. It has several advantages, such as high impact resistance and ductility, excellent optical transparency, flame retardant properties, and relatively low production costs. It is applied in construction panels, safety equipment, optical storage, containers, electronics, automotive, and medical devices. Its monomer, bisphenol A (BPA), is currently considered a xenoestrogen since it has estrogen-like effects in the human body. Despite this, it has not traditionally been recycled significantly. However, the global market demand for polycarbonate is steadily increasing, making the development of its recycling a critical economic and environmental issue.[1]

Our aim was to depolymerise BPA-PC by methanolysis to BPA monomer and dimethyl carbonate (DMC) (**Scheme 1**). In methanolysis, methanol is used as a nucleophilic reagent. By depolymerisation of BPA-PC, pure BPA can be obtained, and from this, BPA-PC can be produced again by transesterification of diphenyl carbonate in a solvent-free melt.

In our work, we have previously used silica gel-supported organocatalysts to depolymerise PET.[2] As a continuation of this study, these catalysts were also applied for the degradation of BPA-PC: three commercially available organocatalysts (Si-TEA, Si-GUA, Si-THU) and one organocatalyst grafted onto silica gel (Si-TBD) prepared by us, were investigated in BPA-PC methanolysis. Among the catalysts applied, Si-TBD showed the highest catalytic activity. The reaction conditions (temperature, catalyst/PC ratio, and methanol/PC ratio) were optimised by a full factorial experimental design. BPA yield was determined by high-performance liquid chromatography (HPLC) and compared with the isolated yield. The recyclability of the Si-TBD catalyst was investigated in several reaction cycles.

In conclusion, the methanolysis of BPA-PC was optimised, achieving 96% BPA yield, and an environmentally friendly method was developed for depolymerising BPA-PC, after which virgin-grade BPA-PC can be reproduced.



Scheme 1: Methanolysis of BPA-PC applying a heterogeneous organocatalyst.

Acknowledgements: This research was funded by the New National Excellence Program of the Ministry of Human Capacities, grants ÚNKP-22-2-II-BME-161 and ÚNKP-22-2-I-BME-146, by the National Research, Development, and Innovation Office (grant number FK138037), and the Richter Talentum Foundation.

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Plastic recycling using commercially available catalysts

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Plastic plays an important role in many sectors, making our lives more comfortable. At the same time, it has a negative impact on our lives due to its non-biodegradable nature, causing environmental and health problems.

Plastic pollution represents not only a global environmental crisis but also a loss of valuable resources. A key strategy to overcome this problem, is regarding plastic waste as a potentially cheap source for the production of value-added products or raw materials for the industry. The reductive depolymerization has emerged as an excellent alternative methodology for the valorization of plastic waste into a variety of valuable products.[1] Catalysts play a key role in the reductive depolymerization of plastic waste. They should be highly active, inexpensive, stable to air, moisture and, if possible, commercially available. In this context, the search for non-toxic and cheap catalysts is very important for the sustainability of depolymerization.

In continuation of our work,[2] in this communication we describe the reductive depolymerization of polyester and polycarbonate plastic waste catalyzed by several commercially available molybdenum, zinc and manganese catalysts with excellent yields (Fig. 1).

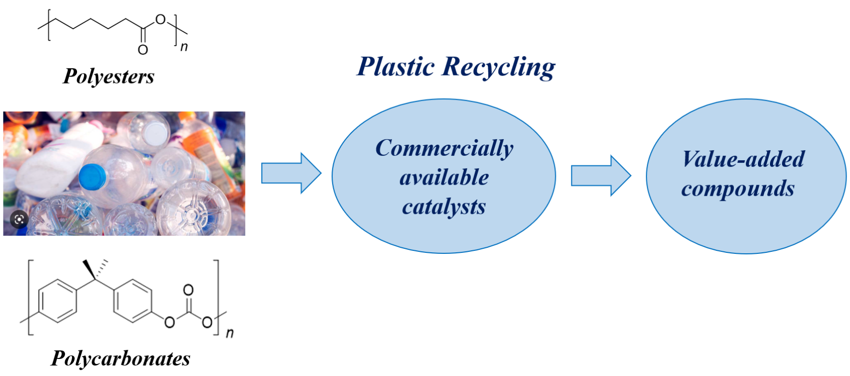

Figure 1: Plastic recycling using commercially available catalysts.

Acknowledgements: This research was supported by Fundação para a Ciência e Tecnologia (FCT) through projects PTDC/QUI-QOR/0490/2020, UIDB/00100/2020, UIDP/00100/2020 and LA/P/0056/2020. DLL thanks to FCT for the grant.

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MeSesamol, a new, bio-based polar aprotic solvent with versatile applications

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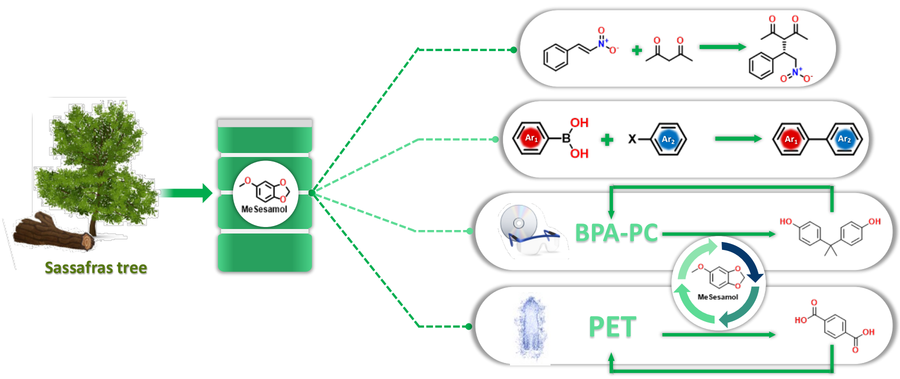
The continued extraction of limited quantities of fossil fuels and the resulting environmental problems is one of humanity's greatest challenges. The research for renewables also focuses on solvents, which represent a major part of the waste generated by the chemical industry.[1] In our work, we propose methyl sesamol (MeSesamol) as a promising new bio-based alternative to polar aprotic solvents. MeSesamol can be produced from sesamol using a environmentally friendly methylating agent, dimethyl carbonate. MeSesamol has a distinctive smell and demonstrates excellent properties as an alternative solvent: high boiling and open-cup flash points, immiscibility with water but miscibility with common organic solvents, and high stability. MeSesamol was successfully used as a solvent in various carbon-carbon coupling reactions, such as Suzuki reactions and asymmetric Michael additions. MeSesamol lies close to dichloromethane (DCM) in Hansen space and achieves a similar or higher yield and enantiomeric excess (up to 97% and 99%, respectively) in the asymmetric Michael reactions compared to DCM. Furthermore, MeSesamol proved to be an excellent solvent for the depolymerisation of poly(bisphenol A-carbonate) and poly(ethylene terephthalate). MeSesamol was recycled in five reaction cycles with excellent efficiency (92–100%) and outstanding cumulative monomer yields (92% bisphenol-A from BPA–PC and 92% terephthalic acid from PET).



Scheme or Figure 1: MeSesamol as a promising alternative for traditional polar aprotic solvents.

Acknowledgements: We are grateful for the financial support of the National Research, Development, and Innovation Office (grant number FK138037), the Richter Gedeon Excellence PhD Scholarship of the Richter Gedeon Talentum Foundation, Richter Gedeon Plc. (G. D.) and the King Abdullah University of Science and Technology (KAUST). Further support was provided by the UNKP-22-1-I-BME-144 and UNKP-22-2-II-BME-145 New National Excellence Program of the Ministry for Culture and Innovation sourced from the National Research, Development and Innovation Fund.

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Combined chemical and biocatalytic approach for asymmetric one-pot reactions

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Nowadays, the main goal of the industrial and academic researchers is to develop an eco-friendlier synthetic process leading to many advantages in terms of reaction times and costs. In order to achieve this purpose, the way of the atom economy implementation could be followed, and the "common" reaction procedures could be improved using green approaches, paving the way for a large-scale application of the entire process. Since the synthesis of chiral pharmaceutical compounds includes many reaction steps, making it difficult and expensive, the idea is to exploit a one-pot reaction (**Figure 1**). This protocol provides the combination in the same reaction environment of two or more different chemical reactions, whose intermediates don't need purification, thus reducing the waste of solvents, but are immediately involved in the following step as starting materials. The here proposed one-pot reaction embrace the use of a chemical catalyst and a biocatalyst, merging their different reactivity and stereoselectivity advantages. In particular, the first step consists in an asymmetric conjugate addition of aryl boronic acids to 3-azaarylpropenones containing pyridine core, using a classical rhodium complex bearing chiral diphosphine as source of chirality,[1] and the second one in an asymmetric transfer hydrogenation of aryl ketones, using an ruthenium complex coordinated to chiral diamine, or an asymmetric biocatalytic reduction of alkyl derivatives, using *Tourolopsis* genera yeast.[2] By setting up the kinetics of the first reaction, the second catalytic step can be successfully carried out affording the desired products in good enantio and diastereopure form. Moreover, there is also the possibility to immobilize both the catalysts on specific supports in order to allow the recycling of the catalysts and their use in flow systems. This combined strategy could be applied to other different types of reactions, matching chemical and biological approaches.[3,4]

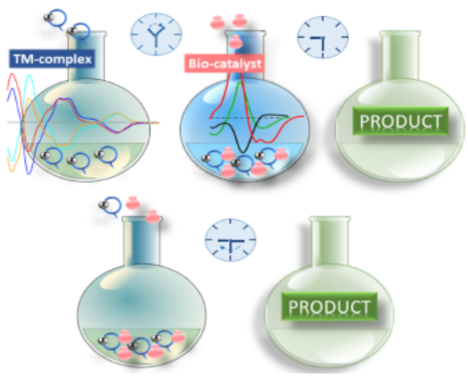

Figure 1. Temporal compartmentalization and one-pot reaction.

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Green design of enzyme-inspired dry-powder polymeric catalyst for fast separation processes

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Catalysis in manufacturing processes is typically homogeneous, expensive and with hard catalyst recovery/regeneration. There is a need of highly selective heterogeneous catalysts, environmentally-friendly, reusable, longer lasting and affordable catalytic processes to replace current, less attractive homogeneous catalyst solutions. Allying molecular imprinting technique (MIT) to catalytic processes, this need can be adressed, thus allowing the production of tailor-made, selective and cost-effective catalysts. Supercritical carbon dioxide ($scCO_2$) is a green alternative solvent/technology for polymer synthesis and processing [1], brings many benefits in comparison to traditional strategies. This applies to the development of molecularly imprinted polymers (MIPs), where homogeneous dry-powders with high controlled morphology and porosity, are obtained ready-to-use, in a single-step, as in high purity without solvent residues [2, 3, 4]. Enzyme-inspired molecularly imprinted polymeric (MIP) particles was designed for fast, selective oxidation of a cholesterol derivative and easy catalyst regeneration [5]. The strategy involved the synthesis of a template-monomer (T:M) complex followed by the crosslinked polymerization in $scCO_2$. A 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)-MIP catalyst was obtained after the cholesterol cleavage from the matrix, and the oxidation of the NH groups turns available TEMPO moieties within the MIP. The oxidation of benzyl alcohol, 5α-cholestan-3β-ol and cholic acid was fast, in high yield and with selective oxidation capacity.

Acknowledgements: The authors thank financial support from Fundação para a Ciência e a Tecnologia, Ministério da Ciência, Tecnologia e Ensino Superior (FCT/MCTES Portugal), through project PTDC/EQU-EQU/32473/2017, a Principal Investigator contract IF/00915/2014 (T.C.). R.V. would like to acknowledge to her doctoral grant SFRH/BDE/51907/2012, a partnership from FCT/MCTES and the pharmaceutical company HOVIONE and the Individual Scientific Employment Stimulus (2020CEEC-IND, 2020.00377.CEECIND) from the FCT/MCTES, Portugal. L.B.M. would like to acknowledge for FCT/MCTES funding with reference CEECIND/03810/2017. The NMR spectrometers in LabNMR@Cenimat are part of the National NMR Facility, supported by FCT (ROTEIRO/0031/2013 - PINFRA/22161/2016), co-financed by FEDER through COMPETE 2020, POCI, and PORL and FCT through PIDDAC (POCI-01-0145-FEDER-007688; UID/CTM/50025/2020-2023). The Associate Laboratory Research Unit for Green Chemistry - Clean Technologies and Processes - LAQV is financed by national funds from FCT/MCTES (UIDB/QUI/50006/2020) and cofunded by the ERDF under the PT2020 Partnership Agreement (POCI-01-0145-FEDER-007265).

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Efficient Pd-catalyzed carbonylation of 'benzyl chloride' type compounds – a rare avenue to underrepresented (het)arylacetate platform

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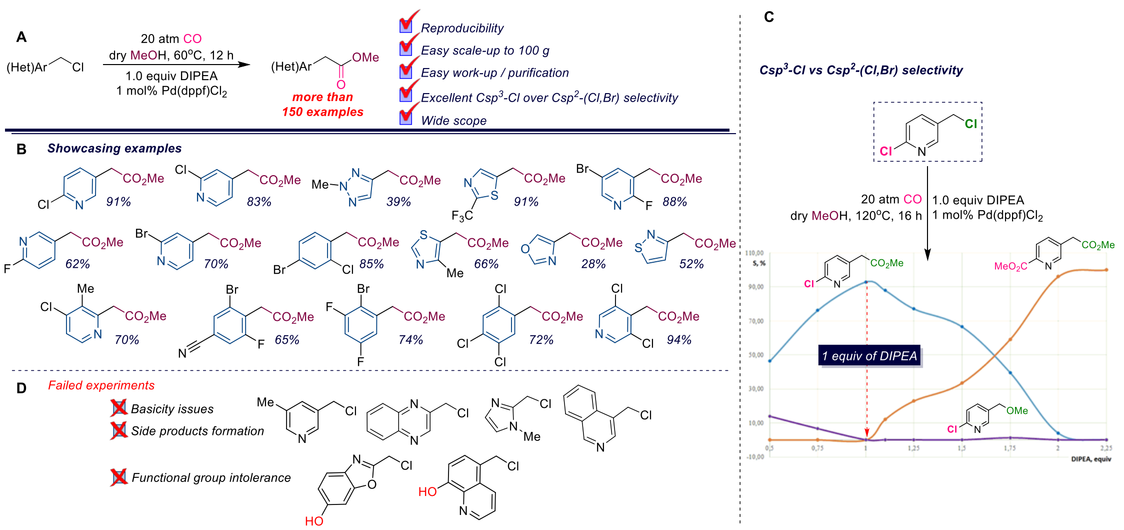
Nowadays synthetic community all over the world is striving for *greener*, *cheaper*, more *atom efficient* and more *reliable* methodologies that can satisfy ever-growing demand of all chemistry branches in versatile building blocks without wasting much time on picking up conditions for every single synthetic case. Pd-supported carbonylation of organic halides is in consistent with all the criteria as it allows the construction of valuable carbonyl compounds in a single step with efficiency, selectivity, and atom economy being compatible with a range of functional groups. While carbonylation of aromatic Csp^2-Hal type compounds is well-reported, the same transformation utilizing 'benzyl halide' type species and leading to *underrepresented* (het)arylacetates was described in only *several works* making no claim to cover the issue sufficiently. Meanwhile, a usual pathway for such a conversion involves tedious multistep 'cyanide' procedure. Herein we report a comprehensive study on carbonylation of impressive range of chloromethyl(hetero)aromatic compounds (**Scheme 1, A, B**). Careful optimization of the reaction conditions provided a protocol allowing for one-step preparation of up to 100 g of corresponding methyl acetates in one synthetic run and featuring excellent reproducibility, convenient work-up and purification steps. Thus, common conditions include interaction at 20 atm of CO, 60°C in MeOH with low loading of Pd(dppf)Cl_2 (1 mol%) in a presence of DIPEA as a base (**Scheme 1, A**). The found conditions are suitable for benzyl chlorides and analogues containing 6- and 5-membered electron-rich and deficient heterocycles. Another point we coped with is the reaction selectivity affecting sp^3-Cl moiety and leaving intact sp^2-(Cl, Br) fragment. A series of experiments has clearly indicated that the reaction outcome is driven by DIPEA amount taken (**Scheme 1, C**). Thus, 1.0 equiv of DIPEA enables for specific sp^3-Cl substitution and increasing its amount up to 2.25 equiv increases the percentage of the diester product. We also observed that elevated basicity of the starting heteroaromatic material is an obstacle towards the target acetates (**Scheme 1, D**). We are trying to overcome this problem as well as another limitation concerning intolerance of OH-containing heterocyclic substrates, which are able to self-alkylation.



Scheme 1: Scope of the carbonylation reaction and selectivity issues investigation.

Directed *ortho* and Remote Metalation Chemistry for the Formation of Substituted Naphthalenes and Azafluorenol Core Liquid Crystals

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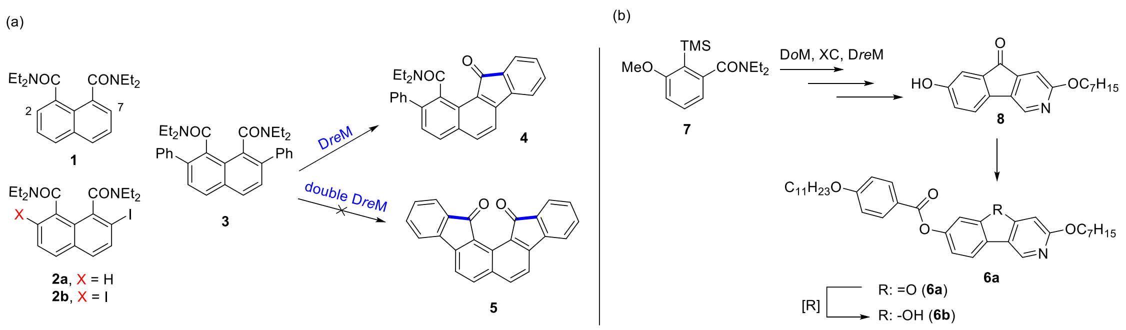
I will present the final two papers published by the Snieckus research group during the life of prof Victor Snieckus. The first[1] **(i)** (see Scheme below) involved the preparation and Directed *ortho* Metalation (D*o*M) of 2- and 2,7-derivatives of *N*,*N*-diethylnaphthalene-1,8-dicarboxamide (**1**), Suzuki−Miyaura cross-coupling (XC) reactions of derived halo derivatives (**2a**, **b**), and Directed *remote* Metalation (D*re*M) of **3** to the monocyclized product **4**. I will also discuss why a double-D*re*M process does *not* occur for **3** to fluoreno[1,2-*a*]fluorenedione **5**, even under excess Lithium Diisopropylamide (LDA) conditions. This work is relevant considering the utility of naphthalene derivatives in chiral catalysts, medicinal compounds, and functional materials such as photoswitches and liquid crystals. Since amides can be transformed to other functional groups or cross-coupled with other materials e.g., with alkenes,[2] this work opens new avenues for materials exploration. The second paper[3] [**Scheme (b)**] focuses on the synthesis of two new smectic C* mesogens containing a hexyloxy side chain and an azafluorenone (**6a**) or azafluorenol (**6b**) core, using a combined D*o*M-D*re*M−Suzuki−Miyaura XC strategy commencing with **7** and progressing through transformations **7** → **8** → **9** → **6a**/**b**. This work was done to expand knowledge around liquid crystals (LCs) containing fluorene and fluorenone cores, known to form different mesomorphic phases depending on the substitution groups of the LC molecules.[4]



Scheme: (a) Directed *ortho* and Remote lithiation chemistry for the formation of substituted naphthalenes **1**-**3** and cyclization reactions of **3** to form **4** (but not **5**). (b) The synthesis of two new smectic C* mesogens containing azafluorenone (**6a**) or azafluorenol (**6b**) core using a combined D*o*M-DreM−Suzuki−Miyaura XC strategy (commencing with **7**).

Acknowledgements: We acknowledge the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement no. 945380. We are grateful to NSERC for support for the Discovery Grant (DG) programs. We are grateful to Compute Canada for computational resources.

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Cyclic Triel Carbenoids as Auxiliary Ligands for Ruthenium-Based Olefin Metathesis Catalysts

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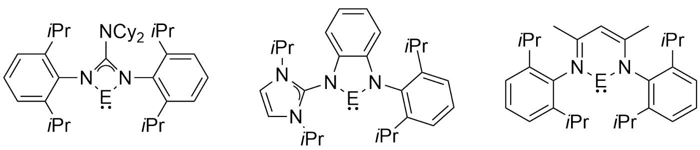
Although carbenes have a long history of being used in organic synthesis as catalysts—both on their own and as auxiliary ligands in transition metal-based species—the same does not apply to carbenoids, close relatives to carbenes, bearing a lone electron pair on a different atom than carbon. One of the most useful reactions which benefit from carbene chemistry is olefin metathesis.[1,2] This type of reactivity has been known for decades, but its main development started in late 1990s when *N*-heterocyclic carbenes began to be used as ligands for ruthenium catalysts.[3] Since then a lot of research has been done to understand the relationship between catalytic activity and structure, and—based on that—synthesize more powerful catalysts, including the arguably most important families introduced by Grubbs and Hoveyda.[2]

In our studies we simulated behavior of Grubbs and Hoveyda-Grubbs type catalysts bearing cyclic triel carbeniods as ligands instead of *N*-heterocyclic carbenes. The most important triel carbenoids include four-membered guanidine-chelated E(Giso), six-membered β-diketiminate-chelated E(NacNac) and the most novel five-membered amidoimidazoline-2-imine-chelated E(AmIm) **(Scheme 1)**.[4] We simulated reaction pathway for selected Grubbs and Hoveyda–Grubbs type catalysts for three different alkenes: ethylene (the simplest possible system), styrene (exhibiting steric hindrance) and isobutylene (forming tetrasubstituted alkene). We show that the most promising candidate for efficient catalysis seems to be the Hoveyda–Grubbs type catalyst with Tl(AmIm) ligand.



Scheme 1: Structures of the most important cyclic triel carbenoides: E(Giso), E(NacNac) and E(AmIm)

Acknowledgements: We acknowledge research support from the National Science Centre grant UMO-2021/43/B/ST4/00122.

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C(sp3)-C(sp3) bond formation reactions through organozinc agents

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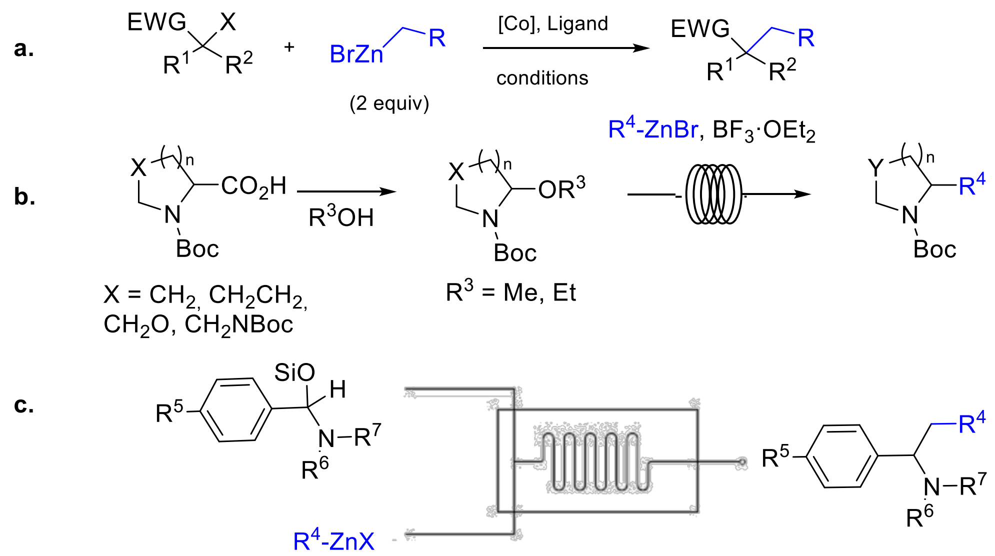
Organozinc halides have been demonstrated to be useful coupling agents in several transformations (e.g. Reformansky and Negishi cross-coupling reactions). They are specially useful in introducing C(sp3)-fractions in drug discovery programs which allows to increase the biological activity of the drug candidates. In order to prepare organozinc halides, a continuous flow version was developed in 2014 by showing several advantages comparing with the traditional batch approach [1]. In this regard, subsequent transformations have been achieved to demonstrate the synthetic value of these organometallic agents [2].

In this work, we demonstrate how these continuous flow generated organozinc agents can be used to achieve C(sp3)-C(sp3) bond formations. First, a new Negishi cross-coupling catalyzed by cobalt is selective over C(sp2)-halides for the generation of quaternary centres (**Scheme 1a**) [3]. Then, we disclose how electrochemistry can be combined with Lewis acids and organozinc agents to achieve the α-functionalization of amines (**Scheme 1b**) [4]. Finally, we show how automated platforms can also we suitable for the coupling of organozinc agents and amides in continuous flow to generate α-functionalized amine derivatives (**Scheme 1c**) [5].



Scheme 1: C(sp3)-C(sp3) bond formation reactions using organozinc halides.

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Unusual silver complexes bearing *N*-heterocyclic carbene ligands: synthesis and their application.

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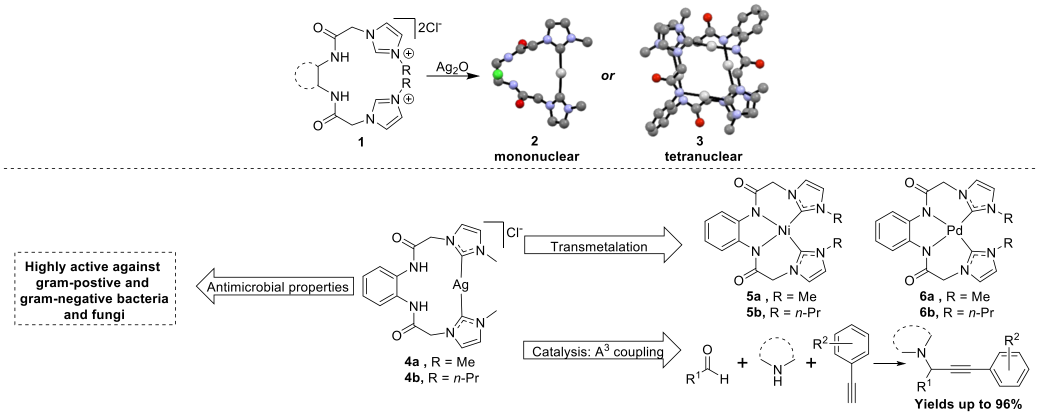
In recent years, there has been a notable increase in interest in *N*-heterocyclic carbenes (NHCs), which have emerged as a subject of considerable significance. Their strong σ-donating ability and steric features make them attractive for application as ligands in transition metal complexes and some NHC-metal complexes proved superior to the respective metal-phosphine complexes analogues and industrial application of others (e.g. Grubbs 2nd generation, Pd-PEPPSI) underline their utility[1a,b] Among the transition metals where NHCs have been applied, silver-NHCs (Ag-NHCs) have gained significant attention due to their simple synthesis, stability, fascinating structural diversity, and wide range of applications.[2] Recently, our group has developed a novel chelating Ag-NHC complex containing a bisamide moiety in its backbone. Complex **2** is synthesized using an equimolar ratio of the silver source and the ligand precursor. Conversely, if the silver source is in excess, the reaction leads to the formation of an unprecedented tetranuclear silver complex **3**, which is stabilized by two equivalents of ligand. This complex is characterized by the coordination of the silver atom to one NHC and one amide moiety. The chelating aspect of the Ag-NHC complex **2** is a remarkable feature that is rarely observed for silver-NHC complexes. The antimicrobial properties and use of these complexes as catalysts in A^3-coupling reactions have also been studied, with the complexes exhibiting extraordinary properties in both directions. The MIC values were as low as 1 µg/ml, and the A^3-coupling products were isolated with yields up to 96% using catalyst loads as low as 0.1 mol%.[3] Additionally, Ag-NHCs complexes have been recognized as effective carbene group transfer agents. As a result, some



of these complexes were used to synthesize NHC complexes of other metals, including nickel **5** and palladium **6**, which had previously failed to be synthesized.[4]

Scheme 1: Synthesis and application of the developed silver complexes.

Acknowledgments: We thank the Charles University Primus program (PRIMUS/20/SCI/017) for financial support.

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Diastereoselective synthesis of highly functionalized indolizidine and pyrrolo[1,2-a]azepine derivatives

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Indolizidine and pyrrolo[1,2-*a*]azepines, a significant part of alkaloids family, are present in numerous natural and synthetic compounds that exhibit a wide range of biological activities.[1] Cycloaddition of nitrones with olefines constitutes a traditional approach to obtain these azabicyclic core through isoxazolidine intermediates.[2] In this context, we recently reported the diastereoselective [3+2]-dipolar cycloaddition of nitrones **1a-c** with reactive alkenes which leads to these scaffolds in one-step (**Figure 1**).

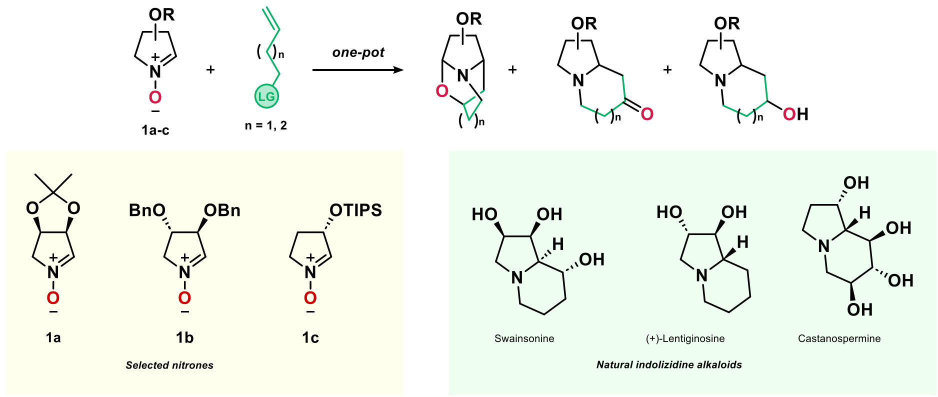

Figure 1: Synthesis of indolizidine and pyrrolo[1,2-*a*]azepine scaffolds in one step.

These derivatives are selectively functionalized to obtain a wide library of iminosugars with potential biological activity (**Figure 2**).

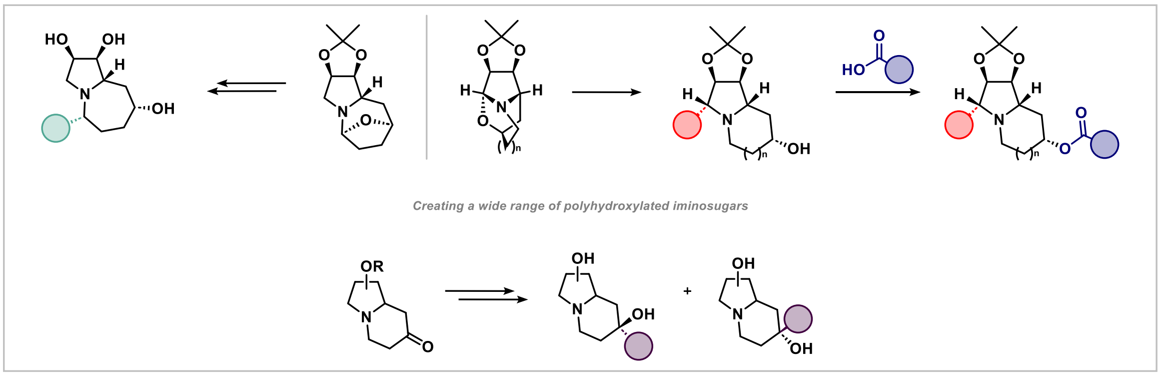

Figure 2: Functionalization and synthetic transformations in azabicyclic scaffolds.

Acknowledgements We thank the government of Castilla y León (SA076P20) and Spanish Ministry of Science and Innovation (PID2020-118303GB-I00) for financial support. N. G. L. thanks Universidad de Salamanca and Banco Santander for predoctoral grant.

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Synthesis of Allyl Functionalized Vinyl Silanes from Propargyl Silanes via 1,2-Silyl Migration

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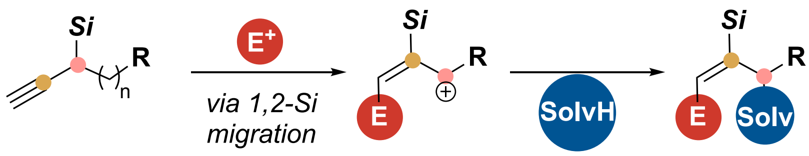
Stabilizing properties of the β-silicon effect have been known to facilitate the rate of the reaction for a variety of transformations that proceed via the formation of β-silyl carbenium ion. This effect can be achieved by two plausible mechanisms – vertical stabilization, where C-Si bond is donating its electrons to vacant π orbital, or non-vertical stabilization by the formation of cyclic 3-atom-4-electron silonium ion. And exactly the latter in combination with other stabilizing effects that might arise is the reason why a variety of such reactions proceed via 1,2-silyl migration.[1] In the highlight of this, recently we have reported the use of Brønsted acids as the catalyst for the synthesis of silyldienes, silylindenes and silylsulfolenes.[2,3]

Herein, we report the expanded use of the concept by using a variety of other non-metal electrophiles (Br^+, I^+, $PhSe^+$) to induce anti-selective 1,2-silyl migration for the formation of the reactive allylic cation.The latter can react in a rapid fashion with a variety of nucleophilic solvents like methanol, dimethylformamide, and acetic acid to form selectively allyl-functionalized vinyl silanes.



Scheme 1: General scheme for electrophile-induced 1,3-difunctionalization of propargyl silanes with solvent as a nucleophile.

The obtained products possess a continuously functionalized atom triad, that can serve as a building block for further transformations like metal-catalyzed Suzuki-Miyaura cross-coupling, C-H activation, electrophilic silicon exchange, and Lewis acid-promoted intramolecular cyclization to selectively obtain alkenes with predetermined double-bond geometry in the 1,2-silyl migration step, or variously substituted indenes.

Acknowledgements: This work was supported by European Social Fund within the project Nr. 8.2.2.0/20/I/008 and Riga Technical University doctoral student grant.

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Stereoisomerism in the synthesis of chiral, bioactive Re(I) tricarbonyl complexes with enantiopure ligands: a drawback or an opportunity?

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Recently, the synthesis and the study of Rhenium di- and tri-carbonyl complexes have gained momentum because of their promising anticancer / antibiotic properties.[1] The intrinsic chirality of the Re(I) metal centers brought by non-equivalent ligands completing the coordination sphere was however largely neglected in these studies. Yet it is well known that the diastereoisomeric interactions with the biomolecules as DNA or membrane transport proteins plays a crucial role which can be evaluated only by testing each stereoisomer. Moreover, the use of enantiopure ligands can enhance the chances of a biological match between the Re(I) complex and the bio-target. However, the drawback here is the increased number of diastereoisomers obtained, whose separation is a supplementary challenge at the synthetic level. Concomitantly, the chiral induction exerted by enantiopure ligands can reduce the number of diastereoisomers, as it was demonstrated when the enantiopure pinene (poly)bipyridine type ligands are coordinated to various transition metal centers with different coordination numbers and geometries.[2]

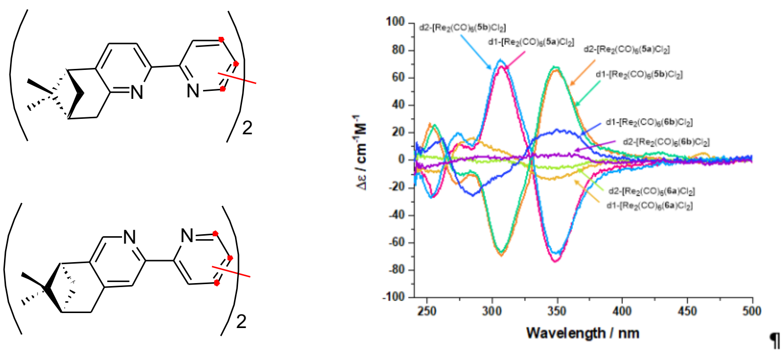

Figure 1: General formula of some enantiopure pinene bipyridine type ligands used in this study (left) and CD spectra of their dinuclear Re(I) tricarbonyl diastereomers.

In this contribution, on overview concerning the synthesis, the characterization and the stereoisomerism of carbonyl Re(I) complexes containing (bis)pinenebypyridine type enantiomers (some of them represented in Figure 1) will be presented. We will show how various factors (ligand's denticity and steric hindrance, nuclearity, number of carbonyls, substitution of the labile halogen ligands by pyridine units) are influencing the outcome of the syntheses *i.e.* the diastereoisomeric distribution and the properties of the isolated Re(I) stereoisomers.

Acknowledgements: We thank HES-SO and Swiss National Science Foundation for financial support.

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Phosphonium Ylide-Mediated CO_2 Utilization for the of Synthesis of α,β-Unsaturated Carboxylic Acids

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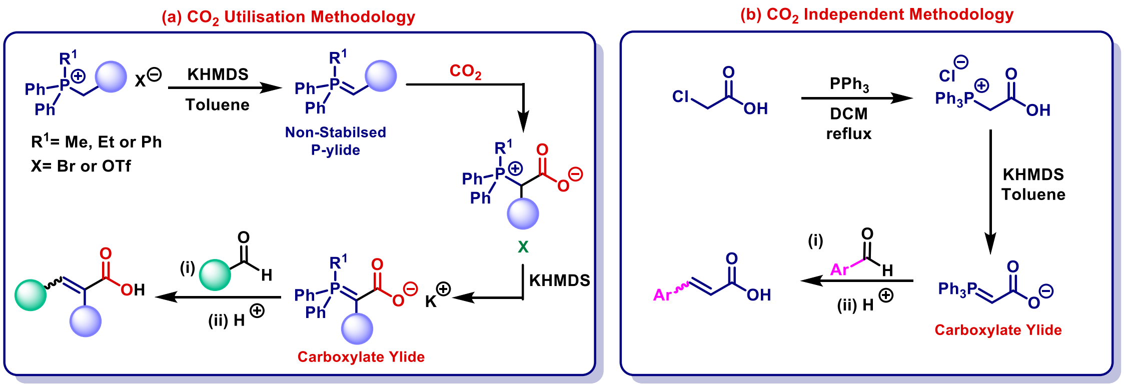
Employing waste products as starting materials for chemical transformations is a key step in addressing the global challenges of sustainable production and consumption. Greenhouse gas CO_2 is perhaps the most significant waste product of the industrialised world.[1] Developing a method for the conversion of a harmful environmental waste product into high-valuable organic products can allow CO_2 to be used as a one-carbon (C1) chemical building block. Phosphonium ylides (P-ylides) have the ability to activate CO_2 into reactive P-ylide CO_2 adducts.[2,3] This activated form of the C1 feedstock can be incorporated into carboxyl-containing products and biologically active compounds.

α,β-Unsaturated carboxyl containing organic products are ubiquitous in nature and this structural motif is responsible for the biological activity of many such organic products.[4] It has been found that α,β-unsaturated carboxylic acids can be synthesised using two comparable synthetic routes, via the P-ylide CO_2 adduct (Compound X, Scheme 1a). The CO_2 utilisation methodology involves activation of CO_2 by a P-ylide to form compound X. Deprotonation of X forms a nucleophilic species (phosphonium carboxylate ylide) that can undergo a novel Wittig-type reaction with various different aldehydes, including aromatic, heteroaromatic and aliphatic aldehydes. The α,β-unsaturated carboxylic acid products are formed in moderate to high yields (see Scheme 1a). This telescoped process has shown a high degree of selectivity for the *E*-alkene. This methodology has also been utilized for the synthesis of pharmaceutically relevant high-value organic products.

A route for CO_2 independent generation of the activated P-ylide CO_2 adduct starting with carboxymethyltriphenylphosphonium chloride has also been developed (see Scheme 1b). This novel route can be used to test substrate suitability and reaction conditions independent of the CO_2 utilisation methodology.



Scheme 1: (a) CO_2 Utlilisation Methodology and (b) Independent Methodology.

Acknowledgements: Financial support for this research was provided by the Irish Research Council (IRC GOIPG/2018/169 and IRC GOIPG/2021/802), and SFI Frontiers for the Future grant (grant code 20/FFP-P/8856).

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Ir-Catalysed (Hetero)aryl C−H Functionalisation *via* N to C Alkyl Transfer

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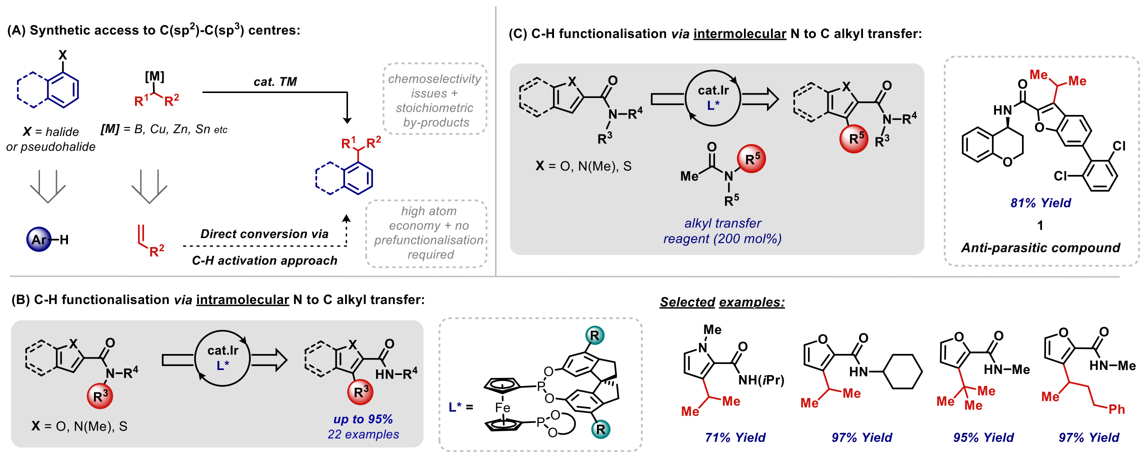
The development of new step economical approaches for the direct formation of C(sp^2)–C(sp^3) bonds is of the upmost importance for the pharmaceutical and agrochemical industries.[1] Specifically, methods that can avoid cumbersome pre-functionalisation steps have the potential to replace traditional cross-coupling reactions (Scheme 1A). Within this context, directing group mediated Ir(I)-catalysed alkene hydroarylation reactions have been previously developed in the Bower group, employing a novel class of bidentate ferrocene-SPINOL ligands, (**L*** in Scheme 1B).[2] This communication will exhibit the application of these ligands in an exciting, newly uncovered intramolecular N to C alkyl transfer reaction (Scheme 1B), which proceeds *via* a unique C–H activation pathway. Furthermore, unexpected intermolecular alkyl transfer, allowing access to products such as complex anti-parasitic compound 1, will be presented, alongside the key mechanistic aspects delineating the hypothesised reaction pathway.[3,4]



Scheme 1: General outlook of alkyl transfer methodology

Acknowledgements: We thank the EPSRC (Engineering and Physical Sciences Research Council) for a studentship, the University of Liverpool analytical services team and the members of the Bower research group.

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Rhodium-Catalyzed Intermolecular Cross-Cyclotrimerization To Access Selaginpulvilins Derivatives and Investigation of Their Medicinal Activity

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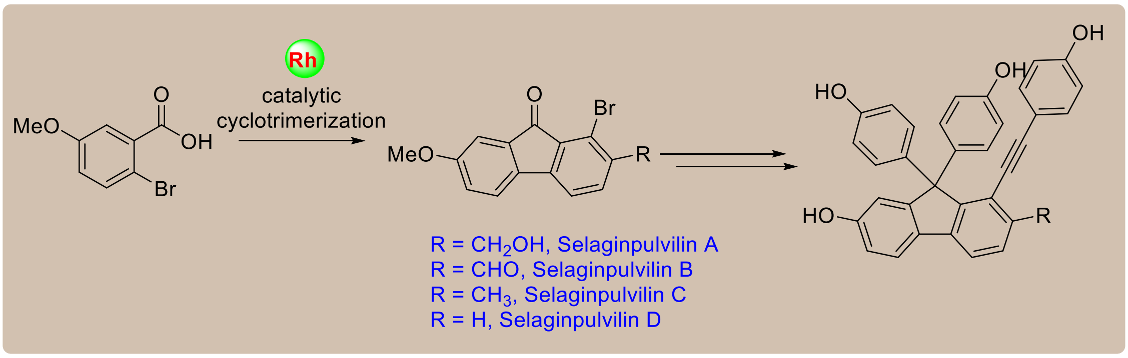
Selaginpulvilin family is a small group of 1-arylethynyl9,9-diaryl fluorene natural products that are likely responsible for the anti-inflammatory properties of Selaginella pulvinata, a plant used widely in traditional Chinese medicine.[1] The densely substituted fluorene scaffold of selaginpulvilins has sparked great interest as a challenging target in the field of total synthesis. Many researchers have attempted to synthesize selaginpulvilin derivatives, nevertheless, most of the reported synthetic strategy relied on (i) a hexadehydro Diels–Alder reaction of a tetrayne (selaginpulvilins A and C) and (ii) a tetrahydro Diels–Alder reaction of an enyne–diyne (selaginpulvilins A, B, and D), and sequences comprising of cross-coupling reactions and an intramolecular SEAr reaction.[2] Very recently our group reported the formal synthesis of selaginpulvilin C and D, however, all these reported methods led to only one of the selaginpulvilin analogs or ceased at some stage of formal synthesis.[3] Herein, we have developed a common methodology to achieve selaginpulvilin derivatives through catalytic cyclotrimerization (**Scheme 1**). The optimized condition was found after a thorough screening of various parameters and metal salts. Also, the biological activity of several intermediates has been tested to understand which core of the molecule is responsible for its known anti-inflammatory properties. Further, DFT calculations have been carried out to have a deep insight into the regioselectivity of cyclotrimerization.



Scheme 1: Rhodium-Catalyzed Total Synthesis of Selaginpulvilins Derivatives Via Catalytic Cyclotrimerisation.

Acknowledgments: We thank the Charles University Primus program (PRIMUS/20/SCI/017) for financial support.

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Batch and Continuous Flow Synthesis of Novel Spiro-β-Lactams with Antiviral Activity

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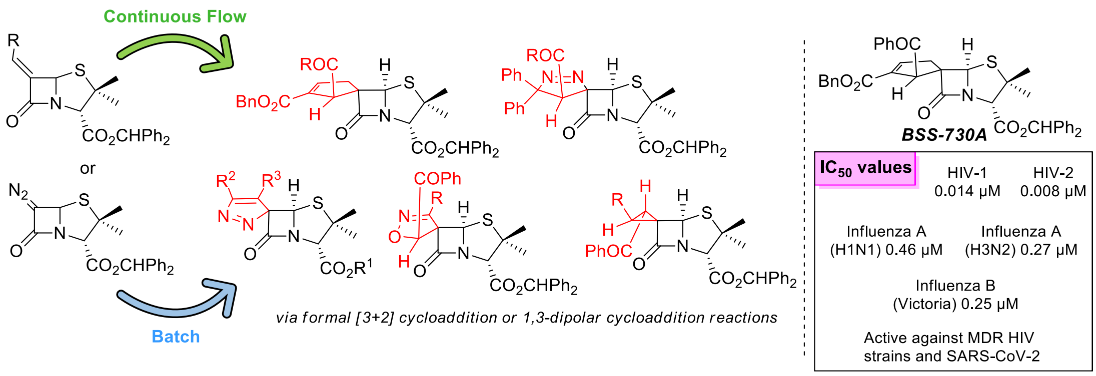
The β-lactam ring has held significant importance in synthetic and medicinal chemistry ever since the discovery of penicillin, due to its highly synthetic versality and biological properties. Recently, studies on the synthesis and biological evaluation of spiro-β-lactams derived from 6-aminopenicillanic acid led to the discovery of lead compounds with remarkable antiviral properties, being the starting point to the rational design of novel spiro-β-lactams.[1] In this communication, we describe the synthesis of a library of spiro-β-lactams by exploring formal [3+2] cycloaddition and 1,3-dipolar cycloaddition reactions of 6-alkylidenepenicillanates and 6-diazopenicillanates allowing the synthesis of novel chiral spiropenicillanates containing carbo- or heterocyclic rings, spiro-fused to the penicillin core. Furthermore, the present work also describes the outcome of these annulation reactions under batch and continuous flow conditions, including our lead compound BSS-730A. The successful use of the continuous flow technique stands out for allowing very short reaction times, and by its inherent characteristics that ensure easy scale-up processes, opening new horizons for the development of chiral spiro-β-lactams. The novel spiro-β-lactams were assayed for their *in vitro* activity against HIV-1, providing relevant structure-activity relationships. Further details of this study will be disclosed.



Scheme 1: Synthesis of chiral spiro-β-lactams from 6-alkylidenepenicillanates.

Acknowledgements: The Coimbra Chemistry Centre-Institute of Molecular Sciences (CQC-IMS) is supported by the Portuguese Agency for Scientific Research, “Fundação para a Ciência e a Tecnologia” (FCT) through projects UIBD/00313/2020 and UIDP/00313/2020 (National Funds) and the IMS special complementary funds provided by FCT. We also acknowledge the UC-NMR facility for producing the NMR data (www.nmrccc.uc.pt).

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Continuous-Flow Electrochemical Oxidation of Abietanes

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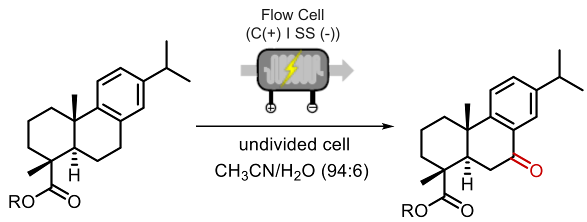
Rosin or Colophony is a natural resin that is extracted from pine trees. Besides having multiple industrial applications, it is also constituted by a group of diterpenes known as abietanes, which, along with its derivatives, has been found to have a wide variety of interesting biological activities, including antimicrobial, antiviral, antitumoral, and anti-inflammatory.[1]

The benzylic oxidation of dehydroabietic acid, and its methyl ester derivative has been previously reported using various oxidative protocols, such as Swern oxidation[2] or using Chromium trioxide in either stoichiometric[3] or catalytic quantities.[4] However, these protocols fail in the context of sustainability for several reasons, such as the use of toxic reagents and stoichiometric amounts.

Herein we present a more sustainable protocol for the oxidation of both dehydroabietic acid and abietic acid, and their methyl ester derivatives. We used modern electrochemical methods to achieve good yields of the ketone for both abietanes. Furthermore, we report the development of an electrochemical flow process towards increase its productivity.[5] Finally, we extended this strategy to colophony and report its successful application both in batch and in flow.[6]



Scheme 1: Continuous flow electrochemical oxidation of dehydroabietic acid (DHA) and its methyl ester derivative (MDHA).

Acknowledgements: We thank CENTRO 2020 Ref. CENTRO-01-0247-FEDER-072630 (BioPINUS) and Fundação para a Ciência e a Tecnologia (FCT, UIDB/04138/2020, UIDP/04138/2020) for financial support. J. A. S. C. thanks the Fundação para a Ciência e a Tecnologia (FCT) for Scientific Employment Stimulus 2020/02383/CEECIND. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996. Centro de Química Estrutural is a Research Unit funded by Fundação para a Ciência e a Tecnologia through projects UIDB/00100/2020 and UIDP/00100/2020. Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020.

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Electrochemically Recoverable Homogeneous Catalyst: Genesis, Application and Capture

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Transition metal ions and their complexes play a crucial role in homogeneous catalysis. However, recovery of homogeneous metallic catalyst is cumbersome. Here we propose a new electrocatalytic approach where the homogeneous catalyst is generated in-situ and recovered by means of electrochemistry. In our study we used Fe and Cu electrodes and applied a potential to allow the dissolution of metal from the anode in the form of ions **(Figure 1)**.

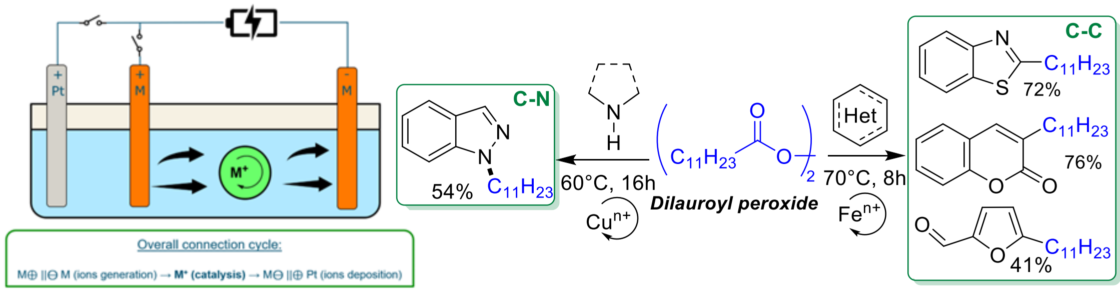

Figure 1. General method and reactions of diacyl peroxides using in situ generated catalysts.

When desired concentration of ions is reached, the potential is removed, and the chemical reaction is performed with generated Fe or Cu ions serving as catalysts. To collect these ions back from the solution, the active anode is substituted by a platinum one. Unlike Fe and Cu, this metal does not dissolve which allows to re-deposit the active metal ions from the solution on the cathode. We studied this electrocatalytic approach on Fe- and Cu-catalyzed transformations of diacyl peroxides used in catalytic C-C and C-N coupling As a result, alkylated benzothiazole, coumarin, furfural and indazole were obtained in moderate to good yields demonstrating that the electrochemically generated ions can indeed serve as active catalysts for these chemical transformation **(Figure 1)**.

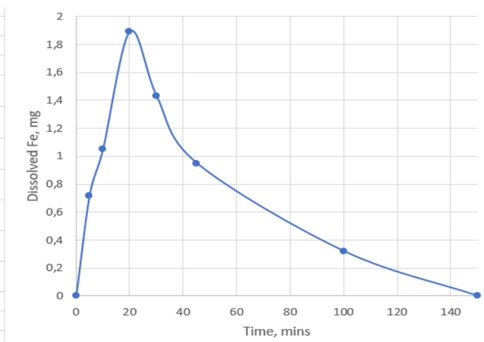

Figure 2. Concentration of dissolved iron vs time, dissolution and deposition

We also investigated the metal dissolution and deposition. **Figure 2** shows the increase in concentration of the Fe ions in the solution under influence of potential (0-20 mins). At this moment iron is the material for both electrodes. At 20 minutes, the anode is switched to platinum and the dissolved iron starts to deposit on the cathode: we observe a decrease of iron concentration with time (20-150 mins) ultimately reaching zero.

Easy access to functionalized sparteine via electrochemical cyanation of quinolizidine alkaloids

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Quinolizidine alkaloids (QA) are largely abundant in the Leguminosae family, especially in the genera Lupinus.[1] Maulide and Afonso's groups developed a process for the extraction of lupanine from *Lupinus albus* seeds wastewater and the preparation of sparteine.[2] These natural products are known for their pharmacological activities, which includes antimicrobial, antihypertensive, antimuscarinic and antidiabetic, as hyperglycemia agents, effects on the central nervous system and uses in asymmetric organic synthesis.[3] Motivated by the potential added value of novel QA derivatives, we explored the selective C-H functionalization of QA using electrochemistry. Over the past years, continuous flow processes have emerged due to their ability to enhance product quality and safety while reducing environmental impact, surpassing traditional batch syntheses.[4] As an attempt to improve the existing methodologies in asymmetric synthesis and, due to the continuous flow advantages, herein we present a new methodology for the cyanation of lupanine (**Figure 1**) under batch and flow conditions.

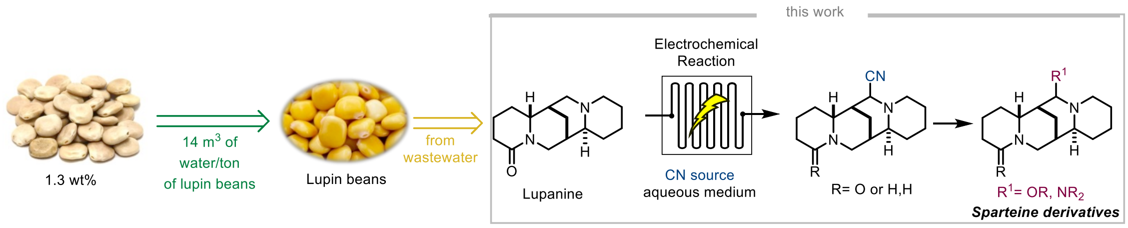

Figure 1: Electrochemical functionalization of quinolizidine alkaloids.

Acknowledgements: We thank the Fundação para a Ciência e a Tecnologia (FCT) for financial support (Ref. 2020/06352/BD, UIDB/04138/2020, UIDP/04138/2020 and PTDC/QUI-QOR/1786/2021). The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996. J.A.S.C. thanks FCT for Scientific Employment Stimulus 2020/02383/CEECIND.

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Synthesis of Imidazolidinones *via* Palladium-catalysis

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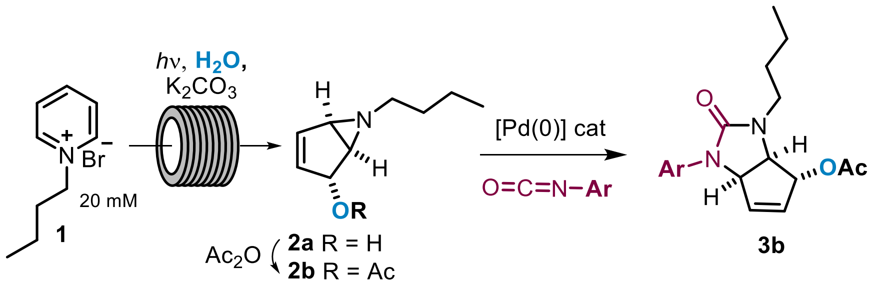
Nitrogen-containing heterocycles can have several applications in the pharmaceutical industry since they contain a wide spectrum of biological activities. Imidazolidinones have shown activity against leukemia, lung cancer and metabolic disorders.[1] These cyclic urea frameworks can be obtained through transition-metal-catalyzed intermolecular cycloaddition using an aziridine moiety as starting material. These reactions often provide effective one-step procedures that result in heterocyclic derivatives, that are challenging to access through conventional approaches.[2,3]

We have previously described the photoreaction of pyridinium salt **1** into the corresponding bicyclic aziridine **2a** under continuous-flow. [4,5] Additionally, we reported that palladium-catalyzed ring opening of bicyclic aziridine **2a-b** with active methylenes presented a new S_N2' selectivity.[6] In this study, the reaction between bicyclic aziridine **2b** and several isocyanates, in the presence of Pd(0)-catalyst is presented (**Scheme 1**). The reactions proceed through ring opening of the aziridine moiety, with the formation of the π-allylpalladium complex, followed by cyclization via nucleophilic addition of nitrogen to the isocyanate, affording regioselectively imidazolidinones **3b**.



Scheme 1: Pd-catalyzed reaction of bicyclic aziridine **2b** with isocyanates.

Acknowledgements: The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996. We thank the Fundação para a Ciência e Tecnologia for financial support (UIDB/04138/2020, UIDP/04138/2020 and 2022.08559.PTDC).

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Photocatalytic transformations of quinic acid derivatives

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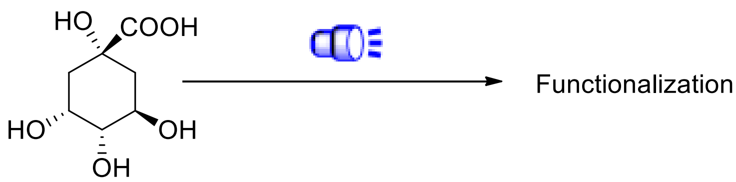
Quinic acid (QA) is a widely occurring metabolite in plants and microorganisms[1].The synthesis of Oseltamivir (Tamiflu)[2] and Bactobolin A[3] are probably the most distinct uses of QA in total synthesis. Exploration of stereoselective metal-free deoxygenation is a recent example of QA's synthetic value[4]. Additionally, the *O*,*O*-silyl group migration on a quinic acid-derived cyclitol gives suitable intermediate for the synthesis of a vitamin D receptor modulator (VS-105)[5]. Photoredox catalysis is a known sustainable alternative to the use of less environmentally superstoichiometric oxidants and reductants. Ruthenium and iridium complexes, in combination with visible light, are efficient photocatalysts when strong reductants or strong oxidants are needed, however, their toxicity and scarcity are a drawback for the evolution of photocatalysis to the next level. Organic dyes represent a good alternative to these metal complexes[6].

The functionalization of QA and its derivatives via photoredox catalysis will be presented. Organic dyes under visible light irradiation can generate radical intermediates from QA under mild conditions. This radical generation unravels innovative ways for the synthetic modification of QA.



Scheme 1: Quinic acid functionalization under visible light

Acknowledgements: The authors acknowledge Fundação para a Ciência e Tecnologia (FCT) for financial support **(PTDC/QUI-QOR/1131/2020, UIDB/04138/2020 and UIDP/04138/2020).** The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

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Accessing Asymmetric Synthesis: Flow Enzymatic Kinetic Resolution of Bicyclic-Aziridines

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The demand for enantiomerically pure compounds in the pharmaceutical industry increases the complexity of the synthetic routes. Among the methodologies to obtain enantiopure compounds, lipase mediated kinetic resolution offers a green process, with a well-established route, distinct advantages of high activity, selectivity, and mild operating conditions.[1]

α-hydroxycyclopenteno-aziridines (bicyclic-aziridines) are an intermediary to achieve molecules with biological properties such as functionalized aminocyclopentitols (*e.g.,* peramivir, ticagrelor, neplanocin A and trehazolin).[2]The bicyclic-aziridines are obtained in a racemic mixture through a photochemical transformation of pyridinium salts, for which we developed a flow reactor for gram-scale preparation.[3] These bicyclic-aziridines have a free secondary alcohol in their structure, allowing for an enzymatic kinetic resolution, which could be achieved by using Novozym 435, an immobilized lipase, CAL B. The obtention of enantiopure bicyclic-aziridines unlocks synthetic routes to complex chiral structures.

We herein disclose the enzymatic kinetic resolution of two bicyclic-aziridines: allyl bicyclic-aziridine and butyl bicyclic-aziridine, from early batch studies to flow **(Figure 1 (B,D) and (C, E)).** We successfully obtained with short residence times (*S*)-allyl bicyclic-aziridine in 98% enantiomeric excess (*ee*) and 46% isolated yield **(Figure 1(C))**, as well the obtention of (*R*)-butyl bicyclic-aziridine acetate in 95% *ee* and 20% isolated yield **(Figure 1(B)).**

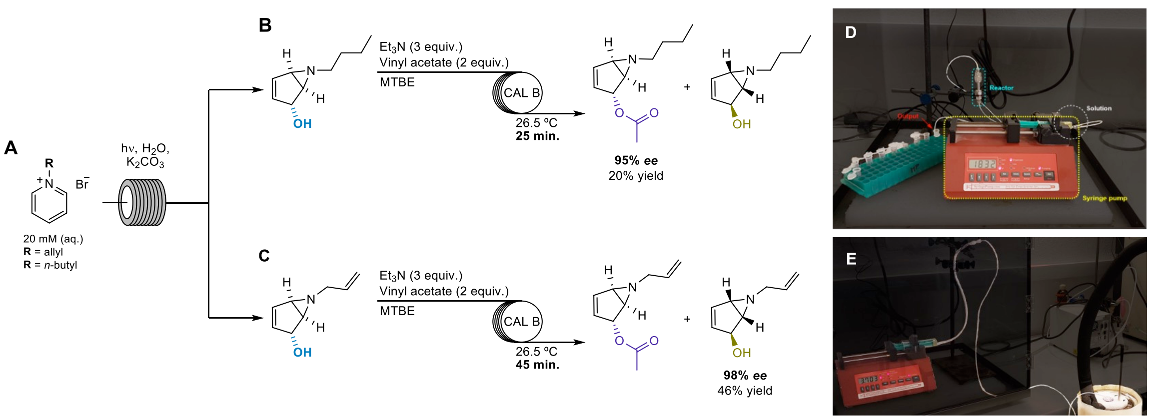

Figure 1: Obtention of enantiomeric pure bicyclic-aziridines: (A) Photochemical transformation of pyridinium salts in flow; Enzymatic kinetic resolution of (B) butyl-bicyclic -aziridine and (C) allyl-bicyclic -aziridine. Flow setup of enzymatic kinetic resolution (D) and (E).

Acknowledgements: The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996. We thank the Fundação para a Ciência e Tecnolgia for financial support (2021.06598.BD, 2022.08559.PTDC, UIDB/04138/2020 and UIDP/04138/2020)

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Semi-Industrial Synthesis of Diverse Pyrazolines and Cyclopropanes via [3+2]-Cycloaddition between Flow-Generated Diazomethane and Alkenes

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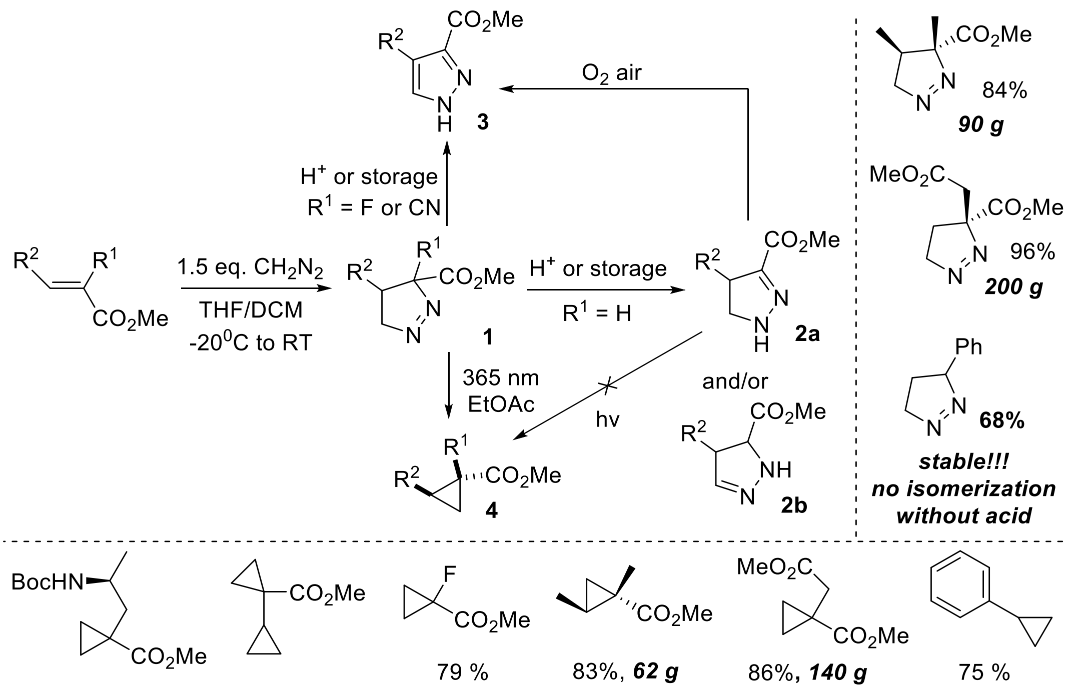
Reactions of CH_2N_2 with acrylic acid derivatives were described[1] in 1930s, however, preparative applications of diazomethane[2] were limited due to its toxicity and explosivity. We elaborated continuous-flow procedure that enables safe and reproducible generation of diazomethane to afford up to 200 g of a cycloaddition product. The initial products, namely 1-pyrazolines **1** are hard to isolate due to isomerization into more stable 2-pyrazolines (**2a** or **2b**) and subsequent oxidation to pyrazoles **3**. Therefore, 1-pyrazolines usually were isolated in mixtures with other isomers or proposed as tentative structures. We confirmed relative stability of 1-pyrazolines bearing tertiary carbon atom or an aryl substituent in the third position, obtained them as individual compounds on a scale up to 200 g and proved the structures with 2D NMR experiments. In case of a leaving group (e.g. F, CN) in the third position of a pyrazoline, corresponding pyrazoles **3** are formed under storage or acidic conditions.

The second part of our investigation is devoted to photochemical synthesis of cyclopropanes **4**. To ensure reaction safety and controllability, syntheses were performed *in flow*. We showed that 1-pyrazolines **1** eliminate nitrogen under 365 nm irradiation, while the other isomers do not undergo the transformation. The reaction sequence is tolerant towards small rings, esters, nitriles, Boc-protected amines and organofluorine compounds; stereochemical configuration is preserved. The desired cyclopropanes were obtained in amounts up to 140 g.



Scheme 1: Performed syntheses and diversity of the obtained products.

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Stereoselective synthesis of an antinociceptive compound by silyl-Prins cyclization

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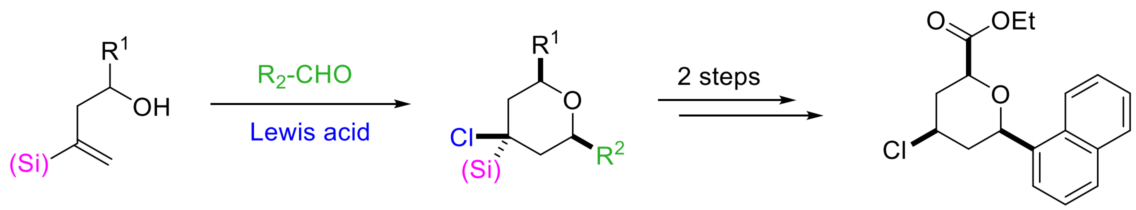
The heterocyclic motif is very abundant in biologically active natural products. Due to their wide variety and complex ring skeletons an always growing number of synthetic approaches to access this type of structures have been described.[1] On the other hand, the use of silicon-containing compounds in the synthesis of natural products has proven to be a powerful tool. [2,3] Our research group has been lately involved in the synthesis of heterocycles starting from vinyl- or allylsilanes.[4]

Here, we present the total synthesis of a compound that has been proved to display antinociceptive properties.[5] The first step is the silyl-Prins cyclization of a vinylsilyl alcohol to obtain a trisubstituted tetrahydropyran. The total stereoselectivity of this reaction results on the formation of a quaternary chloro-containing C4 in a highly selective manner. Two further steps are required to obtain the bioactive compound as a single diastereomer (**Scheme 1**). By this way, a new regio- and stereoselective synthetic route for a bioactive compound is presented.[6]



Scheme 1: Synthetic route for the antinociceptive compound

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Looking for the best selective pathway to obtain *cis*-2,6-dihydropyran derivatives

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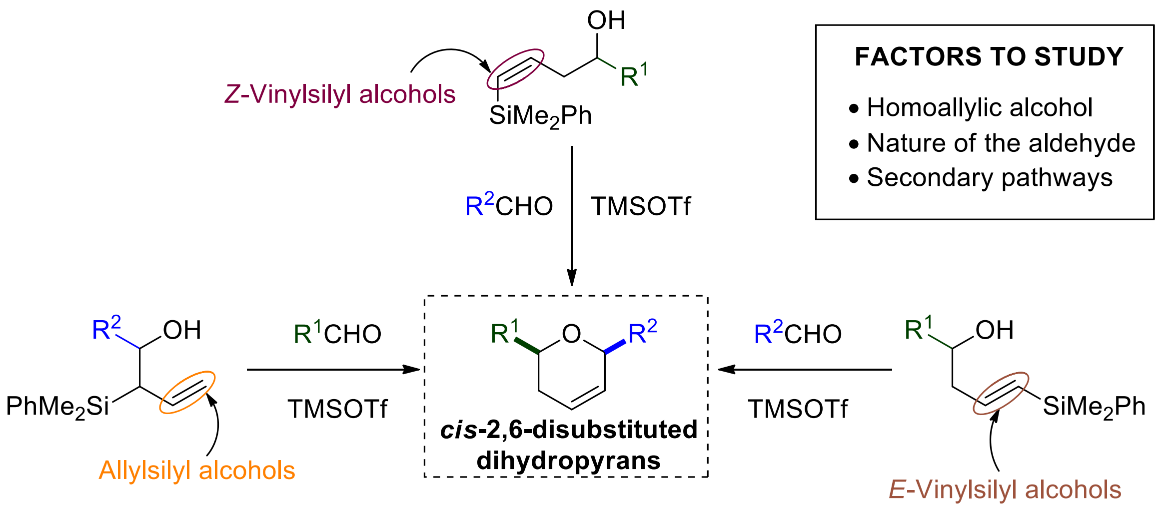
Oxacyclic compounds are common chemical structures found in nature which, due to their biologically active profile, offer promising challenges for drug discovery.[1] The importance of these compounds has evoked great interest for the development of new synthetic methodologies applied to the synthesis of different kind of heterocycles. In this context, numerous research groups have been focused on designing efficient methods for the construction of these cores.[2]

In this communication, we present the study which has been carried out to stablish the best conditions to afford *cis*-2,6-disubstituted dihydropyran derivatives, by silyl-Prins reaction with different alkenols, such as allyl-, *E*-vinyl- and *Z*-vinylsilyl homoallylic alcohols (**Scheme 1**). The influence of the nature of starting materials in the selectivity of the cyclization and the competitive pathways have been explored. Furthermore, computational studies have been performed in order to corroborate the experimental facts.[3]



Scheme 1: Study carried out for the synthesis of *cis*-2,6-disubstituted dihydropyran derivatives.

Acknowledgements: L.F.P. acknowledges a predoctoral grant, funded by the "Junta de Castilla y León".

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New multitarget neuroprotective drugs with 1,3-cyclohexadien-1-als scaffold

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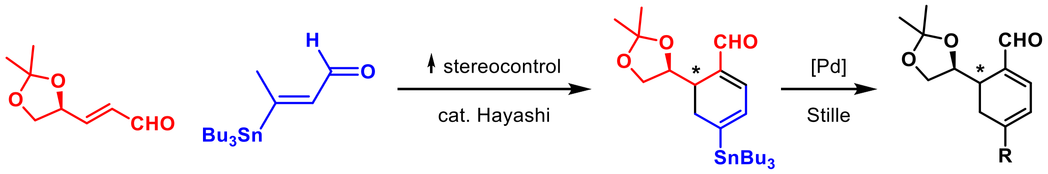
Alzheimer's diseases and other neuroprotective diseases show several neuronal dysfunctions: peptide accumulation and aggregation, modification in neurotransmission and cell-membrane receptors as well as Ca^{2+} homeostasis.[1] These factors collaborate all together to generate excitotoxicity and cell death. A rational approach to the chemotherapy of these diseases consists of the development of multitarget drugs, capable of regulating the pathological routes involved.

In this work, a new synthetic methodology has been developed, allowing a fast and economic procedure to access the chiral 1,3-cyclohexadien-1-als backbone (**Scheme 1**).[2,3] The biological evaluation of these compounds proved the double unsaturated aldehyde scaffold in the neuroprotective activity against oxidative stress thought Nrf2 induction.[4] Besides, the acetylcholinesterase (AchE), butytylcholinesterase (BuChE), MAO-A and MAO-B.

In summary, herein a new horizon to diversity-oriented synthesis has been opened, where the preliminary biological evaluation of the structural influences in Nrf2 induction and neuroprotection shows promising antioxidant and new compounds with selectivity for inhibiting MAO-B against MAO-A.



Scheme 1: Methodology for the obtention for chiral 1,3-cyclohexadien-1-als with biological activity.

Acknowledgements: We thank the government of Castilla y León (SA076P20) and the Spanish Ministry of Science and Innovation (PID2020-118303GB-100) for the financial support, R.B.H. thanks InstituteTeófilo Hernando Foundation for the employment contract.

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Phosphine-mediated Reductive Functionalisation of Aldehydes

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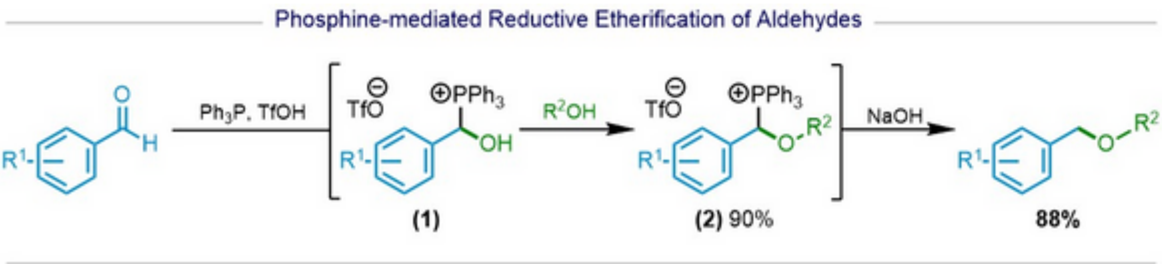
The ether functional group is a common structural feature found in a variety of bioactive compounds including antivirals, antifungals and antimicrobial agents.[1] Tamiflu, an ether-containing antiviral agent used to treat Influenza A and B, generated a market value of $1.1 billion in 2018. Ethers are typically accessed through the Williamson etherification,[2] which involves the reaction of an alkyl halide and an alkoxide to furnish the desired ether. Alkoxymercuration is an alternative strategy which requires toxic mercury reagents and is therefore undesirable. Moreover, in all instances toxic halogenated waste[3] must be carefully removed to avoid contamination.[4]

The methodology proposed herein, employs an aldehyde as the stoichiometric alkyl source and negates the need for alcohol pre-treatment. Aldehydes are abundant alkyl sources, generally non-toxic and more desirable than alkyl halides[5] and as such, exhibit a variety of improvements on alkyl halides as the stoichiometric alkyl source. It has been found that the key intermediate (1) in the formation of benzyl ethers can be obtained in a simple one step reaction. Phosphonium salt hydrolysis with concomitant expulsion of the carbon leaving group,[6] yields the desired benzyl ether in 88% yield. This methodology, will provide an alternative means of accessing this ubiquitous functional group, whilst obviating the use of alkyl halides; which is highly desirable from a Green Chemistry perspective.



Scheme 1: General scheme for reductive etherification of aldehydes.

Acknowledgements: We thank the Irish Research Council for financial support of this project.

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A computational investigation into the Cu-catalysed borylation of α,β-unsaturated compounds

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Boronic esters are versatile building blocks for the synthesis of complex molecules, as they react under mild, functional group tolerant conditions. Boron reagents are also important as starting materials for one of the most common C-C bond-forming reactions in the pharmaceutical industry – the Suzuki reaction. Building a wider library of commercially available boronic ester building blocks would make adding functionality in organic synthesis more accessible. While there are currently many heteroaromatic boronic esters available, there are far fewer saturated heterocyclic boronic esters.[1]

The Partridge Group has developed a method for the synthesis of borylated lactams through the Cu-catalysed borylation of enoates, followed by their cyclisation.[1] These borylated lactams can be made in moderate-to-high yields, and the borylation step can be performed enantioselectively using a chiral catalyst. To aid in the design of future catalysts and new processes, and potentially tune the product selectivity, it would be advantageous to be able to understand how stereoselectivity is induced in these reactions.

This work develops a computational workflow to investigate the origins of stereoselectivity for the borylated lactam synthesis developed by the Partridge group. The main challenges of this work arise from modelling large organometallic complexes with two metal centres and chiral ligands. A simplified mechanism[2] was modelled to determine the general mechanistic pathway, followed by benchmarking of different computational methods. The full reaction was then modelled, and semi-empirical methods such as xTB[3] and CREST[4] were used to find low-energy conformers, before using DFT methods to obtain final geometries. This presentation will provide an overview of the computational benchmarking data, a detailed workflow, and a proposed mechanism with energy profile diagrams for the mechanisms modelled.

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Thermo-responsive foldamers: Switching from supramolecular polymer to heteroduplex through kinetically trapped foldamers

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Foldamers constitute a new family of oligomers that adopt well-defined architectures stabilized by non-covalent interactions.[1] Mostly inspired by the complexity and the amazing variety of functions in biomacromolecules, chemists have dedicated much attention to the synthesis of such species. The latter find numerous applications related to biology, molecular recognition,[2] catalysis,[3] or more recently, stimuli responsive materials.[4] Among the wide diversity of building blocks allowing for the construction of foldamers, some of these structures fold into helical form and hybridize to form double and multiple helices.[5] The corresponding dynamics proved to be affected by parameters, such as temperature, concentration and solvent.[6] However, controlling this equilibrium in a reversible manner remained a challenge to tackle.

In this context, we recently investigated the possibility to elaborate selectively heteroduplex through donor-acceptor interactions. To tackle this challenge, we designed foldamers endowed with planar electroactive rings, such as 1,4,5,8-naphthalenetetracarboxylic diimide (NDI) and 1,5-dialkoxynaphthalene (DAN). Thereby, we observed an unexpected behavior (Figure 1), which involves kinetically trapped species and which will be at the heart of this communication.

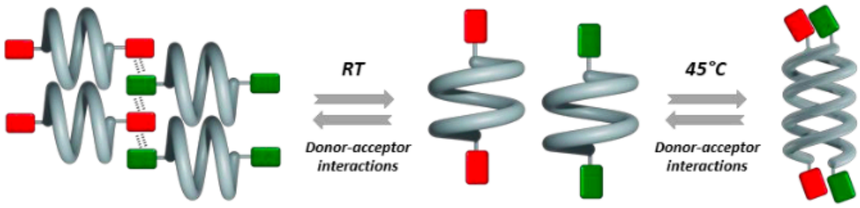

Figure 1. Schematic representation of the behavior of foldamers in solution through donor-acceptor interactions.

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Virtual Screening of New 2-Phenethylamine Hits Targeting μ-Opioid Receptor

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The 2-phenethylamine motif is widely present in nature, from simple, open-chain structures to more complex polycyclic molecular arrangements. From the structural point of view, 2-phenethylamines present a vast therapeutic chemical space, not just as is, but considering different substitutions, functional group decorations, ring enclosures or heteroaromatic analogues.[1] Our group has developed a proptocol to obtain 2-phenethylamines via a novel 1,4-Phenyl radical rearrangement.[2] Considering this innovative approach and the fact several 2-phenethylamine hits were reported targeting the opioid receptors, specially the μ-type receptor,[3] we present here a Virtual Screening campaign to seek novel chemical matter with the aforementioned scaffold (**Figure 1**).

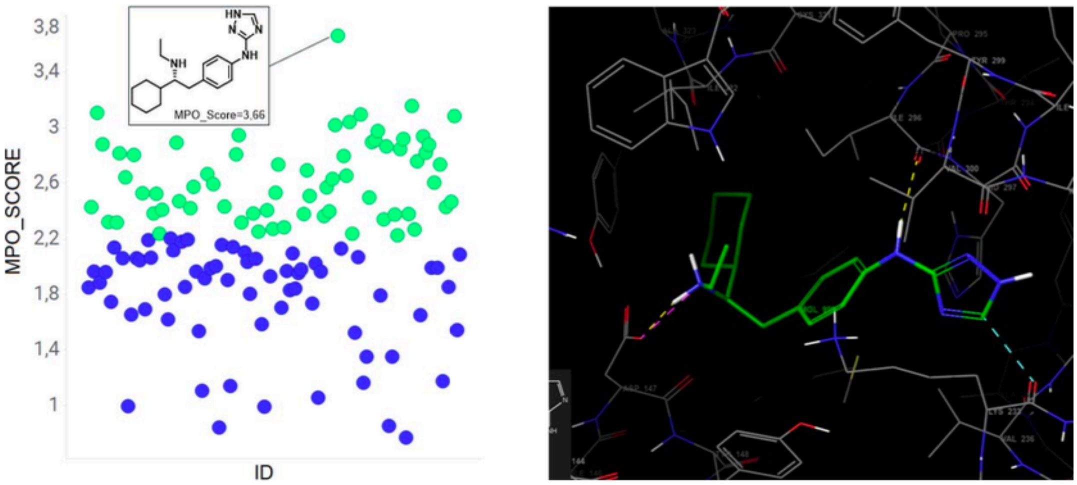

Figure 1: Chemical matter space from the virtual screening campaign.

Physchem properties and molecular docking filters were set up alongside the described synthetic methodology to conform a promising chemical space targeting μ-Opioid receptor, using Discovery Knowledge in Databases techniques.

Acknowledgements: We thank to FEDER Junta de Castilla y Leon (UIC21), and Junta de Castilla y Leon (SA076P20) for financial support.

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Total synthesis: From pyridine to (-)-agelastatin A

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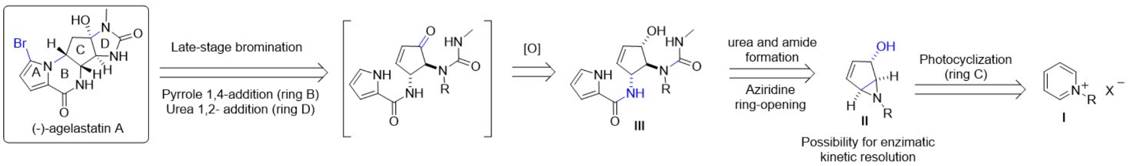
Agelastatin alkaloids have attracted scientific interest since the isolation of (-)-agelastatin A (AglA) from the sponge *Agelas dendromorpha* by Pietra *et al*. in 1993.[1] AglA showed remarkable cytotoxicity against a variety of tumour cells[2] and strong inhibition of osteopontin-mediated neoplastic transformation and metastasis.[3] Additionally, it displays high brine shrimp toxicity and insecticidal properties.[4] Since large quantities of AglA are unreasonable to obtain via natural sources, its total synthesis is highly desirable and some have been developed.[5] Asymmetric synthesis is very challenging and requires laborious steps and protecting groups to construct the four contiguous nitrogen-bound stereocenters of the cyclopentane C-ring. We have developed a strategy that involves the early-stage photochemical transformation of pyridinium salts to bicyclic vinyl aziridines that originate, in one step, the AglA's C-ring with the desired functionality and relative configuration. The presence of a secondary alcohol on the cyclic core allowed enzymatic kinetic resolution in high *ee* (>98%). Both mentioned transformations were performed under flow conditions to increase the efficiency and scale of the processes. Then, a sequence of nitrogen-carbon bond forming reactions culminated in the total synthesis of (-)-agelastatin A in only 12 steps with 4% overall yield, with the use of a single protective group.[6]



Scheme 1: Retrosynthetic analysis of agelastatin A.

Acknowledgements: The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996. The authors acknowledge Fundação para a Ciência e Tecnologia (UIDB/04138/2020, UIDP/04138/2020, SFRH/BD/120119/2016) for financial support.

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2,5-Substituted-1,3,4-oxadiazoles: Synthesis and Protective Activity Against Oxidative Stress

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There are four isomeric forms of oxadiazole and all of them are frequent motifs in drug-like molecules. 1,3,4-Oxadiazole ring is a good bioisoster of amides and esters, which can contribute to hydrogen-bonding driven interactions with receptors. Therefore, they have been extensively used in development of antibacterial[1], antiparasitic[2], anti-tuberculosis[3], analgesic and anti-inflammatory[4], as well as anti-HIV[5] agents. Recently, we have reported synthesis and biological evaluation of 5-(alkylthio)-2-((1*H*-indol-3-yl)methyl)-1,3,4-oxadiazoles[6]. Three of the prepared derivatives were proven to protected Friedreich ataxia fibroblasts against glutathione depletion induced by γ-glutamylcysteine synthetase inhibitor buthionine sulfoximine (BSO). Moreover, two active compounds increased survival of *Caenorhabditis elegans* exposed to juglone-induced oxidative stress.

The goal of this project was to expand the library of 2,5-substituted-1,3,4-oxadiazoles and to extend the study of structure-activity relationships. The synthesis was undertaken in two directions to prepare: 2-(alkylthio)-5-(*N*-heteroaryl)-1,3,4-oxadiazoles and 2-(alkylamino)-5-(*N*-heteroaryl)-1,3,4-oxadiazoles.

Synthesis of 2-(alkylthio)-5-(*N*-heteroaryl)-1,3,4-oxadiazoles was carried out in three-steps. Alkoxycarbamoy-*N*-heterocycles were treated with $NH_2NH_2 \times H_2O$ to get corresponding hydrazides. Subsequently, 5-(*N*-heteroaryl)-1,3,4-oxadiazole-2(3*H*)-thiones were obtained upon base-mediated treatment of hydrazides with CS_2, followed by *in situ* acidification. The last step in this synthesis path was base catalysed *S*-alkylation. Synthesis of 2-(alkylamino)-5-(*N*-heteroaryl)-1,3,4-oxadiazoles was similarly carried out in three-steps. In the first step alkoxycarbamoy-*N*-heterocycles were treated with $NH_2NH_2 \times H_2O$ to get intermediate hydrazides. Subsequently, crude hydrazides were condensed with alkyl isothiocyanates. Finally, 1,3,4-oxadiazole structural unit was formed by intramolecular cyclization reaction.

Upon purification of target products (purity ≥97%, HPLC) their structure was confirmed by detailed NMR, IR and MS spectrum data analysis. The biological investigations of prepared compounds are currently on-going.

Acknowledgements: This work was supported by the Ministry of Education, Youth and Sports of the Czech Republic (program INTER-COST, grant numbers LTC18078 and LTC19030) and by the European Regional Development Fund (Project ENOCH, No. CZ.02.1.01/0.0/0.0/16_019/0000868).

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Development of Readily Accessible Organometallic Capping Reagents for Carbon Labeling of Drugs

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Our group have recently developed methods for carbon isotope labeling of aromatic carbonyls using the unlabeled molecule as the starting material, and readily accessible palladium carboxylate complexes as capping reagents. This work is inspired by previous projects performed in our group and is a part of our goal of developing new organometallic capping reagents.[1] We define this new approach as molecular surgery, a method where drug companies can incorporate a labeled carbon isotope as the last step, or one of the last steps in synthesis. The main advantage of this method is the quantitative incorporation of the carbon isotope label and the minimized loss of the carbon isotope in further reaction steps. This is especially important when drug companies perform ADME studies where ^{14}C-isotope labeling is a mandatory part of the safety study.

As the molecular surgery knife, we employ a variety of methods from literature, where the functional group is cleaved off from the rest of the molecule. This affords the drug core, which can be utilized in a cross-coupling reaction with our capping reagent to afford the carbon isotope labeled molecule. Due to the flexibility of the capping reagents multiple carbonyl analogues of a given drug can easily be synthesized when employing this method.

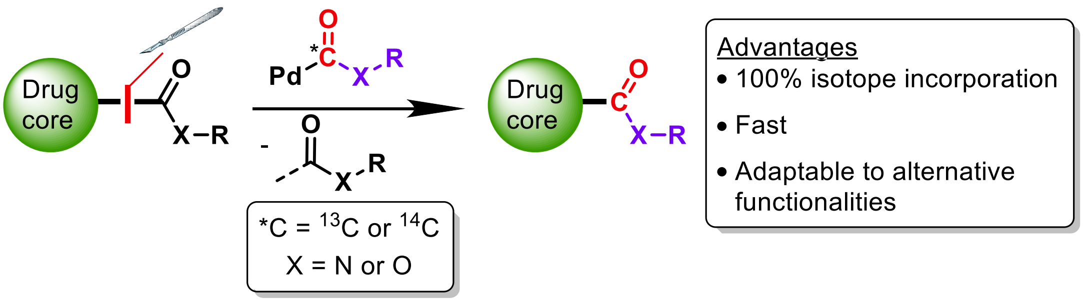

Figure 1: Employing molecular surgery on a carbonyl containing functional group

Acknowledgements: We thank the Novo Nordisk Foundation and Danish National Research Foundation for financial support

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Synthesis and Biological Studies of Functionalized Bipyrazole Compounds

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The progress of the pharmaceutical industry depends on new biologically active substances availability. Pyrazole compounds are major in the fields of organic and medicinal chemistry since they exhibit numerous properties such as antimicrobial, anticancer, anti-inflammatory, antioxidant, antitubercular, etc.[1] Despite the widespread interest in pyrazole chemistry, many unresolved challenges remain, such as the synthesis and biotesting of polycyclic pyrazole derivatives. Based on this, the concept of current work was formulated: the development of novel bipyrazole derivatives synthetic procedures, their functionalization using Pd-catalyzed cross-coupling reactions and bipyrazole derivatives applicability in anticancer therapy. Intermediated hydrazone derivatives also possess broad spectra of biological characteristics ranging from antioxidant, anti-inflammatory, antiviral effects activity and others.[2] The bipyrazole system could not only improve the biological effects of compounds already possessing a pyrazole ring but also provide a new asset of pharmacologically desired properties.[3] The 1-phenyl-1*H*-pyrazol-3-ol was alkylated and then the formylation reaction was performed by the *Vilsmeier-Haack* reaction.[4] Then the obtained different aldehydes were used in the synthesis of hydrazone and bipyrazole derivatives (**Figure 1**). In search of a condensation reaction for the bipyrazole system, various methods were tested. It was found, that sodium nitrite catalyzed cyclization of pyrazole-hydrazones proved to provide the highest yield of the target bipyrazole. Pd-catalyzed *Suzuki-Miyaura* cross-coupling reactions were used for the functionalization of bipyrazole derivatives. AlamarBlue assay was used to assess methabolic activity changes of the cells. Obtained cell viability changes were plotted in order to obtain IC50 value. Here, three cancer cell lines were used: A549, 4T1 and MCF7. A significant cell viability decrease was considered If the IC50 value was less than 20 μM.

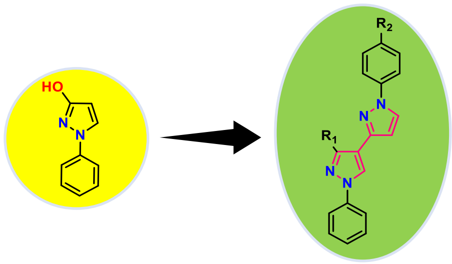

Figure 1: Functionalization of 1-phenyl-1*H*-pyrazol-3-ol.

Acknowledgements: This research has received funding from the Research Council of Lithuania (LMTLT), agreement No [S-SV-22-19] and was funded by a grant (BiPyCellDeath) from funds of the Kaunas University of Technology and Vytautas Magnus University.

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Natural Ionic Systems for Homogeneous and Heterogeneous Catalysis

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The discovery of efficient, sustainable and recyclable homogeneous and heterogeneous catalytic processes is an important challenge for modern science. Nowadays, the use of bioinspired organocatalysts for asymmetric catalysis is relevant for academic approaches as well as pharmaceutical industry. In this context, L-proline is one of the best organocatalysts for different enantioselective transformations [1]. Our recent approaches include the preparation of Bioinspired chiral ionic liquids (BioCILs) as efficient and recyclable organocatalysts or chiral ligands for several asymmetric organic transformations [2, 3].
In parallel, the metal catalysis have been largely used for carbon dioxide conversion into fuels and other valuable products. In this context, Carbon capture and utilization (CCU) is currently under scrutiny at large pilot-plant level as a mitigation strategy for the CO_2 emission problems and global warming [4]. Our recent achievements include the efficient carbon dioxide hydrogenation to methane using Ruthenium nanoparticles (Ru-NPs) prepared and stabilized in task-specific ionic liquids [5]. 1-Octyl-3-methylimidazolim perfluorobutanesulfonate [C_8mim][NfO] is one of the best ionic liquid media producing 84% yield of methane at 150 °C [6]. Other fluorinated anions based ionic liquids exhibited a greater influence on the methane production.

Herein, different catalytic approaches using natural ionic systems (e.g. bioinspired ionic liquids, natural deep eutectic solvents) are presented:

i) **ASYMMETRIC ORGANOCATALYSIS** based on catalytic reaction media composed by suitable combination between proteins and ionic liquids for application in asymmetric Michael reactions with excellent yields and enantiomeric excesses comparable or higher than conventional catalytic systems.
ii) **NANOCATALYSIS** based on ruthenium nanoparticles dispersed on natural ionic systems based on DL-Menthol as alternative media for hydrogenation of CO2 to methane.
iii) **METAL HOMOGENEOUS CATALYSIS** based on zinc complex catalyst and bioinspired ionic systems for preparation of cyclic carbonates from epoxides [7].
iv) **ELECTROCATALYSIS** using protic natural ionic systems as reaction media and zinc anodes for conversion of CO2 into syngas [8].

Acknowledgements: The authors thanks the project Cat4GtL (POCI-01-0247-FEDER-069953), co-funded by ERDF through COMPETE 2020 under PORTUGAL 2020. This work was also supported by FCT/MCTES through projects MIT-EXPL/CS/0052/2021, projects UIDB/50006/2020, LA/P/0008/2020 and UIDP/50006/2020 of the Associate Laboratory for Green Chemistry – LAQV. NMR spectrometers are part of The National NMR Facility, supported by FCT (ROTEIRO/0031/2013-PINFRA/22161/2016) (co- financed by FEDER through COMPETE 2020, POCI, and PORL and FCT through PIDDAC).

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A New Bio-Based Nitrogen-Rich Furanic Platform Alternative for Lignocellulosic Derived Furfurals

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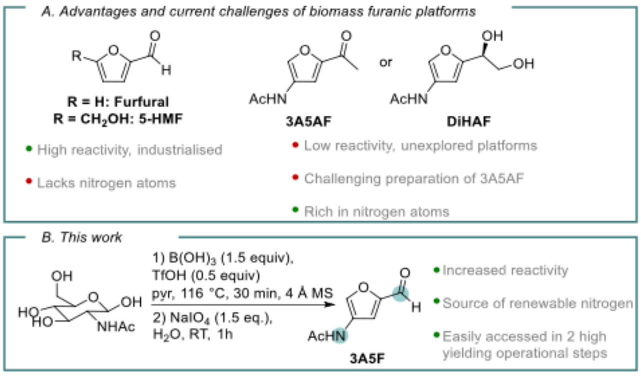
The demand for new biomass-derived fine and commodity chemicals propels the discovery of new methodologies and synthons. Amongst the several examples, furanic platforms obtained from lignocellulosic biomass have emerged as a cornerstone for the sustainable development of new valuable chemicals, as a replacement for oil-based products, and as a starting material for the preparation of "drop-in" chemicals. In fact, furfural is currently being produced in over 250 kTonne/year with over 80 synthons being prepared from it.[1] Despite this, a major limitation of these furans is the lack of nitrogen (**Figure 1A**). Often introducing external nitrogen requires non-sustainable sources, the most common being ammonia. Knowing that circa 1.5% of the total world energy consumption is used to produce ammonia, which is then introduced in fine and commodity chemicals, several academia and industry-based groups have turned their attention to nitrogen-rich biomass sources.[2,3] Besides lignocellulosic biomass, chitin is one of the most abundant waste byproduct. Whereas furfural and 5-hydroxymethylfurfural are cornerstones of sustainable chemistry, 3-acetamido-5-acetyl furan (3A5AF), an N-rich furan obtained from chitin biomass, remains unexplored, due to the poor reactivity of the acetyl group relative to previous furanic aldehydes. Here we developed a reactive 3-acetamido-5-furfuryl aldehyde (3A5F) and demonstrated the utility of this synthon as a source of bio-derived nitrogen-rich heteroaromatics, carbocycles, and as a bioconjugation reagent. (**Figure 1B**) [3]



Scheme or Figure 1: Overview of biomass derived furanics.

Acknowledgements: The authors acknowledge Fundação para a Ciência e Tecnologia (FCT) for financial support (PTDC/QUI-QOR/32008/2017, UIDB/04138/2020, UIDP/04138/2020). Doctoral FCT studentship SFRH/BD/143583/2019 to B.B.S and SFRH/BD/148211/2019 to K.H.S.A. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

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Bimetallic Catalysed Synthesis *N*-heterocycles

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Azaindoles are rare in nature and highly interesting in medicinal chemistry and drug discovery programs. This is mainly due to the fact that its solubility, lipophilicity, target binding and ADME-tox properties can be modulated and tuned, constituting an enormous advantage over other heterocyclic compounds.[1] However, synthesis of azaindoles is challenging, due to the electron-deficient nature of the pyridine ring that alters the electronic properties of the conjugated system. Our group has been focused on the synthesis azaindoles, relying on palladium-catalysed cross-coupling reactions and developed different practical approaches compatible with all azaindole isomers from aminopyridines.[2] In particular, we have been exploring Pd-catalysed one-pot methodologies such as the C–N cross-coupling/Heck reaction[3] also with Pd-nanocatalysts;[4] the *N*-arlyation/Sonogashira/cyclization reaction;[5] Pd-catalysed C–N cross-coupling/C–H functionalization.[6] Recently, we have been investigating the use of Earth-abundant metals, and a bimetallic approach has been disclosed towards *N*-heterocycles.[7] Herein we will present our latest achievements on the one-pot reactions, and simple protocols towards not easy to make *N*-heterocycles (**Figure 1**).

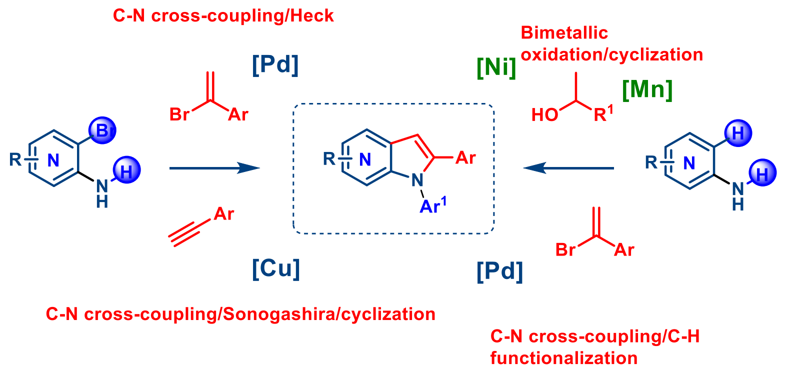

Figure 1: Metal-catalysed synthesis of *N*-heterocycles

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (FCT, projects PTDC/QUI-QOR/0712/2020 and PTDC/QUI-QIN/0359/2021). The author also thank the support by the Laboratório Associado para a Química Verde (LAQV), which is financed by national funds from FCT/Ministério da Ciência, Tecnologia e Ensino Superior.

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Engineering the surface configuration of AgPd alloy catalysts for highly selective oxidation of 5-hydroxymethyl-furfural at room temperature

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Introduction. The production of 2,5-furandicarboxylic acid (FDCA) plays a pivotal role in chemical synthesis as it serves as a highly valuable and renewable platform chemical with diverse applications. For example, FDCA is a key building block for the synthesis of bio-based polymers and materials, such as polyethylene furanoate (PEF), which offers a sustainable alternative to conventional plastics derived from fossil fuels. The selective oxidation of 5-hydroxymethyl-furfural (HMF) to FDCA is a promising pathway to efficiently obtain this valuable compound. However, achieving high selectivity/yield of FDCA at low temperatures is challenging with the currently available catalysts. To address this challenge, our research proposed both thermalcatalysis and photocatalysis systems using AgPd alloy nanoparticles (NPs) supported on CeO_2.

Results and discussion. The aerobic oxidation of HMF using an $Ag_{1.5}Pd_{1.5}/CeO_2$ catalyst at 20°C demonstrates a remarkably high yield of FDCA, making it a promising method for room temperature production of FDCA from sustainable sources. We found increasing the reaction temperature leads to a decline in FDCA yield due to unwanted side reactions. Both the experimental results and density functional theory (DFT) simulations indicate that the selective oxidation process is strongly influenced by the appropriate chemisorption strength of reactants, intermediates, and products on the metal NPs (active sites) at 20°C. Adjusting the Ag/Pd ratio allows for finely tuning the surface configuration to modify its adsorption capabilities and effectively address specific reaction steps. The bimetallic boundary sites of $Ag_{1.5}Pd_{1.5}$ NPs exhibit a moderate adsorption capacity for reactants and intermediates, surpassing the activation energy barriers involved in the oxidation of carbonyl and alcohol groups, while efficiently avoiding side reactions. Mechanism studies reveal the oxidation of alcohols to carbonyl group and carbonyl to carboxyl group in HMF is facilitated by OH• radicals generated from OH^- ions on the alloy NP surface. O_2 molecules act as electron scavengers, completing the reaction loop by efficiently capturing the released electrons. The scale-up results have demonstrated a remarkable FDCA yield at the 100g level, indicating the significant potential of this catalyst for industrial applications. Based on the knowledge of this study, our recent exploration involves the development of an isolated Pd site AgPd photocatalyst, which has shown remarkable success in achieving an FDCA yield exceeding 99% under low-flux light illumination. These results demonstrate the great potential for utilizing solar energy as a driving force for this reaction, paving the way for sustainable and environmentally friendly production of FDCA.

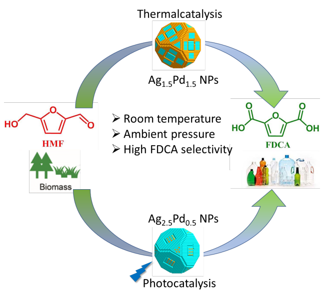

Figure 1. Scheme of thermal catalysis and photocatalysis process of selective HMF oxidation using AgPd alloy catalysts.

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DESIGN OF COCAINE ANALOGUES TO TREAT PSYCHOSTIMULANT USE DISORDERS

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Keywords: *Drug design, Cocaine, Dopamine Transporter, rearrangement.*

The abuse of illicit psychostimulants such as cocaine (**Figure 1**) continues to pose significant health and societal challenges. Despite considerable efforts to develop medications to treat psychostimulant use disorders,none have proven effective. Atypical inhibitors of the Dopamine Transporter (DAT) and are described as promising targets for future drug development. [1]

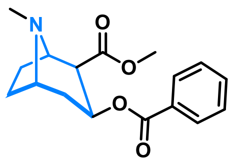
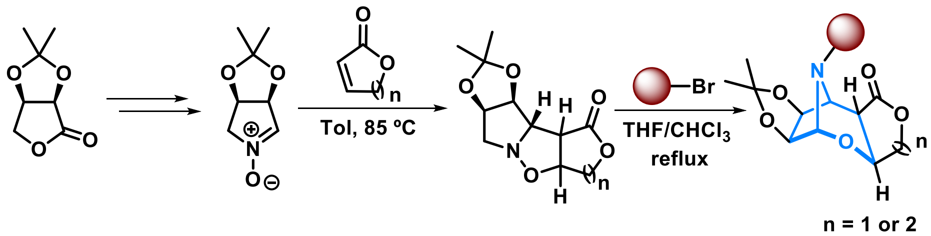


Figure 1: Cocaine structure.

A novel rearrangement reaction has recently discovered in our group leading us to the synthesis of new cocaine analogues in only 4 steps as shown in **Scheme 1**.[2] Shifting the substitution of the bencyl bromide let us modulate bioactivity and toxicity of the final structure.



Scheme 1: Synthesis of cocaine analogues.

A big library of cocaine analogues has been synthesized with promising docking energies as DAT inhibitors. Moreover, a massive virtual screening and docking was carried out to unravel the next generation of cocaine analogues expanding the methodology described.

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Poster Communications

Blue Light Induced Iron-Catalyzed Alkylation of Ketones with Alcohols.

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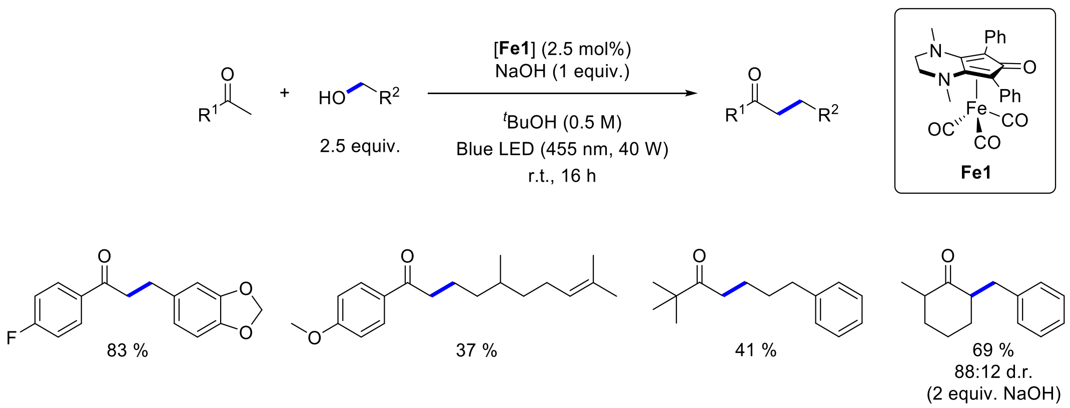
Hydrogen auto-transfer methodology or borrowing hydrogen is an expending and vibrant research area.[1] This reaction consists of the alkylation of a pro-nucleophile (amines, ketones, esters, amides, indoles,…) by an alcohol. this methodology represents a greener and safer procedure than the well-established enolate alkylation for the C-C bond formation, the reductive amination or the nucleophilic substitution for the C-N bond formation. Despite the success of these approaches and catalysts, there is still room to develop C-C or C-N bond formation under milder conditions. The borrowing hydrogen strategy has been applied in the α-alkylation of ketones with alcohols at room temperature under visible light photoirradiation.[2] The reaction was catalysed by a chromophoric phosphine-free diaminocyclopentadienone iron tricarbonyl complex. Different aromatic and aliphatic ketones gave the alkylated products using benzylic and aliphatic primary alcohols (Scheme 1). Preliminar mechanistic investigations highlighted the role of light in both the dehydrogenation and the reduction steps.



Scheme 1: Blue light induced α-alkylation of ketones with alcohols catalysed by an iron complex.

Acknowledgements: We gratefully acknowledge financial support from the "Ministère de la Recherche et des Nouvelles Technologies, Normandie Université, CNRS, "Région Normandie, the Graduate School of Research XL-Chem (ANR-18-EURE-0020 XL-Chem) and the LABEX SynOrg (ANR-11-LABX-0029). A.P. is a Serra Hunter´ Fellow and thanks ICREA Academia prize 2019 and the Spanish MICINN for project PGC2018-097722−B-I00.

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Synthesis of DHFR inhibitors of *M. avium* and *M. abscessus* via late-stage functionalization of 2,4-dichloropyrimidines

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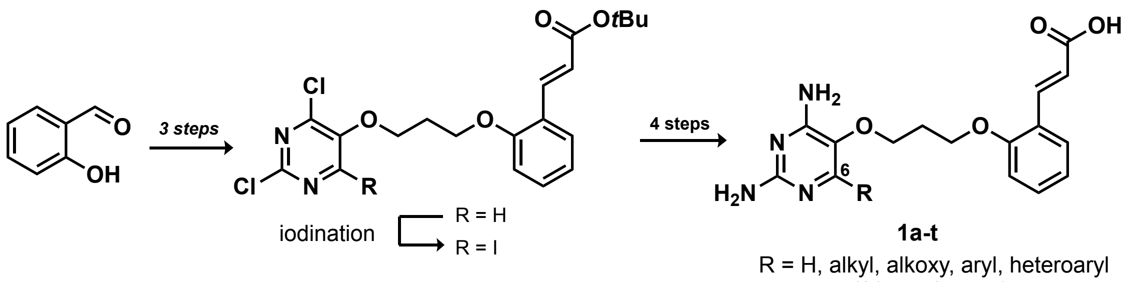
Nontuberculous mycobacteria (NTM) are opportunistic pathogens responsible for lung diseases in immunocompromised patients or patients with pre-existing lung diseases such as cystic fibrosis and chronic obstructive pulmonary disease. The incidence and prevalence of these diseases are increasing worldwide due to the lack of effective drugs.

Here, we describe our results aimed to develop inhibitors of the DHRF (dihydrofolate reductase) of *M. avium* and *M. abscessus*, two microorganisms involved in lung diseases. Our strategy was based on the cocrystal structures of pyrimidine **1** (R = ethyl) complexed to *M. abscessus* and human DHFR (PDB 7k6c)[1], which allowed us to hypothesize that variation in the steric and electronic properties of the C-6 substituent in the pyrimidine ring would increase the selectivity for the Mycobacteria's DHFR.[1] Our approach explored the Pd(0)-catalyzed couplings (Suzuki, Negishi and Sonogashira reactions) after metalation of the C-6 position of the 2,4-dichloropyrimidine ring with 2,2,6,6-tetramethylpiperidine (TMP) bases developed by Knochel and coworkers.[2]



1a-t
R = H, alkyl, alkoxy, aryl, heteroaryl
(20 analogues)

Scheme 1: Synthetic route to diaminopyrimidine inhibitors of *M. avium* and *abscessus*.

Our synthetic work was guided by iterative enzymatic assays with the above mentioned DHFRs which allowed us to unravel four analogues which were potent inhibitors of *M. avium* and *M. abscessus* (K*i* < 1 nM) and inactive against human DHFR (K*i* > 5 μM). Notably, four analogues were more potent than the aminoglycoside antibiotic amikacin used for several bacterial infections, including pneumonia and tuberculosis. Studies are underway to assess the pharmacokinetic properties of the more potent DHFR inhibitors.

Acknowledgements: We are grateful to Fundação de Amparo à Pesquisa do Estado de São Paulo (2019/13104-6 and 2019/20735-1) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (2020/306747) for financial support.

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Selective Catalytic Functionalization of Cavitands

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In the present study, functionalised molecular containers are used as substrates in transition metal-catalysed reactions, a *novel approach to investigate unprecedented supramolecular catalytic synergies*. Metal-catalysed reactions have been sparsely employed to cavitands as convenient tools for molecular enlargement.[1] Based on our previous studies on palladium-catalysed aminocarbonylation and cross-coupling reactions on a of 2-methylresorcinol-based cavitand scaffold,[1f] further unexpectedly highly chemoselective reactions towards tetrafunctionalized derivatives will be presented.

Since the introduction of the carboxamide and formyl functionalities into a framework of practical importance is in the forefront of synthetic chemistry, i) palladium-catalysed aminocarbonylation and ii) platinum/rhodium-catalysed hydroformylation will be discussed.

i) Small-size and deepened cavitands with 4-iodophenyl moieties on the upper rim underwent highly selective aminocarbonylation using various primary and secondary amines as *N*-nucleophiles. Amine nucleophiles range from simple primary amines (for example *tert*-butylamine) via amino acid esters to aminosteroids. High 'tetra-selectivity' was obtained in two aspects: a) tetracarboxamides and tetrakis(2-ketocarboxamides), formed via mono and double carbon monoxide insertion, respectively, were obtained exclusively, b) carboxamides/2-ketocarboxamides possessing the same *N*-substituent were formed even in those cases when two different amines as nucleophiles were used.[2]

ii) Small-size and deepened cavitands with 4-vinylphenyl substituents (i.e., possessing styrene moieties) underwent platinum- and rhodium-catalyzed hydroformylation reaction. As above, the reactions proceeded with high 'tetra-selectivities', that is, all four vinyl groups were either hydrogenated or transformed to the branched or linear aldehydes via hydroformylation. Based on these exceptionally high chemo- and regioselectivities, a cooperation between all the four catalytic reaction centers was supposed.[3]

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Immobilized Cinchonidine-based Catalysts in Deep Eutectic Solvents for Highly Efficient and Sustainable Asymmetric Michael Additions

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In recent years, asymmetric organocatalysis has embraced the use of alternative solvents, contributing to reduced waste formation, often arising from volatile organic compounds used as reaction medium.[1] As the demand for greener chemistry grows, Deep Eutectic Solvents (DESs) have emerged as a promising solution, representing a new generation non-toxic, biodegradable and low-cost solvents that are obtained by simply mixing together two or more safe and cheap components, which are capable of forming an eutectic mixture.[2,3] In this work, we report our studies on immobilized cinchona-squaramide catalyst in three different DESs, namely (Betaine: D-Sorbitol: Water), (Betaine: D-Xylitol: Water) and (Betaine: D-Mannitol: Water), focusing on both catalytic activity and enantioselectivity of the organocatalyst and its recyclability over several reaction cycles using a well-known asymmetric Michael addition.[4] Remarkably, these reactions provided excellent yields (up to 99%) and enantioselectivities (up to 98%) using only 1 mol% of catalyst. It was also possible to achieve 9 cycles in reactions with DES (Betaine: D-Sorbitol: Water), proving the high recyclability of this system. Notably, even in reactions with 0.5 mol% of catalyst, it was possible to achieve 5 cycles and the products were obtained with high yields (up to 95%) and excellent enantioselectivities (up to 94%), using DES (Betaine: D-Sorbitol: Water).[4]

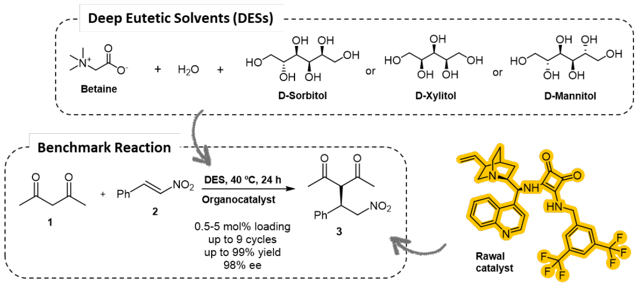

Figure 1: Deep eutetic solvents, benchmark reaction and organocatalyst used for this study.

Acknowledgements: We thank the Fundação para a Ciência e Tecnolgia for financial support through the project UIDB/50006/2020 |UIDP/50006/2020. We are very grateful to ChiraTecnics for the very generous gift of reagents, consumables, and other supports to conduct this work.

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Unveiling the Potential of Phthaloperinones as Active Optoelectronic Compounds for Electronic devices

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Since the electronics revolution in the 20th century, the search and development for new and more efficient electronic devices have been one of the major focuses of our society. These technological advancements have been crucial to improve our quality of life, bringing comfort and pleasure.[1]

Recently, among a plethora of potential compounds, phthaloperinones emerged as promising materials for application in organic electronics due to their unique molecular structure and exceptional electrochemical properties. Additionally, their inherent stability under natural conditions and response to light make them an attractive alternative to other organic based optoelectronic devices.[2,3]

In this communication, we present the syntesis of optoelectronic active phthaloperinone derivatives and their applications in electronic devices such as phtodetectors and OLEDs. Preliminary computational studies were performed revealing the promissing optoeletronic properties of these compounds.

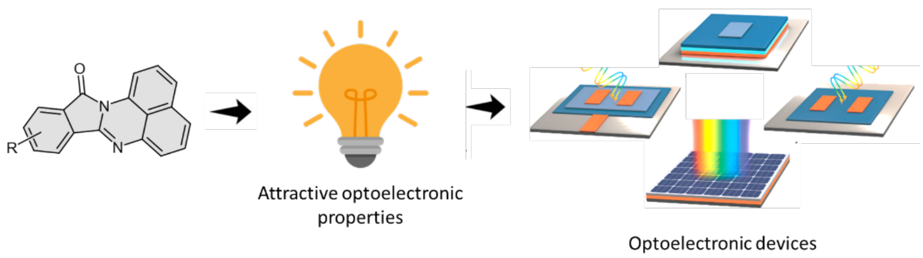

Figure 1: Application of phthaloperinones in organic electronic devices.

Acknowledgements: We thank the Portuguese Foundation for Science and Technology (FCT) for the PhD grant 2021.04769.BD and for funding through project 2022.01391.PTDC.

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Dual Ni/Organophotoredox Catalysed Allylative Ring Opening Reaction of Oxabenzonorbornadienes and Analogs

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A general approach for the allylation of oxa- and azabenzonorbornadienes is reported by merging organophotoredox and nickel catalysis (**Figure 1**).[1] This methodology allowed the diastereoselective allylation of various heterocyclic alkene derivatives with a broader range of allylic acetate compounds compared to previously published procedures.[2] Moreover, no air-sensitive organometallic species and no metal reductants (such as zinc or manganese) are required for the ring opening. Mechanistic studies suggest that the ring opening proceeds through a carbometalation process.[1]

Figure 1: Dual Ni/P.S. allylative ring opening reaction of oxabenzonorbornadienes.

Acknowledgements: We thank the Labex SynOrg and Normandy region for financial support.

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Immobilized and Recyclable Catalysts for the Preparation of Deuterium-Labelled Organic Compounds

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Deuterium(D)-labelled organic compounds are used in many applications e.g., reaction mechanism elucidation,[1] drug development,[2] and organic electronics.[3] In general, D-labelled materials are prepared via:[4] (i) an *indirect* approach (total-synthesis, employing commercially available D-labelled precursors/reagents), or (ii) a *direct* approach, involving late-stage deutero-defunctionalization exchange. Both approaches typically rely on (bio)catalysts to ensure regio- and stereo-selectivity, relatively mild reaction conditions, and a treatment of a broad scope of substrates.[5] However, most (bio)catalysts are expensive to prepare/isolate, and some contain rare and expensive Noble metals (e.g., Ir, Pd, Pt). To address United Nations Sustainable Development Goal 12 (“ensuring sustainable consumption and production patterns”), we need to consider ways to switch from ‘linear’ to ‘circular’ approaches.[6]

This presentation will explore several more-sustainable approaches that have been reported by the scientific community for the synthesis of D-labelled compounds, with a particular focus on immobilized (supported), recyclable (bio)catalysts in batch or continuous flow microreactors.[7] I will also use this opportunity to briefly introduce strategies being explored in our group to immobilize Kerr’s catalyst, a widely used catalyst for the preparation of D-labelled compounds, by connection to the triphenylphosphine and the N-heterocyclic carbene (NHC) ligands (**Figure 1**). Preliminary results indicate that our immobilized catalysts could be recovered and reused while demonstrating activity comparable to the parent catalyst over a few cycles.

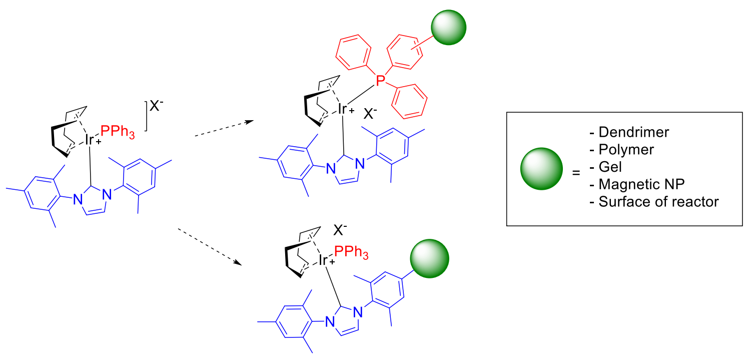

Figure 1: Strategies taken in our research group to immobilize Kerr’s catalyst, either via the PPh_3 or the NHC ligand.

Acknowledgements: We acknowledge the European Union’s Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement no. 945380, and the International Isotope Society (European Division) for financial support.

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Ir-Catalysed (Hetero)aryl C−H Functionalisation *via* N to C Alkyl Transfer

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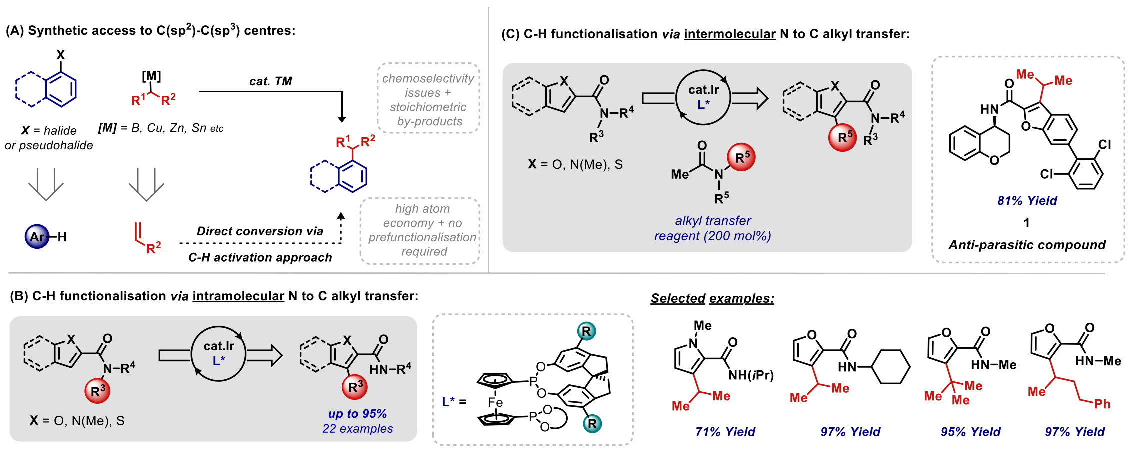
The development of new step economical approaches for the direct formation of C(sp^2)–C(sp^3) bonds is of the upmost importance for the pharmaceutical and agrochemical industries.[1] Specifically, methods that can avoid cumbersome pre-functionalisation steps have the potential to replace traditional cross-coupling reactions (Scheme 1A). Within this context, directing group mediated Ir(I)-catalysed alkene hydroarylation reactions have been previously developed in the Bower group, employing a novel class of bidentate ferrocene-SPINOL ligands, (**L*** in Scheme 1B).[2] This communication will exhibit the application of these ligands in an exciting, newly uncovered intramolecular N to C alkyl transfer reaction (Scheme 1B), which proceeds *via* a unique C–H activation pathway. Furthermore, unexpected intermolecular alkyl transfer, allowing access to products such as complex anti-parasitic compound 1, will be presented, alongside the key mechanistic aspects delineating the hypothesised reaction pathway.[3,4]



Scheme 1: General outlook of alkyl transfer methodology

Acknowledgements: We thank the EPSRC (Engineering and Physical Sciences Research Council) for a studentship, the University of Liverpool analytical services team and the members of the Bower research group.

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Phosphonium Ylide-Mediated CO_2 Utilization for the of Synthesis of α,β-Unsaturated Carboxylic Acids

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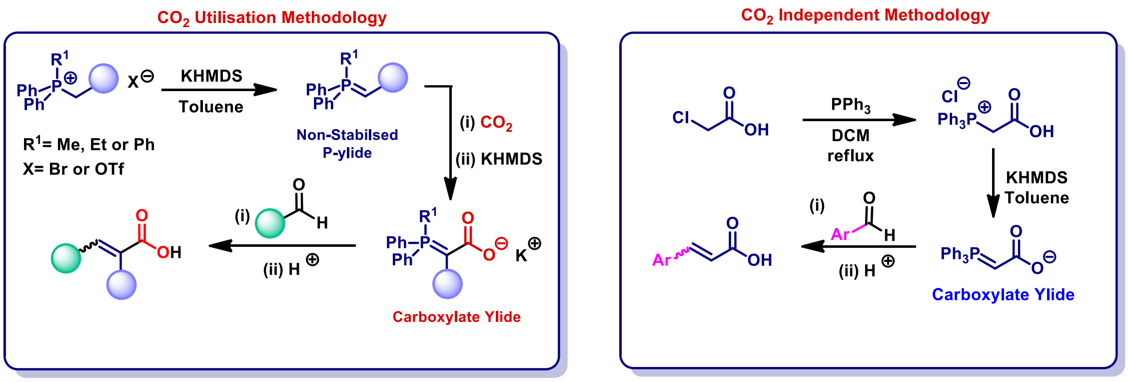
Employing waste products as starting materials for chemical transformations is a key step in addressing the global challenges of sustainable production and consumption. Greenhouse gas CO_2 is perhaps the most significant waste product of the industrialised world.[1] Developing a method for the conversion of a harmful environmental waste product into high-valuable organic products can allow CO_2 to be used as a one-carbon (C1) chemical building block. Phosphonium ylides (P-ylides) have the ability to activate CO_2 into reactive P-ylide CO_2 adducts.[2,3] This activated form of the C1 feedstock can be incorporated into carboxyl-containing products and biologically active compounds.

α,β-Unsaturated carboxyl containing organic products are ubiquitous in nature and this structural motif is responsible for the biological activity of many such organic products.[4] It has been found that α,β-unsaturated carboxylic acids can be synthesised using two comparable synthetic routes, via the P-ylide CO_2 adduct. The CO_2 utilisation methodology involves the in-situ generated P-ylide activating gaseous CO_2, forming the P-ylide CO_2 adduct. A novel Wittig reaction occurs between the P-ylide CO_2 adduct and aromatic, heterocyclic, and aliphatic aldehydes forming α,β-unsaturated carboxylic acids in moderate to high yields. This telescoped process has shown a high degree of selectivity for the *E*-alkene. This methodology has also been utilized for the synthesis of pharmaceutically relevant high-value organic products.

A route for CO_2 independent generation of the activated P-ylide CO_2 adduct starting with carboxymethyltriphenylphosphonium chloride has also been developed. This novel route can be used to test substrate suitability and reaction conditions independent of the CO_2 utilisation methodology.



Scheme 1: CO_2 Utlilisation Methodology and CO_2 Independent Methodology

Acknowledgements: Financial support for this research was provided by the Irish Research Council (IRC GOIPG/2018/169 and IRC GOIPG/2021/802)

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$H(O)P(OPh)_2$-PROMOTED DEOXYGENATIVE HALOGENATION OF ALCOHOLS

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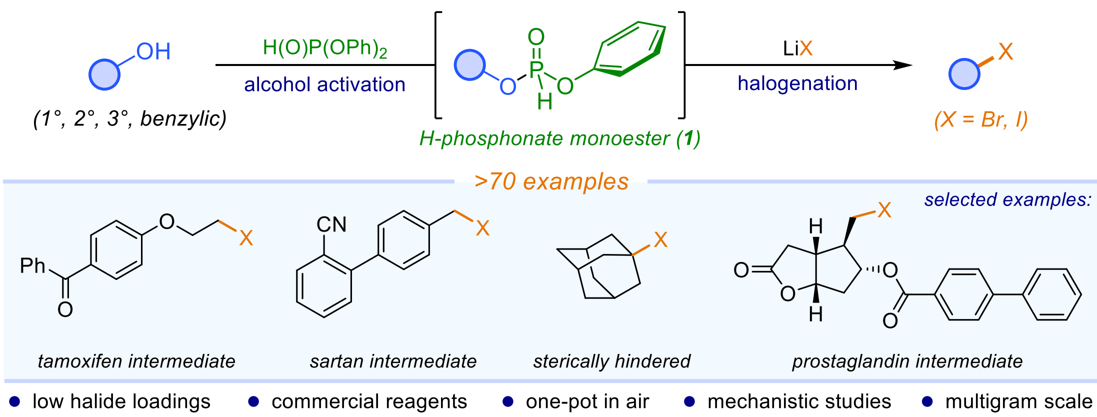
Organic halides are ubiquitous amongst target molecules such as pharmaceuticals, natural products and agrochemicals,[1–3] however, the use of this class of compounds is more often attributed to their inherent reactivity. C(sp^3)–halogenated compounds in particular are synthetically useful reagents as they enable molecular construction by nucleophilic substitution and can serve as precursors to organometallic reagents or carbon radicals. Traditional means of preparing organic halides from alcohols typically make use of hazardous, high-energy reagents and generate stoichiometric quantities of halogenated waste,[4] resulting in processes that are incongruent with the principles of green chemistry.



We report an operationally convenient protocol for the iodination and bromination of alcohols that exploits the inherent behaviour of a commercially available diaryl H-phosphonate promoter, $H(O)P(OPh)_2$.[5] Alcohol activation is achieved by a key transesterification event furnishing the reactive H-phosphonate monoester (1), thus transforming the parent alcohol into an electrophilic intermediate, under halogen-free conditions. Lithium halide salts employed at low loadings carry out the subsequent deoxygenative halogenation, circumventing the requirement for toxic molecular halogens or highly reactive, electrophilic halogenating agents. This strategy has been applied in the synthesis of a variety of primary, secondary, tertiary and benzylic organic halides, demonstrating its synthetic utility as a novel halogenation protocol.

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Synthesis of Carbocyclic Boronic Esters through Intramolecular Lithiation-Borylation and Ring Contraction

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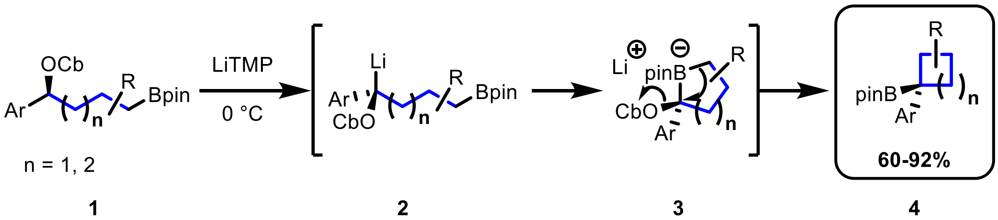
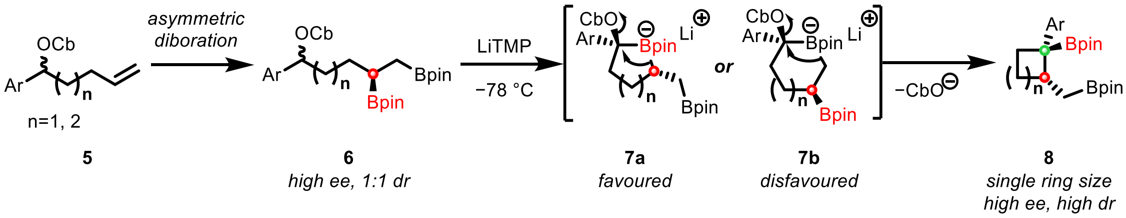
The efficient asymmetric synthesis of sp^3-rich cyclic compounds is of vast importance in the preparation of pharmaceuticals and agrochemicals.[1] The aim of this project is to prepare strained cyclic motifs through ring contraction of thermodynamically more feasible cyclic boronate intermediates. Linear starting materials are prepared in three simple, high-yielding steps in which stereochemistry and substitution pattern can be installed without substrate bias.[2]



Scheme 1: Intramolecular lithiation–borylation and ring contraction to afford carbocyclic boronic esters.

Carbamates **1** are rapidly lithiated using the bulky, non-nucleophilic base lithium tetramethylpiperidine to afford chiral lithium carbenoids **2**. Intramolecular trapping by pendant boronic esters gives cyclic boronate complexes **3**. The leaving group α- to boron allows 1,2-migration and concomitant ring contraction to give desired cyclic products **4**. Development of this method led to excellent yields of both cyclobutyl- and cyclopentylboronic esters.

Under optimised conditions, vicinal bis-boronic esters **6** cyclise towards products **8** with two differentiable synthetic handles. The reaction is regioselective, resulting in products of a single ring size, and diastereoselective, allowing the preparation of cyclobutane and cyclopentane products in high *ee* and *dr* following an enantioselective diboration/cyclisation sequence.



Scheme 2: Regio- and diastereoselective preparation of cyclic bis-boronic esters.

The value of products **8** has been demonstrated through the site-selective functionalisation of both the primary and tertiary benzylic boronic esters, exploiting stereospecific and well-established derivatisations of organoboron compounds.[3] These transformations pave the way for access to a library of enantioenriched cyclobutane and cyclopentane analogues.

Acknowledgements: We thank the EPSRC and Merck Group for their generous funding through the TECS CDT program.

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Modular Synthesis of Teraryl-based alpha-Helix Mimetics

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The inhibition of protein-protein-interactions (PPIs) with small molecules has become a new paradigm in Chemical Biology.[1] Hamilton and co-workers have shown that trisubstituted linear terphenyls can function as α-helix mimetics, displaying the *i*, *i*+4 and *i*+7 amino acid residues.[2] To adress solubility issues, our group has developed a modified design, in which pyridine nitrogen atoms are introduced at the water-exposed face distal to the protein binding site. Most recently, we have achieved comprehensive coverage of the protein sequence space by assembling teraryls from a library of readily available building blocks decorated with the side chains of all proteinogenic amino acids relevant for PPIs (**Figure 1**).[3,4,5]

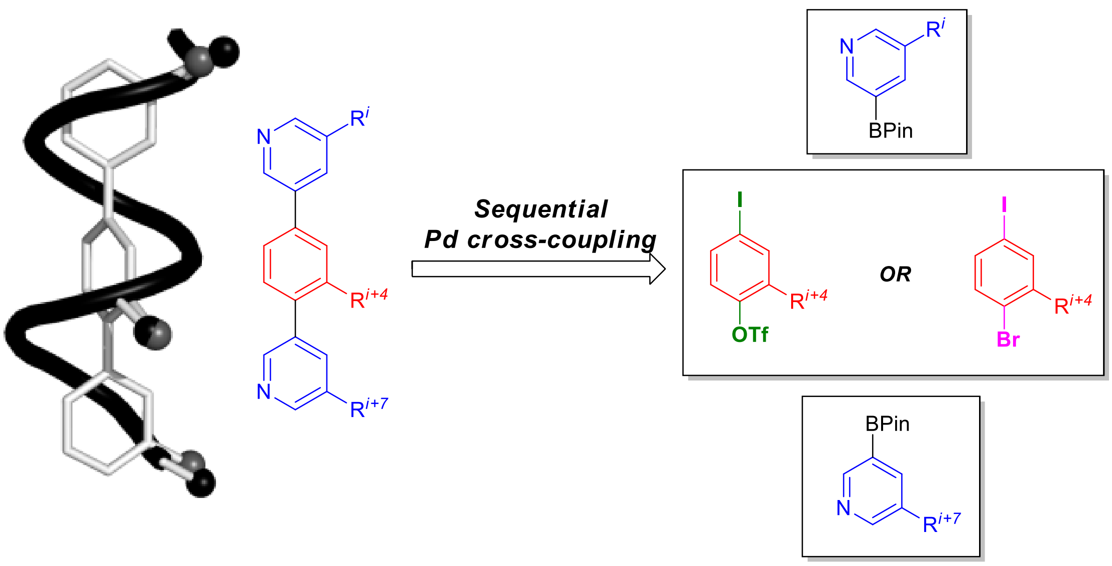

Figure 1: Assembly of teraryl-based alpha-helix mimetics.

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Rh(I) Catalysed Regio- and Enantioselective Ring Opening of Cyclopropanes with Boronic Acid Nucleophiles

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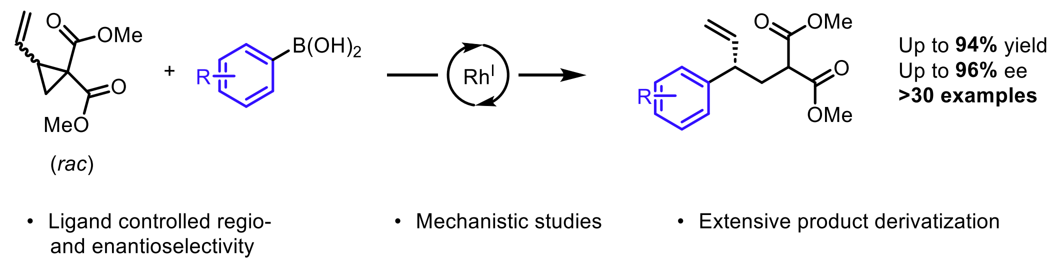
The cyclopropane motif has attracted the attention of synthetic chemists for several decades due to the high ring strain (115 kJ mol-1) and perceived reactivity of the C-C bonds.[1] However, cyclopropanes can be rather kinetically inert and often require activation by vicinal electronic donor and acceptor groups. These donor-acceptor cyclopropanes (D-A cyclopropanes) have experienced a recent renaissance in the pursuit of novel building blocks with multiple functional group handles towards pharmaceuticals.[2] However, few transition metal catalyzed enantioselective ring openings have been reported, and ring openeing with carbon nucleophiles is limited to Friedel-Crafts type reactions.[3] To overcome this limitation, we have developed a Rh(I) catalyzed asymmetric ring opening of D-A cyclopropane using boronic acids as nucleophiles (**Scheme 1**). The products are accessed in up to 94% yield and 96% ee, with excellent regioselectivity observed. The mild conditions tolerate a variety of aryl boronic acids, including halogens, esters, alcohols, ketones and alkenes. Additionally, *ortho*, *meta*¸ *para* and disubstituted aromatics as well as heterocyclic examples are included. The use of boronic acids as nucleophiles greatly expands the scope of nucleophilic D-A cyclopropane ring opening, and the products formed contain multiple functional group handles that can be diversified easily to a variety of industry relevant scaffolds.



Scheme 1: Regio- and enantioselective ring opening with boronic acid nucleophiles

Acknowledgements: Stephen Webster is grateful to the Centre for Doctoral Training in Synthesis for Biology and Medicine for a studentship, generously supported by GlaxoSmithKline, MSD, Syngenta and Vertex.

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Ortho-Functionalization of Polyhalo-Substituted (Hetero)Aryl Tosylates Using an Integrated Continuous Flow/Batch Protocol

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The synthesis of bi(hetero)arene, benzofuran, and pyridofuran scaffolds is of great interest as the (hetero)arenes containing these moieties are used in many therapeutic drugs, fine chemicals and natural products. Therefore, various synthetic strategies to prepare these moieties have been introduced. Among them, the site-selective functionalization of (hetero)aryl polyhalides via Negishi cross-coupling has attracted gradually increasing interest. Notably, directing-group mediated *ortho*-functionalization is one of the most used methods. However, directing-group-mediated *ortho*-metalation is still challenge, due to the competitive elimination of the directing groups. Thus, it is still essential to develop efficient methods for the selective metalation at a desired site of (hetero)aryl polyhalides. Herein, we report the regioselective *ortho* functionalization of polyhalo-substituted (hetero)aryl tosylates using an integrated continuous flow/batch protocol. Formation of arylzinc species under flow conditions is prepared easily and reproducibly in a short residence time. Finally, the method is applied to the synthesis of perampanel, a glutamate receptor antagonist, and benzofuran and pyridofuran derivatives.

Synthesis of Benzofused *N*-Heteropolycycles via Intramolecular Benzyne Cycloadditions using 3-Aminobenzyne Precursors

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Aza-Brook rearrangement has been investigated as a method for the formation of carbon-carbon and carbon-heteroatom bonds in organic chemistry. This rearrangement involves an intramolecular anionic transfer of a silyl group from a carbon to a nitrogen via a hypervalent silicon intermediate. However, there have been few reports on aza-Brook rearrangement due to the relative lack of well-designed amine precursors and the thermodynamic driving force of the weaker N-Si Bond compared to the O-Si bond. Recently, we reported novel 3-amino-2-(*tert*-butyldimethylsilyl)phenyl triflates as aminobenzyne precursors. A base-mediated 1,3-aza-Brook rearrangement occurred on the aryl group, forming aminobenzyne intermediates, resulting in various aniline derivatives. The application of aza-Brook rearrangement for benzyne formation is noteworthy because it allows control of the timing of benzyne formation. As part of our ongoing efforts in uniting aza-Brook rearrangement with benzyne chemistry, we have focused on the intramolecular benzyne cycloaddition for the synthesis of benzofused N-heterocycles. Herein, we show that the possibility of the synthesis of benzofused N-heterocycles by performing intramolecular [4+2] cycloadditions, ene reactions, and HDDA reactions with a benzyne intermediate formed via 1,3-aza-Brook rearrangement, respectively.

Continuous Flow Synthesis of *N*-Sulfonyl-1,2,3-triazoles: Application of Tandem Relay Cu/Rh Dual Catalysis in Microflow Systems

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The copper-catalyzed azide−alkyne cycloaddition (CuAAC) reaction for the highly regioselective synthesis of *N*-sulfonyl-1,2,3-triazoles has received significant attention due to their structural potential. Due to the electron-deficient sulfonyl group in *N*-sulfonyl triazoles, they decompose effectively in the presence of a suitable metal catalyst to produce highly reactive azavinyl carbene. Accordingly, progress has been made in the use of *N*-sulfonyl triazole as an azavinyl carbine precursor in reactions for a wide range of heterocycles and other scaffolds. Despite the benefits involved, the continuous flow synthesis of *N*-sulfonyl triazoles has not been reported. In general, the CuAAC reactions for *N*-sulfonyl triazoles and the decomposition reaction for transition-metal-carbene complexes are highly exothermic reactions. Thus, flow processing would be a versatile tool for the synthesis of them. With these considerations, herein we report the first continuous flow synthesis of *N*-sulfonyl-1,2,3-triazoles, and the first continuous synthesis of *cis*-diamino enones employing tandem relay Cu/Rh dual catalysis.

Synthesis of γ-aminobutyric acid esters *via* ring-opening reaction of cyclobutanones.

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γ-Aminobutyric acid (GABA) to be developed in this research has been known as a neurotransmitter and various compounds with baclofen are also used as therapeutic agents for the nervous system (**Figure 1**). In recent years, there have been increasing opportunities to see foods containing GABA at shop, etc., for the purpose of improving sleep quality and relieving stress. However, its synthesis are require multiple steps, and an exhaustive synthesis method has not yet been sufficiently developed.

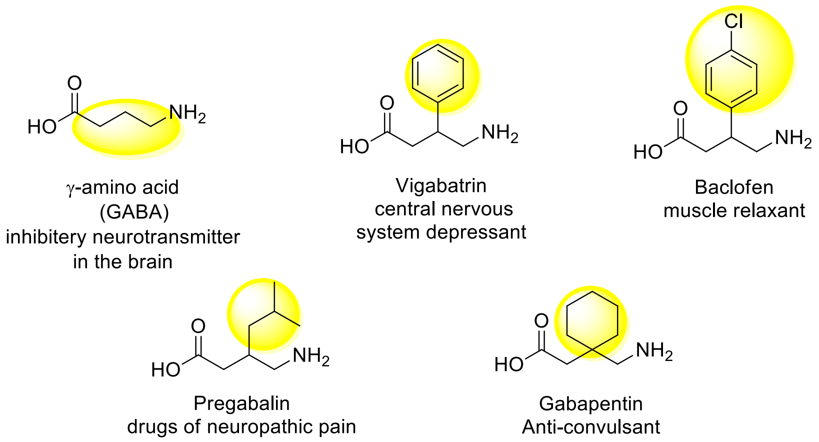
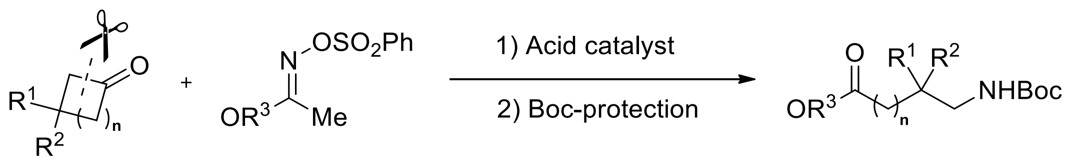


Figure 1: GABA and the derivatives.

In our group, we have performed a deacylative amination reaction using relatively stable oxime reagents as equivalents of hydroxylamine derivatives, which have been unstable and explosive, to convert acetyl arene to aromatic amines[1)]. In this study, based on these findings, we have achieved synthesis of γ-aminobutyric acid esters from cyclobutanones and oxime reagents *via* ring-opening amination rection, which enables to install two functional groups on the both ends (**Scheme 1**). In addition, we were able to obtain amino acid esters, which are precursors of Gabapentin, Baclofen and Pregabalin, which are used as therapeutic agents for the nervous system, by ring-opening the corresponding cyclobutanone. In this presentation, we will report the details about this method.



Scheme 1: .Ring-opening reaction of cyclobutanones for γ-Aminobutyric acid esters

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The reactivity of C(sp^2)-H activated cobalt complexes: a straightforward synthesis of indoles

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The directed C-H bond functionalization methodology using transition metal catalysis has proven itself as a valuable organic synthesis tool.[1] In the last couple of decades this approach has been widely exploited in fields of material sciences, medical chemistry, organic synthesis and total synthesis, mainly due to its atom- and step- economical nature.[2] Besides, nowadays the field of third row transition metal catalyzed C-H functionalization is being extensively studied as a cheaper and attractive alternative to noble metal catalysts.[3]

Our current work is dedicated to the development of cobalt-catalyzed picolinamide-directed C-H bond functionalization of amino acid derivatives. Starting from α,β-unsaturated amino acids **1** we were able to synthesize different C-H activated Co(III) complexes **2** (**Fig. 1**). Moreover, using *N*-fluorobenzenesulfonimide, indole **3** derivatives can be obtained in very good yields.

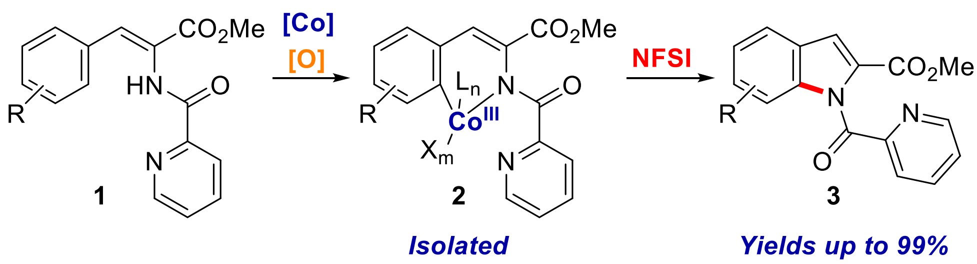

Fig. 1. Synthesis of indole **3** derivatives *via* cobalt catalysis.

Supervisor*: Dr. Chem.* Liene Grigorjeva

Acknowledgements: This research is funded by the Latvian Institute of Organic synthesis internal grant Nr. IG-2023-05.

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Cyclic Triel Carbenoids as Auxiliary Ligands for Ruthenium-Based Olefin Metathesis Catalysts

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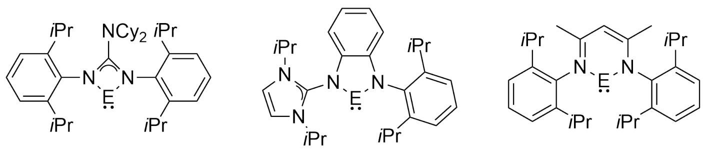
Although carbenes have a long history of being used in organic synthesis as catalysts—both on their own and as auxiliary ligands in transition metal-based species—the same does not apply to carbenoids, close relatives to carbenes, bearing a lone electron pair on a different atom than carbon. One of the most useful reactions which benefit from carbene chemistry is olefin metathesis.[1,2] This type of reactivity has been known for decades, but its main development started in late 1990s when *N*-heterocyclic carbenes began to be used as ligands for ruthenium catalysts.[3] Since then a lot of research has been done to understand the relationship between catalytic activity and structure, and—based on that—synthesize more powerful catalysts, including the arguably most important families introduced by Grubbs and Hoveyda.[2]

In our studies we simulated behavior of Grubbs and Hoveyda-Grubbs type catalysts bearing cyclic triel carbeniods as ligands instead of *N*-heterocyclic carbenes. The most important triel carbenoids include four-membered guanidine-chelated E(Giso), six-membered β-diketiminate-chelated E(NacNac) and the most novel five-membered amidoimidazoline-2-imine-chelated E(AmIm) **(Scheme 1)**.[4] We simulated reaction pathway for selected Grubbs and Hoveyda–Grubbs type catalysts for three different alkenes: ethylene (the simplest possible system), styrene (exhibiting steric hindrance) and isobutylene (forming tetrasubstituted alkene). We show that the most promising candidate for efficient catalysis seems to be the Hoveyda–Grubbs type catalyst with Tl(AmIm) ligand.



Scheme 1: Structures of the most important cyclic triel carbenoides: E(Giso), E(NacNac) and E(AmIm)

Acknowledgements: We acknowledge research support from the National Science Centre grant UMO-2021/43/B/ST4/00122.

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The Design and Synthesis of Anionic Porphyrins Bearing Chiral Cations and Their Exploration in Catalysis

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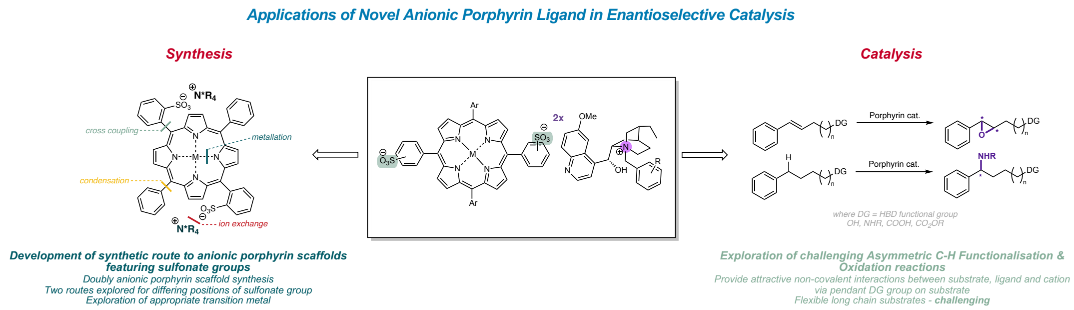
Asymmetric transition-metal catalysed reactions are commonly used to access highly enantioenriched compounds.[1] Classical approaches in this field involve the use of chiral ligands on the metal to induce asymmetry, favouring the major enantiomer through less steric repulsion at the transition state. Whilst a powerful and well-proven approach to enantiocontrol, it is not always universally applicable.

Our group has recently developed a new approach in which achiral anionic ligands are paired with chiral cations based on the readily available cinchona alkaloid scaffold. A network of attractive non-covalent interactions between the anionic ligand, cation and substrate can provide an organised transition state and have been shown to induce enantioselectivity into challenging reaction types; iridium catalysed C-H borylation and rhodium-catalysed C-H amination.[2,3]

One privileged class of ligands that is particularly challenging to render chiral is the porphyrin framework.[4] This could be due to the relative distance between the metal centre and the porphyrin backbone, making asymmetry hard to transfer based on steric repulsion from the ligand to the substrate. Porphyrin ligands are also flat molecules hence, incorporating 3D conformation onto the scaffold is challenging due to geometric constraints.

We have designed and executed the syntheses of novel classes of sulfonated, doubly anionic porphyrins, exploring two different routes to access a variety of catalyst systems. Once in hand, the anionic porphyrin scaffolds were ion-paired to a range of chiral, privileged cationic scaffolds based upon cinchona alkaloids. Since development of two reliable synthetic routes to these privileged chiral ligand scaffolds, we are currently progressing in the discovery of potential catalytic C-H functionalisation and oxidation reactions where inducing chirality is challenging.



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De-Acetylative Amination of Acetyl Arenes and Alkanes *via* Transoximation/Beckmann Rearrangement

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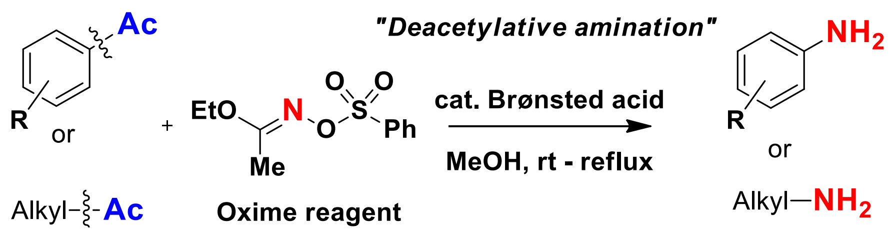
Primary aromatic amino groups are present in pharmaceuticals, dyes, and organic compounds. Therefore, synthetic methods to produce primary amines using transition metal catalysts or organometallic reagents have been developed. However, these methods have disadvantages, such as the use of costly transition metals and designer ligands, the need to remove trace metal impurities from the product, and inability to control reaction site selectivity under non-directing group conditions during C-H amination. From these point of view, transition metal-free amination is an attractive method. In this study, we focused on the acetyl arenes, which was useful starting materials for metal-free aromatic primary amination. Reaction of acetyl arene with hydroxylamine to form a ketoxime, followed by conversion of the ketoxime to an amide *via* Beckman rearrangement. Hydrolysis of the amide to the corresponding amine completes the synthesis, although these methods required multi-steps.

In contrast, we recently developed transoximation using an oxime considered equivalent to hydroxylamine and derivatives such as *O*-(mesitylsulfonyl)hydroxylamine (MSH reagent).[1,2] This reagent enable to perform direct amide synthesis from ketone *via* transoximation and Beckmann rearrangement.[3] In this work, we performed de-acetylative amination of acetyl arene and alkanes using oxime reagent via transoximation, Beckmann rearrangement and alcoholysis (Scheme 1).[3] These methods could be applied to synthesis of *γ*-aminobutyric acid (GABA) derivatives. The strategy offers the possibility of novel synthetic routes for pharmaceuticals and other useful compounds. In this presentation, we described the details about scope of substrates and mechanistic study.



Scheme 1: De-acetylative amination of acetyl arenes and alkanes

Acknowledgements: This work was supported by the Ube Industries Foundation and 2023 Kindai University Research Enhancement Grant (SR09).

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Metal-catalyzed C-H functionalization of azaarenes with nitroolefins

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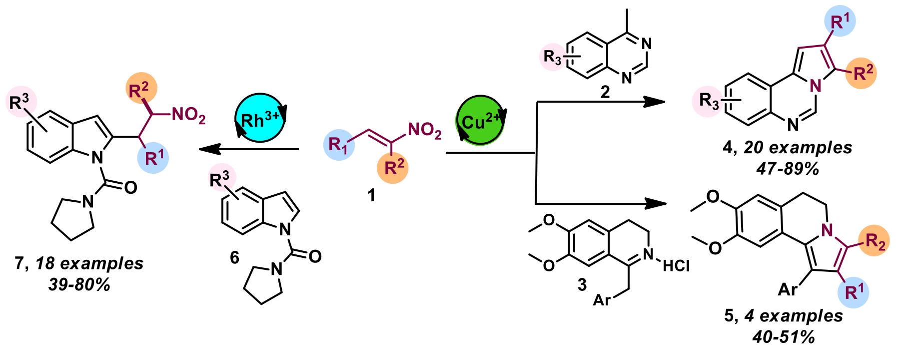
Reactions involving C(sp^3)-H bonds of azaarenes have been widely studied in recent years as they allow direct functionalization of these *N*-heterocycles without the use of harsh reaction conditions.[1] We have previously reported a Cu(I)-catalyzed one-pot Michael addition/dehydration cascade reactions, using β-nitroolefins and 2-methyl-azaarenes, furnishing 3-(*N*-heteroarenyl)acrylonitriles.[2] The use of nitroolefins as partner is very attractive, since the nitro groups of the products allow subsequent versatile transformations. Herein, we describe the synthesis of new pyrrolo[1,2-*c*]quinazolines **4** from readily available β-alkyl-β-nitrostyrenes **1** and 2-methyl-quinazolines **2** promoted by Cu(II) (**Scheme 1**). We then turned our attention to the isoquinolines **3** aiming the formation of pyrrolo[2,1-*a*]isoquinolines **5**, which could lead, for example, to the synthesis of analogs of the lamellarins.[3] Under the optimized conditions, it was possible to synthetize 19 pyrroloquinazoline derivatives in 57-89% yield, 1 pyrazoloquinazoline in 47% yield and 4 pyrroloisoquinolines with 40-51% yield. Control experiments and mass spectroscopy analysis indicated that the formation of pyrroloquinazoline derivatives proceeds via an ionic mechanism.
Continuing our efforts in this area, we have synthesized indole derivatives **7** via Rh(III)-catalyzed C-2 alkylation with nitroolefins. Indoles substituted at the C-2 position have shown important biological activities.[4] Under the optimized condition, 18 examples were prepared with 39-80% yield. Furthermore, the nitro group was reduced to the corresponding amine and then submitted to the Ugi reaction furnishing highly functionalized indole derivatives.



Scheme 1: Metal-catalyzed functionalization of *N*-heterocyclic compounds.

In summary, we have developed a simple and efficient method for the synthesis of fused nitrogen heterocycles using inexpensive copper catalysis. Furthermore, we have described the nitroalkylation of indoles at the C-2 position via a C-H activation protocol using easily accessible nitroolefins.

Acknowledgements: We thank FAPESP, CNPq, CAPES and GSK for financial support and fellowships.

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N-Aryl-*N*´-silyldiazenes as Masked Aryl Nucleophiles for the Arylation of Imines and α-Trifluoromethylstyrene Derivatives

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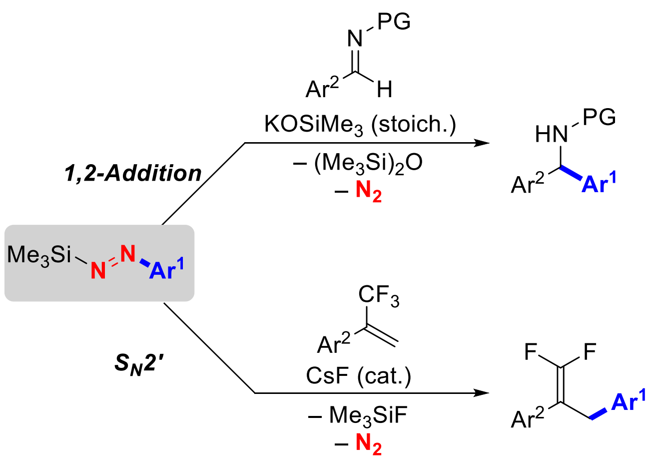
Our group recently rediscovered the use of *N*-aryl-*N*´-silyldiazenes as latent aryl nucleophiles.[1,2] Upon activation by a Lewis base, an aryl-substituted diazenyl anion is generated that further releases dinitrogen and the desired aryl nucleophile. Catalytic amounts of alkali metal trimethylsilanolate salts initiate an autocatalytic silylarylation of carbonyl compounds, in which the transferable aryl group can be decorated with a variety of functional groups, thereby revealing the full potential of these *N*-aryl-*N*´-silyldiazenes.[2] We then envisioned engaging these silicon-masked, functionalized aryl pronucleophiles in the arylation of more challenging electrophiles such as aldimines and α-trifluoromethylstyrene derivatives.

At the outset, we identified two challenges for the arylation of aldimines. Firstly, aldimines are poorer electrophiles than aldehydes and secondly, the N–Si bond is less stable than the O–Si bond, rendering an autocatalytic process less likely. However, employing stoichiometric amounts of Lewis-basic potassium trimethylsilanolate in the reaction of unactivated aldimines and silylated diazenes, the corresponding benzhydryl-substituted amines were obtained in good yields (Scheme 1, upper equation).[3]

To further study the reactivity of the *N*-aryl-*N*´-silyldiazenes, we investigated their potential to arylate α-trifluoromethylstyrene derivatives. Upon desilylation with a catalytic amount of CsF and concomitant loss of dinitrogen, the aryl nucleophile attacks the trifluoromethylstyrene electrophile through an S_N2' mechanism to furnish the corresponding *gem*-difluoroalkene. The released fluoride anion in turn activates another diazene molecule and propagates the autocatalytic reaction. A broad range of functional groups is tolerated in both the aryl nucleophile and the trifluoromethylstyrene derivative, providing access to various novel 1,2-bisarylated 3,3-difluoro-2-propene derivatives in moderate to good yields (Scheme 1, lower equation).[4]



Scheme 1: *N*-Aryl-*N*´-silyldiazenes as latent aryl nucleophiles for the arylation of imines and α-trifluoromethylstyrene derivatives.

Acknowledgements: This research was supported by the Deutsche Forschungsgesellschaft (Oe 249/23-1).

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Enantioselective Preparation of Spiro Compounds Using NHC Catalysis

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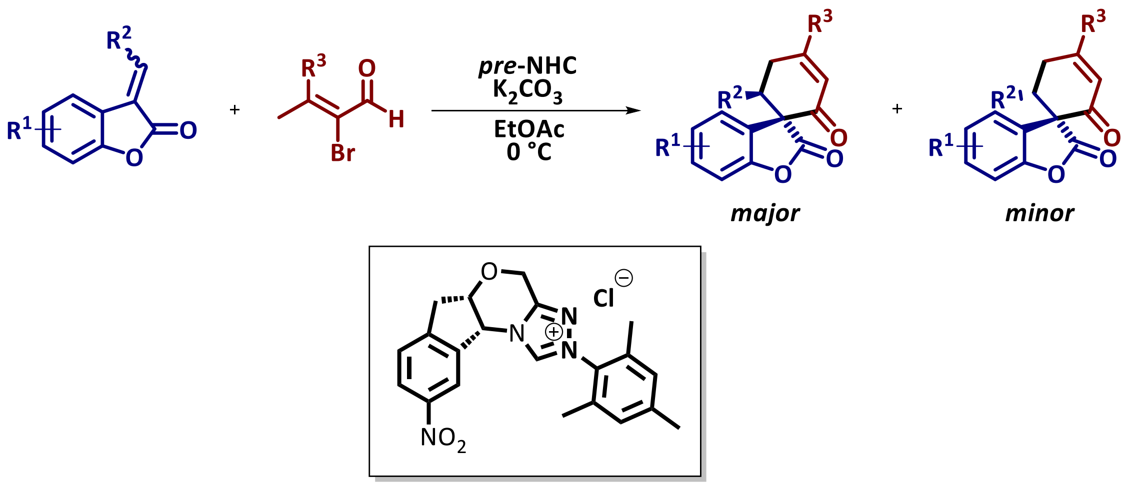
Carbenes are organic molecules with a divalent neutral carbon atom carrying six electrons in the valence sphere. Nowadays, a widely used group is stable *N*-heterocyclic carbenes which are used as ligands in transition metal catalysis, but they also found application as organocatalysts. Since the beginning of this millennium, organocatalysis has become a valuable alternative to catalysis using enzymes and transition metals.[1]

Herein, we would like to demonstrate the enantioselective formal [4+2] cycloaddition reaction between substituted benzylidene benzofuranones containing polarized C=C bond and substituted 2-bromo-*α*,*β*-unsaturated aldehydes. The reaction proceeds under catalysis with *N*-heterocyclic carbenes without additional oxidants *via* an azolium dienolate intermediate[2,3] and produces various chiral spiro compounds (**Scheme 1**). So far, a number of spiro compounds with different biological activity (for example, antibacterial, antifungal, anticancer effect) have been isolated and prepared.



Scheme 1: Enantioselective preparation of spiro compounds using NHC catalysis.

Acknowledgements: This work was supported by the Charles University Grant Agency (286323) and Czech Science Foundation (22-11234S).

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Enantioenriched 1,4-Benzoxazepines via Chiral Brønsted Acid Catalyzed Enantioselective Desymmetrization of 3 substituted Oxetanes.

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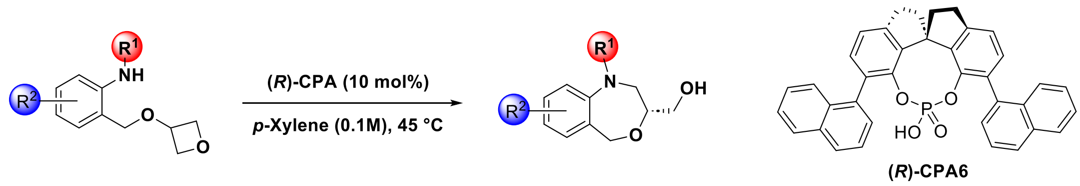
Seven membered 1,4-benzoxazepine scaffold (1,4-BZO) is a fascinating versatile pharmacophore that constitutes the integral backbone of a significant proportion of pharmaceutical drugs[1], including TAK-475,[1a] bozepinib,[1b] (1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl) pyrimidines[1c] and loxapine[1d]. The structural diversity coupled with biological activity of 1,4-BZOs has attracted a great deal of interest, which has led to the development of an innovative set of compounds, essentially in achiral or racemic form.[2] The exploitation of catalytic asymmetric strategies for these seven membered heterocycles presents a significant challenge and remains in its infancy.[3] Here we present a highly enantioselective desymmetrization of 3-substituted oxetanes, enabled by confined chiral phosphoric acid (Scheme 1). The method provides effective access to chiral seven membered 1,4-benzoxazepines with one stereogenic center. We also investigate a broad substrate scope accompanied by versatile synthetic transformations and applications.



Scheme 1: Organocatalytic Enantioselective Desymmetrization.

Acknowledgements: This work was supported by Charles University Grant Agency (290923) and Czech Science Foundation (22-11234S).

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A computational investigation into the Cu-catalysed borylation of α,β-unsaturated compounds

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Boronic esters are versatile building blocks for the synthesis of complex molecules, as they react under mild, functional group tolerant conditions. Boron reagents are also important as starting materials for one of the most common C-C bond-forming reactions in the pharmaceutical industry – the Suzuki reaction. Building a wider library of commercially available boronic ester building blocks would make adding functionality in organic synthesis more accessible. While there are currently many heteroaromatic boronic esters available, there are far fewer saturated heterocyclic boronic esters.[1]

The Partridge Group has developed a method for the synthesis of borylated lactams through the Cu-catalysed borylation of enoates, followed by their cyclisation.[1] These borylated lactams can be made in moderate-to-high yields, and the borylation step can be performed enantioselectively using a chiral catalyst. To aid in the design of future catalysts and new processes, and potentially tune the product selectivity, it would be advantageous to be able to understand how stereoselectivity is induced in these reactions.

This work develops a computational workflow to investigate the origins of stereoselectivity for the borylated lactam synthesis developed by the Partridge group. The main challenges of this work arise from modelling large organometallic complexes with two metal centres and chiral ligands. A simplified mechanism[2] was modelled to determine the general mechanistic pathway, followed by benchmarking of different computational methods. The full reaction was then modelled, and semi-empirical methods such as xTB[3] and CREST[4] were used to find low-energy conformers, before using DFT methods to obtain final geometries. This presentation will provide an overview of the computational benchmarking data, a detailed workflow, and a proposed mechanism with energy profile diagrams for the mechanisms modelled.

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New triazine-phosphonate dopants for proton exchange membranes (PEM)

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The establishment of a new paradigm for energy is underway demanding new energy sources for the increasing needs of society with none or lower environmental impact. To reach the ambitious and well-defined targets for decarbonized energy systems it is needed new clean technologies. Some of them rely on well-established or emerging electrochemical devices, including batteries, fuel cells and CO_2 and water electrolysers, whose applications and performances depend on key components such as their separators/ion-exchange membranes.[1,2] The most studied and already commercialized membranes go by the brand name of Nafion, which showed great chemical stability, but their high proton conduction depends on their water content, markedly limiting their operating temperature range. Our previous studies have demonstrated that the incorporation of aryl or heterocyclic phosphonic acid dopants into Nafion, by casting, results in an enhancement of the proton conductivity[1-4] and stability[5] of the Nafion doped membranes.

This work reports the synthesis and characterization of a new series of triazine-phosphonate derivatives for use as dopants in the preparation of Nafion modified membranes. Several arylphosphonate compounds were prepared bearing an amino or a hydroxy functional group at the *para*-position of the aryl ring. These compounds react with 2,4,5-trichloro-1,3,5-triazine through a nucleophilic substitution reaction to obtain the 2,4,6-(*p*-substituted)phosphonate-1,3,5-triazine dopants (**Figure 1**). The new compounds were characterized by NMR, IR spectroscopy and mass spectrometry, allowing the assignment of their structure.

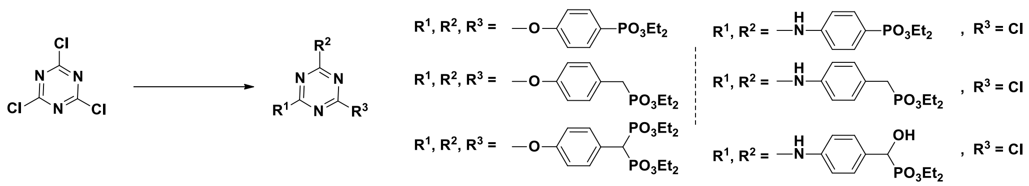

Figure 1: Syntheis of new triazine-phosphonates.

In the anticipation that these synthesized phosphonates can act both as a source of protons and proton acceptors, facilitating the intermolecular proton conduction throughout the modified membranes, new Nafion modified membranes were prepared by casting, through the incorporation of these synthesized 1,3,5-triazine-phosphonate derivatives. The new membranes were characterized, and their proton conduction properties were evaluated by electrochemical impedance spectroscopy (EIS), at different temperature and relative humidity (RH) conditions.

Acknowledgements: This work was financed by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P., within the scope of the project PTDC/EQU-EPQ/2195/2021 - CO2RED, and LAQV-REQUIMTE, project UIDB/50006/2020 and UIDP/50006/2020. We also acknowledge the project "HYLANTIC" - EAPA_204/2016, co-financed by the European Regional Development Fund in the framework of the INTERREG ATLANTIC program.

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Next Generation Bioisosteres – Photocatalytic Construction of Azabicycles

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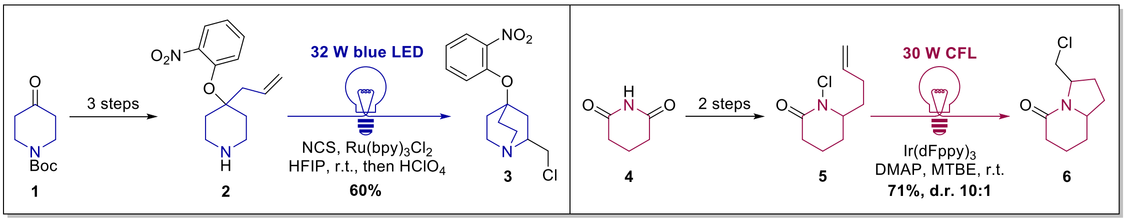
Drug candidates with a higher fraction of sp3 (Fsp3) centres have a greater likelihood of passing clinical trials and becoming a commercial drug.[1, 2] Possibly the most explored strategy to enhance Fsp3 is the replacement of aromatic rings with caged hydrocarbons including bicyclo[1.1.1]pentane and bicyclo[2.2.2]octane fragments. While the chemical, physical and pharmacological properties of benzene bioisosteres have been more widely explored,[3] the bioisosteres of heteroaromatic molecules constitute an emerging field, with quinuclidine-containing drugs largely derived from naturally occurring cinchona alkaloids.

In this project, we have designed a synthetic route to quinuclidine **3**, centred around the development of a photocatalytic 6-exo-trig cyclisation for the construction of the [2.2.2]-bicyclic motif. We have established a pathway to the key allylpiperidine intermediate **2**, and optimised the conditions for the radical cyclisation, with current work focusing on employing the chloride and nitro groups as handles for further functionalisation.

In parallel, we have developed an orthogonal photocatalytic method to access fused bicyclic heteroaromatic structures, a highly prevalent motif amongst medicinally and biologically active molecules. We are currently expanding this methodology towards building a library of functionalised fused bicyclic lactams of varying ring sizes, saturation levels and substitution patterns.

In this presentation, we will explore the different synthetic approaches undertaken towards both quinuclidine **3** and bicyclic lactam **6**, detail the different strategies' limitations and expand on their use in constructing the successful robust routes.



Scheme 1: Photocatalytic synthesis of bridged and fused azabicycles.

Acknowledgements: We thank the Centre for Doctoral Training in Synthesis for Biology and Medicine and to Lincoln College Oxford for a studentship.

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Zinc and Alkaline Earth Metal Complexes for the Activation of CO_2

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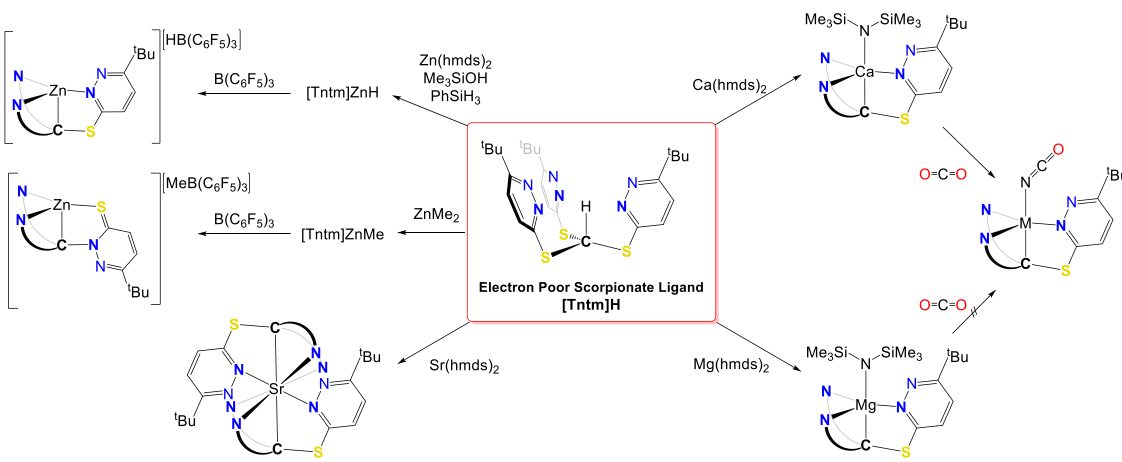
The functionalization of CO_2 has been a major challenge for many years. We recently reported a homogeneous zinc hydride catalyst bearing a scorpionate ligand [Tntm]ZnH (Tntm = tris(6-tert-butyl-3-thiopyridazinyl)methanide) capable of the hydrosilylation of CO_2 under ambient conditions without any additives.[1] The electron deficient ligand renders the metal centre more Lewis acidic, leading to efficient catalysis.

Here we present the reactivity of $B(C_6F_5)_3$ as a hydride acceptor. Addition of the borane to [Tntm]ZnH gave [[Tntm]Zn][$HB(C_6F_5)_3$], which was only stable for a limited amount of time. The zinc methyl complex [Tntm]Zn(Me) is conveniently prepared by addition of $ZnMe_2$ to the ligand and in contrast to the hydride complex, the well-defined zwitterionic complex [[Tntm]Zn][$MeB(C_6F_5)_3$] was also isolated and characterised by ^{1}H, ^{11}B, ^{13}C and ^{19}F NMR analysis. Further structural information was gained by X-ray diffraction analysis. The catalytic hydrosilylation of CO_2 by [Tntm]Zn(Me) and $B(C_6F_5)_3$ is presented.



Scheme 1: Reactivity of [Tntm]H towards several divalent metal precursors.

In contrast to [Tntm]Zn(Me), the more Lewis acidic methyl magnesium complex [Tntm]Mg(Me) can only be observed up to -30 °C. More stable Tntm complexes with Mg and Ca can be obtained by using a hexamethyldisilazane (hmds) co-ligand. The heteroleptic [Tntm]M(hmds) (M = Mg, Ca) complexes were isolated and characterised. Contrary to them, $Sr(hmds)_2$ reacts with [Tntm]H to the homoleptic C_3 symmetric complex $[Tntm]_2Sr$, where the ^{t}Bu groups on the ligand proved to be insufficiently bulky to stabilize the heteroleptic product. Further reactivity for the Mg and Ca complexes towards silanes and CO_2 is discussed. In case of [Tntm]Ca(hmds), a reaction with CO_2 quantitatively leads to [Tntm]Ca(NCO), while the Mg complex was found to be stable.

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Formal Enone α-Arylation via I(III)-Mediated Aryl Migration/Elimination

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Classical approaches to the synthesis of α-arylated carbonyl compounds often rely on transition-metal-catalyzed coupling reactions of enolates, generated from the parent carbonyl under highly basic conditions, with aryl moieties functionalized with either halides or pseudohalides (**Figure 1A**).[1] In contrast, many more recent methods employ electrophilic aromatic reactants that facilitate arylation under milder conditions and can be based on sulfur(IV), bismuth(V), or iodine(III) reagents, as well as arynes (**Figure 1B**).[2] Among these transformations, those based on rearrangements are particularly intriguing, as they offer access to products bearing substitution patterns that are otherwise difficult to access, while also sometimes allowing more atom-economical reactions.

In continuation of our interest in rearrangement reactions of high-energy intermediates,[3] particularly such that can be considered the products of umpolung of the α-position of carbonyls, we have developed an oxidative rearrangement reaction of β-arylated carbonyls to afford α-arylated, α,β-unsaturated carbonyl compounds (**Figure 1C**).[4] This transformation, enabled by hypervalent iodine promoters formed *in situ* from commercially available reagents, allows the formation of a range of products in good yields and, in the case of additional β-substitution, high levels of double-bond stereoselectivity.

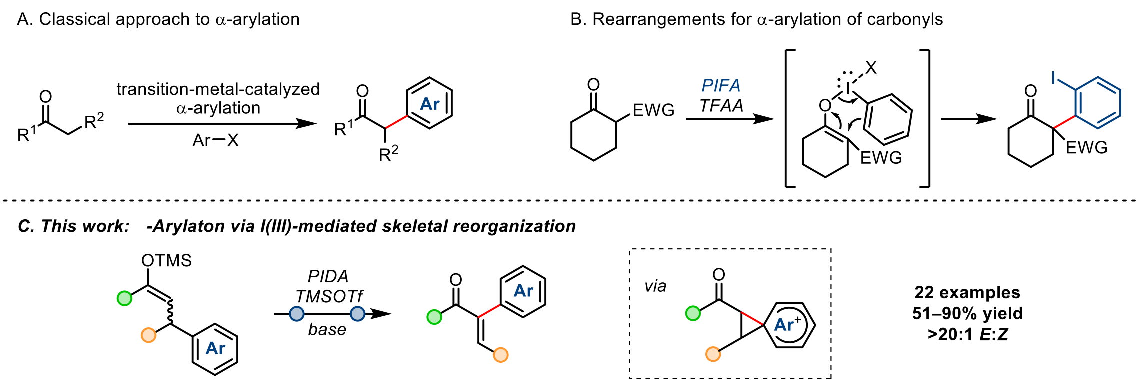

Figure 1: A & B – Selected approached to the α-arylation of carbonyls; C – α-Arylation through oxidative skeletal reorganization.

Acknowledgements: Generous support of this research by the University of Vienna, the European Union (CoG 682002 to N.M.) and the Austrian Science Fund (P32607 to N.M. and J 4202-N28 to D.K.) is acknowledged.

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ENANTIOSELECTIVE PHOTOCATALYTIC SYNTHESIS OF SATURATED BICYCLIC SCAFFOLDS AS PHENYL BIOISOSTERES

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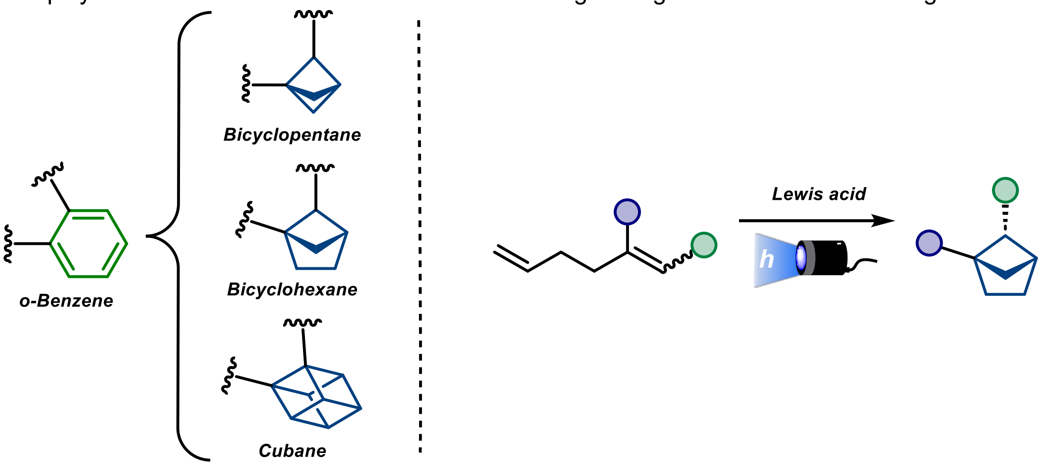
Benzene rings are one of the most abundant structural motifs present in drugs and bioactive molecules. The replacement of these scaffolds for sp^3-rich analogues as suitable bioisosteres represents an interesting approach when seeking diversity in medicinal chemistry.[1]

Over the last years, some saturated bicyclic structures have been described and validated as appropriate bioisosteres of disubstituted benzenes. The substitution of sp^2-hybridized scaffolds with rigid three-dimensional building blocks with well-defined exit vectors, open access to a novel and unexplored chemical space. Pharmaceutical properties of drugs, such as solubility and metabolic stability can be improved with the replacement of planar aromatic rings with their saturated bioisosteres. These compounds have also the advantage of avoiding conflict with patents concerning benzene and its various substitution.[2] Despite these facts and even though the enantioenriched drug analogues could potentially result in an improvement of their biological properties, the enantioselective catalytic synthesis of disubstituted benzene bioisosteres remains unexplored, and no methodology has been reported yet.

Herein we will describe a unique approach for the enantioselective catalytic synthesis of 1,5-disubstituted bicyclo[2.1.1]hexanes based on a Lewis acid-catalyzed [2+2] photocycloaddition. The pharmaceutical properties were evaluated for the individual enantiomers of biologically active compounds in which the bicyclic scaffold was implemented, indicating that the developed catalytic strategy has the potential to be employed for the construction of enantioenriched drug analogues with enhanced biological activity.



Scheme 1: Examples of ortho-disubstituted benzene bioisosteres, and proposed method for the synthesis of enantioenriched bicyclo[2.1.1]hexanes.

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Hydrogen-bond donor enabled photocatalyzed intramolecular [2+2]-cycloaddition reaction

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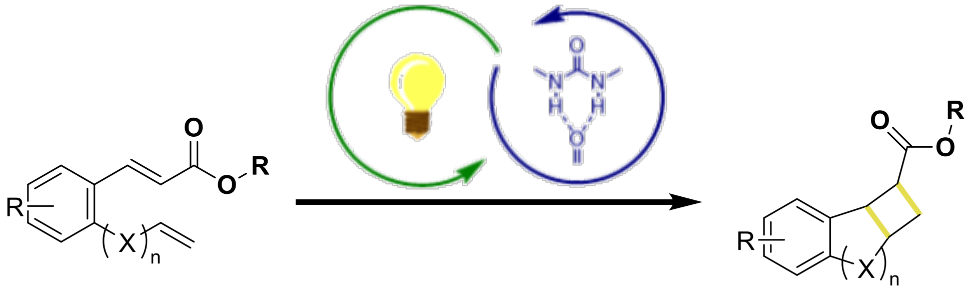

Photocatalysis proved to be a useful and efficient methodology for the development of new synthetic pathways. From 2009 to 2018 a rising number of articles (nearly sixty thousand papers) have been published including “photocatalytic” as a keyword. [1] Looking at these numbers we may have the impression there is nothing else that can be discovered in this field. However, the interest in developing and investigating dual catalytic strategies has still increased over the last years. [2]

Giving space to the investigation of new fields, like the combination of photocatalysis with hydrogen bond catalysis. [3, 4]. Inspired by these new possibilities, we present a merged photocatalytic - hydrogen bond catalysed intramolecular [2+2]-cycloaddition reaction. Herein, we demonstrate that the presence of a hydrogen catalyst is a powerful tool to activate both photocatalysts and substrates. In addition, we demonstrated the potential of our procedure with the exploration of a wide scope.

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Synthesis and characterization of photochemical properties of novel donor-acceptor photosensitizers based on perylene skeleton

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The current rise in a drug resistance among bacteria is prompting the search for new solutions to eliminate pathogenic microorganisms living on an usable surface that surrounds us. One of possible solutions is singlet oxygen ($^1O_2$), which is characterized by antibacterial, antiviral and antifungal properties.[1] The mechanism of action of singlet oxygen is based on its high chemical reactivity. An excited $^1O_2$ molecule seeks to reduce its energy state, which is achieved in the oxidation of various substances. It reacts readily with lipids, proteins and nucleic acids, changing their structure.[2] Singlet oxygen can be created by photogeneration, in which a suitable photoactive molecule, called a photosensitizer, is excited by light and transfers excess energy to triplet oxygen to form reactive oxygen species (ROS).[3]

In the present work, new triplet photosensitizers based on perylene derivatives were obtained. Perylene dianhydride, as a compound with radiation energy acceptor properties, was modified to obtain compounds with better solubility and by attaching donor groups - phenothiazines, which are highly bioactive and have wide applications. Phenothiazines are electron donors and transfer charge with multiple acceptors, yielding compounds that are promising triplet photosensitizers. An attempt was made to attach surface-anchoring groups, like (3-aminopropyl)triethoxysilane APTES, to such a compound for futher immobilization of PDI-derivatives on a surface.. As a result, it is possible to obtain an antimicrobial surface with non-selective and multipotential activity having wide applications in the medical sector, among others.

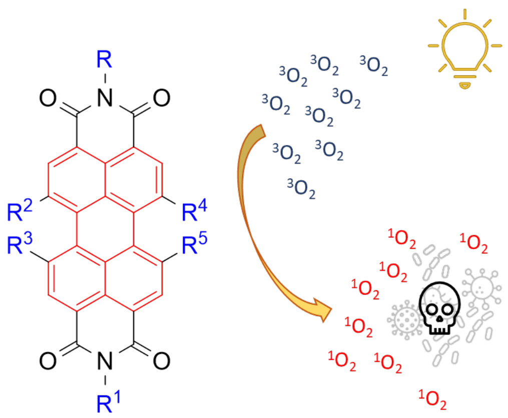

Figure 1: Perylene derivatives applied for singlet oxygen generation.

Acknowledgements: Research funded by the National Science Center as part of the SONATA Bis 2021/42/E/ST5/00110 project. K.S. thanks the OCTA project (Organic Charge Transfer Applications, 778158, Horizon 2020). Research work financed from the funds for science in the years 2018-2023 allocated to the implementation of an international co-financed project.

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Imine hydrosilylation: A theoretical validation through experimental results

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Hydrosilylation reactions have been extensively used in the enantiomeric reduction of imines due to their economic advantages in the utilization of inexpensive reagents.[1,2] While metallic catalysts have been primarily used for this reaction, organocatalysts have recently emerged as a promising alternative that provides similar or better results.[3] Specifically, picolinamide-cinchona organocatalysts have been demonstrated to achieve high enantioselectivity of up to 91% *ee* and a high turnover frequency when paired with trichlorosilane.[4] However, our understanding of the enantioselective hydrosilylation catalysed by picolinamide-cinchona has stagnated following the work of Barrulas et. al.[4] In this work, we attempt to unveil the mechanism of this reaction by comparing the energies calculated using well-established DFT methods (at the B97/Def2-TZVP/D3 level of theory) to the experimental yields of the reaction.The reaction mechanism is as described by the intermediaries and transition states depicted in **Figure 1**, as well as their corresponding energy gaps. The mechanism found is indeed similar to the one proposed previously by Matsumura and co-workers.[5] Additionally, these findings allow for a better understanding of the factors that govern selectivity and overall yields. This is imperative to further develop new and more efficient catalytic systems, thus having sizeable impact in organocatalysis, specially in imine reductions.

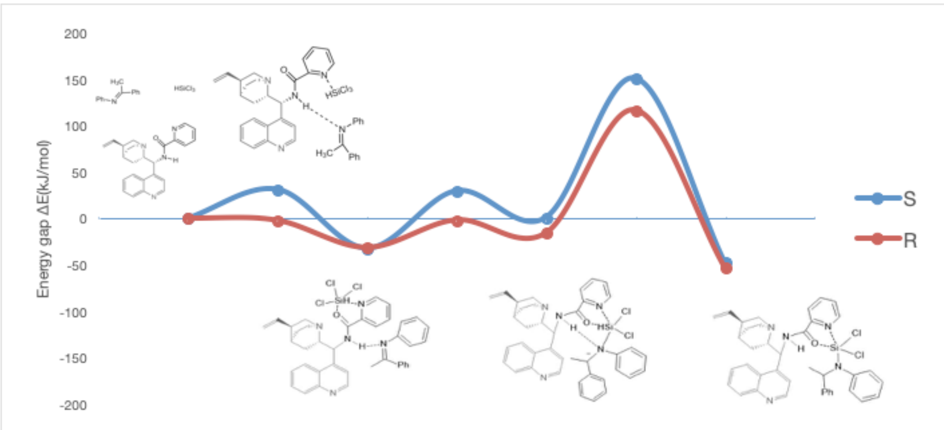

Figure 1: Picolinimide-cinchona based catalysed hydrosilylation energy profile.

Acknowledgements: This work was supported by FCT/MCTES through national funds and co-financed by FEDER (Project UIDP/50006/2020). Computational resources were also provided by project Search-ON2: Revitalization of HPC infrastructure of UMinho" (NORTE-07-0162-FEDER-000086), co-funded by the North Portugal Regional Operational Programme (ON.2 – O Novo Norte). The author further acknowledges FCT/MEC for the funding of a doctoral grant.

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Synthesis of dibenzodiazepinones via Buchwald-Hartwig Amination/Carbonylation

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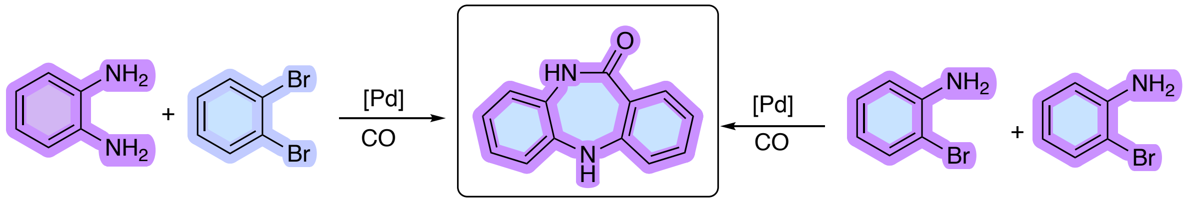
Dibenzodiazepinone units have been shown to be highly potent structures, endowed with numerous medicinally relevant properties, notably for their anti-anxiolytic and anti-depressant activities. Recently, dibenzodiazepinone-based scaffolds were reported to exhibit significant anti-cancer properties, as they were found to effectively inhibit tumor invasion in-vitro,[1] and induce apoptosis among several cancer cell lines.[2] Additionally, several dibenzodiazepinone-based structures were proven to act as p21-activated kinase (PAK) inhibitors, and Chk1 inhibitors.[3] Buchwald-Hartwig amination remains a fundamental tool to deliver structurally diverse nitrogen-containing heterocycles.[4] In this work, we considered accessing this unit using a strategy that involves Buchwald-Hartwig amination/Carbonylation starting from two different precursors *o*-phenylene diamine and 2-bromoaniline (**Scheme 1**).[5] The optimisation of the catalytic sequential B-H amination/ carbonylation conditions led to the disclosure of important structures and revealed important aspects related to this procedure.



Scheme 1: Synthetic pathway adopted to access dibenzodiazepinone structures.

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Hydroboration of carbon dioxide catalyzed by zinc complexes of borane-tethered *bis*(pyrazolyl)methane ligands

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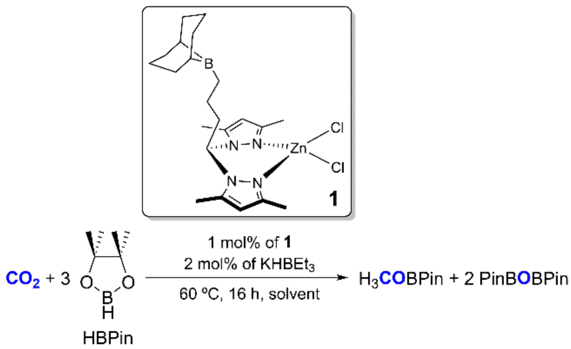
The growing concentration of greenhouse gases in the atmosphere, of which carbon dioxide (CO_2) corresponds to 80%, has had serious ecosystem implications.[1] Industrial CO_2 mitigation technologies range from physical to chemical but present low efficiency and massive operatory costs.[2] The development of readily accessible, active, selective, and inexpensive catalysts capable of converting CO_2 into added value compounds such as methanol (CH_3OH) is still a hot topic. The hydroboration of CO_2 to CH_3OH utilizing homogeneous catalysis is a relatively recent and scarcely explored approach that promises to avoid harsh operatory conditions while maintaining high reaction selectivity.[3]

We have been developing new ligands derived from *bis*(pyrazolyl)methane containing pendant borane moieties. This strategy allows for the reversible activation of CO_2 by the reaction intermediates via incorporation of a very Lewis acidic moiety in the second coordination sphere of a metal complex.[4] In particular, the dichloride zinc complex **1**, stabilized by a *bis*(3,5-dimethylpyrazolyl)methane scaffold containing a pendant 9-borabicyclo[3.3.1]nonane (9-BBN) moiety, has been synthesized and characterized in the present work. Complex **1**, when activated by $KHBEt_3$, catalyzes the hydroboration of CO_2 with pinacolborane (HBPin, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane) to the respective methyl ester $H_3COBPin$ in 42% yield, at 60 ºC, 1 bar of CO_2 pressure and 1 mol% of complex **1** (**Scheme 1**). Compound $H_3COBPin$, which resulted from the triple reduction of CO_2, yields CH_3OH via hydrolysis.[5] The present catalyst system is therefore a promising platform to convert CO_2 to CH_3OH under mild conditions.



Scheme 1: Hydroboration of CO_2 catalyzed by **1**/$KHBEt_3$.

Acknowledgements: Centro de Química Estrutural is a Research Unit funded by Fundação para a Ciência e Tecnologia through projects UIDB/00100/2020 and UIDP/00100/2020. Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020.

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Synthesis of polycyclic compounds containing quaternary carbon centres using tandem carbopalladation/Suzuki-cross coupling reaction and epoxide-arene cyclisation

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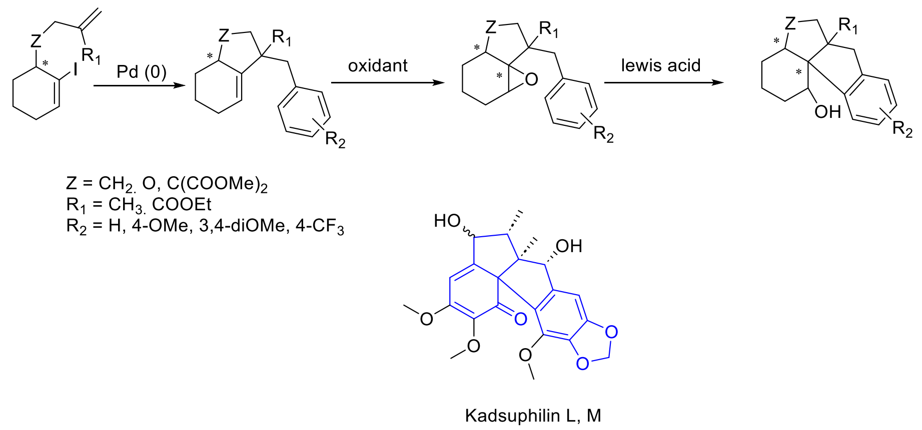
Polycyclic natural products containing quaternary carbon centres are important targets in organic synthesis research due to their biological properties. As examples of such compounds, kadsuphilin L and M were extracted from *Kadsura philippinensis*.[1] This plant is known for its biological properties such as anticancer,[2] antiviral,[3] hepatoprotective[4] and antioxidant.[5]

Our work is focused on the synthesis of polycyclic compounds with quaternary carbon centres that have a structural core similar to the above-mentioned kadsuphilins. One of the key steps of the synthesis is tandem carbopalladation/Suzuki-cross coupling reaction where alkenyl iodides with a six-membered ring were used to react with aryl halides boronic acids to generate a bicyclic intermediate. The following step is an epoxidation reaction, and finally an epoxide-arene cyclisation where the epoxide ring is opened by the aromatic ring, forming the quaternary carbon centre. Several strategies to improve the stereoselectivity of the synthesis will be described.



Scheme: Synthesis of polycyclic compounds containing quaternary carbon centres using palladium-catalysed tandem reaction

Acknowledgements: We thank the Charles University Grant Agency (project No. 197123) for financial support.

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Design and Synthesis of a Library of Novel Hole Transport Materials based on [2.2]Paracyclophane

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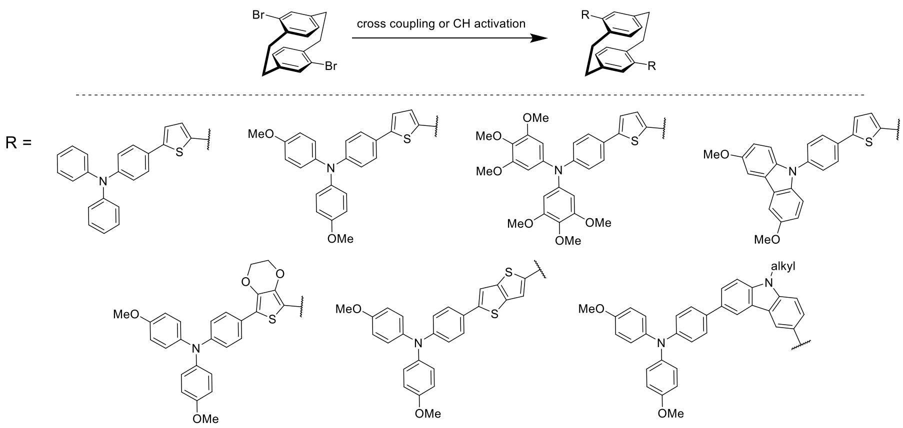
With the conversion from the use of fossil fuels to more sustainable energy sources such as sunlight, wind and water, there is a high demand for research in optimizing these sustainable sources. The recent development of new active materials for third generation solar cells (dye-sensitized, organic and perovskite) has also led to an immediate rise in research for appropriate charge transport materials. To ensure high power conversion efficiencies (PCE), the properties of charge transport materials and their optimization are of crucial importance.[1] With organic hole transport materials (HTM) currently being a big bottleneck for perovskite solar cells to reach higher PCEs, new materials, which are easy to synthesize, stable and quick to adjust to novel active materials, are in high demand. Known organic semiconductors can solve only part of these problems. The currently most used organic small molecule HTM, spiro-OMeTAD, for example, only shows high PCEs through insertion of dopants. The hydrophilic properties of most dopants strongly decrease the stability and lifetime of developed modules and result in the possibility of exposition to hazardous lead compounds.[2] To work towards a solution, we are targeting the issue by providing a systematic synthetical approach to a large library of two to four Donor-π-arms attached to different core systems like [2.2]paracyclophanes[3] and porphyrins. Further variations include different triarylamine and carbazole derivatives as donors, thiophene and related moieties such as benzothiophene or thieno[3,2-b]thiophene as well as the associated chalcogen structures as π-linkers (**Scheme 1**). By comparing the changing properties each synthesized molecule shows, the ideal HTM for any active layer can be chosen. Furthermore, finetuning of properties such as solubility, fill factor or molecule stacking can be addressed. Hereby we allow our materials to not only be implemented on the currently most used perovskite MAPbI, but in addition to be used for any emerging new active layers such as lead-free or oxide-based perovskites. By now, the library consists of 35 molecules with an undoped PCE up to 7.2% and ionisation potentials between 5.14 and 5.86 eV.



Scheme 1: Exemplary organic semiconductors as part of the growing library.

Acknowledgements: We thank the KeraSolar project funded by the Carl Zeiss foundation for financial support.

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DFT methods as a tool in the search for bifunctional catalysts active in the dual process of polymerization and depolymerization

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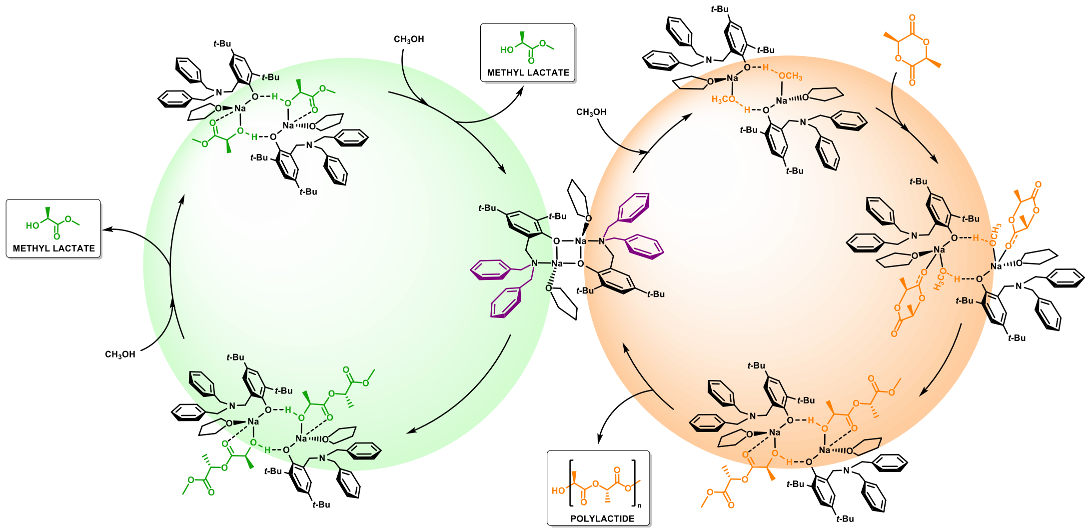
Bifunctional complexes active in both polymerization and depolymerization processes are an interesting alternative to traditional polymer synthesis and recycling methods. Using this type of compounds allows minimizing costs associated with both processes and, moreover, to close the LCA loop by obtaining recycled monomers that are the starting product for the synthesis of esters used in the ring-opening polymerization (**Scheme 1**). The most active catalyst in the dual process of polymerization and depolymerization is being sought. In this context, sodium aminophenolates are prominent candidates. The most important issue for the evaluation of their catalytic potential seems to be the selection of a suitable amine arm with a dangling motif and -N or -O donor atoms.[1]
Sodium complexes with different amine arms have been studied. Their ability to coordinate lactide, alcohol and PLA was verified by DFT methods. The studies indicate that the use of dangling amine arm motif allows the metal atom to decoordinate the amine arm and simultaneously coordinate the lactide or polymer. Complexes with that motif are active in both polymerization and depolymerization processes.[2]



Scheme 1: Catalytic cycles of *L*-lactide polymerization (orange) and polylactide depolymerization (green) processes catalyzed by sodium compound.

Acknowledgements: This work was financially supported by the National Science Centre, Poland. Grant No. 2017/25/B/ST5/00597. The Authors would like to express gratitude to the Wrocław Centre for Networking and Supercomputing (WCSS) for providing computational time and facilities.

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Photocatalytic Generation of Trifluoromethyl Nitrene and its Use in Alkene Aziridination

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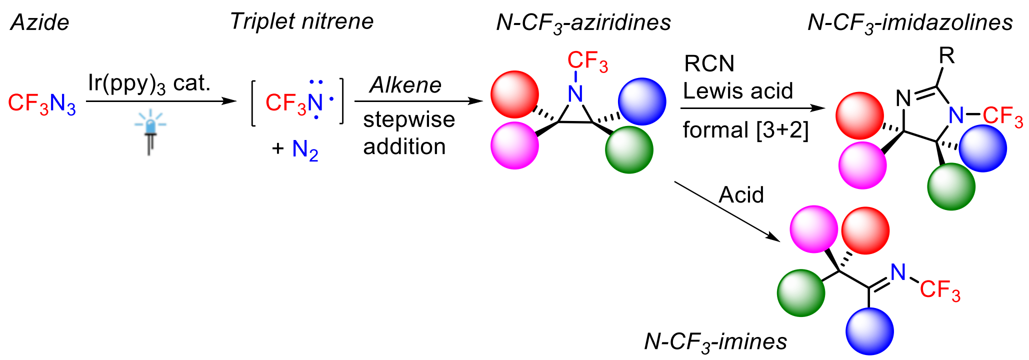
Nitrenes are highly reactive, uncharged species bearing strongly electrophilic properties. Despite their limited stability and in some cases explosive nature, azides have been exploited as potential nitrene precursors.[1] Nowadays, photo, thermal decomposition or microwave-assisted methods with transition metals or organocatalysts are used to sensitize the precursors and stabilize the formed nitrene species to achieve highly selective reactions such as aziridination, C-H amination and addition to electron rich heteroatoms.[2]
Although several new *N*-(per)fluoroalkylated azides have been synthesized recently,[3] their ability to efficiently generate nitrenes is unknown.
We report a facile, atom-efficient method for the generation of triplet trifluoromethyl nitrene and its application in alkene aziridination reactions to provide unique *N*-trifluoromethyl aziridines. Furthermore, we discovered Lewis acid-mediated formal [3+2] cycloaddition of aziridines with nitriles to provide novel *N*-CF_3-imidazolines and Brønsted acid-mediated group migration of aziridines to *N*-CF_3-imines (**Scheme 1**).



Scheme 1: Preparation and reactivity of *N*-trifluoromethylated aziridines.

Acknowledgements: We thank the Czech Academy of Sciences (Research Plan RVO: 61388963) and the Czech Science Foundation (Projects 23-04659S and 23-07066S).

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Synthesis of 5*H*-pyrazino[2',3':4,5]pyrrolo[3,2-*d*]pyrimidin-4-amine as a core structure for potential antivirals

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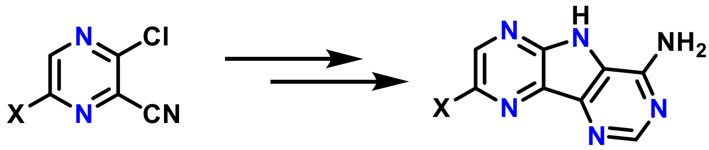
Various compounds bearing 9-deazapurine core show a wide range of biological activity, such as anticancer[1, 2], antibacterial[3] and antiviral[4] properties. Significant number of these bioactive molecules are tricyclic, heteroaromatic derivatives of this isosteric pyrrolo[3,2-d]pyrimidine[5, 6], or share identical core-geometry.[7, 8, 9] Moreover, a number of nucleoside analogues bearing such heterocycles as nucleobase have emerged in recent years and found intriguing applications in the synthesis of oligonucleotides, that are utilized – for instance – in the antisense technology[10].

As the 9-deazapurine structure does not occur in nature, the search for its efficient synthesis and the preparation of its further derivatives through novel strategies is ongoing. One of the least explored structure is 5*H*-pyrazino[2',3':4,5]pyrrolo[3,2-*d*]pyrimidin-4-amine: only one direct derivative is known in the literature.[11]

Herein, we present a successful synthesis of this crucial (pentaaza-fluoren-1-yl)-amine core molecule **1** (**Scheme 1**). Synthetic strategies, their challenges and further modifications of this novel structure will be discussed in detail.



1a: X = H
1b: X = Br

Scheme 1: Synthesis of the 5*H*-pyrazino[2',3':4,5]pyrrolo[3,2-*d*]pyrimidin-4-amine core structure (**1**)

Acknowledgements: The work was supported by the National Institute of virology and bacteriology (Programme EXCELES, ID Project No. LX22NPO5103) - Funded by the European Union - Next Generation EU and the Czech Academy of Sciences (RVO:61388963).

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Sequential Reactivity of Molecular Flavin Catalysts

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Flavoenzymes are highly versatile biocatalysts that share the same catalytically active moiety, the isoalloxazine core. It can switch between three distinct redox states (*inter alia* the quinoid, semiquinoid, and hydroquinoid) by undergoing one- and two- electron transfers and can be excited by visible light. These catalytically active states mediate a plethora of chemical transformations including halogenations, desaturations and activation of molecular oxygen.[1] However, despite the vast reactivity of flavoenzymes, the use of molecular flavins in synthetic chemistry is limited since significantly reduced activity is observed outside of the enzymatic environment, which stabilizes the flavin and tunes its reactivity.[2] Our group focuses on the synthesis and application of stable, molecular flavin catalysts for biomimetic and synthetically useful non-enzymatic transformations.

In a first example, we synthesized a C_2-symmetric bisflavin **1** and successfully applied it in the biomimetic bromination of phenolic substrates (**Figure 1A**), where it showed increased reactivity and stability compared to (–)-riboflavin tetraacetate (RFTA).[3] In a second example, we substituted the ribityl ester backbone of RFTA with a methyl group to increase its stability and applied it in a sequential desaturation-epoxidation reaction (**Figure 1B**). Desaturation of silyl enol ethers **5** by photoexcited flavin **4** takes place under an atmosphere of argon forming α,β-unsaturated ketones **6**. Changing the atmosphere to oxygen in presence of a reductant leads to aerobic epoxidation of **6** to α,β-epoxyketones **7** in a one-pot fashion (**Figure 1**). In total, 13 examples of **6** and 12 examples of **7** were prepared using **1**, where parent RFTA on the other hand exhibited decomposition after the first step inhibiting the subsequent one-pot epoxidation.[4]

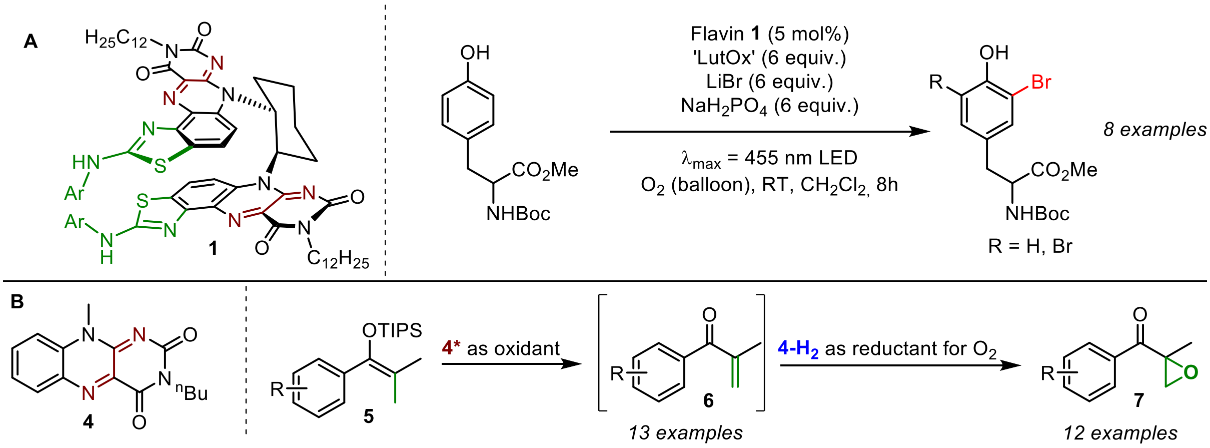

Figure 1: A) Aerobic bromination of phenolic substrates. B) Sequential one-pot desaturation-epoxidation reaction.

Acknowledgements: We thank the Fonds der Chemischen Industrie for a Ph.D. Fellowship to A.W and Liebig Fellowship to G.S.

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Decarboxylative-Carbonylative Nickel-Catalyzed Cross-Coupling for the Efficient Isotopic Labeling of Aryl-Alkyl Ketones

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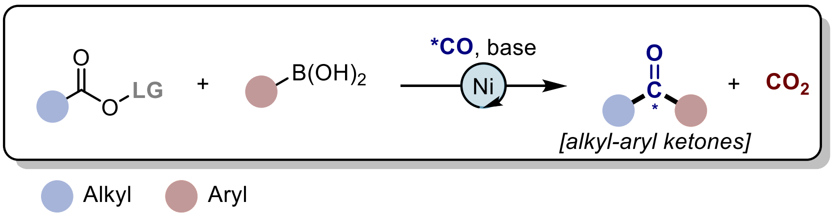
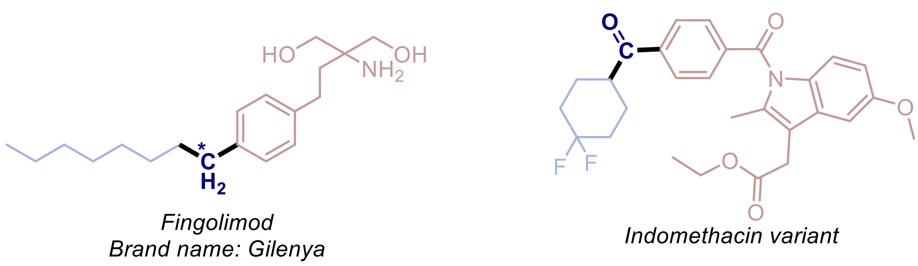
Isotopically labeled compounds are crucial in the drug development and approval process. Isotopologues enriched with stable isotopes, such as deuterium and carbon-13, are invaluable in quantitative bioanalysis investigations, being used as internal standards for LC-MS/MS based assays. Isotopologues enriched with a radioactive isotope, such as tritium or carbon-14, provide access to essential ADME data through *in vivo* studies, both in animals and humans.

The isotope labeling of drug candidates is challenging since the isotope label must be located at a chemically and biologically stable position in the molecule to track its fate. It is often necessary to conduct multiple syntheses with different labeling patterns. Additionally, there is only a limited and generally highly expensive pool of radiolabeled starting materials. Therefore, time and money can be saved by incorporating the labels at a late or even the last stage of the synthesis, and using CO as the (radio)labeling source.

An efficient methodology for the nickel-catalyzed carbonylative cross-coupling of alkyl carboxylic acids with aryl boronic acids to obtain aryl-alkyl ketones and their isotopologues is described. The method uses stoichiometric amounts of (labeled) CO released from SilaCOgen or COgen in combination with a common nickel catalyst and ligand. A wide range of aryl-alkyl ketones bearing various functionalities were successfully synthesized under mild conditions. Moreover, the methodology was expanded to the synthesis of pharmacologically relevant compounds and their $^{13/14}$C-enriched isotopologues. The reaction mechanism was investigated experimentally and supported by DFT calculations.



stoichiometric (labeled) CO
1° and 2° acids
aryl and heteroaryl boronic acids
mild conditions



Scheme 1: Decarboxylative-carbonylative cross coupling of redox-activated esters and boronic acids for late-stage isotope labeling of pharmaceuticals and pharmaceutical analogues.

Acknowledgements: We thank the Danish National Research Foundation (grant no. DNRF118, CADIAC), and the European Union's Horizon 2020 research and innovation program (grant no. 859910, CO_2PERATE and 862179, FLIX) for financial support.

N-Heterocyclic Carbenes as Versatile Tool for Molecular Surface Modification

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The successful isolation of an N-heterocyclic carbene in 1991 opened up a new class of organic compounds for investigation. From these beginnings as academic curiosities, N-heterocyclic carbenes today rank among the most powerful tools in organic chemistry, with numerous applications in commercially important processes.[1,2] Here we provide a concise overview of on-surface chemistry of N-heterocyclic carbenes, summarizing their general properties, their binding modes and their self-assembly on metal surfaces.[3,4,5] We give insight into common preparation methods[3] (**Figure 1**) and highlight various fields of application (**Figure 2**), including surface protection[1,3], biosensing[6], (photo) switchable surface properties[7,8], microelectronics[9,10] and heterogeneous catalysis[11].

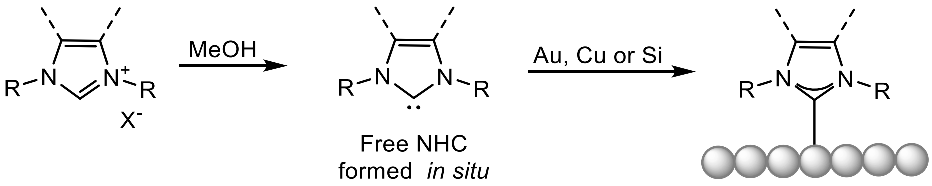

Figure 1: General preparation procedure for N-heterocyclic carbene monolayers on metal surfaces.

a) b

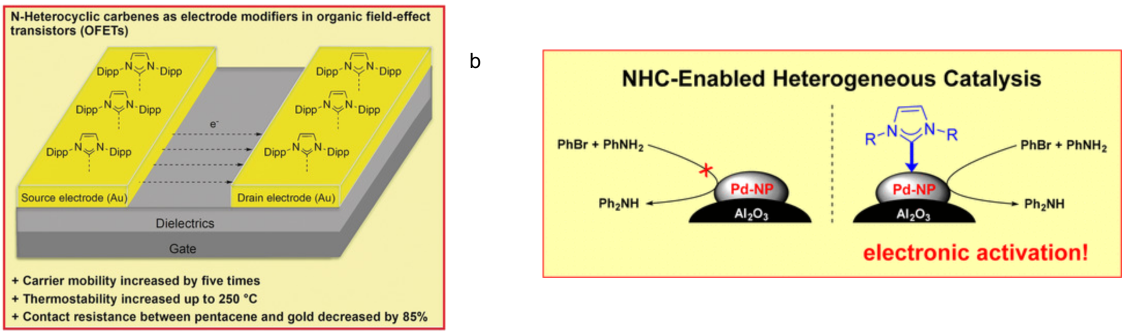

Figure 2: Two exemplary applications for N-heterocyclic carbene monolayers. a) Microelectronics, b) catalysis.

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Photoredox-Catalyzed Defluorinative Functionalizations of Polyfluorinated Aliphatic Amides and Esters

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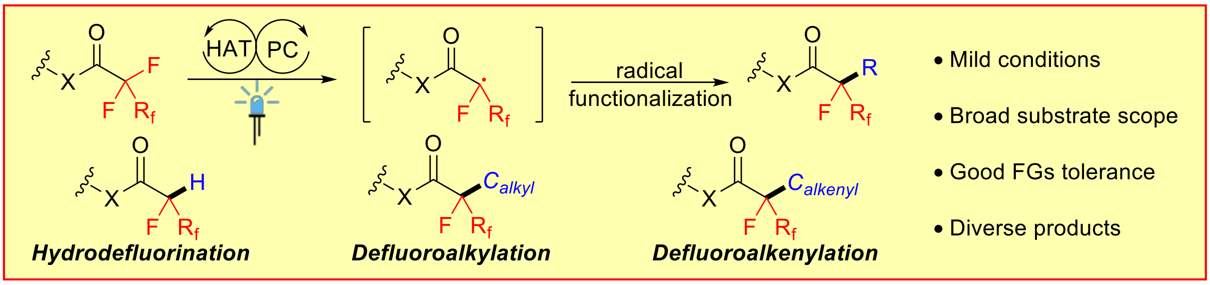
Organofluorine compounds are of particular interest to the pharmaceutical, agrochemical, and materials sciences due to their unique biological and physical properties.[1] Accessing functionalized organofluorine compounds by selective functionalization of the C–F bond in per- or oligofluorinated compounds has great potential. However, the high C–F bond strength[2] and selectivity control pose synthetic challenges.



Our work introduces a new visible-light-promoted pathway to selectively defluorofunctionalize strong C–F bonds in polyfluorinated aliphatic esters and amides. Various transformations, including hydrodefluorination, defluoroalkylation, and defluoroalkenylation, affording a variety of important partially fluorinated motifs, can be realized. The mild reaction conditions of our photoredox-catalyzed approach enable a remarkable substrate diversity and functional-group compatibility. Straightforward downstream chemistry towards fluorinated amines and alcohols as well as the access to new drug derivatives further emphasizes the potential of the protocol.

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Cobalt-pincer complexes based on triazine backbone - application in the synthesis of organometalloid compounds

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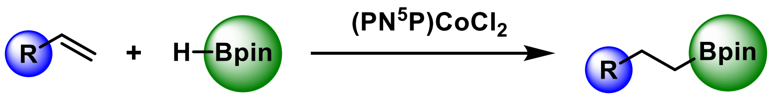
Organoboron compounds, due to their unique properties, are essential resources used in organic synthesis for the introduction of new functional groups, and for obtaining bioactive molecules or fine chemicals.[1] Boron moiety is commonly introduced into a molecule by hydroboration of unsaturated compounds (alkenes, alkynes). However, in most cases expensive precious metal complexes (rhodium, ruthenium) are used as catalysts for this process.[2] Therefore, a vast majority of current research work is devoted to the development of new alternative complexes which will be based on inexpensive and easily accessible Earth-abundant metals.[3]

A particularly interesting example of such catalysts are pincer cobalt complexes. They are known in the literature for their high stability and activity in many catalytic reactions (hydrosilylation, hydrogenation, coupling).[4] Their important feature is the possibility of affecting their selectivity by simply changing the reaction conditions or the structure of the ligand.[5]

Therefore, in my communication, I will present a procedure for the hydroboration of alkenes catalyzed by low-cost pincer cobalt complexes. The developed methodology proceeds under mild conditions regarding principles of sustainable chemistry, leading to the obtaining of a highly valuable group of compounds.



Scheme 1: Syntheses of organoboron compounds catalyzed by pincer cobalt complexes.

Acknowledgements: This work was supported by a National Science Centre Grant: UMO-2018/30/E/ST5/00045. We would like also to acknowledge Adam Mickiewicz University in Poznan for its financial support as part of the "Initiative of Excellence - Research University" project.

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Unique synthesis of new heterodimeric zinc complexes

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The new synthetic strategy for heterodimeric zinc compound formation is based on considerations regarding the classic redistribution of ligand reactions in a mixture of chiral complexes and monomer-dimer equilibria. In the case of racemic mixture selective chiral sorting generated heterodimers, complexes with ligands in which each of the zinc metal centers is coordinated to the ligand enantiomer with the opposite configuration. Exploring the mechanism of this reaction, we have been proved that the dynamic behavior of in the solution of chiral complexes involves a reaction between homodimers towards the selective formation of heterodimers. The mechanism of this intriguing reaction has been proposed based on theoretical studies.[1,2]

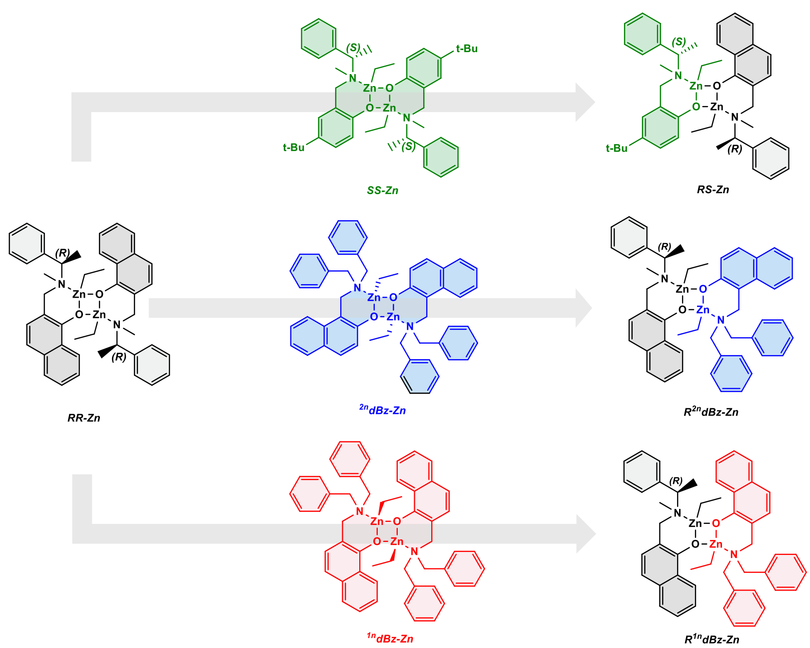

Figure 1: Synthesis of aminophenolate heterodimeric zinc complexes.

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Palladium-Catalyzed C(sp^3)-H Arylation Of Pentacyclic Triterpenoids

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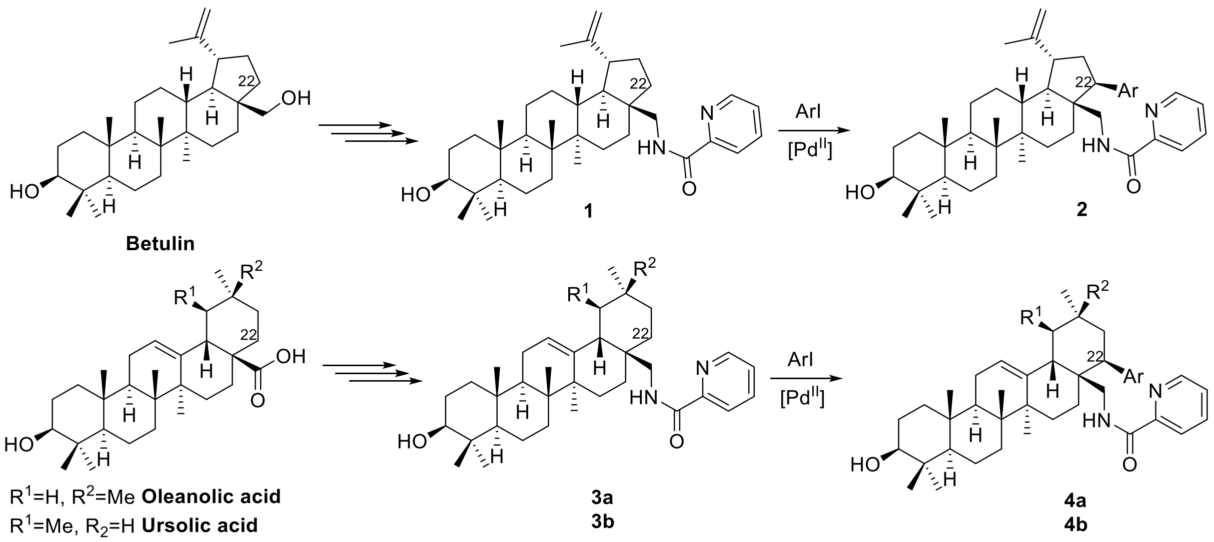
Naturally abundant pentacyclic triterpenoids are significant secondary metabolites which have aroused huge interest by possessing wide range of remarkable biological activities such as antitumor[1] antidiabetic[2] anti-inflammatory[3] and antiviral activities[4]. Oleanolic, ursolic acids and betulin, are the most recognizable compounds of this branch, which are isolated from various plants. The aim of this work is to obtain novel triterpenoic derivatives by C-H arylation at C(22). For this purpose, precursors bearing picolinic amide directing groups were synthesized (**Scheme 1**).



Scheme 1: C-H activation of betulin, oleanolic acid and ursolic acid.

Obtained picolinic amides **1**, **3a**, **3b** were successfully combained with aryl iodides employing Daugulis conditions and C-H arylated products **2**, **4a**, **4b** were obtained.[5]

Acknowledgements: We thank the European Social Fund within the Project No 8.2.2.0/20/I/008.

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Post-Synthesis Strategies to Prepare Mesostructured and Hierarchical Silicate Catalysts for Olefin Epoxidation

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Olefin epoxidation is an important transformation for the chemical valorization of olefins, which may derive from renewable sources or domestic/industrial waste, contributing to a sustainable biobased/circular economy. The use of adequate catalysts, preferably heterogeneous ones, in olefin epoxidation processes is important to achieve high productivity. In this work, different post-synthesis strategies, namely incipient wetness impregnation (IWI) and solid-state impregnation (SSI), were employed to introduce molybdenum species into mesostructured and hierarchical micro-mesoporous catalysts of the type TUD-1 and BEA zeotype (hierBEA), respectively, to confer epoxidation activity for the conversion of relatively bulky C8 olefins (*cis*-cyclooctene, 1-octene, *trans*-2-octene) and biobased olefins (methyl oleate, *DL*-limonene) to epoxide products, using *tert*-butyl hydroperoxide (TBHP) as oxidant, at 70 ºC (**Figure 1**).[1] The influences of (i) the type of metal precursor, (ii) type of post-synthesis impregnation method (SSI versus IWI), (iii) type of support (TUD-1 versus BEA) and (iv) top-down versus bottom-up synthesis methodologies were studied to achieve superior catalytic performances. Higher epoxidation activity was achieved for a material prepared via IWI of $MoO_2(acac)_2$ (acac = acetylacetonate) on (pre-treated) siliceous TUD-1 and calcination; for example, methyl oleate was converted to the corresponding epoxide with 100 % selectivity at 89 % conversion (24 h) and *DL*-limonene was converted to the corresponding mono- and diepoxide products in 69 % and 8 % yields, respectively, at 81 % conversion (4 h). Catalytic and solid-state characterization studies were conducted to shed light on material stability phenomena.

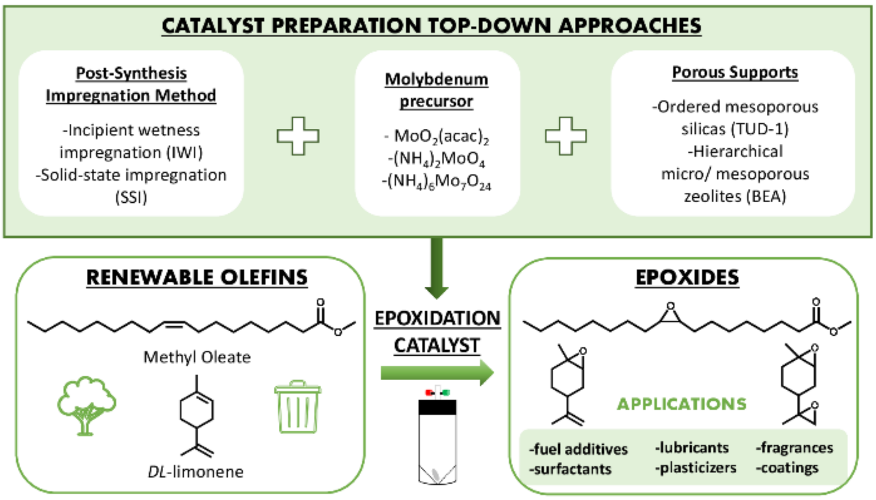

Figure 1: Silicate catalysts possessing mesoporosity, prepared via top-down strategies, for epoxidation of biobased olefins.

Acknowledgements: This work was carried out with the support of CICECO—Aveiro Institute of Materials (FCT (Fundação para a Ciência e a Tecnologia) ref. UIDB/50011/2020, UIDP/50011/2020 and LA/P/0006/2020) and the COMPETE 2020 Operational Thematic Program for Competitiveness and Internationalization (Project POCI-01-0145-FEDER-030075), co-financed by national funds through the FCT/MCTES (PIDDAC) and the European Union through the European Regional Development Fund under the Portugal 2020 Partnership Agreement. D.M.G. (grant ref. 2021.04756.BD) acknowledges the FCT for PhD grant (State Budget, European Social Fund (ESF) within the framework of PORTUGAL2020, namely through the Centro 2020 Regional Operational Program). The position held by MMA was funded by national funds (OE) through FCT, IP, in the scope of the framework contract foreseen in the numbers 4, 5 and 6 of article 23 of the Decree-Law 57/2016 of 29 August, changed by Law 57/2017 of 19 July.

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Application of *N*-Amino pyridinium salts in photochemistry

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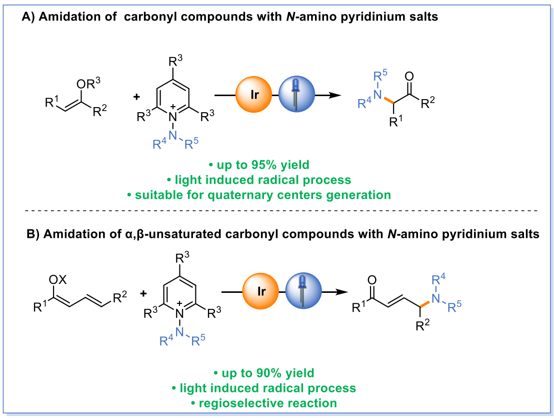
Amines play crucial roles as biologically active compounds in medicine, as synthetic intermediates in organic chemistry.[1] Along this line, *N*-amino pyridinium salts have recently received a lot of attention as precursors to generate *N*-centered radicals via photochemical means.[2] These are attractive for generating new C-N bonds, giving access to α-amino carbonyl- or γ-aminocarbonyl moieties (**Scheme 1**). [3,4]
Upon light irradiation, electron transfer from the excited state of the Ir(III)*-catalyst to the *N*-amino pyridinium salt results in the N-N bond cleavage generating an amidyl radical. Subsequent addition of the radical to the enolate affords a carbon-centered radical, which after oxidation and to cation and removal of the protection group leads to α – and γ- aminated products.[3,4] The broad synthetic utility of the developed method is demonstrated by functionalization of ketones, aldehyde, esters, vinyl ethers and 1,3-diketones.[3] *N*-amino pyridinium salts as electrophilic radical precursors can also generate γ-aminocarbonyl compounds in photochemical conditions from unsaturated enones. The photocatalytic vinylogous reaction of dienolates give products in high-yield, it is scalable, and tolerates a broad range of unsaturated α,β-unsaturated carbonyl, including biologically relevant compounds as starting materials.[4]



Scheme 1: Amidation reactions with *N*-amino pyridinium salts.

Acknowledgements: Financial support for this work was provided by the National Science Center (PL): MAESTRO UMO-2020/38/A/ST4/ 00185 to K.F.S. and D.G. and ETIUDA 7 UMO-2019/32/T/ ST4/00303 to K.G.

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Suzuki-Miyaura coupling using a recycled and reusable homogeneous palladium catalyst

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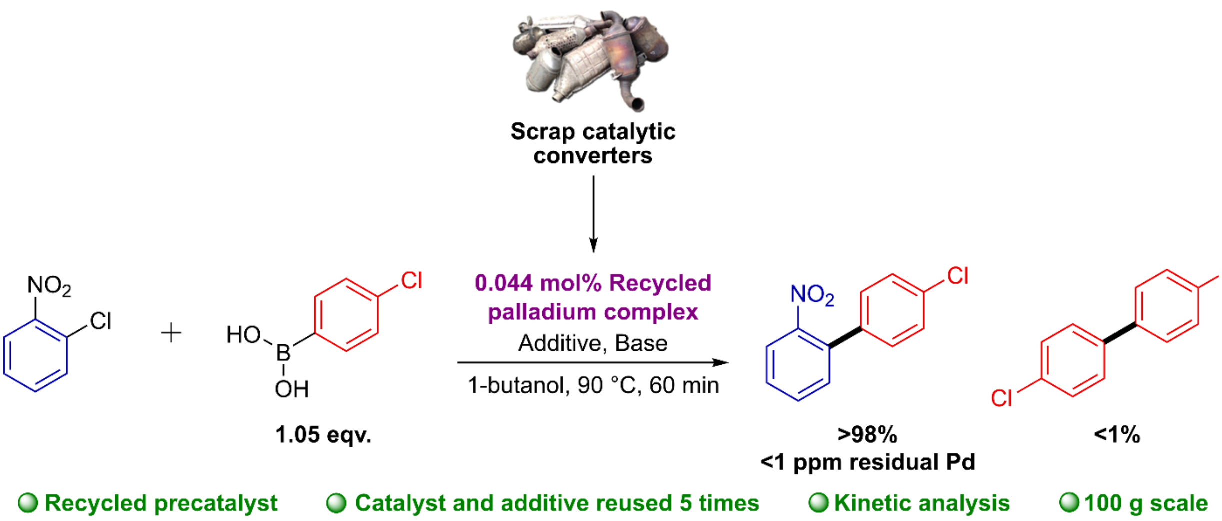
Unrelenting demand for the finite natural supply of palladium has resulted in supply deficits and record prices (~350% price increase since 2012).[1] Palladium production is also plagued with the environmental impact of mining and refining processes.[2] As a result, palladium consumption in its current form is unsustainable and improvements to the lifecycle of the metal are needed.[3] Owing to their short lifetime and rich palladium content (2000 ppm versus <10 ppm in ore), scrap catalytic converters (SCCs) offer a valuable 'urban mine' of palladium. Despite this, existing recovery technologies are limited by energy intensive pyrometallurgy (temperatures >1000 °C) and undesirable hydrometallurgical processes e.g. *aqua regia* and multi-step liquid-liquid extractions. This has led to our research on molecular palladium compounds recovered directly by solvometallurgy from solid SCCs for use as catalysts.[4-6]

Herein, a molecular palladium complex recyclable from SCCs has been applied as a homogeneous Suzuki-Miyaura catalyst. A design of experiments (DoE) optimisation on a model reaction (**Scheme 1**, Boscalid intermediate, BASF) provided conditions for high conversions (>98%) and cross-coupling selectivity (99:1) on a 100 g scale. A novel strategy for both catalyst and additive recycling has been demonstrated over five reuse cycles by kinetic reaction profiles. ICP-MS, TEM and kinetic analysis revealed that palladium speciation and recycling was influenced by water leaching during work-up. Kinetic and mechanistic analysis also revealed the role of catalyst aggregates and an unusual catalyst deactivation pathway. Finally, kinetic profiles illustrate that the recycled and recyclable palladium catalyst perform comparably to traditional catalysts. Our results offer a unique strategy for achieving 'closed-loop' sustainable consumption of palladium in the chemical industry.



Scheme 1: Graphical abstract – Model Suzuki-Miyaura coupling.

Acknowledgements: We are grateful for a studentship to S.M. funded by the EPSRC Centre for Doctoral Training in Next Generation Synthesis and Reaction Technology (Imperial College London, EP/S023232/1).

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The Use of Azide-Tetrazole Equilibrium in the Modification of Fused Pyrimidines

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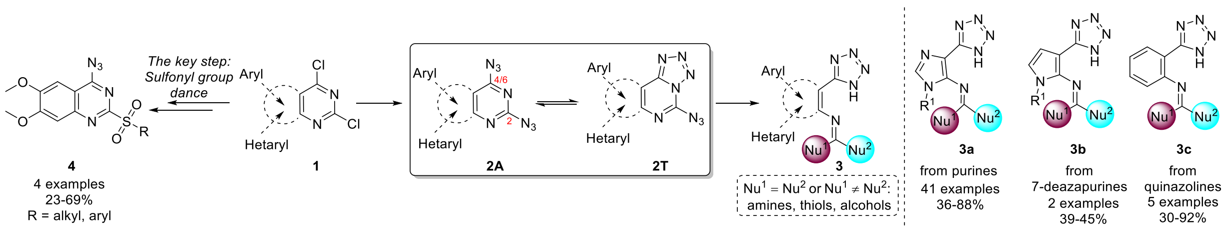
Both pyrimidine and imidazole rings can be opened in purine derivatives.[1] Our research introduces a new method for the ring-opening reactions of fused pyrimidines such as purines, deazapurines, and quinazolines. By utilizing various nucleophiles and the presence of azide-tetrazole equilibrium in structure **2**, we have established a unique approach toward imidazolyl/pyrrolyl/aryl tetrazole derivatives **3a**–**c** (**Scheme 1**). In our case, the tetrazole ring acts initially as a protecting group, encouraging nucleophiles to attach to the less active C2 position of fused pyrimidine. Then it acts as a leaving group when the pyrimidine ring undergoes a second nucleophile attack, eventually leading to the formation of tetrazolyl derivatives **3**. We have confirmed the structures of these compounds using X-ray analysis. Besides, the opened products can be used as starting materials to prepare diazepine-type structures.

Additionally, an approach was developed for sulfonyl group migration from the quinazoline's C4 position to its C2 position via a "sulfonyl group dance" during S_NAr reactions with NaN_3 using the azide-tetrazole equilibrium and based on our previous studies toward 6-azido-2-sulfonylpurine derivatives[2] and thiosubstituted tetrazoloquinazolines[3] (**Scheme 1**).

We will discuss the ways to synthesize ring-opening products for fused pyrimidines and substituted quinazoline derivatives.



Scheme 1: General synthetic approaches toward derivatives **3** and **4**.

Acknowledgements: The authors thank the Latvian Council of Science grant No LZP-2020/1-0348 for financial support.

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Mechanochemical borylation of aryl diazonium salts promoted by sodium chloride

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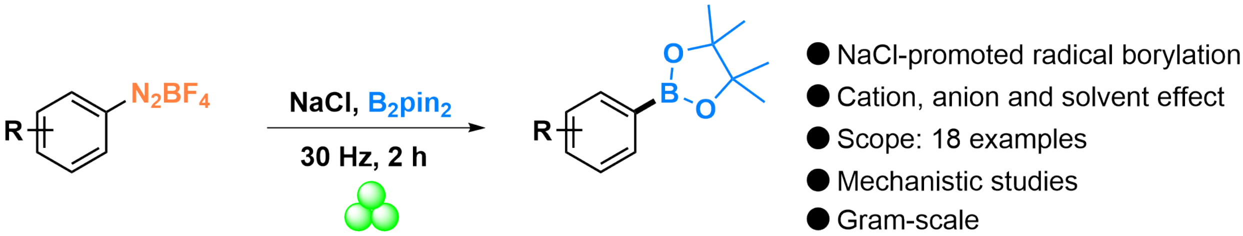
Arylboronates represent an essential tool in organic synthesis with a broad option of applications, serving as precursors for important chemical transformations, with the Suzuki-Miyaura coupling possibly being the most prominent. Outside of their synthetic use, aromatic boron-bearing compounds have found their way into other fields such as sensors, medicinal chemistry or covalent organic-frameworks. Traditional preparation of arylboronates relied on reactive organometallic reagents and thus limiting the scope to molecules that can tolerate strong bases and nucleophiles. The breakthrough in developing synthetic methods to access arylboronates in a radical manner led to the discovery of the radical borylations of aromatic compounds.[1]
Herein we present mechanochemically induced radical borylation of aryl diazonium salts promoted by sodium chloride. This transformation was discovered serendipitously while intending to use sodium chloride as inert milling auxiliary. To our surprise reaction proceeded smoothly, which led us to investigation of the utility of this transformation (**Scheme 1**). In this work, we report full optimization and scope for this transformation alongside with mechanistic studies by quantum chemical calculations as well as investigation of the influence of different cations, anions and solvents on this transformation. Finally, this reaction could be successfully upscaled to a obtain the boronic esters on a gram scale, providing a facile access to interesting building blocks.[2]



Scheme 1: Mechanochemical borylation of aryl diazonium salts promoted by sodium chloride.

Acknowledgements: This work has been supported by VEGA grant no. 1/0332/19 and project CAPELE (ERC StG, grant no.: 101078608).

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Synthetic Pathways Toward Designed Purine Derivative for the Photo-Catalysis

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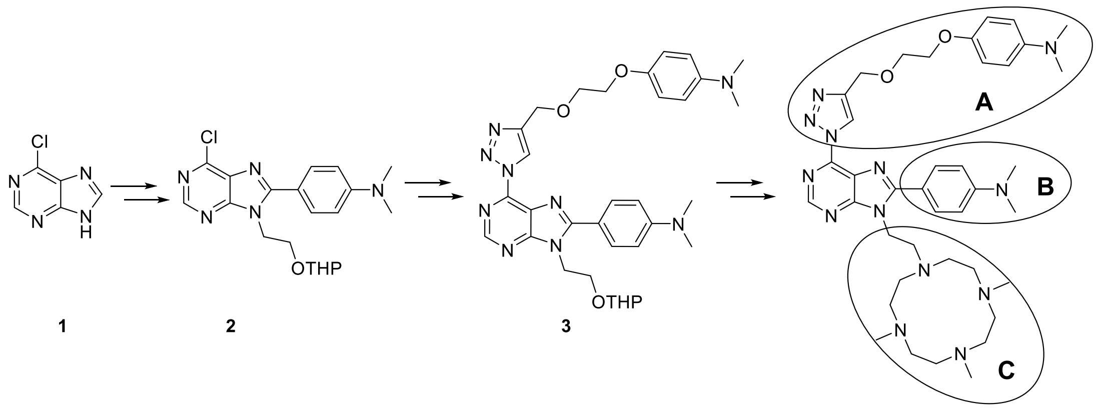
Fluorescent purine derivatives have a variety of uses in analytics – they can be used as a metal ion and pH sensors.[1] They also can be used for cell imaging[2] and as photo-catalysts.[3]
Target purine compound **4** was designed with an aim to be used as a potential molecular system for the photo-catalysis. Several synthetic pathways were designed and have been tested to obtain it (**Scheme 1**). For the synthesis of **4**, 6-chloropurine (**1**) needs to be derivatized at *C*(6), *C*(8) and *N*(9) positions by introducing **A**, **B** and **C** moieties. In the end, target compound **4** was obtained in 9 steps, using the combinations of S_NAr, S_N2, CuAAC, C-C metal catalyzed coupling, alkylation and Mitsunobu reactions. Further, it is planned to test its fluorescence properties and complexation abilities.
We will discuss approaches toward purine derived photo-catalyst **4** and its application.



Scheme 1: Synthetic route toward target compound **4**.

Acknowledgements: The authors thank MEPS co-project LV-LT-TW/2022/9 for financial support. A.B. thanks the European Social fund within project Nr. 8.2.2.0/20/I/008 and Riga Technical University.

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Azide-Tetrazole Equilibrium Driven Reactions of Fused Diazido Pyrimidines and Characterization of Tautomerism Therein

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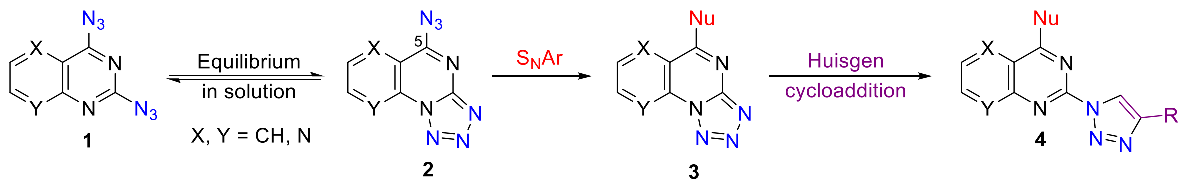
Pyrimidine-fused heterocycles are privileged scaffolds that attract great interest due to their biological properties.[1] Modification and refinement of such scaffolds is a promising strategy for development of novel drugs. Recently a new class of tetrazole-fused pyridopyrimidines have been evaluated as anti-depressants and epilepsy drugs.[2]

From synthesis perspective, heterocycles with azido-azomethine structural entity are interesting due to present dynamic azide tetrazole equilibrium in solution phase.[3] The equilibrium can be shifted towards one or other tautomer by altering ambient conditions such as solvent polarity and/or temperature. Thus, azide tetrazole ring-chain tautomerism is known to influence S_NAr reactivity and regioselectivity.[4]

Herein we describe an efficient and straightforward synthesis method toward fused tricyclic tetrazolopyridopyrimidines (**Scheme 1**). We discovered that diazido-substrate **1** undergoes azide-tetrazole equilibrium which directs S_NAr to take place at the *C*-5 position displacing residual azide as a leaving group. FT-IR and X-ray analysis of **3** reveals tetrazole to be the major tautomeric form present in the solid state. On the other hand, the equilibrium in solution phase liberates azido group that can be further functionalized in Huisgen cycloaddition reactions. Calculated thermodynamic heats of tautomerization in solutions *via* variable temperature NMR and DFT support the observed experimental results.



Scheme 1: Synthesis of tetrazolopyridopyrimidines.

Acknowledgements: The authors thank the Latvian Council of Science Grant LZP-2020/1-0348 for financial support and A. Mishnev for X-ray analysis.

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Pyridine-2-carboxylate Palladacycle Catalyzed Addition of Arylboronic Acids to Electron-deficient Alkenes

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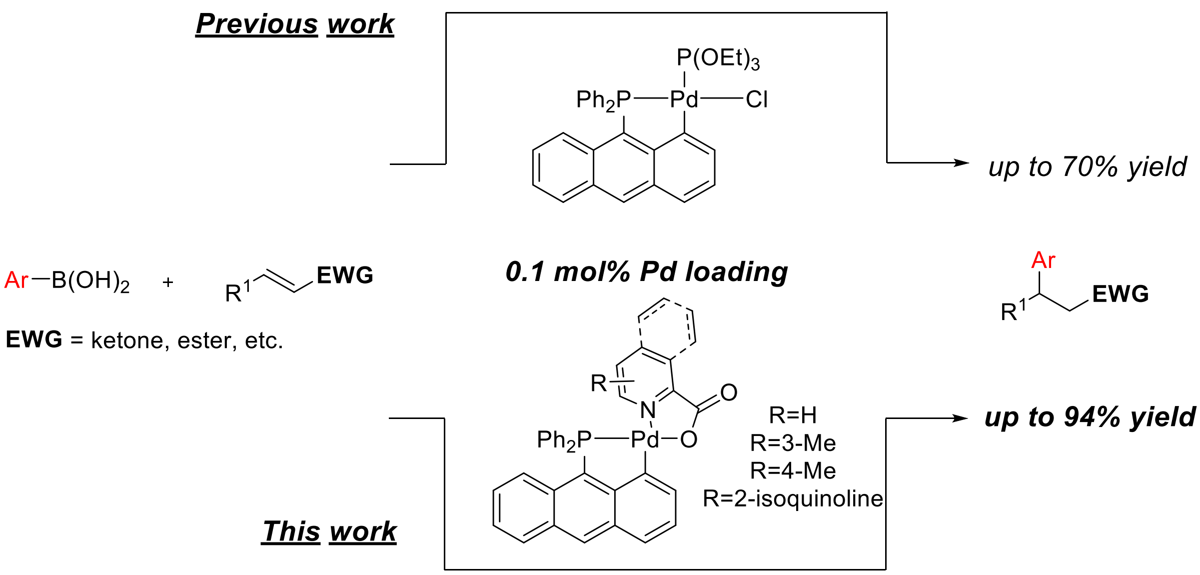
Naphthyl-based (P,C)-cyclometalated palladium complexes show high catalytic activity in various carbon-carbon bond reactions.[1] However, anthracene-based (P,C)-cyclometalated palladium complexes are superior catalytic activity to naphthyl-based (P,C)-cyclometalated palladium complexes in the addition of arylboronic acids to electron-deficient alkenes.[2] Anthracene-based (P,C)-cyclometalated palladium complexes with phosphite as a co-ligand performed a large substrate scope in the addition, but the highest turnover number was 700. Herein, we will report that changing the co-ligand of the anthracene-based (P,C)palladium complex from phosphite to pyridine carboxylate markedly enhances the catalytic activity in the addition.



Scheme 1

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Synthesis of Chiral 3-Allyl-isoindolinone Derivatives via Optical Resolution

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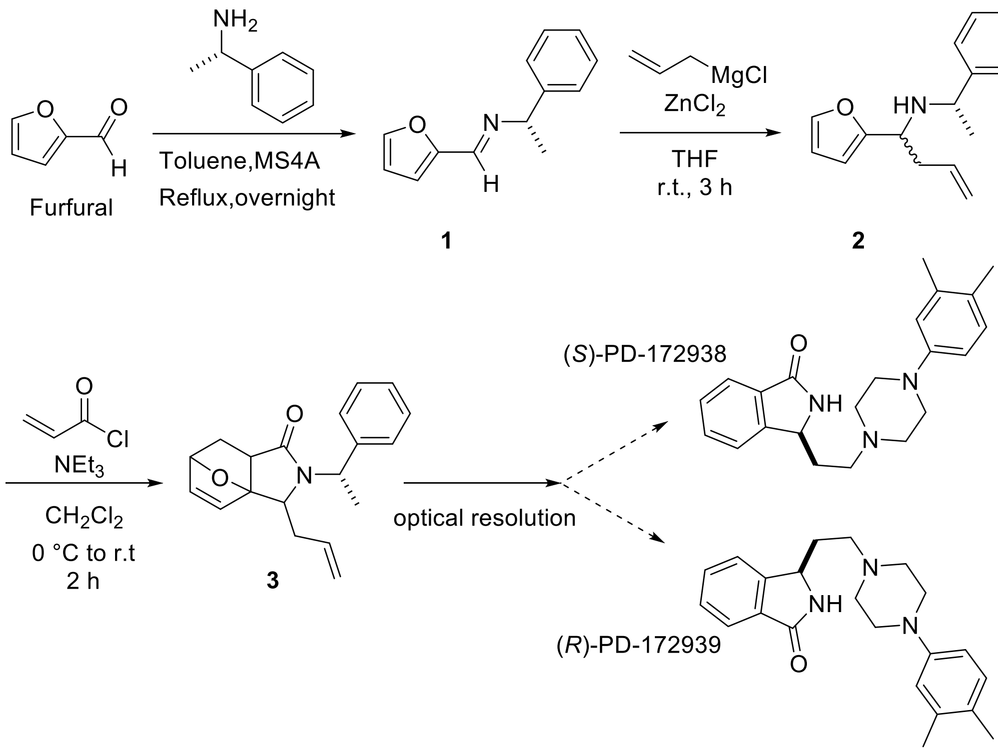
Many chemicals are currently produced from petroleum as the predominant feedstock, but the use of biomass as an alternative feedstock to petroleum is attracting attention for the realization of a carbon-neutral society.[1)] Furfural is one of the versatile chemicals that can be obtained from biomass and is a starting material for various functional chemicals; for example, aromatic compounds can produce from furfural and olefin via the Diels-Alder reaction. Herein, we will report the synthesis of chiral isoindolinone derivatives such as (*S*)-PD-172938 and (*R*)-PD-172939 via intramolecular Diels-Alder reaction of furans (IMDAF)[2)] as a key step and the optical resolution of their diastereomers **3** (Scheme 1).



Scheme 1. Proposed synthetic route of (S)-PD-172938 and (R)-PD-172939 via IMDAF

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Redox-active esters as key intermediates in the synthesis of sulfur-derivatives of oseltamivir

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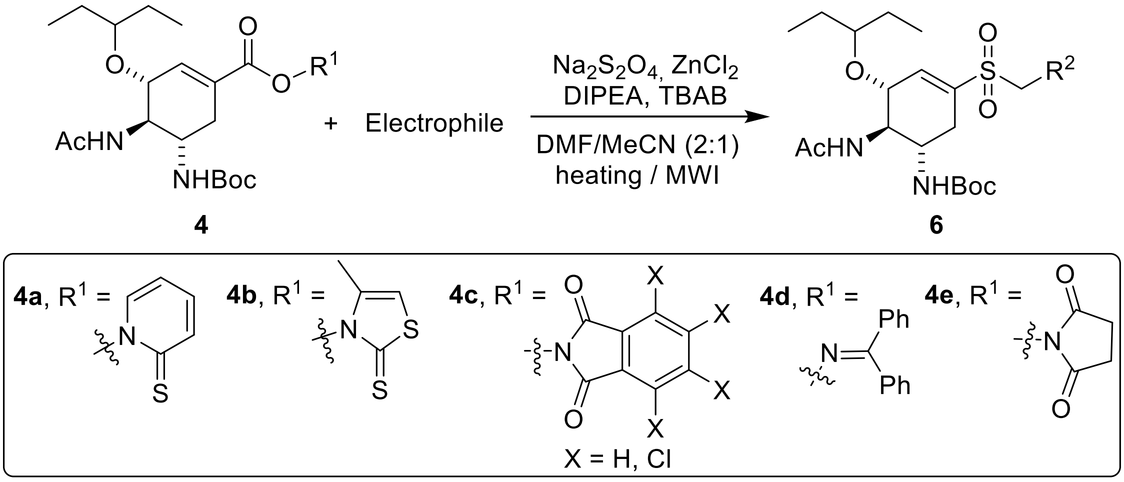
Redox-active esters play a pivotal role in various cross-coupling reactions[1] and were used in reactions catalyzed by transition metals.[2] Active ester **4b** was used as one of the crucial intermediates in the multistep synthesis of different derivatives of oseltamivir.[3] We have chosen to test redox-active esters as a suitable intermediate in the synthesis of the sulfur analogs of oseltamivir. Compounds bearing sulfone group possess significant biological activities and are active pharmaceutical ingredients in various drugs. Hence, the incorporation of SO_2 may lead to improving the biological activity of oseltamivir toward the influenza virus. Sodium dithionite was used as the source of SO_2 in decarboxylative sulfonylation as a synthetical approach to tertiary sulfones.[4] We have tested several esters bearing various activating groups, electrophiles (e.g. R^2-Br, R^2-OTs, $PO(OR^2)_3$), and inorganic salt $Na_2S_2O_4$ as a source of SO_2.



Scheme 1: Synthesis of sulfur derivatives of oseltamivir

Acknowledgments: We thank Comenius University for the financial support of this work under contract no. UK/84/2023.

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Development of Readily Accessible Organometallic Capping Reagents for Carbon Labeling of Drugs

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We have developed a method for carbon isotope labeling of secondary amides from the original secondary amide and a readily accessible palladium carboxylate complex **Pd-1**. This work is inspired by previous projects performed in our group and is a part of our goal of developing new organometallic capping reagents.[1] We define this new approach as molecular surgery, a method where drug companies can incorporate a labeled carbon isotope as the last step, or one of the last steps in synthesis. The main advantage of this method is the quantitative incorporation of the carbon isotope label and the minimized loss of the carbon isotope in further reaction steps. This is especially important when drug companies perform ADME studies where ^{14}C-isotope labeling is a mandatory part of the safety study.

As the molecular surgery knife, we employ a method from literature, where an aromatic Boc protected amide is cleaved off from the rest of the molecule. This affords the **Ni-1** complex[2], which can be utilized in a cross-coupling reaction with our capping reagent to afford the carbon isotope labeled molecule. Due to the flexibility of the capping reagents multiple secondary amide analogues of a given drug can easily be synthesized when employing this method.

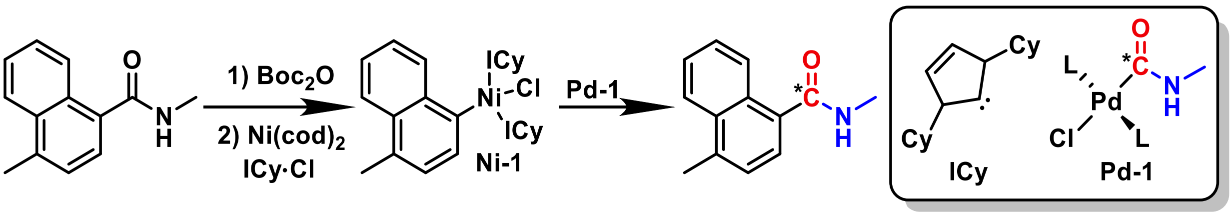

Figure 1: Employing molecular surgery on a secondary amide

Acknowledgements: We thank the Novo Nordisk Foundation and Danish National Research Foundation for financial support

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Synthesis and Photophysical Properties of Phosphorescent Purine-Iridium Complexes

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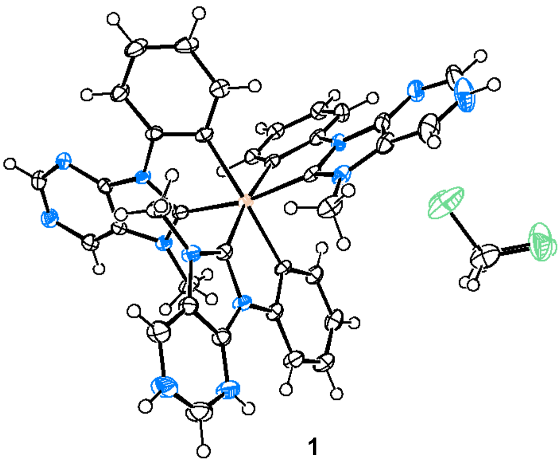
There is ongoing research towards more efficient emitters in organic light-emitting diodes (OLED), and especially for structures, that emit light in the blue region. Highly efficient emitters can be achieved using phosphorescent transition metal complexes, that can utilize excited triplet states for emission. To the best of our knowledge, there are only 2 publications that have examined the photophysical properties of iridium complexes with purine carbenes.[1] So further research in this field is necessary to yield optimized emitters for OLEDs.

The purine ligand was prepared from a functionalized pyrimidine via *de novo* synthesis. *Mer* isomer **1** was selectively formed in a AgOAc mediated reaction, while *fac* isomer **2** was prepared in an acid catalyzed isomerization.[2] XRD structures were achieved to prove the identity of both isomers (**Figure 1**). Both isomers emitted blue light, with *mer* isomer showing a bathochromic shift compared to *fac* isomer. Emission also exhibited a bathochromic shift, when comparing PMMA doped solid state to DCM solution. Quantum yields in PMMA reached up to 100%.



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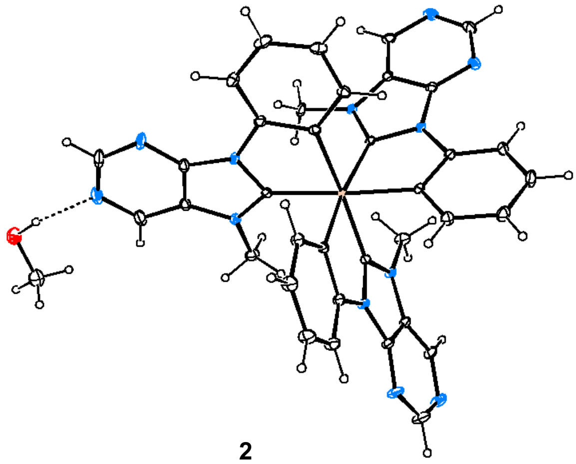

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Figure 1: XRD structures of *mer* **1** and *fac* **2** purine-iridium complexes.

Acknowledgements: This work was supported by the Latvian Council of Science grant No. LZP-2020/1-0348. *Dr. phys.* A. Mishnev is acknowledged for X-ray analysis.

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Anion-Binding Catalyzed Asymmetric Dearomatization of 4-Oxy-quinolinium Salts

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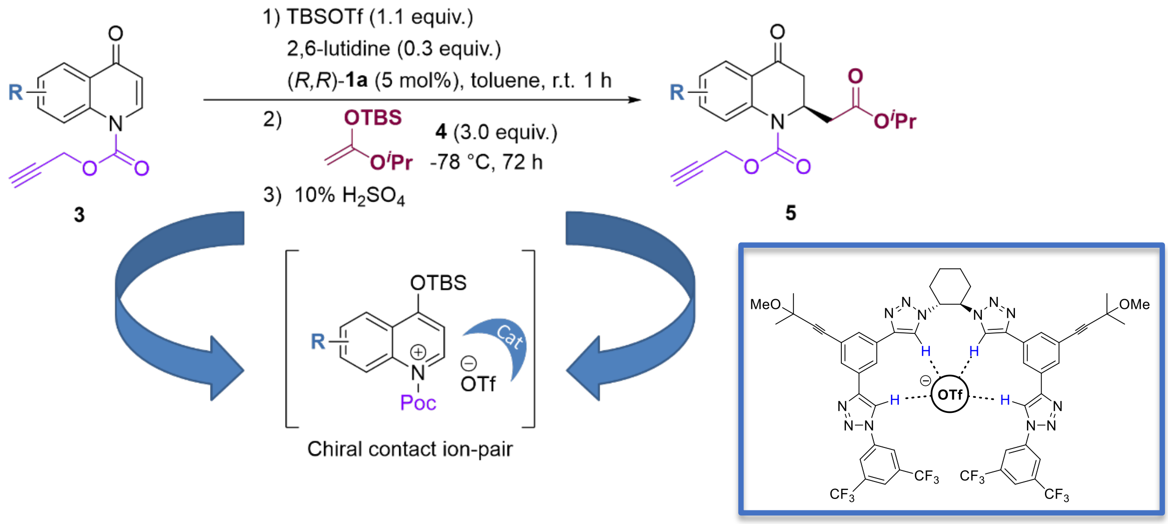
The 4-quinolones and their derivatives are important scaffolds in medicinal chemistry due to their broad spectrum of antibacterial activity.[1] For this reason, the development of new synthetic pathways is of great importance. Anion-binding catalysis,[2] which is based on the activation of an ionic electrophile by binding of the catalyst to its counter-anion, has become a powerful tool for asymmetric organic transformations. Thus, this strategy provides an alternative straightforward approach for the preparation of enantioenriched 4-quinolones. The family of helical triazole-based hydrogen bond-donors **1**, developed in our group, has already shown a great potential as anion-binding catalysts in enantioselective dearomatization reactions of different substrates such as Isoquinolines,[3] quinolines,[4,5,6] pyridines,[5,6,7] and pyrylium derivatives[8] among others. Herein, we present an asymmetric Reissert type reaction of 4-quinolones employing silyl ketene acetal as nucleophile and propargyloxycarbonyl (Poc) as a protecting group, towards the synthesis of different kinds of chiral 4-quinolone derivatives.



Scheme 1: Anion-binding dearomatization of poc-protected quinolones.

Acknowledgements: We thank IRTG-2678 and DAAD for the generous financial support.

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Switching from Ionic to Radical Type Chemistry: Radical NHC-Catalysis Enables the Regiodivergent C–H Acylation of (Hetero)Arenes

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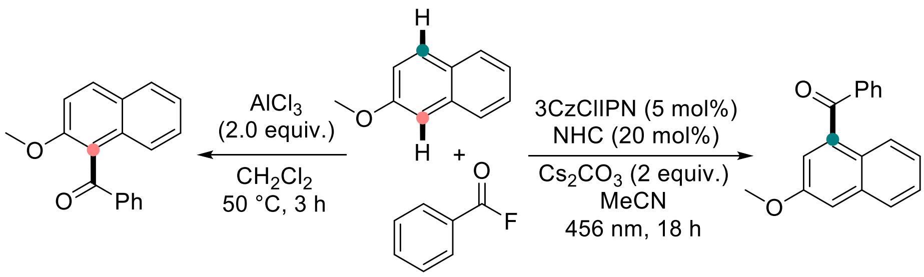
The Friedel-Crafts acylation which belongs to the class of electrophilic aromatic substitutions is a highly valuable and versatile reaction in synthesis. The regioselectivity is well predictable and determined by electronic as well as steric properties of the (hetero)arene substrate.[1] Herein, a radical approach for the C–H acylation of arenes and heteroarenes is presented which is achieved by mild cooperative photoredox/NHC catalysis (**Scheme 1**).[2] Key step is the cross coupling of an arene radical cation with an NHC-bound ketyl radical controlled by the persistent radical effect (PRE).[3] Compared to the classical Friedel-Crafts acylation, a regiodivergent outcome is observed upon switching from the ionic to the radical mode. In these divergent reactions, aroyl fluorides act as the acylation reagents in both the ionic and the radical process.



Scheme 1: Regiodivergent benzoylation of (hetero)arenes realized by using either Friedel–Crafts type conditions or employing cooperative NHC/photoredox catalysis.

Acknowledgements: We thank the Deutsche Forschungsgemeinschaft (DFG) for supporting this work.

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Masked malondialdehydes - efficient synthons for functionalized heterocycles

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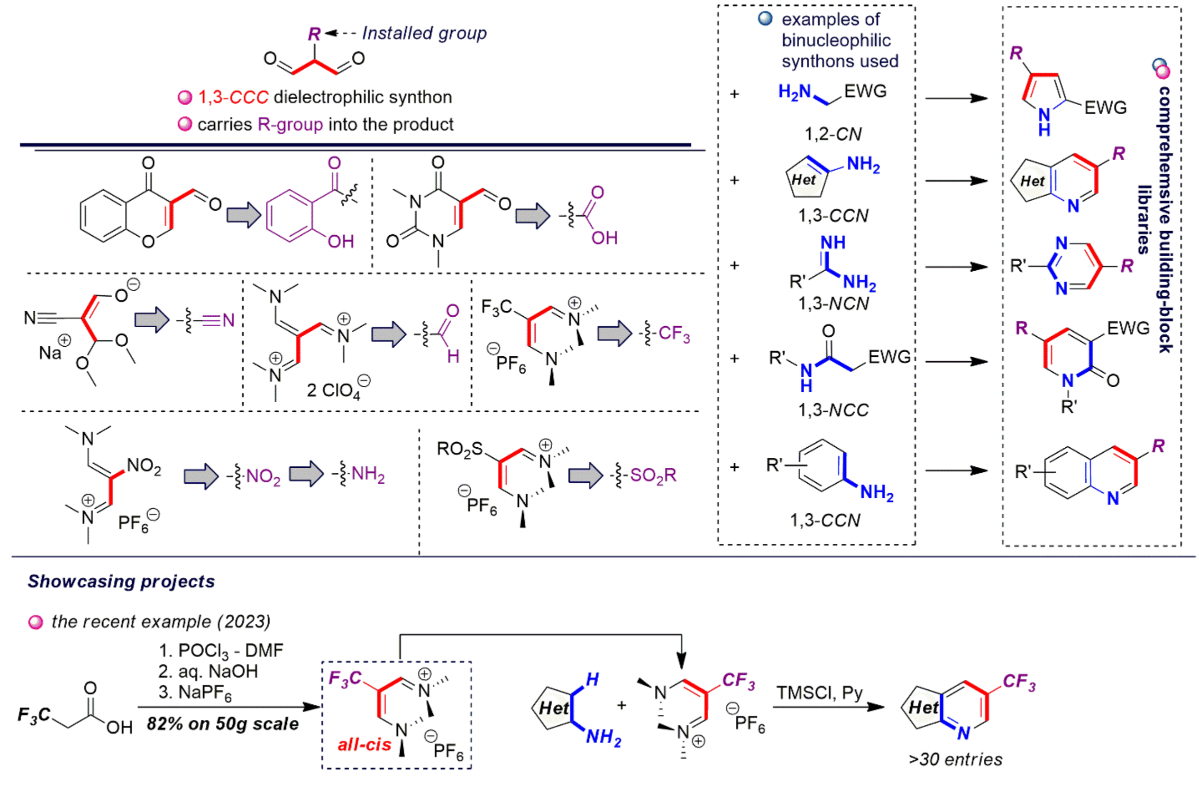
1,3-CCC dielectrophile moiety, which can formally be regarded as a masked malondialdehyde-derived portion, is a well-established and versatile synthon with enormous synthetic power. Its recognition within organic frameworks and careful selection of binucleophilic partners provides a convenient instrument for the construction of various 5- and 6-membered heterocyclic systems. Herein we outline the development of ideas related to the application of frameworks with incorporated malondialdehyde moiety in heterocyclization reactions and share the experience gained from working with them in our labs. The reported period covers 20 years and proceeds from the first our object formylchromones to a recent example of trifluoromethylvinamidinium salt (**Scheme 1**). Apart from the construction of a heterocyclic core, the methodology enables installing demanded functionalities, e.g. CO_2H, CHO, CN, NO_2, NH_2, SO_2Cl and CF_3 groups. In the report, we will discuss crucial for these interactions regarding regioselectivity issues, scope and limitations of the cyclizations as well as touch on the scalability of the elaborated protocols. For representative examples of our works on the topic see ref. 1(a-e).



Scheme 1: Outline of the investigations involved malondialdehyde masked scaffolds.

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Beyond the noble-metal-contained catalytic systems - solutions for Pd-crisis

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Hydrogenation of unsaturated organic compounds is one of the most demanded processes both in large-scale chemical production (synthesis of components of motor fuels and oils, solvents, compounds for the preparation of dyes, as well as in the food industry) and in the fine organic synthesis (preparation of active substances for pharmaceuticals and agrochemistry). At present, the most active hydrogenation catalysts used in industry are based on platinum metals, first of all palladium. Raney nickel or similar systems are used as an alternative to platinum metals, but their catalytic activity and selectivity are usually not high enough for the complete replacement of palladium. However, the cost of palladium increased more than 8 times in the last 10 years, which was one of the main reasons for the so-called "palladium crisis". In addition, the toxicity of platinum metal compounds gives rise to the need for thorough purification of hydrogenation products, especially the ones consumed in pharma and agrochemistry.

In this report, we present the results of the development of nanosized palladium and nickel-containing composites, which were used in experimental production processes at Ukrainian enterprises Enamine Ltd. and UORSY Ltd. for the heterogeneous catalytic hydrogenation of organic compounds on a laboratory and semi-industrial scale.

The catalysts were developed taking in mind two possibilities. The content of platinum metals can be significantly reduced due to (i) deposition of nanoparticles possessing higher catalytic activity, with a capacity of re-used. The catalysts based on 3D metals (Ni and Co), compounds of Mo, Re and others, which have catalytic activity comparable to Pd but lower cost, can be created. Simple and efficient approaches to the creation of composites of Pd or 3D metal nanoparticles with porous carriers were proposed, based on thermolysis of the complexes of Pd0, Ni0 (such as Pd2(dba)3, Ni(Cod)2, where dba = dibenzoylacetone, COD = cis,cis-1,5-cyclooctadiene), Co^{II} complexes with 1,2-diaminobenzene, 1,10-phenantroline, melamine. The composites showed high catalytic performance in the processes of hydrogenation of a wide range of unsaturated organic compounds (alkenes, alkynes, nitro compounds, carbonyl compounds, heterocyclic compounds of various structures), amination of carbonyl compounds with amines and acetonitrile. Notably, the catalytic performance of the Pd-based composites in the processes of hydrogenation of organic compounds was an order of magnitude higher than those for commercially available analogues, allowing to reduce palladium consumption significantly in the processes of hydrogenation. The methods for scale up of the Pd-based composites in up to 200 g batches were developed.

Hydrogenation of halogen-containing N- and S-containing heterocycles in the presence of Re-based composites could be performed with high selectivity, and the halogen atom could be preserved in the aromatic core, opening up a unique possibility to obtain halogen-containing saturated heterocyclic compounds.

All these achievements as well as statistics of using the catalysts in our laboratories last 3 years, comparison analysis, scale-up and perspectives of reusing and recycling will be discussed in the report.

Evaluation of Potential Small and Macromolecular Anti-SARS-CoV-2 Agents

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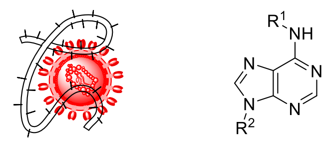
Since early 2020, SARS-CoV-2 pandemic has affected a majority of the world forcing unprecedented measures of public health safety.[1] On the other hand, it has attracted the brightest scientific minds and has mobilized resources to battle the infection. While big pharma companies have delivered innovative vaccines that helped containing the pandemic by activation of immune response, consortia of research institutes devoted efforts in determining the detailed structure and mode of action of the virus to deliver tailored anti-viral agents that would stop the infection/transmission.[2] It is known that polyanionic macromolecules, such as sulfated polysaccharides, can inhibit viral infection by binding to virus in a similar manner as the cell membrane anionic saccharides, eg. heparan sulfate or sialic acid.[3] Such a non-specific inhibition is a prospective mode of action for developing topical antiviral formulations based on natural components. At the same time, small molecules, such as nucleosides, are well known therapeutics for fast-progressing deseases. By combining our expertise in isolation of natural polysaccharides and in synthetic organic chemistry, we have investigated a potential for battling the virus (Figure 1). A library of prospective nucleosides and serine adenosylmethionine (SAM) analogues was subjected to molecular docking studies to identify hit compounds with competing or allosteric binding to SAM-dependent 2'-O-methyl transferases. Some selected compounds were subjected to enzyme inhibitory assays to evaluate their efficiency.

At the same time, various sulfated carbohydrates such as natural or chemically modified galactans (carrageenans and furcellaran) isolated from algae abundant in the Baltic sea or polysaccharides produced in an enzymatic synthesis were tested for antiviral activity employing nanoluciferase assays. Synergistic effect of various combinations with known antivirals was also studied.



Polysaccharides for antiviral formulations

Small molecule antivirals

Figure 1: Schematic depiction of studied antivirals.

Acknowledgements: We thank the Estonian Research Council grant COVSG7 and Latvian Research Council grant VPP-COVID-2020/1-0014 for financial support.

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EnTdecker: Predicting excited state properties of organic molecules to accelerate substrate discovery for energy transfer catalysis

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Energy transfer (EnT) catalysis is a powerful synthetic strategy to enable valuable transformations under mild conditions.[1] Machine-learning approaches have the potential to expedite the discovery of novel substrates for EnT catalysis by enabling a rapid exploration of the compound space based on excited state properties. Accurate predictions for diverse chemical structures, however, require high-quality data on which such models can be trained on. To achieve this, a dataset is created that is unique in its chemical diversity in order to cover a vast fraction of synthetically relevant compound space for EnT catalysis. Using this dataset, predictive models are trained to obtain valuable excited state properties, e.g., the triplet energy as well as the spin density distribution, which help to assess a molecules suitability for EnT catalysis.[2] The models predictive performances and their ability to generalise are investigated and found to be suitable for in-lab applications. This is further demonstrated by rediscovering successful substrates from literature as well as experimental validation through luminescence-based screening (Figure 1). By reducing the computational effort for the determination of excited state properties by four orders of magnitude compared to quantum mechanical calculations, the presented framework represents a tool to guide substrate selection and increase the experimental success rate for EnT catalysis.

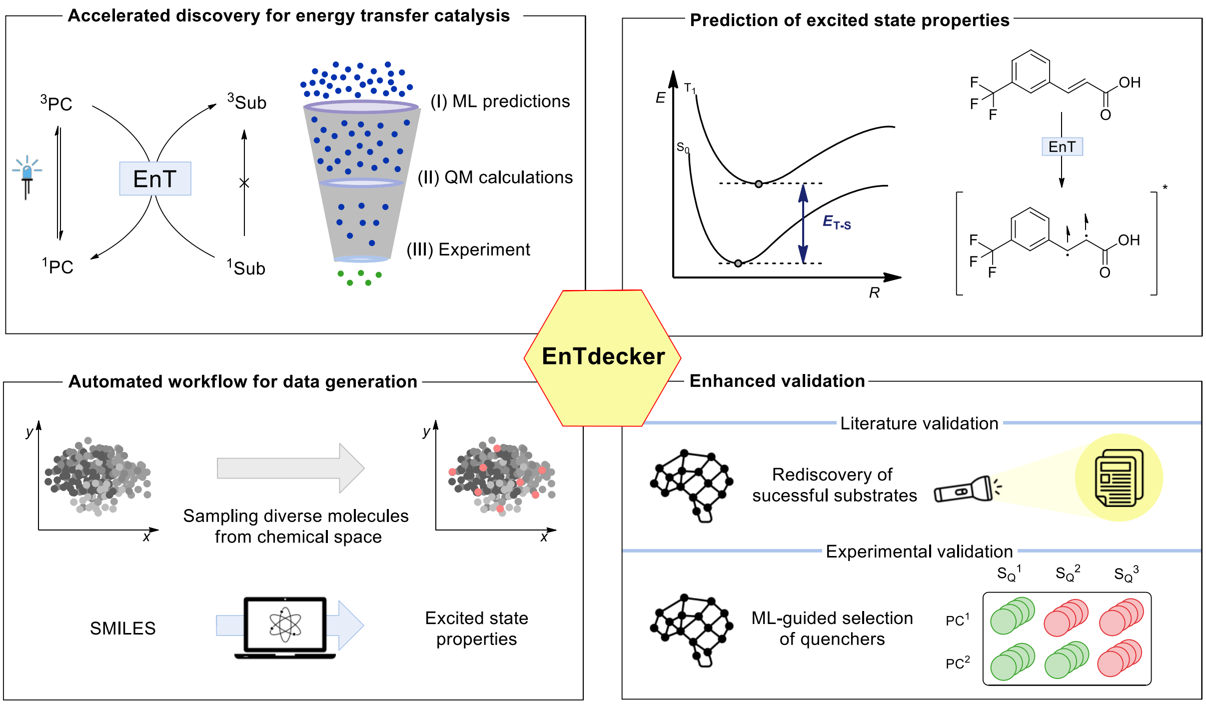

Figure 1: Schematic overview of the EnTdecker framework to accelerate the discovery of substrates for EnT catalysis.

Acknowledgements: We thank the Deutsche Forschungsgemeinschaft (SPP 2363) for financial support.

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C-H Amination of Pentacyclic Triterpenoids

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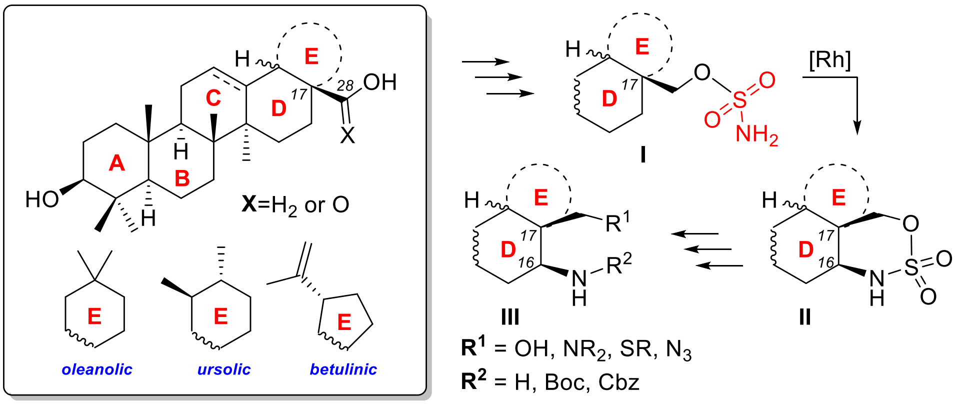
Betulin, erythrodiol and uvaol are naturally occurring secondary metabolites found in various plants. These pentacyclic triterpenoids and their semi-synthetic derivatives demonstrate significant pharmacological properties, including anti-tumor, anti-inflammatory, antiparasitic, and anti-viral activities.[1] The aim of this research is to establish a synthetic method for the unexplored introduction of amino functionality at the C(16) position of triterpenoid scaffold.



Scheme 1. C-H amination of pentacyclic triterpenoids

For this purpose, precursors **I** bearing sulfamate ester moiety were obtained, and converted to oxathiazinanes **II** *via* Du Bois γ-C(sp3)-H bond amination (Sheme 1).[2] Key intermediates **II** are further converted into variously functionalized compounds **III** through the ring opening reactions (X=N_3,OSO_3H,. *etc*.). The target products are expected to posses better water solubility and thus bioavailability.

Acknowledgements: This work has been supported by the State Research Program of Latvia ”BioMedPharm”. V.K. thanks European Social Fund within the project 8.2.2.0/20/I/008 and Riga Technical University.

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Catalytic Disconnection of C–O Bonds in Epoxy Resins and Composites

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Fiber-reinforced epoxy composites are well established for load bearing applications in the aerospace, automotive and wind power industries, due to their light weight and high durability. These composites are based on thermoset resins, consisting of s bond linkages and aromatic backbones, embedding glass or carbon fibers. *In lieu* of viable recycling strategies, end-of-use composite-based structures such as wind turbine blades are commonly landfilled. Due to the negative environmental impact of plastic waste, the need for circular economies of plastics has become pressing. However, recycling thermoset plastics is not trivial. Here, we present a transition metal catalysed protocol for recovering the base chemical bisphenol A and fibers from thermoset epoxy resins. Our approach is based on disconnecting C(alkyl)–O bonds of the most common linkages of the polymer, using a ruthenium-catalysed dehydrogenation/bond cleavage/reduction cascade. We showcase the application of this methodology to relevant unmodified amine-cured epoxy resins as well as commercial composites (Figure 1), including the shell of a wind turbine blade. The high quality of the recovered fibers was confirmed using X-ray micro-computed tomography, X-ray photoelectron spectroscopy and scanning electron microscopy. Our results demonstrate that chemical recycling approaches for thermoset epoxy resins and composites are achievable.[1]

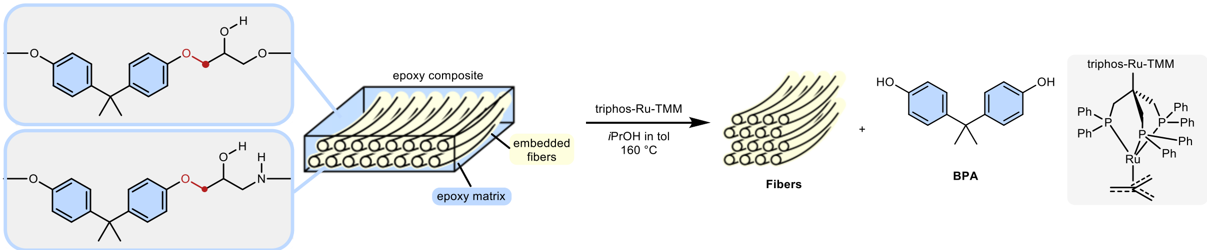

Figure 1: Disconnection of C–O bonds in epoxy composites using ruthenium catalysis.

Acknowledgements: We thank the Innovation Fund Denmark, Carlsberg Foundation, Danish National Research Foundation, Novo Nordisk Foundation for financial support.

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Borylative Transition-Metal Free Cross Couplings with Vinyl Iodides

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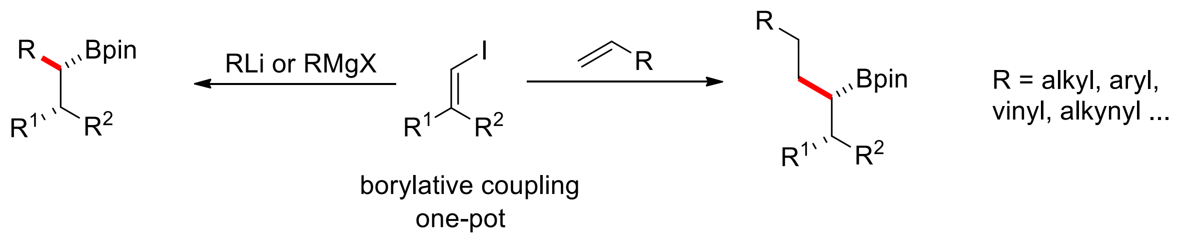
Alkyl boronic esters are highly valuable compounds in organic chemistry and related fields due to their good stability and highly versatile reactivity. In this work, stereoselective borylative cross coupling of vinyl iodides either with organolithium compounds or Grignard reagents or with alkenes is reported. These coupling reactions proceed via stereospecific hydroboration[1] and subsequent stereoselective 1,2-metallate rearrangement.[2] The cascades utilize readily available reagents and proceed without the need of a transition metal catalyst (**Scheme 1**).



Scheme 1: Borylative coupling of vinyl iodides with organolithiums, grignard reagents or alkenes.

Acknowledgements: This work was supported by the Fonds der Chemischen Industrie (doctoral fellowship to G.S.), the European Research Council ERC (advanced grant agreement No. 692640) and the International Research Training Group IRTG 2678 funded by the Deutsche Forschungsgemeinschaft DFG.

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An efficient alcoholysis of primary amides

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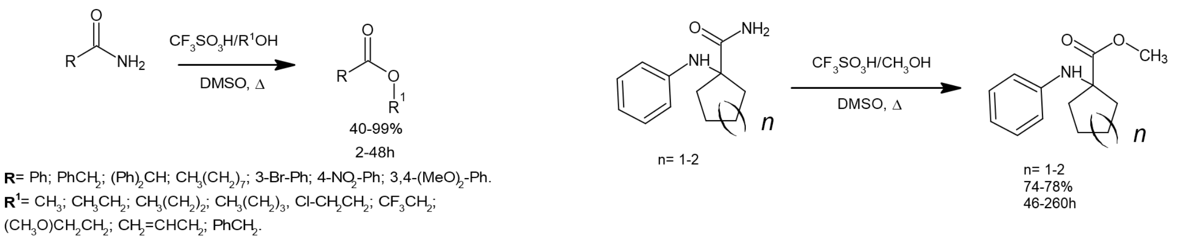
Synthesis of esters is usually performed via acylation of alcohols and phenols by carboxylic acids, acid anhydrides or via alkylation of carboxylates.[1] Conversion of amides to esters is much less common. Nevertheless, synthesis of complex compounds bearing an ester funcional group often proceeds via nitriles or amides and is rather complex and challenging. Recently we have reported a convenient conversion of α-aminoamide to the corresponding methyl ester in the presence of trifluoromethanesulfonic acid (TfOH) and DMSO additive in 65% yield. [2] Further, the initial methanolysis reaction was optimized using benzamide and methanol as the substrates and the optimal conditions were applied to alcoholysis of various primary amides bearing different functional groups (alkyl-, arylalkyl-, branched arylalkyl-, nitro-, bromo- and methoxy), 2 α-aminoamides containing C5-C6 cyclic aliphatic moieties and one more complex primary amide bearing an aryl-alkyl ether and a cyclic tertiary amide group. C1-C4 primary alcohols, benzyl and allyl alcohols, as well as 2-chloro-, 2-methoxy- and 2,2,2-trifluoroethanol were used as a reaction media (**Scheme**) in the presence of DMSO. [3]



Scheme: Alcoholysis of primary amides in the presence of TfOH.

Substrate structure and boiling point of the reaction media had a great effect on the reaction speed. The observed times of reaction were consistent with typical steric and electronic effects on the electrophilicity of the carbonyl group and temperature effect on reaction kinetics. Attempt to perform benzamide alcoholysis in benzyl alcohol resulted in complex mixture containing dibenzyl ether. Alcoholysis of benzamide in 2,2,2-trifluoroethanol was completely unsuccessful. Cycloxehyl substituted α-aminoamide demonstrated the longest reaction time extending up to 260 h. Methanolysis of a more complex primary amide bearing an aryl-alkyl ether and a cyclic tertiary amide moiety demonstrated selective reactivity of the primary amide group. To sum up, we have developed and optimized a universal, reliable, robust and selective method for converting primary amides to esters in the presence of several functional groups.

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Synthesis of Phosphonate Derivatives of Pentacyclic Triterpenoids

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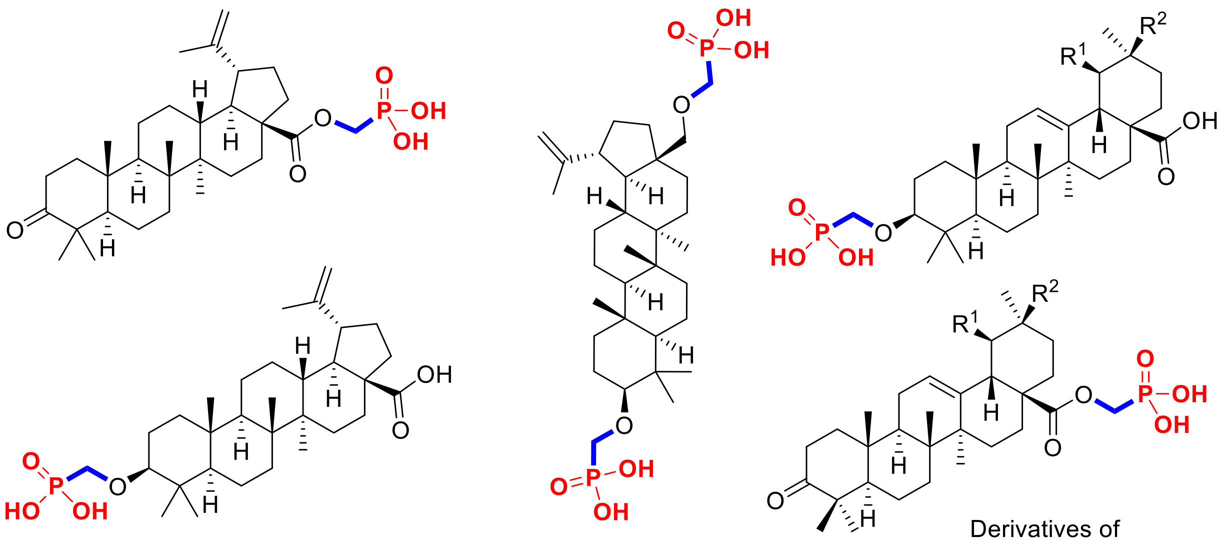
Natural pentacyclic triterpenoids are important secondary metabolites which have attracted interest due to the wide range of their biological activities such as antitumor[1] antidiabetic[2] anti-inflammatory[3] and antiviral activities[4]. Betulin and betulinic, oleanolic, ursolic acids are the most recognizable compounds of this branch, which are isolated from various plants. However, the medicinal application of these natural products are hindered by their extremely low water solubility and thus – low bioavailability.[5] One option to overcome this limitation is introduction of polar anionic functional groups such as phosphates and sulfates, which, however, are prone to hydrolysis.

Here we describe the synthesis of novel anionic triterpenoid phosphonates, which bear methylene-bridged phosphonate side chains. The latter are suitable for both the enhanced water solubility and complexing / salt formation with metal ions like Ca^{2+}, which is important for their further applications as bioactive additives to various calcium phosphate-based biomaterials.



Betulinic acid derivatives

Betulin derivative

Derivatives of
Oleanolic acid: R^1=H, R^2=Me
Ursolic acid: R^1=Me, R^2=H

Acknowledgements: This work has been supported by the State Research Program of Latvia "BioMedPharm". V.K. thanks European Social Fund within the project 8.2.2.0/20/I/008 and Riga Technical University.

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Mild and Operationally Simple Transformation of Boronic Esters to Amines

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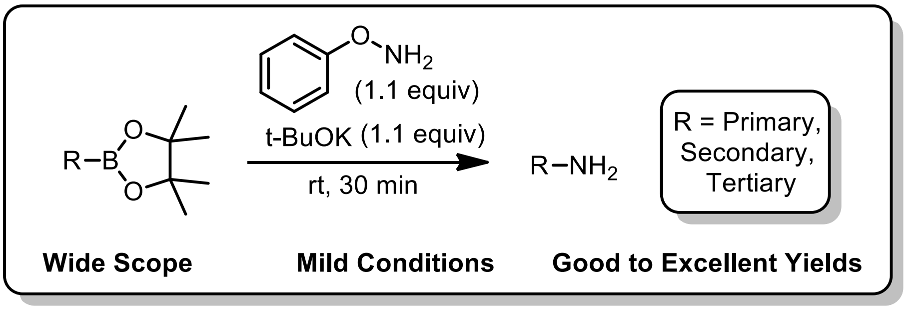
Despite the ubiquity of amines, they are difficult groups to carry through extended synthesis requiring protection and deprotection. Late-stage functional group interconversion to amines is an appealing solution and boronic esters are ideal precursors. Boronic esters can be installed stereoselectivity and transformed with retention or inversion of stereochemistry and are therefore an ideal starting material.[1] The transformation has as of yet required high temperatures and extended reaction times.[2,3] Herein, we report a novel aminating reagent, phenoxyamine, for the transformation of primary, secondary, tertiary, and aromatic boronic esters under room temperature and short reaction times with improved yields and wider scope. (Scheme 1).



Scheme 1: Mild and Operanationally imple conversion of boronic esters to amines

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Towards the Total Synthesis of Mycapolyol E

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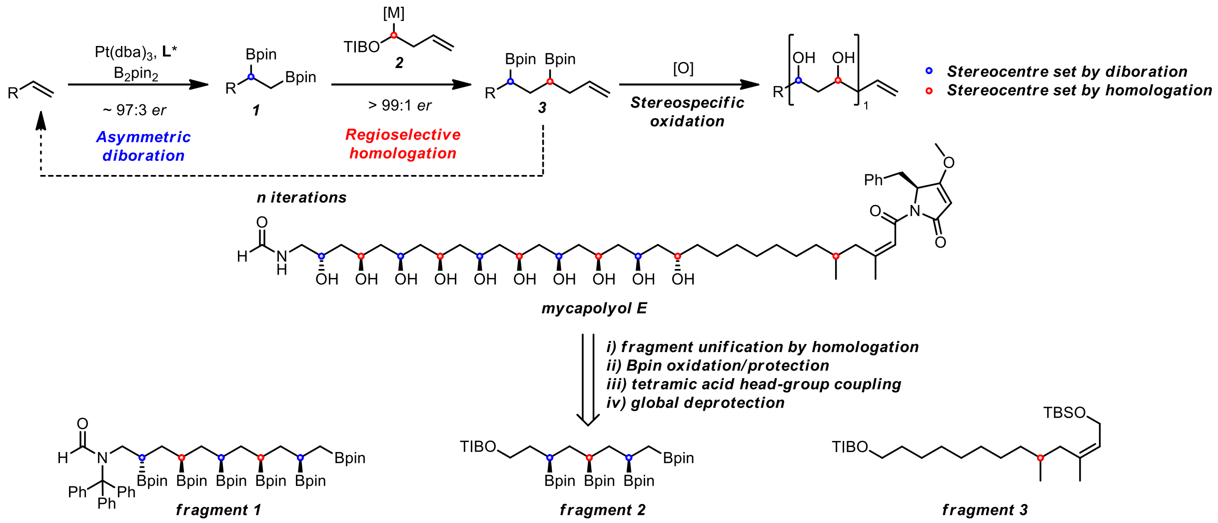

Polyketides are arguably the most important class of natural products, given their extensive application as small-molecule drugs. Due to their assembly-line like biosynthesis from small repeating building blocks, these compounds often possess repeating motifs. This is true for polyacetates, a sub-class of polyketides, which display repeating 1,3-hydroxyl stereocentres.

Our research group recently reported a two-step iterative strategy for the rapid synthesis of stereodefined 1,3-polyol motifs. This strategy harnesses asymmetric diboration of terminal alkenes, furnishing an enantioenriched 1,2-bis boronic ester **1**. This is then followed by a regioselective homologation of the primary boronic ester with enantiopure metal carbenoid **2**, yielding an enantioenriched 1,3-bis boronic ester **3**, which bears a terminal alkene primed for subsequent iterations. Finally, stereospecific oxidation of the enantioenriched polyboronic ester provides the desired 1,3-polyol motif.

We now aim to apply this methodology towards the first total synthesis of Mycapolyol E, a member of a family of polyketide metabolites which display cytotoxicity towards HeLa cell. These compounds bear 9-14 contiguous, stereodefined, skipped hydroxyl groups and are flanked by a tetramic acid derived and formamide head groups.

Our retrosynthetic analysis of Mycapolyol E disconnects to three fragments of equal complexity, of which two would utilise our iterative strategy to set the 1,3-polyol stereocentres. The synthesis of these fragments, and their unification by regioselective homologation of primary boronic esters, has now been optimised. All that remains to complete the first synthesis of any member of the Mycapolyol family is downstream manipulations to install the tetramic acid derived head-group, where our efforts are currently focused.

Acknowledgements: DR thanks VKA for his continued support and guidance and to the EPSRC sponsored TECS CDT and Vertex Pharmaceuticals for a PhD studentship.

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Reductive depolymerization of polyester and polycarbonate plastic waste catalyzed homogeneous and heterogeneous manganese catalysts

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The sustainable production of value-added compounds and the protection of the environment and public health are two very important concerns that both academia and industry are facing. Nowadays, one of the biggest pollution concerns is related to the huge amount of plastic waste that is generated around the world. Plastic waste represents not only a global pollution problem, but also a carbon-rich, low-cost, globally available feedstock. In this context, the conversion of plastic waste into value-added compounds is an extremely important research area.

The development of methodologies for the reductive depolymerization of polyester plastic waste using inexpensive catalysts based on an earth-abundant metal would be an important advancement in achieving the requirements of an ecologically and economically benign process.

Manganese, as the third richest transition metal in the Earth's crust, is cheap and less toxic, has been applied as a catalyst in a variety of organic reduction. In continuation of our work,[1] in this communication we report the depolymerization of plastic waste into valuable compounds using commercially available homogeneous and heterogeneous manganese catalysts with good to excellent yields (Fig. 1).

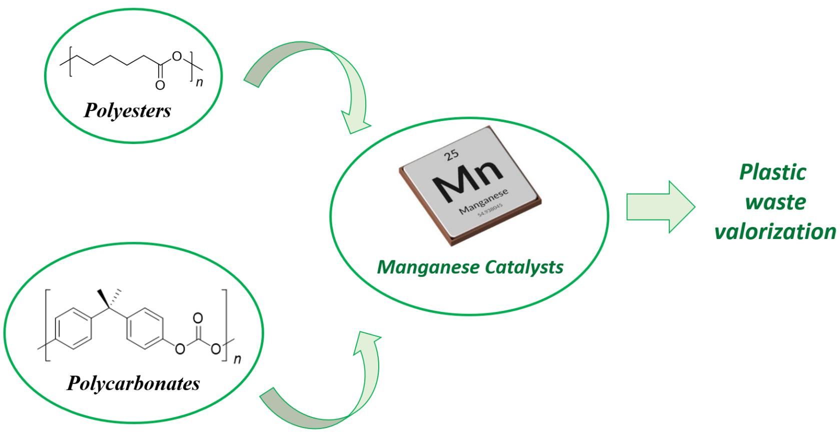

Figure 1: Reductive depolymerization of plastic waste catalyzed by manganese compounds.

Acknowledgements: This research was supported by Fundação para a Ciência e Tecnologia (FCT) through projects PTDC/QUI-QOR/0490/2020, UIDB/00100/2020, UIDP/00100/2020 and LA/P/0056/2020. DLL thanks to FCT for the grant.

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New Synthetic Pathway to 7-Arylpurines from Substituted Pyrimidines

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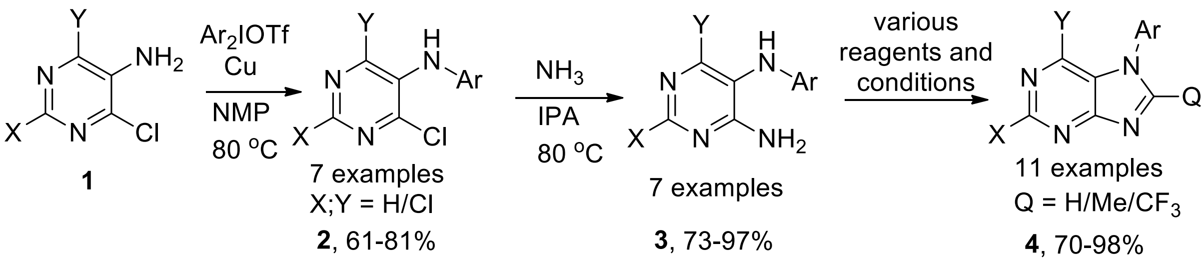
The *N*(9) position of the purine ring is the most reactive for alkylation and arylation reactions. Some synthetic methods for introduction of alkyl substituents at *N*(7) position exist,[1] however direct *N*(7) arylation is more complicated. Often for purines utilized Cu catalyzed Chan-Lam reaction[2] and arylation with iodanes[3] yield only *N*(9) substituted products. There are few methods that result in arylation mostly at purine *N*(7) position, however *N*(9) arylated byproduct also forms and these methods are substrate dependent,[4] so we have developed a new efficient approach starting from substituted pyrimidines.

The optimal synthetic pathway involves transformations starting from pyrimidine derivative **1**: Amino group was arylated in a Cu catalyzed reaction and yielded 5-arylaminosubstituted pyrimidines **2**. S_NAr reaction with ammonia at 80 °C proceeded with only one of the chlorine atoms and yielded compounds **3**. Final step was a ring closing reaction with orthoester under acidic conditions that yielded compounds **4**. Variously substituted 7-arylpurines were prepared by utilizing different pyrimidine starting materials, diaryliodanes and ring closing reagents.[5]



Scheme 1: *De novo* synthetic pathway to 7-arylpurines.

Acknowledgements: This work was supported by the Latvian Council of Science grant No. LZP-2020/1-0348.

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Rhodium-Catalysed Cross Coupling of Azetines

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Azetidines are of interest to both synthetic and medicinal chemists, appearing in natural products and biologically active molecules and finding use as bioisosteres, synthetic intermediates and in catalysis[1]. However their synthesis is underexplored and routes to substituted azetidines are few and often limited in scope.

The Fletcher group has previously demonstrated a rhodium-catalysed sp^2-sp^3 coupling of cyclobutenes with arylboronic acids to form substituted cyclobutanes[2] (see **Figure 1**).

This work extends the reaction to the coupling of 2-azetine substrates, giving substituted azetidine products. It is shown that the identity of the nitrogen protecting group in the azetine substrate affects the reaction's regioselectivity, giving preference for arylation at either the 2 or 3 position (see **Figure 2**). Using an N-benzoyl protecting group the reaction is optimised to give 3-substituted azetidine products (see **Figure 3**).

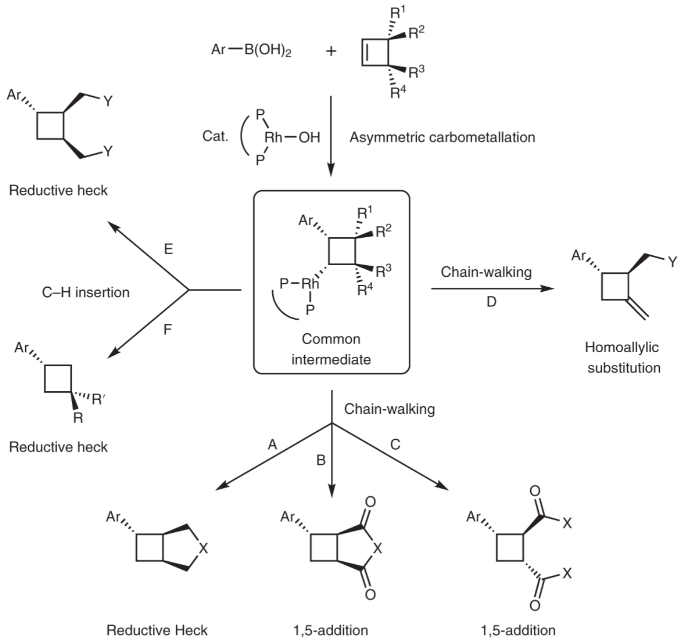

Figure 1: Previous work by the Fletcher group, figure from reference 2.

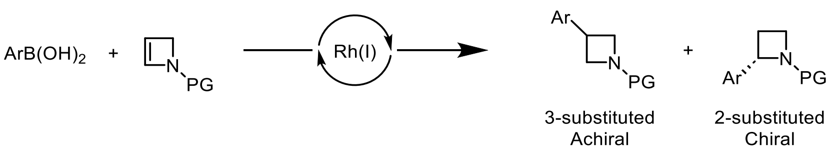

Figure 2: General reaction scheme for the Rh-catalysed coupling of 2-azetines

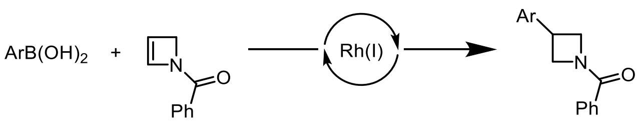

Figure 3: Reaction scheme for Rh-catalysed cross-coupling of N-benzoyl protected azetine substrates

Acknowledgements: MRJ thanks the ESPRC and GSK for financial support

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Sulphur-Resistant Ruthenium Catalyst for the Hydrogenation of N-Heteroarenes

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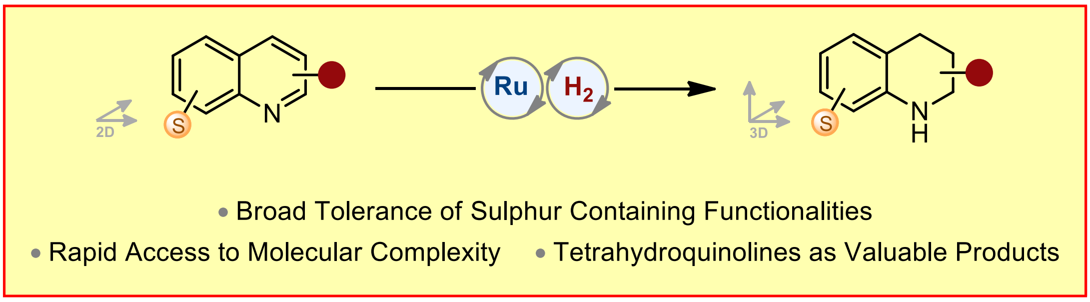
Sulphur is next to oxygen and nitrogen one of the most important heteroatoms in nature and ubiquitous in a plethora of natural products.[1] Due to its many different oxidation states and functionalities it is especially essential for medicinal chemistry or drug discovery, serving as a hydrogen bond donor/acceptor or as a polarity handle.[2] However, its free electron pairs render sulphur as very Lewis basic and therefore poisoning catalysts, in particular heterogeneous ones.[3] The resistance of heterogeneous catalysts to sulphur poisoning has been seldomly demonstrated in hydrogenation or other catalytic processes.[4] Herein, we present a novel heterogeneous Ru-W-S catalyst that tolerates various sulphur functionalities in the hydrogenation of N-heteroarenes. The utility of the products was further demonstrated by subsequent diversifications of the sulphur functionalities.



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Acknowledgements: Generous financial support by the European Research Council (ERC Advanced Grant Agreement No. 788558) and the Alfried Krupp von Bohlen und Halbach Foundation are gratefully acknowledged.

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Synthesis of chiral *N*-heterocyclic carbene-transition metal complexes *via* transmetalation of their respective silver complexes.

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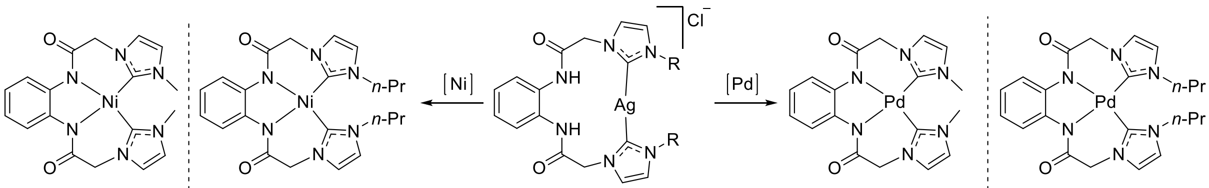
Chiral *N*-heterocyclic carbene (NHC) transition metal complexes have emerged as valuable tools in asymmetric catalysis. NHCs are strong σ-donor ligands that can form stable complexes with transition metals. Chiral NHC-metal complexes have been successfully applied in a variety of catalytic processes, including cross-coupling reactions, asymmetric hydrogenations, C-H activations, and cycloadditions, among others. These complexes offer a versatile platform for accessing a wide range of chiral compounds, making them valuable in synthetic chemistry and the production of pharmaceuticals and fine chemicals. The design and development of novel chiral NHC-metal complexes continue to be an active area of research, aiming to expand the scope of asymmetric transformations and advance the field of catalysis.[1a,b] Recently, our group has developed a novel chelating Ag-NHC complex containing a bisamide moiety in its backbone.[2] From the organometallic point of view, Ag-NHCs complexes have been recognized as effective carbene group transfer agents.[3] Herein such transmetalating properties were used to synthesize NHC complexes of other transition metals, including nickel **2a** and palladium **3a**, which had previously failed to be synthesized.[4] Both complexes exhibited axial chirality due to the coordination of the ligand to the metal center in a helical manner and were both analysed in solid and liquid state. Furthermore, DFT calculations were performed to better understand the transition state of the configurational flip and energy barrier of such transition state. The scope was extended with the synthesis of nickel complex **2b** and palladium complex **3b** containing a bigger side chain on the imidazole moiety. These two complexes proved to be configurationally more stable than their previous analogues.



Scheme 1: Transmetalation of the silver complexes (**1**) to their correspondence nickel (**2**) and palladium complexes (**3**).

Acknowledgments: We thank the Charles University Primus program (PRIMUS/20/SCI/017) for financial support.

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Electrochemical oxidation of glycerol on bimetallic-zeolite modified electrodes

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Zeolites with a hierarchical structure are different from the as-synthesised zeolite structures due to their secondary mesoporous network, which can be either inter- or intra-crystalline. This unique feature facilitates mass transfer and enhances access to the active acid sites [1]. In this study, the use of zeolite, hierarchical zeolites, bimetallic-zeolite modified electrodes based on Carbon Toray in aqueous media at different pH were investigated for the electrochemical oxidation of glycerol. Glycerol is a by-product of biodiesel production that can be utilized as raw material for the synthesis of other valuable chemicals. The oxidation of glycerol is a highly interesting process due to the presence of three distinct alcoholic functions, which enables the production of a wide range of oxidized products (Figure 1) [2]. The electrochemical stability of the bimetallic-zeolite modified electrodes was verified by cyclic voltammetry studies. Cyclic voltammograms show different oxidation processes, which confirm the occurrence of interactions between glycerol and the catalyst surface necessary for the direct oxidation reactions. Multiple studies, including our previous works, reported that metal-zeolite modified electrodes exhibit excellent mechanical and chemical stability, with no observed leaching of the metal phase [3]. The structural differences between the zeolites and hierarchical zeolites enhance different catalytic behaviour in the electrolyses of the glycerol oxidation.

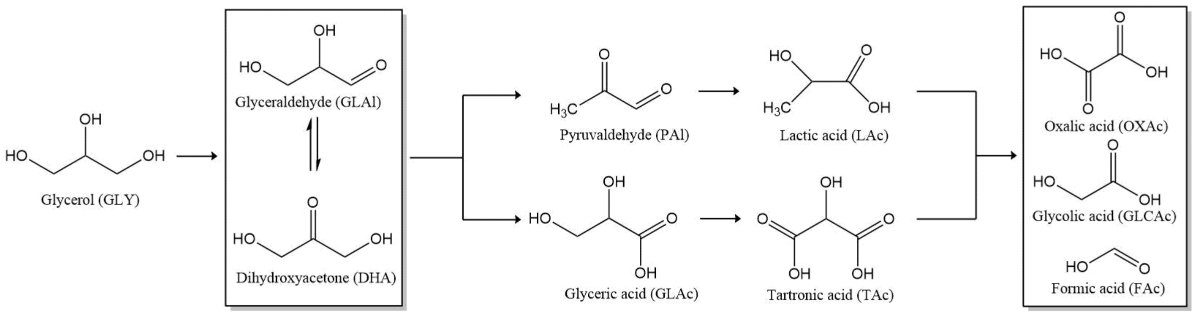

Figure 1: Simplified scheme for glycerol oxidation [2].

Acknowledgements: We thank the Fundação para a Ciência e Tecnolgia for financial support by the projects CQE(UIDB/00100/2020. UIDP/00100/2020) and IMM (LA/P/0056/2020), Centre of Chemistry (UID/QUI/0686/2020), CEB (UIDB/04469/2020) and LABBELS (LA/P/0029/2020).

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Fenton-like catalysts based on Mn-zeolites obtained by chemical and mechanochemical methods for health applications

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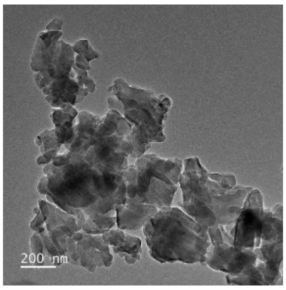
The use of inorganic nanoparticles without toxicity as Fenton heterogeneous catalysts for health applications is appealing as it can take advantage of *in situ* conditions of some pathologies, such as mild acidity and the overproduction of hydrogen peroxide (H_2O_2) in cancer [1]. This study focuses on the development of modified Mn-zeolite nanoparticles as Fenton-like catalysts for health applications. The zeolite nanoparticles present a high chemical and thermal stability in biological environments making them good candidates for medical applications [2,3]. Chemical and mechanochemical methods were used to modify ZSM-5 and BEA zeolites to obtain catalysts with controlled particle size and texture while maintaining their crystal structure. ZSM5 and BEA are two distinct commercial zeolites that have varying average particle sizes where BEA present the smallest average size of 20 nm, which form large aggregates (Figure 1). ZSM5 zeolite comprises of irregular particles, including large aggregates, medium-sized and small particles. In the case of this structure, mechanochemical treatments, with frequencies of 10 Hz during 10 or 5 min allowed to reduce the size of aggregates when compared to the starting material (Figure 2). The characterization data indicated that the modified zeolite nanoparticles retained their crystal structure but showed some textural changes. To evaluate the catalytic behaviour of metal-ion loaded with Mn^{2+}, the Fenton-like reaction was performed using mild acidic and physiological conditions (pH 6.4 and 7.4, 37 ºC and 50 µM H_2O_2). The MnBEA series exhibited the most favourable results in Fenton-like reactions, demonstrating the immense potential of metal-zeolite nanomaterials in health-related applications. Preliminary results in cancer cell lines (melanoma and lung) show promising cytotoxic activity.



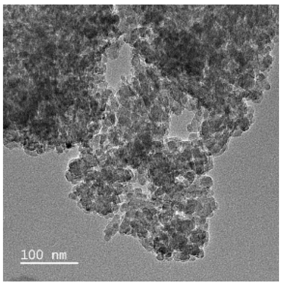


Figure 1: TEM images of pristine zeolites: ZSM5 (left) and BEA (right)

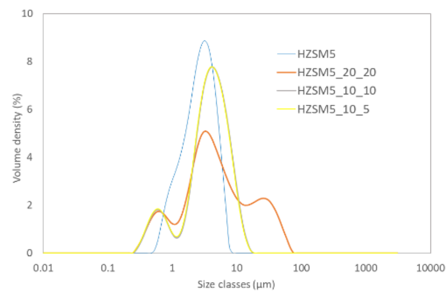


Figure 2: Particle size distribution (HZSM5_Freq_time)

Acknowledgements: V.I. and A.R.B. thank for the PhD grant, UI/BD/152219/2021 and SFRH/BD/141058/2018, respectively. ASM thanks FCT for the Assistant Researcher contract CEECIND/01371/2017 (Embrace Project). This work was supported by FCT by the projects: UIDB/00100/2020. UIDP/00100/2020 and LA/P/0056/2020, CQ/UM (UID/QUI/0686/2020), CEB (UIDB/04469/2020) and LABBELS (LA/P/0029/2020), and Instituto Politécnico de Lisboa (IPL) through Project IPL/2022/ZeoMed ISEL.

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Solvent-controlled regioselectivity of alkenes addition to β-dicarbonyl compounds

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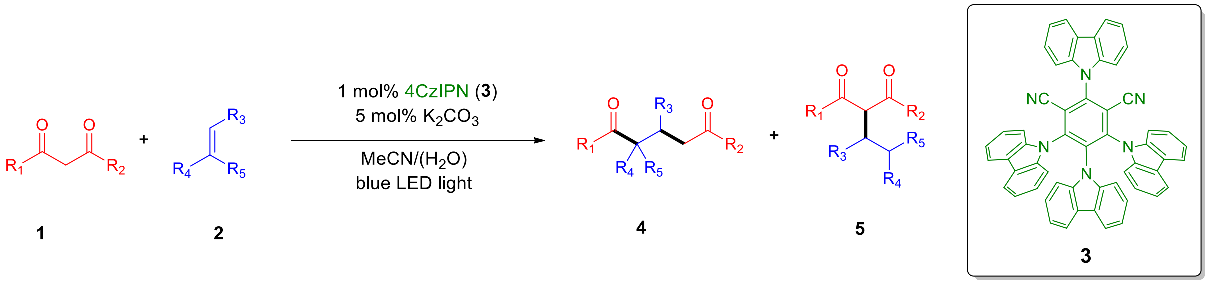
Photocatalysis, especially its version incorporating visible light, is a field of chemistry that has attracted a lot of attention in recent years. Its increasing popularity is caused by the possibility of performing reactions that meet the requirements of Green Chemistry, aimed at reducing the harmful effects of chemistry on the environment and applying milder and sometimes less expensive reaction conditions.[1] This approach was recently implemented in a number of publications describing methods for C-C bond formation between molecules with activated CH_2 group and olefins.[2]

In this work, the reaction of alkenes with β-dicarbonyl compounds catalyzed by an organic photocatalyst - 4CzIPN induced by visible light, was studied (**Scheme 1**). In the developed methodology, depending on the reaction conditions, in particular, the presence/absence of water in the reaction mixture, a variable preference was observed for the formation of de Mayo reaction type products (**4**) or radical addition to the double bond products (**5**). The impact of different factors and parameters on the yield and selectivity of the obtained compounds (**4** or **5**) was examined, and optimal conditions that provide the best regioselectivity of the process were determined. Screening of the substrates scope including various alkenes, esters, and diketones were performed and the mechanistic aspects affecting the observed results were analyzed.



Scheme 1: Reaction of alkenes with β-dicarbonyl compounds catalyzed by 4CzIPN.

Acknowledgements: The research has been supported by a grant from the Priority Research Area Anthropocene under the Strategic Programme Excellence Initiative at Jagiellonian University.

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Rhodium Catalysed Deconstruction of Epoxy Resin in Water

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Thermoset epoxy resins and their fibre reinforced composites have excellent resistances to chemical exposure and mechanical stress. Therefore these materials have become crucial for demanding applications, such as coatings and laminations, construction of air planes and wind turbines, as well as manufacturing of sporting goods. In general, epoxy polymers are applied for structures designed to last, with the flipside, that deconstruction and recycling strategies are highly challenging, and thus underdeveloped.[1] In order to achieve cirular economies for plastics, which reduce waste accummulation as well as resource consumption, efficient depolymerisation strategies are necessary. In order to achieve sustainability, these strategies must adhere to the principles of green chemistry, such as atom efficiency and the use of green solvents.[2] For the valorisation of lignin, terpy-Rh complexes have been shown to be efficient depolymerisation catalyst in water.[3]

Here, we present a rhodium catalysed approach to selectively cleaving $C_{(Alkyl)}$–O bonds in thermoset epoxy resins in mild conditions with water as sole solvent. The reactivity was investigated on model compounds mimicking the linkages of epoxy polymers (Figure 1). Furthermore, we demonstrate the recovery of the polymer building block bisphenol A from commercial and widely used thermoset epoxy polymers and show preliminary mechanistic studies on the rhodium catalysis. The method is based on an alcohol dehydrogenation coupled to a C-O bond activation.

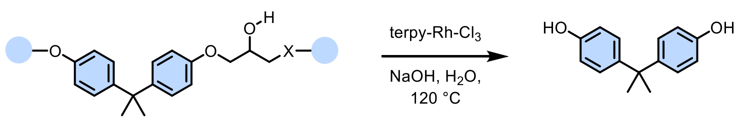

Figure 1: Terpy-Rh catalysed C-O bond disconnection of epoxy motifs in water.

Acknowledgements: We thank the Innovation Fund Denmark, Carlsberg Foundation, Danish National Research Foundation, Novo Nordisk Foundation for financial support.

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Acidolysis of Polyurethane Foam for Polyol and Aniline Recovery

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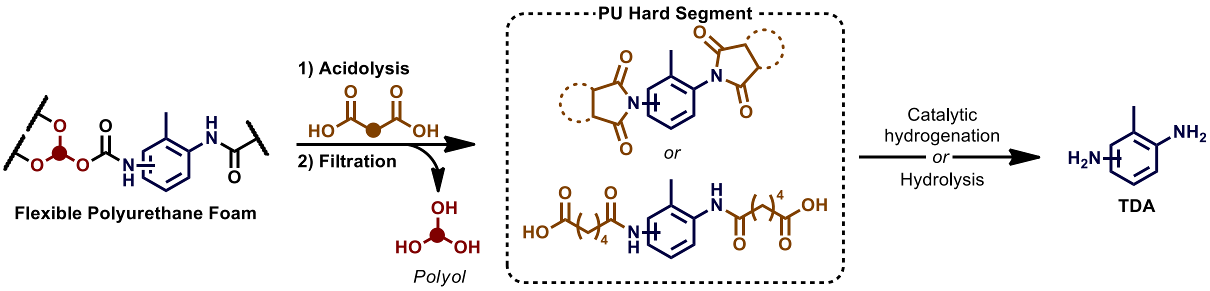
Polyurethane (PU) is a thermoset plastic with a wide range of applications, where it's for example used in mattresses, shoes, and automobiles. Due to PUs highly cross-linkages in the polymeric structure, PU waste cannot melt and therefore exclude the possibility for remolding as a recycling technique.[1] A newer promising recycling technique for deconstructing PU waste is acidolysis. Acidolysis is an industrial method for recovering the original polyol from polyurethane foams (PUF).[2] Here, a dicarboxylic acid is reacted with PUF at elevated temperature, resulting in a polyol and a solid PUF hard segment, which is separated by filtration (**Scheme 1**). While the polyol is valorized, the hard segment is normally discarded.



Scheme 1: Acidolysis of flexible polyurethane foam followed by catalytic hydrogenation or hydrolysis of the hard segment resulting in TDA.

First, we present a method for valorizing the hard segment via a ruthenium catalyzed hydrogenation. Second, we present a cost-effective method and straightforward method for industrial applications, which involves the recovery of aniline through acidic and alkaline hydrolysis of the hard segment. This approach has demonstrated its effectiveness when implemented on a larger scale, with a remarkable recovery up to 91% for the utilized TDA on a 10g quantity of PU. Furthermore, this method has exhibited promising outcome in the deconstruction of rigid polyurethane foam, resulting, resulting in the recovery of MDA.

Acknowledgements: We deeply appreciate the financial support from the Innovation Fund Denmark (Grant no. 9069-00017B), the Danish National Research Foundation (Grant no. DNRF118), and Aarhus University

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Integrating Hydroformylations into a Methanol Economy

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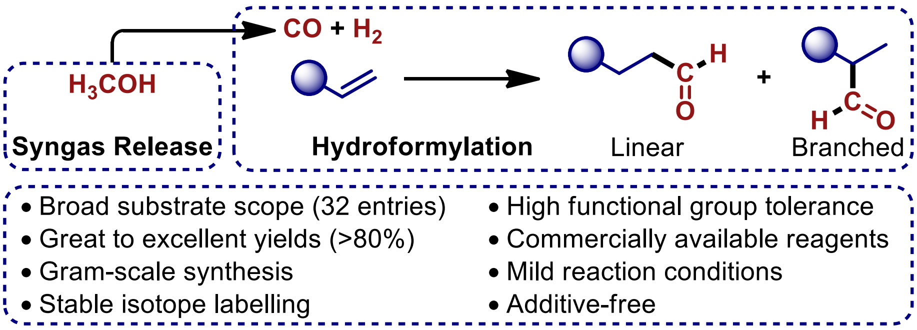
Most chemicals produced to date originate from fossil-derived resources. Within the framework of a green transition, introducing CO_2 as a carbon feedstock for synthesis is a necessity. Doing so by redesigning a multitude of interconnected chemical processes from scratch would be a herculean challenge. Instead, accessing established production chains from an alternative entry point would be a more achievable path to decarbonisation. Presently, a methanol economy that makes use of methanol as energy carrier is emerging. As green methanol is becoming more available from CO_2 hydrogenation, it presents an ideal entry point to rethink platform chemicals.

In this work, we present a proof-of-concept for decarbonising the important oxo process, a process using transition metal-based catalysts carried out on multimillion-ton scale annually. We demonstrate that the conversion of methanol to syngas (CO/H_2 mixture) can be utilised for efficient hydroformylations. If combined with methanol-to-olefin (MTO) processes and green methanol production, oxo products could thus be generated using solely CO_2 as carbon feedstock through a methanol platform. Our protocol uses a two-chamber reactor, which allows for separating a ruthenium-catalysed dehydrogenation of stochiometric amounts of methanol with the hydroformylation of olefins (**Figure 1**). A broad substrate scope containing 32 entries from aliphatics, styrenes, and allylbenzenes containing electron withdrawing and donating groups to natural products and drug precursors with yields between 80 to >95% is presented. In addition, the use of stoichiometric methanol (1.5 equivalents) further enables the methodology for cheap stable isotope labelling of pharmaceuticals and relevant compounds by simply using isotopically labelled methanol.



Scheme 1: Overview of the methodology presented.

Acknowledgements: We thank the Danish National Research Foundation (grant no. DNRF118), NordForsk (grant. no. 85378), the European Union's Horizon 2020 research, the innovation program under grant agreement no. 862179, the Marie Sklodowska-Curie grant agreement no. 859910, and Aarhus University for financial support.

Non C2-Symmetrical Phosphoramidites:

An Approach to Novel Asymmetric Conjugate Addition Reactions

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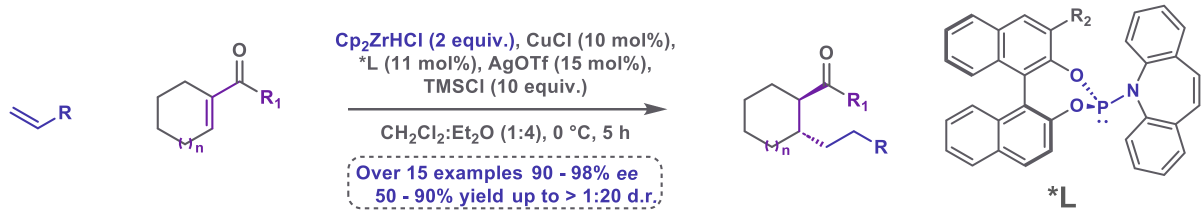
The Copper-catalysed Asymmetric Conjugate Addition (ACAs) of carbon nucleophiles to a,b-unsaturated carbonyl compounds is a powerful transformation for making new C–C bonds and is often used as a key step in syntheses. Over 200 examples in literature exist for cyclic and linear substrates using a myriad of different organometallic nucleophiles such as Grignard reagents, trialkylaluminiums and dialkylzincs between others[1,2]. The Fletcher group has been active in the field of ligand design towards copper-catalysed ACAs. The groups methodology utilizes the schwartz reagent which can form an organometallic species *in situ* when mixed with an alkene[3].

When comparing cyclic to exocyclic substrates a shocking contrast is evident. Only two examples in literature are observed for exocyclic substrates (72%, 82% *ee*)[4]. Encouraged on our groups history in the field we attempt to solve this problem by developing a general procedure for ACAs of exocyclic substrates by utilizing the chemistry developed by the group and our expertise on ligand development (**Scheme 1**).

Herein we expose the limitations of C_2-Symmetric phosphoramidites and how their non-C_2 symmetric equivalents can overcome this issue portraying the ACA of a,b-unsaturated ketones as a clear example. We investigate the robustness of the reaction by using different ketones and alkenes, the scalability of this transformation and finally the derivatization of these novel products.



Scheme 1: Asymmetric conjuagete addition on exocyclic substrates utilizing non-C2 symmetrical phosphoramidites.

Acknowledgements: We thank the University of Oxford and Vertex Pharmaceutical Ltd for financial support.

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Design, synthesis and characterization of multifunctional D-A compounds to TADF-OLEDs application

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Over the last few decades, there has been significant progress in the research of organic light-emitting diodes (OLEDs). More recently, there has been a growing interest in materials that exhibit room-temperature phosphorescence (RTP) emission or thermally activated delayed fluorescence (TADF).[1] These applications have shown excellent properties when molecules with donor-acceptor structures (D-A) are designed. Specifically, electron-deficient azaaromatic compounds like pyrazines and pyridazines-fused compounds have received considerable attention across various research fields, particularly in materials sciences.[2] Within this context, our work focuses on the design, synthesis, and photophysical characterization of new compounds with a D-A structure. We utilize acenaphtopyridopyrazine as the acceptor core and incorporate different donors such as phenothiazine, phenoxazine, acridine derivatives, carbazole, diphenylamine, and dibenzoazepine derivatives to investigate the relationship between structure and properties (see figure 1). To obtain these compounds, we successfully employed N-C coupling reactions, resulting in good yields. The photophysical properties were investigated in both solution and solid state, utilizing time-resolved spectroscopic analysis in different matrices, such as Zeonex and CBP. Our findings revealed that the materials exhibited TADF and/or RTP properties, with distinct behaviors influenced by structural modifications and matrix dependence. Additionally, when employing a solution processable technique in OLEDs, we achieved an impressive EQEmax of up to 15.3% when using CBP as the host material, what exceed the barrier of 5% of fluorescent devices. Moreover, the materials displayed aggregation-induced emission (AIE) and/or aggregation-induced enhancement emission (AIEE), depending on the specific modifications of the donors. This implies that these materials possess versatile and multifunctional characteristics suitable for optoelectronic applications.

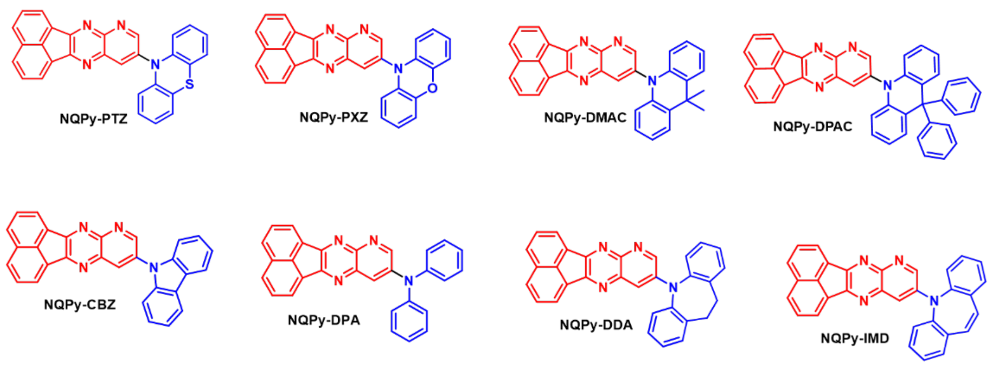

Figure 1: Molecular structures of the D-A compounds synthesized.

Acknowledgements: Preludium 20: 04/040/PBU22/0204; Exceed: H2020-WIDESPREAD-2018-2020-6/952008; Rektor Grant: 32/014/SDU/10-22-04.

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Enantiospecific One-Pot Synthesis of Enones from Boronic Esters

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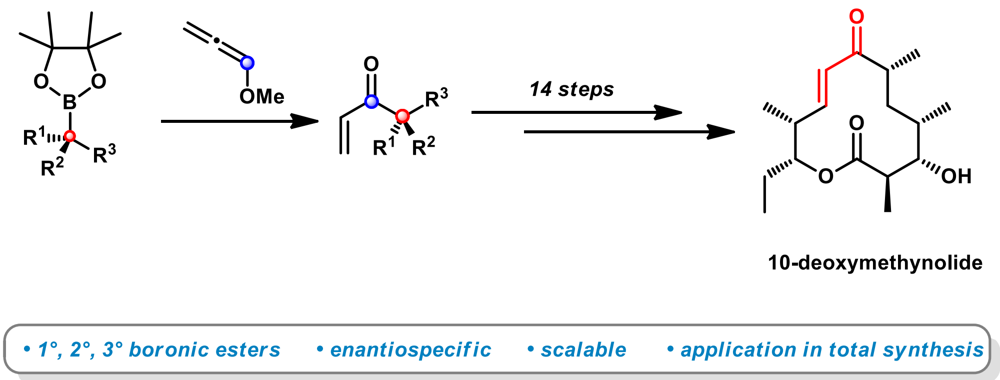
Boronic esters have come to occupy a privileged position as diverse functional handles.[1] In particular lithiation-borylation, the coupling of boronic esters with an enantioenriched metal carbenoid followed by 1,2-migration, affords a subsequent homologated boronic ester with precise stereocontrol. Applying this process in an iterative fashion yields a powerful tool by which stereocentres may be meticulously crafted.[2] This process, termed 'assembly-line' synthesis has found widespread application in the synthesis of polyketides.[3]

Despite the success of assembly-line synthesis, limitations remain. In the case of polyketide synthesis, many ubiquitous functional groups are inaccessible from boronic esters. In particular, there are no current means by which enones may be introduced from assembly-line synthesis, despite their frequent presence in the carbon skeleton of an array of natural products. Furthermore, where enones are not present in the final structure, they are frequently utilised as diverse synthetic handles in the total synthesis of natural products.[4] This is owed to the ability of enones to act as platforms from which a variety of powerful transformations may be launched. Including Michael additions, Diels-Alder reactions, and ring-closing metathesis.

We report, a one-pot, enantiospecific transformation of boronic esters to enones, using methoxyallene as a cheap, commercially available, 3 carbon building block in the application of lithiation-borylation chemistry (Scheme 1). A wide-ranging substrate scope demonstrates the applicability of this chemistry to primary, secondary, and tertiary boronic esters. Furthermore, a variety of functional groups are tolerated, leading to a range of enones being accessed in moderate to excellent yields. As demonstration of the broad ranging applicability of this chemistry, the total synthesis of the polyketide 10-deoxymethynolide has been completed.



Scheme 1: A one-pot synthesis of enones from boronic esters

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Electrophile Induced 1,2-Silyl Shift In Terminally Functionalized Propargyl Silanes For The Synthesis Of Small Heterocycles

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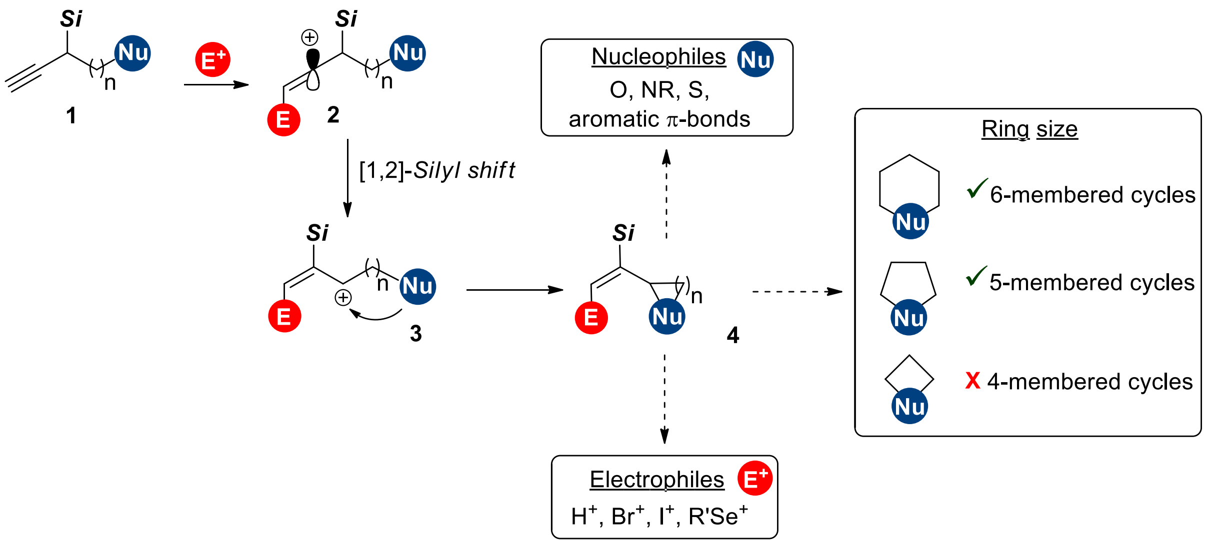
About 80% of all FDA approved drugs consist of small molecules, among which 59% are nitrogen heterocycles,[1] 27% are oxygen heterocycles, but 26% are sulfur-containing drugs.[2] Their extensive use in medicinal chemistry offers perspective to the development of new synthetic pathways towards heterocyclic structures, especially those containing at least one *N*-, *O*- or *S*-atom.

Previously our group studied electrophilic activation of propargylsilanes for the synthesis of 3-silylated 3-sulfolenes[3] and indenes.[4] These transformations were made possible by the stabilizing properties of the *β*-silicon effect and 1,2-silyl migration, which is observed in activated propargylic systems.[5] To further expand the concept of propargyl silanes as precursors for heterocycles, we designed a series of terminal-nucleophile-containing substrates **3**, which upon electrophilic activation underwent intramolecular cyclization, yielding *N*-, *O*- and *S*-containing heterocycles **4** (**Scheme 1**). Various electrophiles have been shown to induce the discussed transformation, such as H^+, Br^+, I^+ and $PhSe^+$, providing diverse substitution patterns for the resulting alkene side chain. To demonstrate the reaction scope, substrates containing alcohol, carboxylic acid, aldehyde, oxime, acyl amide, carbamate, sulfonamide and thioacetate functionalities have been cyclized. In case of aryl-moiety containing substrates, an intramolecular Friedel-Crafts reaction was observed, yielding bicyclic structures. The provided methodology allows the synthesis of 2-vinylsubstituted heterocycles with double or triple functionalized C=C bond with a distinct preference for *E*-geometry.



Scheme 1: Heterocyclization of propargyl silanes.

Acknowledgements: R.K. thanks the European Social Fund project Nr. 8.2.2.0/20/I/008 and Riga Technical University doctoral student grant for funding.

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Enantioselective Lewis Base catalyzed Allylation of C-Centered Latent Pronucleophile

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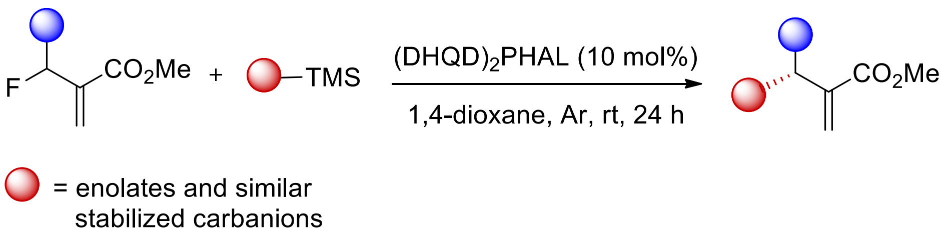
The scope of Lewis base catalyzed reactions is often limited, particularly with respect to the identity of the nucleophilic coupling partner.[1] For example, in Lewis base promoted allylations of C-nucleophiles using MBH carbonates, the reactions require stoichiometric amounts of chiral Lewis base promoter,[2] and the substrate scope is limited to sufficiently acidic C-H pronucleophiles.[3][4] To address these issues, Vilotijevic group has developed the concept of latent nucleophiles in Lewis base catalysis which addresses this problem through the use of latent pronucleophiles that feature a modification which lowers their nucleophilicity and enables their activation at an opportune moment during the reaction when the activated electrophile is already present in the reaction mixture.[5] In a proof-of-concept study, silylated pyrroles, indoles and carbazoles were used as latent N-centered nucleophiles and silyl enol ethers as C-centered latent pronucleophiles in chiral Lewis base catalyzed allylic substitutions of Morita-Baylis-Hillman (MBH) fluorides.[5a] Here we report the application of the concept of latent pronucleophiles to C-C bond formation and the development of enantioselective Lewis base catalyzed allylation of C-centered latent pronucleophiles with allylic fluorides.[5b]



This poster describes the development and optimization of reactions conditions, evaluation of the reactions scope and mechanistic studies with a detailed discussion of factors influencing regioselectivity and stereoselectivity of substitution. The optimized reactions proceed as dynamic kinetic resolutions of the allylic fluorides and provide the products in high yields and with high enantioselectivity. The reaction products are amenable to rapid conversion to common structural motifs present in natural products and biologically active compounds.

Acknowledgements: This work was a part of a German Science Foundation (DFG) funded project number 445755502. S. K. is grateful to DAAD for a graduate fellowship.

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Enabling Ring-Opening Reaction of Cyclopropanols with Decatungstate Anion Photocatalysis

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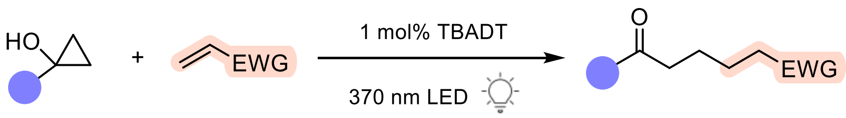
Cyclopropanols have emerged as valuable building blocks in organic synthesis due to their facile preparation by the Kulinkovich reaction[1] and their distinct reactivity. Oxidative activation and radical ring opening of cyclopropanols leading to the formation of β-keto radicals can be achieved using transition metal catalysts, stoichiometric oxidants and photoredox catalysts.[2] Herein, we report a photocatalyzed reaction of cyclopropyl alcohol and electron-deficient olefine using tetrabutylammonium decatungstate (TBADT) as a catalyst. In contrast to the typical behavior of TBADT, we believe that the reaction follows single-electron transfer mechanism and is based on oxidation of cyclopropanol and reduction of alkene.[3] The reaction can be successfully scaled-up under the continuous-flow conditions.



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Rhodium-Catalyzed Intermolecular Cross-Cyclotrimerization To Access Selaginpulvilins Derivatives and Investigation of Their Medicinal Activity

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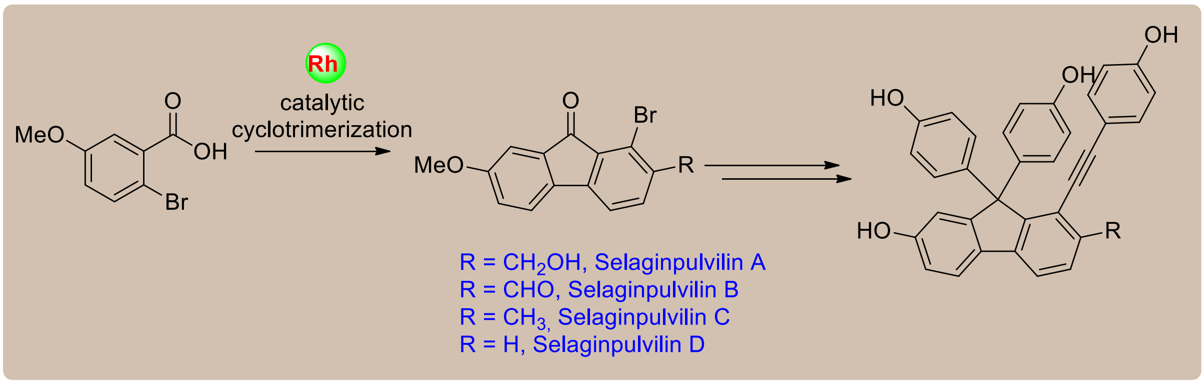
Selaginpulvilin family is a small group of 1-arylethynyl9,9-diaryl fluorene natural products that are likely responsible for the anti-inflammatory properties of Selaginella pulvinata, a plant used widely in traditional Chinese medicine.[1] The densely substituted fluorene scaffold of selaginpulvilins has sparked great interest as a challenging target in the field of total synthesis. Many researchers have attempted to synthesize selaginpulvilin derivatives, nevertheless, most of the reported synthetic strategy relied on (i) a hexadehydro Diels–Alder reaction of a tetrayne (selaginpulvilins A and C) and (ii) a tetrahydro Diels–Alder reaction of an enyne–diyne (selaginpulvilins A, B, and D), and sequences comprising of cross-coupling reactions and an intramolecular SEAr reaction.[2] Very recently our group reported the formal synthesis of selaginpulvilin C and D, however, all these reported methods led to only one of the selaginpulvilin analogs or ceased at some stage of formal synthesis.[3] Herein, we have developed a common methodology to achieve selaginpulvilin derivatives through catalytic cyclotrimerization (**Scheme 1**). The optimized condition was found after a thorough screening of various parameters and metal salts. Also, the biological activity of several intermediates has been tested to understand which core of the molecule is responsible for its known anti-inflammatory properties. Further, DFT calculations have been carried out to have a deep insight into the regioselectivity of cyclotrimerization.



Scheme 1: Rhodium-Catalyzed Total Synthesis of Selaginpulvilins Derivatives Via Catalytic Cyclotrimerisation.

Acknowledgments: We thank the Charles University Primus program (PRIMUS/20/SCI/017) for financial support.

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Pd-catalyzed allylic substitution between C-based nucleophiles and Bicyclic Aziridines

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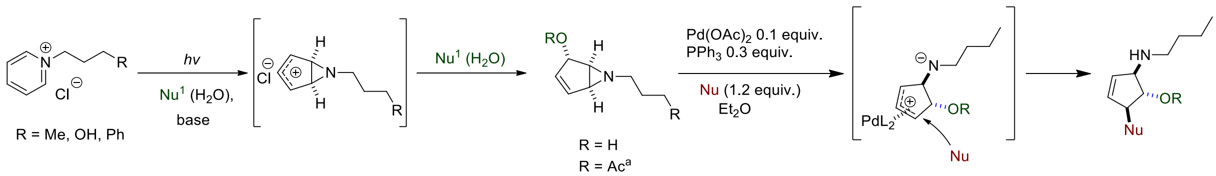
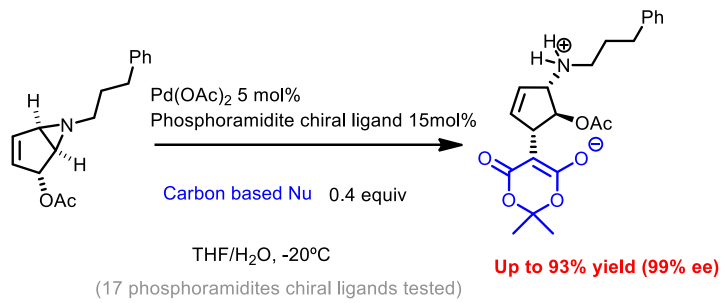
Aziridines are highly reactive three-membered heterocycles. They are well known to organic chemists for their great potential as building blocks for the synthesis of carbocycles with significant biological activity, such as aminocyclopentitols and β-lactams.[1]

A short route for the synthesis of these structures is the photochemical transformation of pyridinium salts to bicyclic-aziridines. The photochemical rearrangement forms a *cis*-fused cyclopenteno-aziridine allylic cation which reacts stereospecifically with poor nucleophiles/solvent devising a stable bicyclic-aziridine containing a new C-Nu bond in *trans*-position (Scheme 1).[2]



Scheme 1 Photochemical transformation of pyridinium salt and palladium catalysis followed by nucleophilic attack.

Considering the peculiar structure of the above described α-oxycyclopenten-aziridines in connection with our long-standing interest in Pd-catalyzed allylations, we were intrigued by the thought of investigating the behaviour of such cyclic substrates against soft carbon-based pro-nucleophiles under Pd(0) catalysis. Within this framework, we have previously developed a palladium-catalyzed ring opening of vinyl aziridines. This process proceeds takes place through η^3-allylpalladium complex formation via aziridine cleavage, and γ-reactivity of carbon-based nucleophiles leading to new carbon-carbon bonds (Scheme 1).[4] In this line, efforts on an asymmetric approach for aziridine opening via Pd catalysis, was achieved successfully with a good range of substrates. (Scheme 2).



Scheme 2 . Enantioselective opening of bicyclic aziridine via palladium catalysis.

Acknowledgements: The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996. We also thank the Fundação para a Ciência e Tecnologia for financial support (PhD grant 2020.04589.BD) and projects (2022.08559.PTDC, UIDB/04138/2020 and UIDP/04138/2020)

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Novel corrole-based photosensitizers for photodynamic therapy of endometrial cancer

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Endometrial cancer (EC) is the second most common gynaecological cancer in developed countries.[1] The primary treatment for this type of cancer involves a total hysterectomy. Therefore, there is an urgent need to find an effective conservative therapy for EC.[1] Easy access to the uterine cavity and a low incidence of side effects makes photodynamic therapy (PDT) a potentially useful approach for EC treatment.[1] In recent years, our research group has been exploring the reactivity of azoalkenes and nitrosoalkenes for the synthesis and functionalization of various heterocyclic systems.[2a] Recently, an innovative synthesis of oxime- and hydrazone-functionalized *trans*-A_2B-corroles was described, exploring the chemistry of nitrosoalkenes and azoalkenes toward dipyrromethanes.[2b,c] All the previously synthesized corroles containing a hydrazone moiety were subjected to *in vitro* evaluation for their potential use as photosensitizers in lung cancer PDT, showing promising results, namely IC_{50} in the nanomolar range and low or non dark cytotoxicity.[2c] In this communication, *in vitro* PDT activity against endometrial cancer of some of these hydrazone-functionalized corroles as well as of *de novo* synthesized corroles will be presented. The design of new corroles aimed to modulate their hydrophilic/lipophilic character and to establish structure-photoactivity relationships. Details of the synthesis, photophysical characterization, photocytotoxicity and dark cytotoxicity in endometrial cancer cell lines will be disclosed.

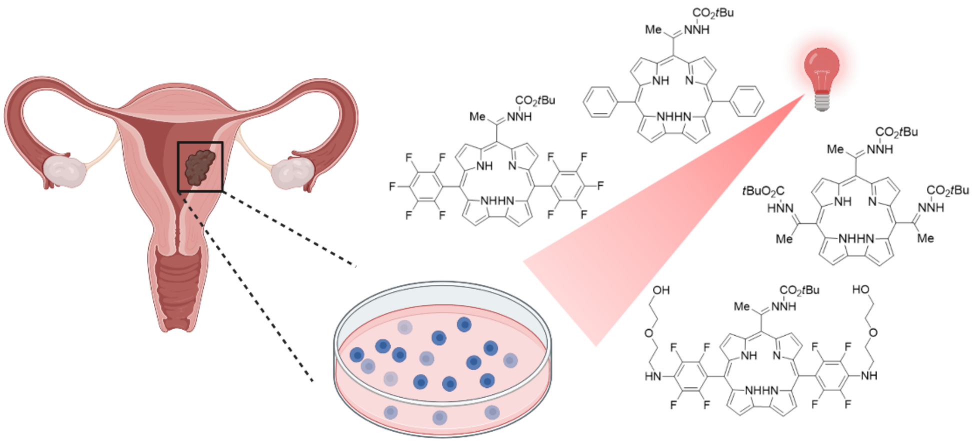

Figure 1: *In vitro* PDT activity against endometrial cancer. Created with Biorender.com.

Acknowledgements: Coimbra Chemistry Centre (CQC) and Centre for Innovative Biomedicine and Biotechnology (CIBB) are supported by the Portuguese Agency for Scientific Research, “Fundação para a Ciência e a Tecnologia” (FCT) through projects UIDB/00313/2020 and UIDP/00313/2020 (CQC), UIDB/04539/2020 and UIDP/04539/2020 (CIBB). This work was also supported by Project PTDC/QUI-QOR/0103/2021, funded by national funds (PIDDAC) via FCT. Bruna D. P. Costa also thanks to the FCT for financial support (2022.12013.BD). We also acknowledge the UC-NMR facility for obtaining the NMR data (www.nmrccc.uc.pt).

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Unified Bioinspired Approaches toward complex pyrazinoquinazoline alkaloids

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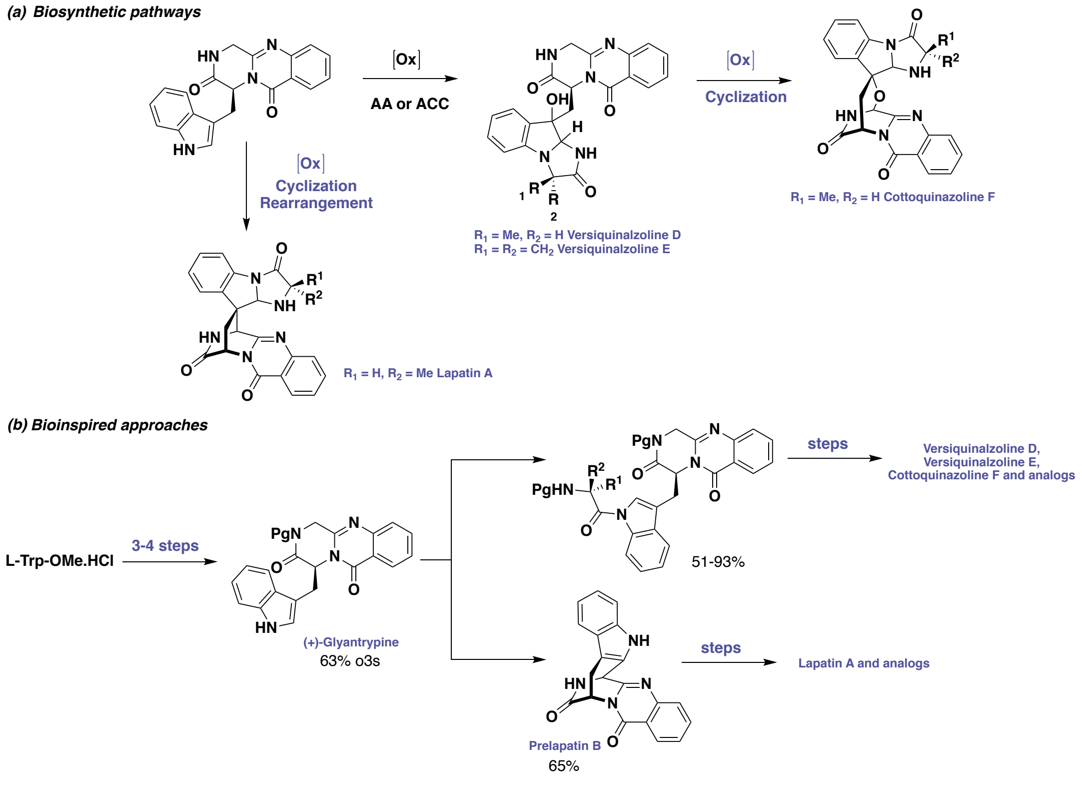
The pyrazino[2,1-b]quinazoline-3,6-dione motif is the core fragment found in many terrestrial and marine fungal metabolites showing interesting biological properties and therefore might serve as powerful chemotherapeutic agents [1, 2]. (+)-Glyantrypine, was proposed as the biosynthetic precursor of numerous of them [2] (scheme 1). The biosynthetic studies support that through an intermolecular condensation with amino acids followed by further oxidation-cyclisation Versiquinazolines D and E are obtained. The total synthesis of Fumiquinazolines family, slightly differing from glyantrypine-based alkaloids in structure, has been achieved by Snider and Zeng but involved a long 13-16 step synthesis [3]. Our proposed total synthesis for Versiquinazolines D and E, Cottoquinazoline F and the Lapatin A family consists of a bioinspired diversity-generating approach (scheme 1): synthesis of (+)-glyantrypine and its acylation with diverse protected amino acids followed by bioinspired oxidation/amination strategy to the Versiquinazoline D and E, base-mediated oxygenation and substitutive cyclization to the Cottoquinazoline F and Lapatin A derivatives.



Scheme 1: a) Biosynthetic pathways to Versiquinazolines D, E, Cottoquinazoline F and Lapatin A, b) Bioinspired approaches

Acknowledgements: We thank the *Grant Agency of Czech Republic (GA ČR) (Project: 21-30730S) and IOCB (RVO:61388963).*

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Unified Bioinspired Total Syntheses of Complex Indolodiketopiperazine Alkaloid Terpene Hybrid Natural Products and Their Analogs

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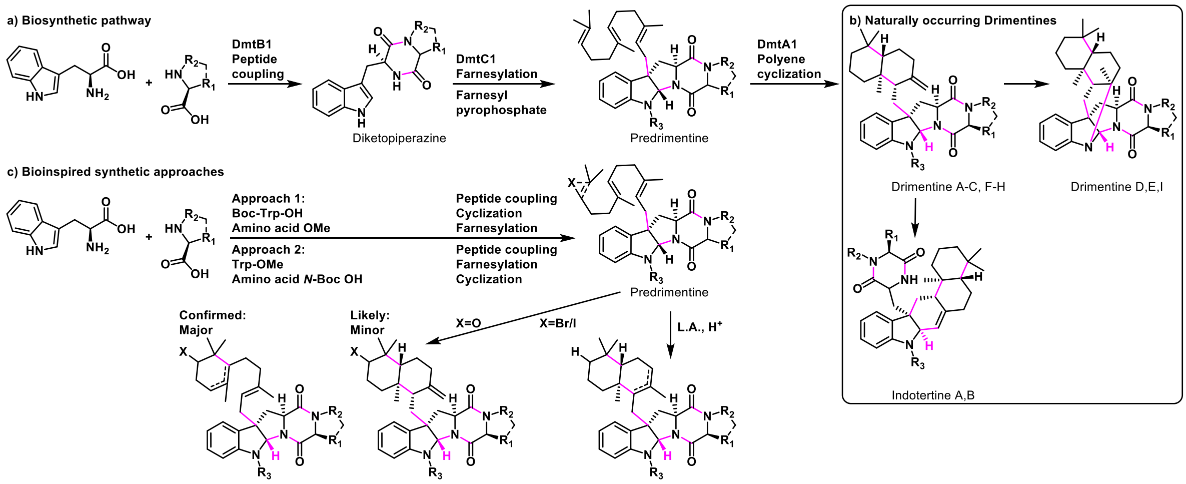
Drimentines and indotertines are a class of terpenoid containing alkaloids with interesting pharmaceutical properties. These molecules exhibit activity against cancer, parasites, bacteria and fungi. Drimentines and their naturally occurring analogues are secondary metabolites produced by Actinomycetes.[1] The biosynthetic pathway has been studied in detail (scheme 1a).[2] To the best of our knowledge, there is not yet an approach available to synthesize the multitude of drimentines and their analogues (scheme 1b). Both natural and non-natural analogues are desired. Based on the biosynthesis, two similar synthetic approaches were proposed (scheme 1c). Tryptophan, the common amino acid in every drimentine, is coupled with another selected amino acid to form a dipeptide. The choice of protecting groups on the substrates is dependent on the subsequent chemistry involved in the selected approach. In approach 1 the diketopiperazine is formed by a cyclization followed by farnesylation to form the corresponding predrimentine. In approach 2 these two steps are reversed. The methodology is identical in both approaches. The cyclization occurs by a thermally induced condensation. The introduction of the farnesyl moiety is performed by known methodology using palladium catalysis.[3] The key step to prepare drimentines A-C, F-H is proposed by a polyene cyclization.[4] The methodologies that are being explored are: (X=H) Lewis-Acid catalysis provides endocyclic decalin; (X=H) halonium ion mediated cyclization results in premature termination of the cascade (X=Br/I) where the minor product was likely to contain an exocyclic methylene; (X=O) oxirane Lewis Acid ring-opening also provides monocyclization (X=OH) but here no exocyclic methylene was observed. Substrates where X is Br/I or OH can be transformed to the desired naturally occurring drimentine by reduction.



Scheme 1: a) Biosynthetic pathways to Drimentines A-C. F-H b) Target structures of naturally occurring Drimentines and analogues c) Bioinspired synthetic approaches.

Acknowledgements: We thank the *Grant Agency of Czech Republic (GA ČR) (Project: 22-32466S) and IOCB (RVO:61388963).*

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Selective α-Oxygenation of Glycine Derivatives to Access Short Peptides Containing Non-Natural Amino Acids

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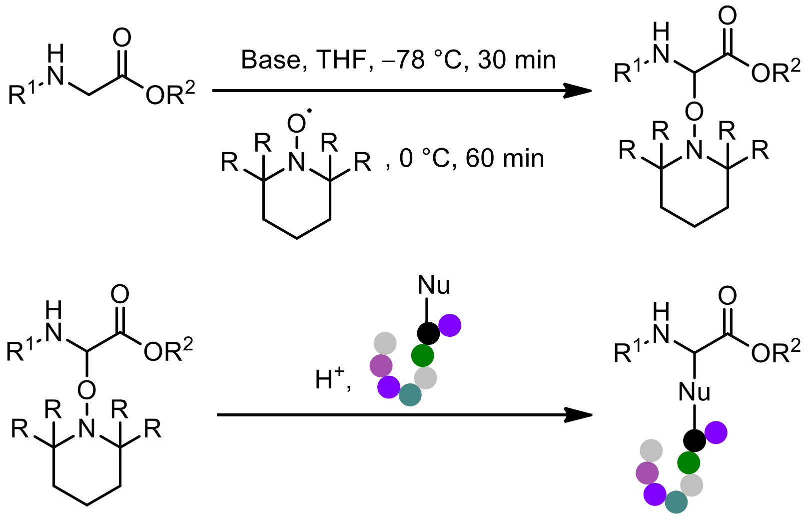
Peptides and proteins have always been important target molecules for biochemical and pharmaceutical applications. Introduction of non-natural changes to these biomolecules have gained much interest in the field since these modifications may grant them novel properties.[1]

We present the methodology for the modification of glycine derivatives by a very mild oxidizing agent; the nitroxide radical, to generate glycine alkoxyamines.[2] The methodology was extended to short peptides and interesting orthogonal reactivity of amino acids were unwrapped. The alkoxyamines can be further modified by thermal homolysis or acid-mediated heterolysis to generate a library of non-natural amino acids (**Scheme 1**). Thermal homolysis was extensively studied and a correlation between the structure of glycine alkoxyamines and homolysis temperature was found. Acid-mediated heterolysis paved the way to the modification of glycine containing peptides to access non-natural peptides under physiological conditions. This novel strategy may lead to interesting potential biological applications such as peptide fusion.



Scheme 1: Modification of glycine derivatives

Acknowledgements: We thank the Gilead Science & IOCB Research Center, IOCB Prague and the European Regional Development Fund; OP RDE; Project: ChemBioDrug (No.CZ.02.1.01/0.0/0.0/16_019/0000729) for supporting this work.

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Bimetallic Catalyzed Synthesis of 2-Arylindoles

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The synthesis of indole derivatives, which possess significant pharmacological properties as anticancer, antioxidant, and anti-inflammatory drugs, has garnered considerable attention in the field of synthetic and medicinal chemistry.[1] To improve the synthetic methodologies for indole-based compounds, a focus has been placed on metal-catalyzed methods involving imine intermediates to generate N-heterocycles.[2] In recent years, bimetallic catalysis has emerged as a promising approach for constructing C–C and C–heteroatom bonds, particularly by combining palladium catalysts with inexpensive and Earth-abundant metals, not commonly used in cross-coupling reactions.[3]

In this study, a novel bimetallic synthesis strategy for 2-arylindoles was presented, using alcohols and anilines as starting materials. The dehydrogenation or oxidation of secondary alcohols was achieved through nickel- or manganese-catalyzed reactions, respectively. The resulting ketone was subsequently converted into an imine intermediate, which was cyclized to form the desired 2-arylindole via a palladium-catalyzed oxidative cyclization. Notably, the synthesis was performed without isolating the intermediates, streamlining the process. Furthermore, the compatibility of the catalysts was investigated and an optimized protocol was developed, integrating Earth-abundant metals and palladium complexes, thereby enhancing the sustainability of N-heterocycles synthesis. (**Figure 1**).[4]

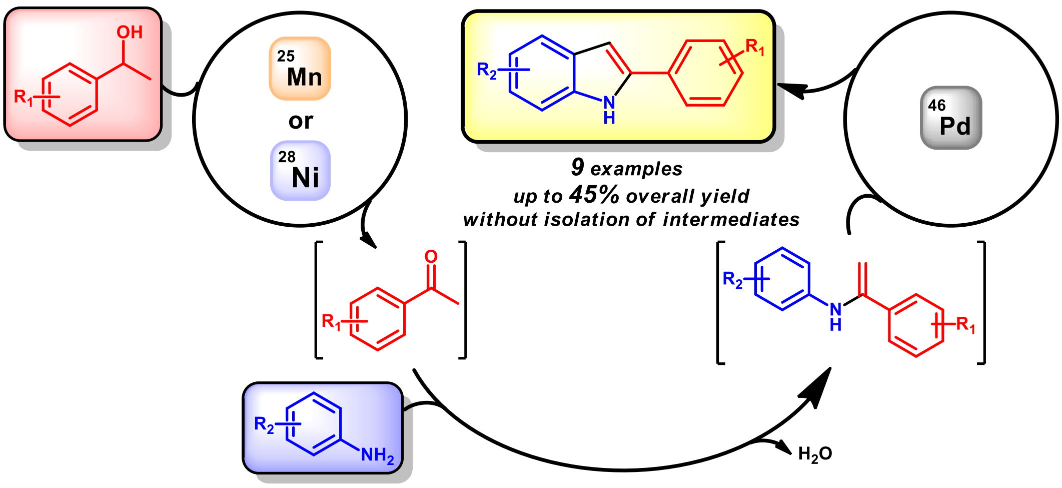

Figure 1: Bimetallic synthesis of 2-arylindoles from 1-phenylethanol derivatives and aniline derivatives.

Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (FCT, projects PTDC/QUI-QOR/0712/2020 and PTDC/QUI-QIN/0359/2021). The authors also thank the support by the Laboratório Associado para a Química Verde (LAQV), which is financed by national funds from FCT/Ministério da Ciência, Tecnologia e Ensino Superior and MOSTMICRO-ITQB, UIDB/04612/2020 and UIPD/04612/2020. The National NMR Facility is supported by FCT, ROTEIRO/0031/2013–PINFRA/22161/2016, co-financed by FEDER through COMPETE 2020, POCI, and PORL and FCTthrough PID-DAC) and CERMAX (022162).

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Rhodium-Catalyzed Asymmetric Arylation of Cyclobutenone Ketals

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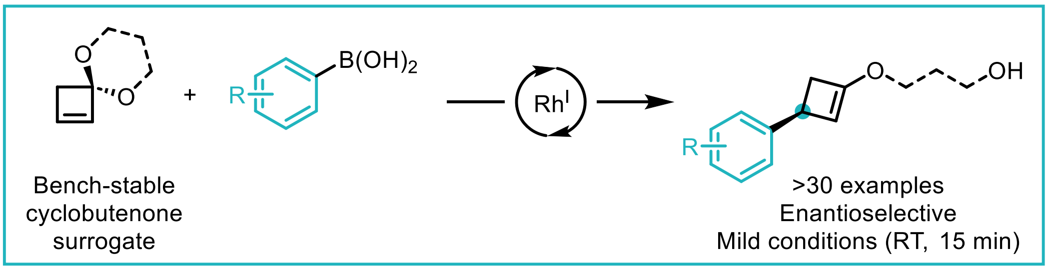
We describe rhodium-catalyzed enantioselective additions of aryl and vinyl boronic acids to cyclobutenone ketals. This transformation involves enantioselective carbometalation to give cyclobutyl-rhodium intermediates, followed by β-oxygen elimination to afford enantioenriched enol ethers. Overall, this addition serves as a surrogate for the elusive Rh-catalyzed 1,4-additions to cyclobutenone.



Scheme 1: This work: cyclobutenone ketals serve as bench-stable surrogates for cyclobutenone that can undergo carbometallation initiated transformations to access enantioenriched enol ethers.

Acknowledgements: Financial support from the U.K. Engineering and Physical Sciences Research Council (EP/W007363/1) is gratefully acknowledged. DEA thanks Department of Chemistry, University of Oxford, for funding.

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Photocyclization by a triplet-triplet annihilation upconversion pair in water – avoiding UV-light and oxygen removal

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Photon upconversion is a photochemical process, which converts low energy photons into high energy photons. Triplet-Triplet annihilation gained interest in many research fields due to the possibility to use low energy light. In addition, high quantum yields and tuneability in terms of absorption and emission have been observed. The first step of the procces is absorption of the triplet-sensitizer by visible light and subsequent intersystem crossing leading to its triplet state. The subsequent triplet-triplet energy transfer to an annihilator leads to annihilator molecules populating the triplet state. When two triplet annihilators are in close proximity an annihilation process can be observed, where one annihilator is deactivated to its ground state and the other annihilator populates its singlet state. This highly energetic singlet state can be applied in photochemical transformations, where this excited state can be used as a SET reductant or as an energy transfer agent. Although the process is well-known for more than half a century, the application of those systems in organic transformations is to this day limited.

Herein, we present an intramolecular [2+2] cycloaddition of an α,β-unsaturated ketone *via* Green-to-Violet Triplet-Triplet Annihilation under micellar conditions. The corresponding cyclobutane products can be formed in good to excellent yields. The application of micelles enables a highly O_2 sensitive photochemical process to take place under aerobic conditions without the need for oxygen-removing protocols.

Synthesis of Zinc Oxide Nanoflowers and Nanoneedles and Application in Photocatalytic Antibiotic Ofloxacin Degradation by UV Irradiation

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In recent times, nanoparticles have attracted more attention due to their new properties and wide applications in various technology and research fields. Based on their physical and chemical properties, some well-known classes of nanoparticles include metal nanoparticles, oxide nanoparticles, ceramic nanoparticles, semiconductor nanoparticles, and polymer nanoparticles. One particular class of nanoparticles, zinc oxide nanoparticles, has gained significant attention as a versatile material with numerous applications, thanks to its unique physical, chemical, and biological properties. ZnO is one of the compounds that exhibits the highest morphological diversity, including nanorods, needles, helixes, springs, rings, ribbons, tubes, belts, wires, nanoplates, nanosheets, nanoflowers, snowflakes, etc. Precipitation is a simple method for synthesizing ZnO particles with diverse morphologies at a relatively low cost. ZnO has emerged as a potential photocatalyst for the degradation of organic contaminants due to its high activity, large bandgap, ability to reduce the recombination of electron-hole (e^-–h^+) pairs, high electron mobility, low cost, and eco-friendly nature. For the last several years, many harmful organic compounds from the pharmaceutical industry (antibiotics) have been discharged into the environment, directly influencing human health. These organic contaminants are not naturally self-degradable and tend to accumulate in the human body and living organisms, which leads to poisoning and resistance of organisms. Among the methods of eliminating antibiotics, photocatalysis using ZnO is an effective strategy with a low operating cost and no production of polluting secondary products when complete decomposition occurs.

In this work, zinc oxide nanoflowers and nanoneedles samples were prepared from zinc acetate dihydrate and ammonium hydroxide using ethanol aqueous solutions by the homogeneous precipitation method. It was established that ZnO nanoflowers formed from a 0.1 M ethanol solution with a yield of 35.2%, whereas ZnO sheets were precipitated from a 16.8 M ethanol solution with a low yield of only 1.3%. Therefore, the more concentrated ethanol solution did not favor the zinc oxide yield.

The structure of the synthesized zinc oxides was studied using XRD, SEM, FTIR, z-potential measurements, and low-temperature nitrogen adsorption/desorption isotherms. The particle sizes of the ZnO nanoflowers and nanoneedles nanoparticles, determined by Debye-Scherrer's equation based on the dominant diffraction peak of (101), are 39.7 and 11.5 nm, respectively. The specific surface area of ZnO nanoflowers was 7.9 and ZnO nanoneedles – 29.9 m^2g^{-1}, and the total pore volumes were 0.35 and 0.06 cm^3g^{-1}, respectively.

The obtained zinc oxide samples were used in the photocatalysis of the photodegradation reaction of ofloxacin under UV irradiation (9 W, λ = 369 nm). The bulk experiment showed that photodegradation of ofloxacin did not occur under UV treatment. Moreover, the antibiotic concentration remained the same after stirring with ZnO for 3 minutes in darkness. Therefore, the non-catalytic photodegradation reaction, as well as adsorption, could not be taken into account.

ZnO nanoneedles demonstrated better photocatalytic activity. The photocatalytic effectiveness of the antibiotic ofloxacin reached values of 55% for 1 hour and 98% for 3 hours for ZnO nanoflowers, whereas it reached 83% for 1 hour and 100% for 3 hours for ZnO nanoneedles. The photodegradation reaction of ofloxacin, catalyzed by zinc oxide nanoflowers and nanoneedles under UV irradiation, follows a pseudo-first-order model very well.

Thus, the obtained results indicate that zinc oxide nanoflowers and nanoneedles can be successfully synthesized using the homogeneous precipitation method and applied in the photocatalytic degradation of the antibiotic ofloxacin under UV irradiation.

Acknowledgements: This research is funded by the EU NextGenerationEU through the Recovery and Resilience Plan for Slovakia under the project No. 09I03-03-V01-00108 and project APVV-19-0302.

Reductive Amination as a Powerful Tool in the Stereoselective Synthesis of Selected Medicinal Drugs and their Analogues

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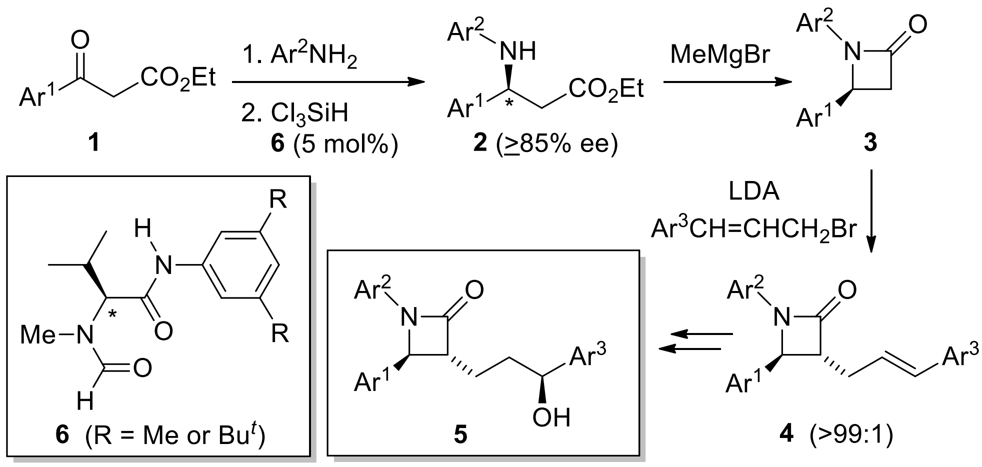
In industry, about a quarter of C-N bonds are constructed via reductive amination, being second only to amide formation.[1] Over the years, we have developed an enantioselective reduction of imines (generated in situ from ketones or aldehydes) with Cl_3SiH, catalysed by Lewis-basic chiral formamides, such as **6**.[2] The enantioselectivity typically exceeds 90% ee[2] and the method is tolerant of a number of vulnerable functional groups, in particular CN, NO_2, N_3, P(O), (pin)B, C≡C bonds, etc.[3]

Herein, we present the synthesis of Ezetimibe itself (a medication currently used to treat high blood cholesterol) and its analogues. The key strategy steps (**Scheme 1**) are the synthesis of amine **2** from β-keto ester **1**, where the imine reduction was carried out with Cl_3SiH in the presence of **6** as an organocatalyst, cyclization and allylation of the resulting β-lactam **3** to afford **4**. The latter derivative was then converted in two steps into Ezetimibe analogues **5**.



Scheme 1: Principal steps in synthesis of Ezetimibe analogues.

Acknowledgements: We thank Charles University and IOCB, Prague for financial support....

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Hypervalent Iodine(III) Reagents with Transferable Primary Amines for Electrophilic α–amination of Stabilized Enolates

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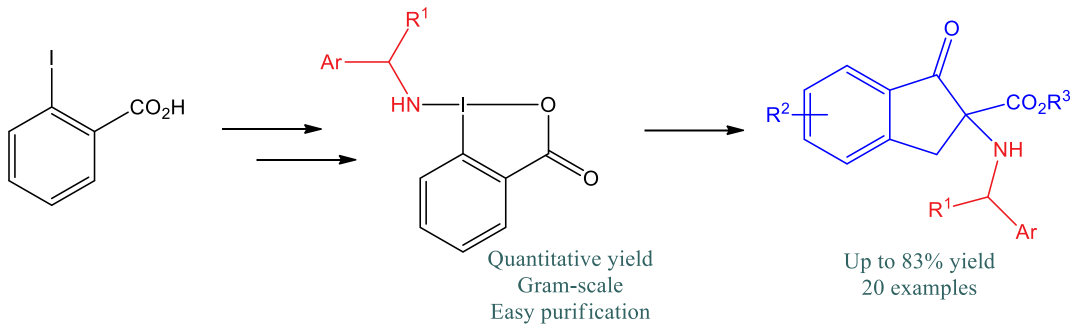
The C–N bond is one of the utmost importance due to its abundance in organic compounds showing biological activity.[1] Furthermore, the α–amino carbonyl moiety plays a significant role as it is the structural component of α–amino acids. Driven by the broad scope of their biotechnological application, unnatural amino acids bearing atypical side chains have attracted attention in the scientific community making the search for efficient construction of C–N bonds a current topic.[2]

Iodine(III) compounds have been explored as electrophilic synthons of usually nucleophilic functionalities. The electrodeficient iodine atom and the reactivity of the hypervalent bond causes an inversion of the polarity of a bound moiety.[3] Cyclic benziodoxoles and benziodoxolones are particularly interesting as they show enhanced stability when compared to their acyclic analogues due to conjugation between the aromatic ring and the iodine atom.[4] Iodine(III) reagents for the transfer of electrophilic nitrogen-containing groups such as azides[5], bissulfonimides[6] and imines[7] have been established. Taking advantage of the *umpolung* reactivity, our group has previously reported the use of hypervalent iodine reagents for the transfer of sulfonyl groups to amines.[8] In the follow-up of this work, we recently developed four novel benziodoxolone-derived iodine(III) reagents for electrophilic α–amination and reported its employment in the α-amination of stabilized enolates (**Scheme 1**). In this communication our results will be presented.[9]



Scheme 1: Electrophilic α–amination of carbonyl compounds with benzylaminobenziodoxolone.

Acknowledgements: We would like to thank Fundação para a Ciência e Tecnologia for the fellowships 2022.04623.PTDC and 2022.13650.BD. This work was supported by the Associated Laboratory for Sustainable Chemistry - Clean Processes and Technologies-LAQV which is financed by national funds from FCT/MEC (UID/QUI/50006/2013) and co-financed by the ERDF under the PT2020 Partnership Agreement (POCI-01-0145-FEDER-007265). The NMR spectrometers are part of The National NMR Facility, supported by Fundação para a Ciência e Tecnologia (RECI/BBB-BQB/0230/2012).

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Oxidative Transformations with Photoactivated Phenanthrenequinone and Its Electron-Deficient Derivative

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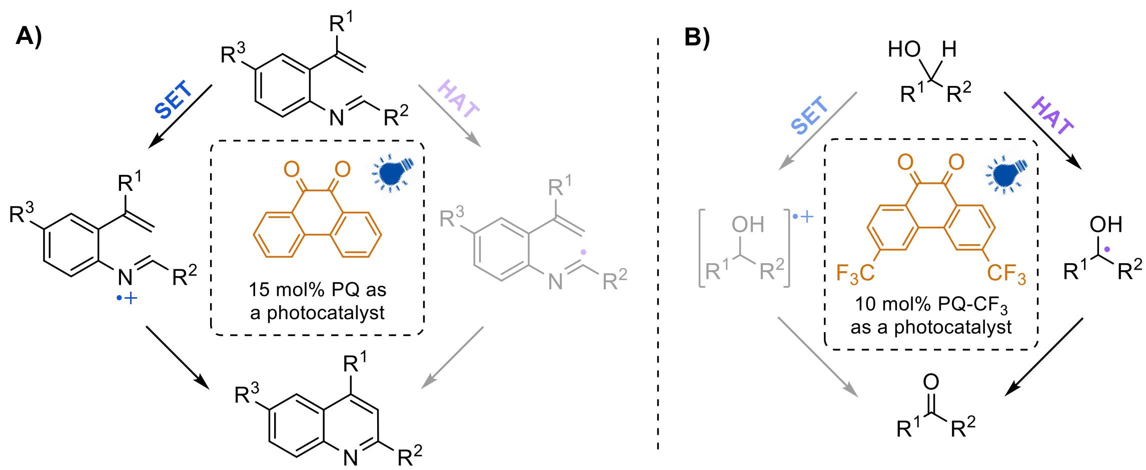
During recent years, photoredox chemistry has emerged as a milder strategy to perform oxidative reactions. Especially organophotocatalysts provide an interesting and greener alternative to more traditional methods, which generally require high temperatures or pressures, expensive metal catalysts, or strong Lewis acid reactants. 9,10-Phenanthrenequinone (PQ) is known to act as a photoactivated oxidant[1], and the interest on using PQ as a visible-light-excited photocatalyst has been rapidly growing over the past few years. We developed a method where PQ catalyzes electrocyclization of 2-vinylarylimines to polysubstituted quinolines, producing up to quantitative yields already after 1 h of excitation with blue LEDs at room temperature.[2] On the basis of experimental and DFT studies, we propose that excited-state PQ induces one-electron oxidation of the imine substrate, which triggers the electrocyclization mechanism (**Scheme 1A**).

Most secondary alcohols exhibit higher oxidation potentials than vinylarylimines, limiting efficient PQ-catalyzed oxidation of alcohols to electron-rich benzylic alcohols. To improve the photooxidation performance, we designed a high-yielding synthetic route for a novel, more electron-deficient PQ derivative, 3,6-bis(trifluoromethyl)-9,10-phenanthrenequinone (PQ-CF_3).[3] With PQ-CF_3 as an organophotocatalyst, oxidation of secondary alcohols occurred efficiently in mild conditions, even when electron-deficient aryl alcohols or aliphatic alcohols were used as substrates. The comprehensive mechanistic studies suggested that contrary to the electrocyclization of imines, the mechanistic pathway of the alcohol oxidation is dependent on the electronic properties of both the catalyst and the substrate. As the key mechanistic discovery, we showed that the newly developed PQ-CF_3 operates as a highly efficient hydrogen atom transfer (HAT) catalyst.



Scheme 1: A) PQ-catalyzed electrocyclization of 2-vinylarylimines via single-electron transfer (SET). B) PQ-CF_3-catalyzed alcohol oxidation via hydrogen atom transfer (HAT).

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Distal meta-alkenylation of formal amines enabled by catalytic use of hydrogen-bonding anionic ligands

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Pd-catalyzed distal C–H activation using covalently attached directed groups (DG) is well explored. However its limitation lies in the pre-installation and post-functionalization detachment of the DG. Additionally, the stoichiometric amount of transient DG employed in distal C–H activation, further hinders the efficacy. In an attempt to overcome these challenges, we have utilized the catalytic use of directing ligands to promote such distal *meta*-C–H activation. Non-covalent interactions are a ubiquitous process that promotes the spontaneity of various natural and biological transformations, thus playing a prominent role in controlling the regioselectivity and site selectivity of various organic transformations. However, the primary requirement of employing such non-covalent interactions is the presence of milder reaction conditions. Consequently, its involvement in transition-metal catalysis has, to date, remained in the infant stage. Non-covalent interactions among a target, a suitably designed directing ligand and palladium can establish an optimum arrangement that allows selective distal C–H activation of arenes. The catalytic use of directing ligands, through H-bonding interaction with the substrate helps us to achieve site-selective Pd-catalyzed distal C–H activation. The current protocol illustrates a series of directing ligands that enables selective *meta*-alkenylation of aromatic amines with varying chain lengths, signifying the generality of the work developed.[1]

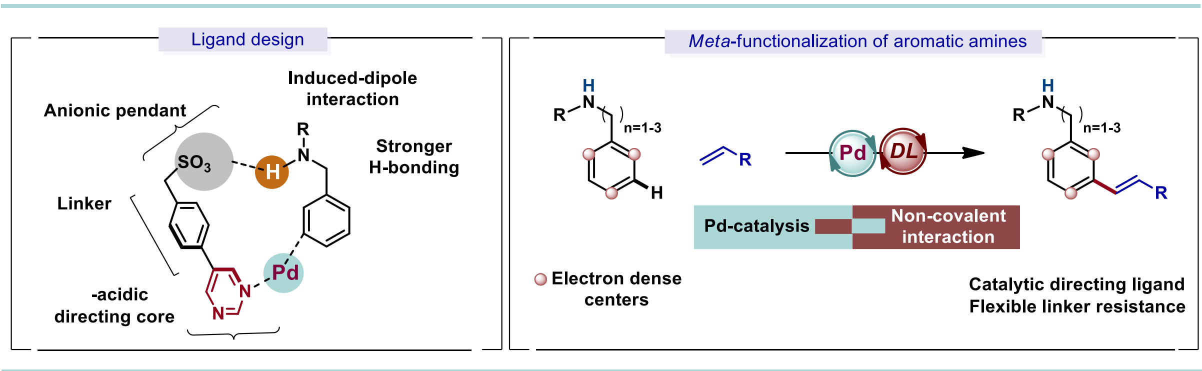

Figure 1: This Work- Non-covalent interactions to promote Pd-catalyzed distal *meta*-C-H activation

Acknowledgements: We thank the SERB, India (RD/0121-SERB020-001) for financial support....

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Homogeneous *versus* Heterogeneous Catalysts in CO_2 Addition Reactions to Epoxides

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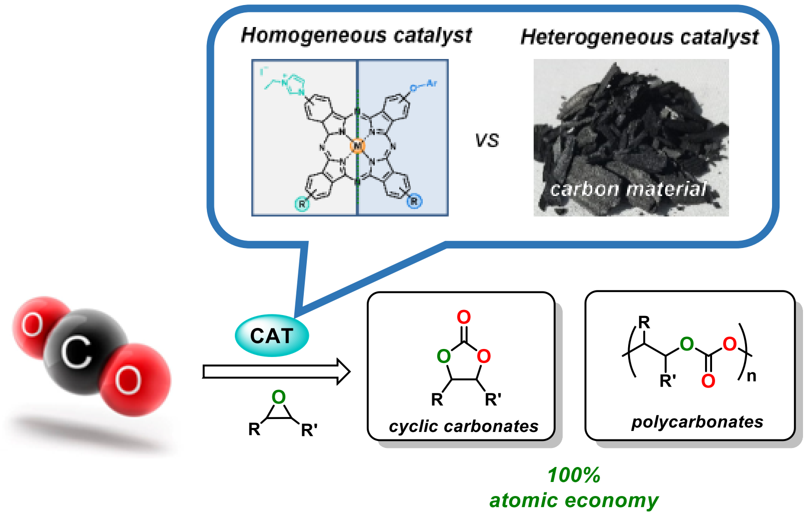
Carbon dioxide (CO_2) is an abundant greenhouse gas produced by human action, being currently considered a non-toxic, inexpensive and versatile reagent in organic synthesis. However, due to its chemical inertness, chemical reactions involving CO_2 activation usually face large energy barriers and require the development of highly effective catalysts.[1] Among the CO_2 catalytic transformations, we highlight the CO_2 addition reaction to epoxides, which can selectively afford two types of products: cyclic carbonates or polycarbonates, both with relevant applications, namely as green solvents, lubricants, cosmetics, electrolytes in lithium batteries or in plastic engineering, respectively.[2,3] Such reactions have been mainly accomplished through the use of homogeneous catalysts, such as metal complexes of N- and O-donor ligands, as well as with heterogeneous catalysts, such as supported metal salts, metal organic frameworks and carbon materials.[4,5]

In this work, we describe the synthesis, characterization and catalytic evaluation of different types of homogeneous and heterogeneous catalysts in CO_2 addition reactions to epoxides. On the one hand, we report the application of phthalocyanine-based metal complexes in this reaction, where the effect of the aromatic macrocycle structure in the catalytic activity and selectivity towards polycarbonates *versus* cyclic carbonates will be discussed. Moreover, we also present the application of biomass-derived carbon materials (vegetable charcoal, biochar, and activated charcoal) as renewable heterogeneous catalysts.



Scheme 1: CO_2 addition reactions to epoxides using homogeneous or heterogeneous catalysts.

Acknowledgements: The authors thank FCT for funding through projects UIDB/00070/2020, UIDP/00070/2020, UIDB/00313/2020, UIDP/00313/2020 and UIDB/00285/2020, PRR - Recovery and Resilience Plan and the European Union (EU), Next Generation Funds, for funding through Project Nº 6979 - PRODUTECH R3 [Recuperação-Resiliência-Reindustrialização], Notice 02/C05-i01/2022, the University of Coimbra and Santander Universidades for funding Project CO2BioFilter (PT0047.F.02.C), and Fundo Ambiental (Ministério do Ambiente e da Ação Climática) for funding Project EducaPlast (Call Educação Ambiental + Transversal + Aberta + Participada 2022, Notice 14199/2022, application no 201). The authors also thank BioGreenWoods SA for providing the carbon materials. A.C.S. Gonzalez thanks FCT for PhD grant UI/BD/150804/2020.

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ELPIS: Engaging Libraries of Promising Oxindoles as Tyrosine-Kinase InhibitorS in Cancer Target Therapy

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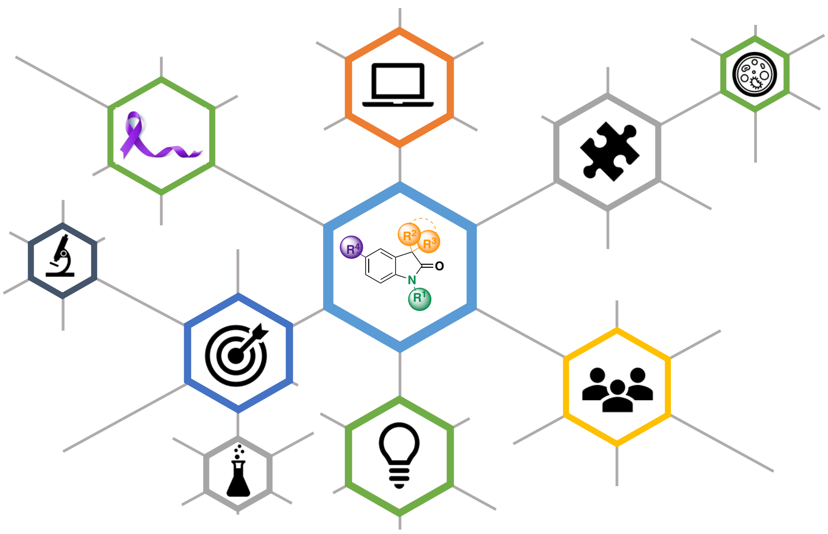
Tremendous efforts have been made by the scientific community to transform the world in a better place. Particularly concerning healthcare, scientists are committed to fight against complex and mortal diseases, study their behaviour and intervening in the discover of new drugs, treatments, or best ways to provide patients long (and quality!) lives. Cancer is massively diagnosed worldwide, is cruel, complex, and fatal disease. Current available treatments are still linked with terrible side-effects (chemotherapy) and the future trusts on target therapy: drugs that safely exterminate the malignant cells and are safe for normal ones. There is an urgent need to develop these drugs, targeting specific proteins inside the cells. Although it is extremely challenging to invent new medicines, the difficulty increases when sustainable, innovative, and economically favoured processes must be considered. This project application fits within the United Nations 2030 Agenda for sustainable development. Our work-plan is based on the synthesizes of new promising molecules to treat cancer and it is expected to reduce substantially the waste generation through prevention, reduction, and reuse during the work schedule. In this presentation we would like to disclose our latest findings and preliminary outcomes regarding this challenging task within this multidisciplinary project.



Acknowledgements: This work received financial support from PT national funds from Fundação para a Ciência e Tecnologia/Ministério da Ciência, Tecnologia e Ensino Superior (FCT/MCTES): 2022.02910.PTDC, UIDB/50006/2020, UIDP/50006/2020.

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Synthesis of new superhydrophobic and environmentally friendly coatings for stone protection

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The decay diagnosis and conservation of stone-built heritage is increasingly becoming a worldwide concern. Among the known causes of stone decay, water has been identified a key factor in the alteration of the original stone's properties and aesthetics, directly impacting its sociocultural and socioeconomical value.[1,2] This work aims to synthesize novel environmentally friendly superhydrophobic coatings for stone protection, based on dendritic polymer technology and composed of natural occurring building blocks such as amino acids, amines and carboxylic acids, capable of imparting hydrophobicity into various surfaces. These derivatives are created to develop a class of novel, low-cost, highly efficient, durable and eco-friendly protective coatings for application to contemporary and historical stone structures and objects. Preliminary results include the use of L-Lysine as the base component to construct novel coatings for heritage applications using the convergent synthesis method of Generation 1 (G1) and Generation 2 (G2) dendrons (figure 1).[3] The novel coatings, their identification and characterization will be carried out by one- and two-dimensional nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS) and infrared spectroscopy (FTIR).

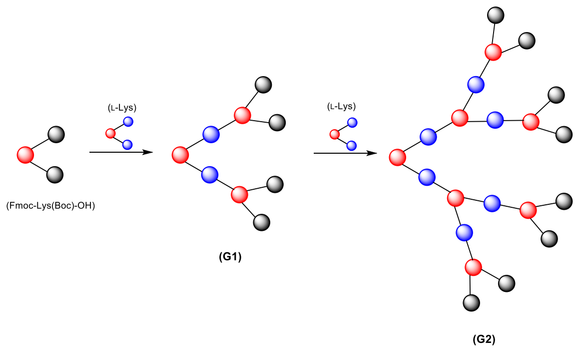

Figure 1: The convergent synthesis method of Generation 1 (G1) and Generation 2 (G2) dendrons using L-Lysine (L-Lys) as the base compound.

Acknowledgements: This work has been financially supported by the Eco-STONEPROTECT – Eco-friendly superhydrophobic hybrid coatings for STONE PROTECtion project (EXPL/CTA- GEO/0609/2021) and by the UIDB/04449/2020 and UIDP/04449/2020 projects, which were funded by Fundação para a Ciência e Tecnologia (FCT) and by the European Regional Development Fund.

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Mechanochemistry for the Transformation of Furanes through Multicomponent Reaction Catalysed by Zn

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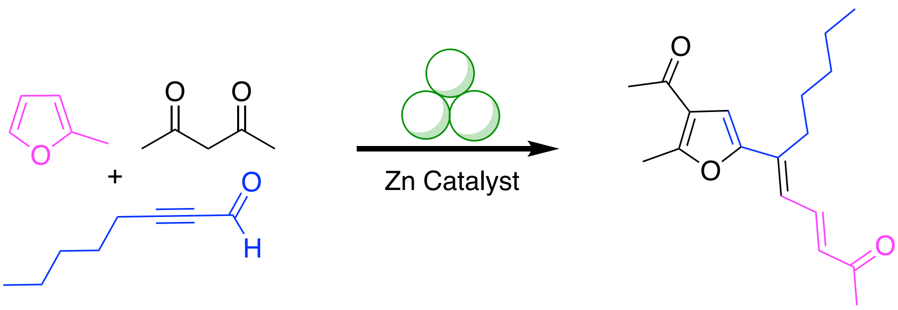
Due to its rich chemistry, furan is an important scaffold in organic synthesis and has been explored as a building block in the construction of a wide range of heterocyclic and acyclic structures, some of which have found applications in natural product synthesis and medicinal chemistry.[1] In addition, 2-methylfuran is a biomass platform molecule obtained by hydrogenation and hydrogenolysis of furfural, which is one of the top added-value chemicals that is being produced from biomass. The effective use of renewable reagents obtained from biomass requires the development of sustainable synthetic methodologies capable of increasing the chemical diversity of the compounds derived from renewable reagents. The aim of this work is to develop a multicomponent reaction for the synthesis of furan polyenes from 2-methylfuran, catalysed by zinc under mechanical action (**Scheme 1**), and to study the effect of the catalyst and different variables inherent to mechanochemistry on the same reaction.

Under ball milling conditions carried out in stainless steel jars with two balls (7 mm), using ZnX_2 salts (X = Cl, Br, I) as catalyst, the desired compound was obtained as a mixture of isomers in 2 h and with an overall yield of 32-59%. The use of $Zn(OAc)_2$ as catalyst gave, exclusively, the product from the Knoevenagel condensation between acetylacetone and octinal. Similar results were obtained using Zinc(II) scorpionates as catalyst, however, these catalysts were recoverable from the reaction media by selective solubilization with ethyl acetate. The reaction mechanism, the influence of the catalyst (including zinc ligand), and of the number and mass of balls will be discussed.



Scheme 1: Multicomponent synthesis of 2-methylfurane derivatives catalysed by Zn.

Acknowledgements: Authors thanks CQC supported by the Portuguese Agency for Scientific Research, “Fundação para a Ciência e a Tecnologia” (FCT) through projects UIDB/00313/2020 and UIDP/00313/2020, cofounded by COMPETE2020-UC, and projects UIDB/04585/2020 of the Research Unit CiiEM and UIDB/04565/2020 and UIDP/04565/2020 of the Research Unit Institute for Bioengineering and Biosciences—iBB, and LA/P/0140/2020 of the Associate Laboratory Institute for Health and Bioeconomy—i4HB.

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Flavonoid-Triazole Hybrids as Potential Anti-Alzheimer's Agents: Synthesis and Biological Assays

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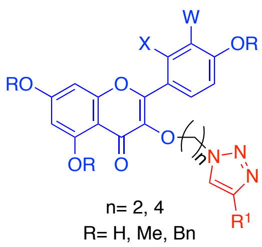
Alzheimer's disease (AD) is a neurodegenerative disease with high mortality and morbidity, for which there is still no cure, despite all the efforts of researchers in the last three decades.[1] Flavonoids, a class of polyphenols present in our diet, possess multiple biological activities, including anti-AD effects. However, flavonoids have low bioavailability and permeability, which compromises their therapeutic efficacy.[2] Molecules containing the 1,2,3-triazole unit in their structure also have a wide range of pharmacological properties, including anti-AD.[3] To improve the therapeutic efficacy of flavonoids (quercetin and morin), it was decided to combine them with the 1,2,3-triazole unit through a molecular hybridization approach.

The main objective of this work is the quest for more effective anti-Alzheimer agents. Herein we report a new library of flavonoid (quercetin or morin)-1,2,3-triazole hybrids which were designed, synthesized and investigated for antioxidant, neuroprotective, and butyrylcholinesterase (BuChE) inhibitory activities. Flavonoid-1,2,3-triazole hybrids were prepared with very good to excellent yields through Copper(I)-Catalyzed Alkyne–Azide Cycloaddition (CuAAC) - "Click" Reaction (Figure 1).[4] Some of the new hybrids showed potent *in vitro* inhibitory activity on BuChE (IC_{50} values between 10 and 50µM) along with antioxidant and neuroprotective effects. Moreover, toxicity evaluation for the most promising hybrids was performed using the *Artemia salina* toxicity assay, showing low toxicity.



Quercetin-1,2,3-triazole hybrids X=H; W=OR
Morin-1,2,3-triazole hybrids X=OR; W=H

Figure 1: Flavonoid-1,2,3-triazole Hydrids.

Acknowledgements: We acknowledge the Fundação para a Ciência e a Tecnologia (FCT) for funding through the strategic project to LAQV-REQUIMTE (FCT/ MCTES; UIDB/50006/2020|UIDP/50006/2020).

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Synthesis and structural and photophysical characterizations of Diketopyrrolopyrroles for technical and biological applications

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Diketopyrrolopyrroles (DPP) represent a class of brilliant red and strongly fluorescent high-performance pigments that have exceptional light, heat, and environmental stability [1,2]
The synthetic versatility of diaryl DPP is immense. These compounds possess several reactive centers that can be attacked by nucleophiles or electrophiles. This fact is attractive for exploring their chemical reactivity towards transformation into derivatives with improved performance or novel application properties [1,3].
This work presents a series of new diketopyrrolopyrrole derivatives synthesized from the cheap commercial Pigment Red 254 (DPP) [4]. The structures of all new compounds were confirmed by several spectroscopic techniques, and their photophysical properties were evaluated.

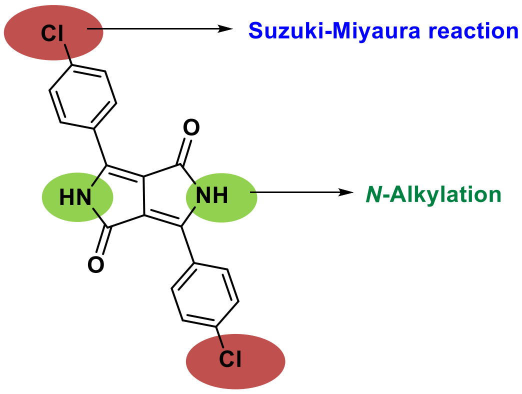

Figure 1. Pigment red 254

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Funding
This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) for LAQV-REQUIMTE through the projects UIDB/50006/2020 and UIDP/50006/2020.

Acknowledgements
Thanks are due to the University of Aveiro and FCT/MCTES for the financial support through PT national funds for LAQV-REQUIMTE (UIDB/50006/2020 and UIDP/50006/2020), within the PT2020 Partnership Agreement, and to the Portuguese NMR Network. Vítor A. S. Almodovar thanks FCT/MCTES for her doctoral grant (SFRH/BD/135598/2018).

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Synthesis of Ultra-High Molecular Weight Polyethylenes Catalyzed by Vanadium(V) Aroylhydrazine-Arylolates

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Synthetic polymers play important roles in our daily life due to their good properties and easy preparation. Polyethylene materials account for a significant share of the polymer market, with production estimated at 120 million tons per year. Applications range from packaging, water and gas pipelines, car parts, toys, furniture, medical devices to building materials and so-forth. They are also irreplaceable as copolymers for the synthetic rubber and elastomer manufacturing industries, even for the manufacture of photovoltaic films or artificial lungs, and in the production of cyclic olefin copolymers [1]. Research into the development of new catalysts remains an important topic, since they control the final polymer morphology, which can be of interest with the growing demands for the production of new specialized polymers and could also help to improve the performance of the existing ones, manufacturing processes and technologies, and costs [2]. Vanadium catalysts have played important roles [3]. We prepared a series of vanadium(V) aroylhydrazine-arylolates and employed them in ethylene polymerization to produce ultra-high molecular weight polyethylene (UHMWPE) [4]. MAO or DMAC could activate the complexes **V1–V3** (**Figure 1**) to catalyze the polymerization reaction with an activity up to 3.37 × 10^6 g mol^{-1} h^{-1} at 60 °C. The polyethylene obtained has a molecular weight around 3 million g mol^{-1}, being the highest molecular weight achieved by a vanadium catalyst of this type so far. The cocatalyst MAO was generally less active than DMAC (0.43 vs. 3.37 × 106 g mol^{-1} h^{-1}), but it led to higher molecular weight polyethylenes.

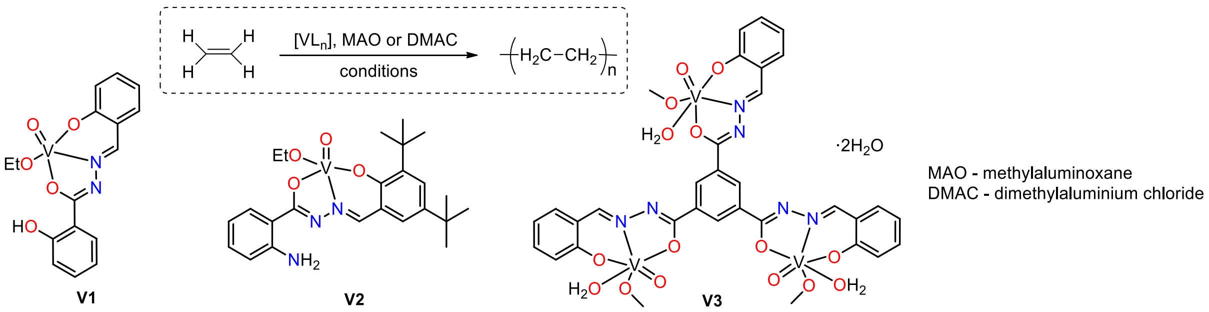

Figure 1: Ethylene polymerization catalyzed by vanadium (V) catalysts **V1-V3**.

Acknowledgements: This work was supported by the National Natural Science Foundation of China (No. 21871275, 52103011), the Natural Science Foundation of Shandong Province (ZR2021QE211), and Fundação para a Ciência e a Tecnologia (FCT), Portugal, in the form of projects UIDB/00100/2020 and UIDP/00100/2020 of Centro de Química Estrutural and project LA/P/0056/2020 of the Institute of Molecular Sciences. It has also been supported by the RUDN University Strategic Academic Leadership Program (recipient A.J.L.P., preparation).

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Design and Synthesis of a Covalent Organic Polymer Towards the Environmental Remediation

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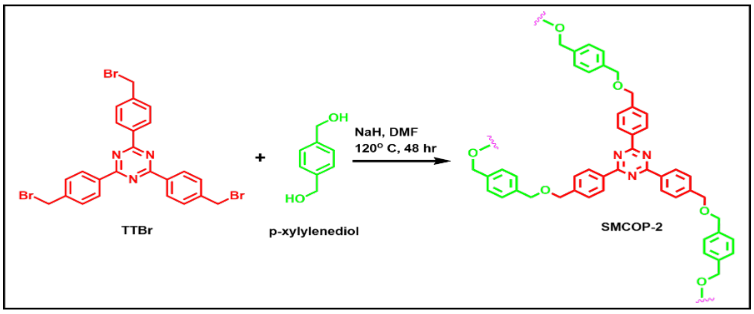
Covalent organic polymers (COPs) are highly acclaimed among the functional materials for efficiently resolving environmental issues. Several reports are available on N-rich COPs having imine bonds for various applications in environmental remediation. Herein, we have designed and synthesized an ether-linked robust covalent organic polymer (SMCOP-2)[1a] with triazine core by an elementary S_N2 reaction and was characterized by FTIR, UV-DRS, ^{13}C CP/MAS, PXRD, FE-SEM, thermogravimetric analysis (TGA), etc.

Upon exposure to the acid vapor, SMCOP-2 changes its color. We've categorically explored the phenomenon and explained the sensing mechanism with the help of UV-DRS and FTIR. This way, the polymeric material could detect any leakage of HCl gas in the laboratories and in industries.

$Cr_2O_7^{2-}$ ions are known for DNA damage and the development of tumors. We've observed that the fluorescence emission of SMCOP-2 gets quenched in the presence of $Cr_2O_7^{2-}$ ions; corresponding ksv and LOD values are quite low, which makes it a suitable luminescent sensor for the $Cr_2O_7^{2-}$ ions present in water. Malachite green dye known to be carcinogenic in nature. SMCOP-2 can degrade malachite green photo catalytically in visible light, which follows the pseudo-first-order kinetics.



Scheme 1: Synthesis of SMCOP-2

Acknowledgements: We thank IIT Indore for instrumental and financial support.

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Ficha Técnica:

Título: ISySyCat – International Symposium on Synthesis and Catalysis, Évora, 2023

Editores: Carolina S. Marques, Elisabete P. Carreiro, Anthony J. Burke

Impressão: Cromotema

Tiragem: 228 exemplares

Designer Capa: Susana Oliveira, Gabinete de Comunicação, Universidade de Évora

ISBN: 978-972-778-309-0 (printed edition)
978-972-778-310-6 (digital edition)

Notes: