UNIVERSITÉ DE SHERBROOKE

24TH QUEBEC-ONTARIO MINI-SYMPOSIUM ON BIOORGANIC AND ORGANIC CHEMISTRY

8-10 Nov. 2013

Hôtel Delta Sherbrooke

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Welcome to Sherbrooke !

It is my pleasure to welcome you in Sherbrooke, at the 24th Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry (QOMSBOC). Dedicated to the exhibition of scientific development at the graduate level, the QOMSBOC is a premier regional conference in this field that provides students with an opportunity to showcase their latest research.

Three prestigious lectures will be given by keynote speakers from academia and industry:

- Professor Masad J. Damha, McGill University;
- Dr Lawrence G. Hamann, Novartis Institute for biomedical research, Cambridge (US), and;
- Professor Marc L. Snapper, Boston College.

I want to thank all the people that have been involved in the organization of this event: Professor Alexandre Drouin (Bishop's University, scientific program), Sophie Beauchemin, the Université de Sherbrooke, the students from my research group for their precious help, and all the volunteers.

I hope you will enjoy your stay in Sherbrooke. Looking forward to making this new edition of QOMSBOC a success!

Bienvenue à Sherbrooke !

Il me fait plaisir de vous accueillir à Sherbrooke, pour ce 24ème Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry (QOMSBOC). Dédié à l'exposition du développement scientifique au niveau des études supérieures, le QOMSBOC est une conférence régionale de premier plan offrant aux étudiants l'occasion de présenter leurs récentes avancées en recherche.

Trois conférences prestigieuses seront données par des conférenciers provenant du milieu universitaire et de l'industrie :

- Professeur Masad J. Damha, Université McGill;
- Dr Lawrence G. Hamann, Novartis Institute for biomedical research, Cambridge (É-U) et;
- Professeur Marc L. Snapper, Boston College.

Je tiens à remercier toutes les personnes qui ont été impliquées dans l'organisation de cet événement : le professeur Alexandre Drouin (Université Bishop, programme scientifique), Sophie Beauchemin, l'Université de Sherbrooke, les étudiants de mon groupe de recherche pour leur aide précieuse et tous les bénévoles.

J'espère que vous apprécierez votre séjour à Sherbrooke. Au plaisir de faire de cette nouvelle édition de QOMSBOC un succès!

Prof. Guillaume Bélanger
Université de Sherbrooke
Chairman

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Vendredi / Friday 8 nov. 2013

Lac Mégantic	19h00 - 21h00	Inscription / Registration
	19h00 - 22h00	Cocktail de bienvenue / Mixer

Samedi / Saturday 9 nov. 2013

Lobby	7h45	Inscription / Registration
Sherbrooke C	8h30	Mot de bienvenue / Opening remarks
	8h40	**OR1**. Goeffrey Phillips (University of Western Ontario)
	9h00	**OR2**. Jennifer Farmer (York University)
	9h20	**OR3**. Roya Mirabdolbaghi (Brock University)
	9h40	**OR4**. Gaëtan Maertens (Université du Québec à Montréal)
	10h00	**OR5**. Cyrus Lacbay (McGill University)
Lobby	10h20	Pause / Break
Sherbrooke C	10h40	**OR6**. Thomas Johnson (University of Toronto)
	11h00	**OR7**. Vimal Varghese (Brock University)
	11h20	**PL1**. Prof. Masad J. Damha (McGill University)
Sherbrooke B	12h10	Dîner / Lunch (installation des affiches / poster set up)
Sherbrooke C	13h40	**OR8**. Stéphane De Cesco (McGill University)
	14h00	**OR9**. Ramsay Beveridge (University of Toronto)
	14h20	**OR10**. Michaël Raymond (Université de Montréal)
	14h40	**OR11**. Jean-François Vincent-Rocan (Université d'Ottawa)
Lobby	15h00	Pause / Break
Sherbrooke C	15h20	**OR12**. Pascal Léveillé (Université de Sherbrooke)
	15h40	**PL2**. Dr Lawrence G. Hamann (Novartis Institutes for Biomedical Research)
Sherbrooke A	16h30 - 18h30	**Séance par affiche / Poster session** – cocktail
Sherbrooke C	18h30	Délibération des juges pour affiches / Meeting of posters judges
Sherbrooke B	19h00	**Banquet**

Dimanche / Sunday 10 nov. 2013

Sherbrooke C	8h30	**OR13**. Adam Zajdlik (University of Toronto)
	8h50	**OR14**. Keller Guimarães (Queens' University)
	9h10	**OR15**. Avid Hassanpour (Concordia University)
	9h30	**OR16**. Philippe McGee (Université d'Ottawa)
	9h50	**OR17**. Carolyn Ladd (Université de Montréal)
Lobbby	10h10	Pause / Break (délibération des juges des présentations / meeting of presentation judges)
Sherbrooke C	10h30	**OR18**. Starr Dostie (Institut de recherches cliniques de Montréal)
	10h50	**PL3**. Prof. Marc L. Snapper (Boston College)
	11h40	Mot de la fin / Closing remarks

Professor Masad J. Damha

"Structural and Functional Studies of Nucleic Acid Analogues"

Chemically modified oligonucleotides have found remarkable utility in an exceptionally diverse range of applications. Modified nucleic acids can now be found in clinically approved drugs, and chemically modified nucleotide analogues have provided valuable tools for studying the structure of oligonucleotides and their interactions with enzymes. Fluorinated nucleosides (arabinonucleosides, ribonucleosides, etc), and ring expanded nucleosides are of particular interest in our research. I will discuss the synthesis and development of new fluorinated furanose nucleosides and ring expanded (oxapane) nucleosides for a) chemical modification of nucleic acids and b) to probe the nucleotide excision processes of HIV Reverse Transcriptase (RT). Furthermore, I will present results investigating the consequences of our nucleotide modifications on duplex and higher order structures, conformation, stability, and nucleic acid interactions with enzymes such as gene silencing enzymes (RISC).

MASAD JOSÉ DAMHA was born in and raised in Managua, Nicaragua and immigrated to Canada in 1978. He attended McGill University, completing a B.Sc. in Chemistry (1983) and then a Ph.D. (1987) in Organic Chemistry there with Professor Kelvin K. Ogilvie. His Ph.D. work focused on the synthesis and conformational analysis of nucleic acids (RNA). In 1987, he accepted a position of Assistant Professor at the University of Toronto's Erindale College (UTM). In 1992, he returned to his Alma Mater, where as James McGill Professor of Chemistry, he is working in the field of bio-organic and bio-medicinal nucleic acid chemistry. His research is bearing fruit in the development of new therapeutic drugs based on protein and RNA targeting. With his students, he has authored over 150 publications, and filed/received several patents worldwide.

In 1999, Professor Damha co-founded Anagenis, Inc. - a start up company with proprietary antisense technologies that was later acquired by Topigen Pharmaceuticals, Inc., a Montreal-based biotechnology company.

Prof. Damha is Chair of the Department of Chemistry (2013-2018), President of the Oligonucleotide Therapeutics Society (2013-2014), and Treasurer of the International Society of Nucleosides, Nucleotides and Nucleic Acids (2012-2014). Recently, he served as Associate Vice-Principal (Research & International Relations) at McGill (2010-2011). He has also served in the Editorial Board of the journal *Bioconjugate Chemistry* (1999-2003).

Other honors include: The John Charles Polanyi Chemistry Prize (Ministry of Colleges and Universities, 1989), The IUPAC Award (Chemical Institute of Canada, 1991), Ichikizaki Awards for Young Chemist (1989-94), the Merck-Frosst Award for Therapeutic Research (CSC, 1999), the Fellowship of the Chemical Institute of Canada (F.C.I.C.), the James McGill Professorship (McGill University, 2004-2011), the Bernard Belleau Award of the CSC (2007), the Fessenden Professorship in Science Innovation (McGill University; 2010), the David Thomson Award in Graduate Supervision and Teaching (McGill University; 2010), the Leo Yaffe Award for Excellence in Teaching (McGill University; 2011-12), and the Queen Elizabeth II Diamond Jubilee Medal (The Governor General of Canada; 2012).

Dr Lawrence G. Hamann

"Synthetic Methods Development in Drug Discovery"

Adapting cutting edge synthetic methods to enable construction of pharmaceutically relevant heterocyclic molecules is critical to efficiently access broader chemical space on the way to innovative medicines. Additionally, the consideration of sustainable or "green" chemistry practices in medicinal chemistry is of high importance, and can have significant downstream benefit as methods used in a discovery setting are perpetuated into drug development. These two aspects have led us to focus some efforts on telescoped reaction sequences, and late-stage derivatization afforded by C-H functionalization methods. Recently reported methyliminodiacetic acid (MIDA) protected boronic acids allow us to use cross-coupling retrosynthetic strategies in alternate bond construction sequences, and slow *in situ* release of the free boronic acid in a subsequent step enables telescoped reaction sequences. We have developed one-pot sequences including a variety of reaction types together with SM cross-coupling to demonstrate the utility of this concept. We have also begun to develop methods for efficient C-H functionalization of drug-like molecules which contain Lewis basic heterocycles, which has been a long-standing challenge in the field of C-H activation chemistry.

LAWRENCE G. HAMANN received his BS degree in Chemistry from the University of Detroit and his PhD in Organic Chemistry from the University of Michigan working with Professor Masato Koreeda. He then joined Ligand Pharmaceuticals in San Diego in 1992, where he participated in the discovery of some of the first known non-steroidal modulators of nuclear hormone receptors. Moving to Bristol-Myers Squibb in 1999, he led drug discovery teams targeting cardiovascular and metabolic disease, sarcopenia, hepatitis C and HIV, delivering multiple clinical development candidates, including the FDA approved DPP4 inhibitor saxagliptin (Onglyza™) for type 2 diabetes, and the first-in-class HCV NS5A inhibitor daclatasvir, currently in Phase III clinical trials.

He joined the Novartis Institutes for BioMedical Research (NIBR) in Cambridge, MA in 2008 as Executive Director, Global Discovery Chemistry. At NIBR he has had responsibility for the Early Discovery Chemistry group, working closely with the Developmental and Molecular Pathways Biology Group to help progress novel drug discovery programs from target validation through candidate characterization focusing on orphan genetic diseases, oncology, infectious disease and cardiovascular disease.

In addition, Dr. Hamann has been actively engaged with the academic community, including initiation of a broad collaboration with the Center for C-H Functionalization, a NSF-sponsored Center for Chemical Innovation, for which he is a member of the Scientific Advisory Board. He is a co-inventor on more than 70 patents and has more than 60 research publications.

Professor Marc L. Snapper

"Asymmetric Functionalization of Alcohols: Four Lewis Basic Functionalities Working Cooperatively"

Nathan Manville, Hekla Alite, Fredrik Haeffner, Amir H. Hoveyda, and Marc L. Snapper, Department of Chemistry, Merkert Chemistry Center, Boston College Chestnut Hill, MA 02467, marc.snapper@bc.edu

New reactions offer opportunities to shorten synthetic routes to important targets. We will describe our efforts to develop catalytic asymmetric silylation and sulfonylation of alcohols. Our initial rational selection strategies brought us to an effective, but slow imidazole catalyst. Subsequent computations studies then allowed us to identify a co-catalyst that accelerates significantly this asymmetric transformation. The net result is a selective and practical catalytic asymmetric functionalization of diols and polyols.

MARC L. SNAPPER received a B.S. in Chemistry/Biology from Union College in Schenectady, N.Y. After four years as a Research Chemist at Sterling Organics (Rensselaer, N.Y.), he entered the graduate program at Stanford University where he obtained a Ph.D. under the guidance of Professor Paul A. Wender. Following postdoctoral studies at Harvard University under the supervision of Professor Stuart L. Schreiber, Snapper joined the Boston College Chemistry Department faculty in 1993 as an Assistant Professor. In 1999 he was promoted to Professor of Chemistry. Research interests of the Snapper group include the development of new transformations that allow for the efficient construction of molecules of importance; as well as, the use of these molecules to study biological processes.

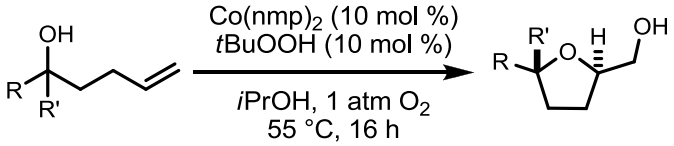
In addition, Prof. Snapper has been actively engaged with the academic community, including initiation of a broad collaboration with the Center for C-H Functionalization, a NSF-sponsored Center for Chemical Innovation, for which he is a member of the Scientific Advisory Board. He is a co-inventor on more than 70 patents and has more than 60 research publications.

Prof. Snapper served in several Review Panels for the NIH and the NSF, coauthored 95 research publications and 2 patents. He received several honors and awards, including the Lilly Grantee Award (1997-1999), DuPont Young Professor Award (1998-2001), Glaxo Wellcome Chemistry Scholar Award (1999-2001), Merck Chemistry Councyl Grant (2000-2002), and the Japanese Society of Synthetic Organic Chemistry Lectureship Award (2004).

OR1 Formation of 2,5-*trans*-tetrahydrofurans through oxidative cyclization employing a second generation catalyst

Geoffrey Phillips and Brian L. Pagenkopf* Department of chemistry, The University of Western Ontario, London, ON, N6A 5B7, bpagenko@uwo.ca

The tetrahydrofuran (THF) ring is a prolific motif found in wide array of natural products with potent and varied biological activity. The Mukaiyama aerobic oxidative cyclization has emerged as a facile method for the synthesis of 2,5-*trans*-THFs in high yield and excellent levels of diastereoselectivity. Our group has developed a second generation catalyst, $Co(nmp)_2$, for use in the oxidative cyclization which circumvents purification issues associated with first generation catalysts. The new second generation catalyst has been applied to the synthesis of 2,5-*trans* and 2,5,5-tri-substituted THFs in good to excellent yields and high levels of diastereoselectivity.[1]

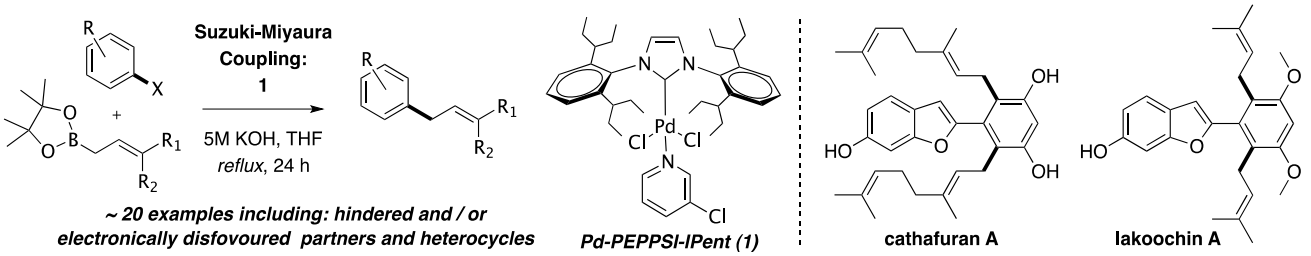


Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B.; Machin, B. P.; Pagenkopf, B.L. *Org. Lett.* **2009**, *11*, 5614-5617.

OR2 Regioselective Suzuki-Miyaura coupling of allylboronic acid pinacol ester derivatives with aryl halides via Pd-PEPPSI-IPent

Jennifer L. Farmer, Howard N. Hunter and Michael G. Organ* Chemistry Department, York University, Toronto, ON, M3J 1P3, organ@yorku.ca

Pre-catalyst *Pd-PEPPSI-IPent* (**1**) has been shown to be very reactive in the Suzuki-Miyaura coupling (SMC) of allylboronic acid pinacol ester derivatives with various aryl and heteroaryl halides.[1] Essentially, exclusive regioselectivity for the linear product was observed with prenylboronic acid pinacol ester (R_1 = R_2 = Me). In the case of *E*-trisubstituted allylboronates with different substituents on the olefin, minor olefin geometry isomerization was observed (*E/Z* ≈ 80/20). The high linear selectivity demonstrated by **1** over other Pd-catalysts has significant synthetic value as this process can now be used with high-reliability to produce such allylated aromatics. Using this method the first total synthesis of cathafuran A, lakoochin A, and their derivatives is being investigated. Their structural features combined with their important biological and pharmacological activities make them interesting synthetic targets.

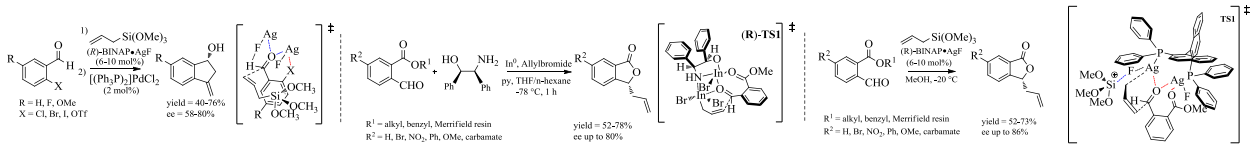


1. Farmer, J. L.; Hunter, H. N.; Organ, M. G.* *J. Am. Chem. Soc.* **2012**, *134*, 17470.

OR3 Allylation of sterically hindered *ortho*-substituted arylaldehydes as a route to medicinally useful products

Roya Mirabdolbaghi and Travis Dudding* Department of Chemistry, Brock University, St. Catharines, ON, L2S 3A1. Canada. *tdudding@brocku.ca*

We have developed a sequential Ag(I)/Pd(II) catalyzed asymmetric Sakurai-Hosomi-Yamamoto allylation/Heck reaction that affords biologically active C_1-chiral 3-methylene-indan-1-ols with enantiomeric excess (ee) up to 80%.[1] Notably, this protocol allowed for the use of various *ortho*-substituted arylaldehydes (usually considered to be challenging substrates) and afforded respectable levels of enantioselectivity. Moreover, we have recently advanced two complementary synthetic approaches to functionalized C_3-chiral phthalides, a class of medically useful compounds, which proceed *via* one-pot allylation/transesterification sequences; (1) an indium-mediated approach and (2) a Ag(I)-catalyzed reaction that afford ee's up to 80 and 86%, respectively.[2,3] Key features of these works include the allylation of *ortho*-substituted arylaldehydes and DFT-calculations to rationalize the observed enantioselectivities. This talk will provide an overview of these develops and ongoing studies related to this area of research.

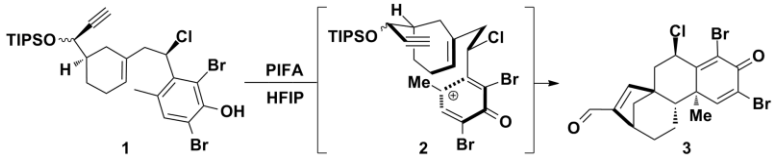


1) Mirabdolbaghi, R.; Dudding, T. *Tetrahedron* **2012**, *68*, 1988. 2) Mirabdolbaghi, R.; Dudding, T. *Org. lett*. **2012**, *14*, 3748. 3) Mirabdolbaghi, R.; Dudding, T. *Tetrahedron* **2013**, *69*, 3287.

OR4 Asymmetric synthesis of the main core of Kaurane family members triggered by an oxidative Polycyclization-Pinacol tandem process.

Gaëtan Maertens, Samuel Desjardins, Sylvain Canesi*, Département de Chimie, Université du Québec à Montréal, Montréal, QC, H3C 3P8, canesi.sylvain@uqam.ca

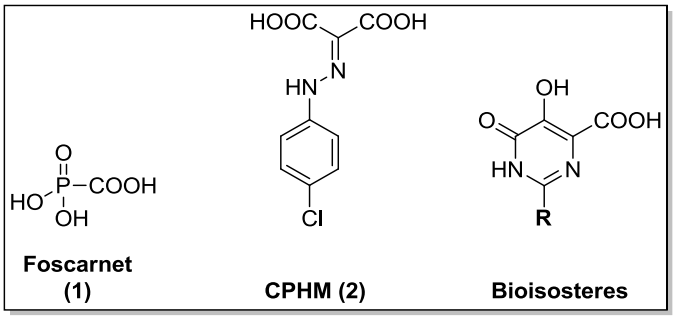
We propose an asymmetric synthesis of the main tetracyclic core ***3*** of natural diterpenes belonging to the large family named Kaurane. Our strategy is based on cationic polycyclizations of poly-unsaturated compounds concluded by a pinacolic rearrangement, two powerful synthetic tools that can provide quick access to complex natural structures with high selectivity. Moreover, our interest in oxidative dearomatization of electron-rich aromatic compounds led us to envisage triggering the polycyclization cascade by formation of a phenoxonium ion. The later results from the activation of the functionalized phenol ***1*** with bis(trifluoroacetate)iodosobenzene, an environmentally benign hypervalent iodine reagent. During the processus of cyclization, the configuration of the first quaternary center is controlled by the benzilic stereocenter via the chair transition state ***2***, minimizing steric and electronic interactions. The synthesis of phenol ***1*** is performed in 18 steps from a known benzaldehyde derivative. Key steps used include asymmetric Yamamoto allylation and hydrocyanation processes as well as a metathesis.



OR5 Studies toward the development of a new class of HIV-1 Reverse Transcriptase inhibitors

Cyrus Lacbay[1], Jean Bernatchez[2], Matthias Götte[2,3] and Youla Tsantrizos[1,2*], [1]Department of Chemistry, McGill University, Montréal, QC, H3A 0B8; [2]Department of Biochemistry; and [3]Microbiology and Immunology, McGill University; Youla.Tsantrizos@mcgill.ca

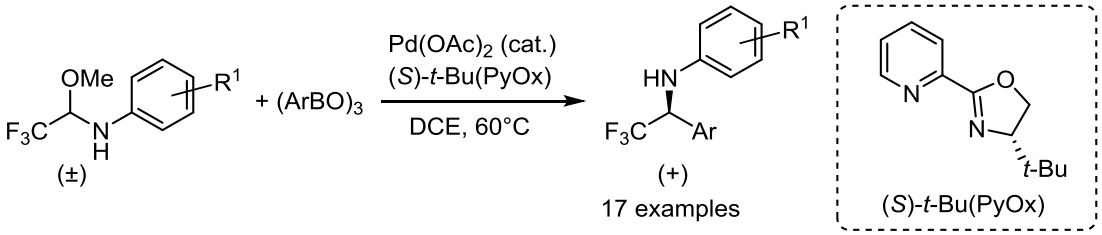
Reverse transcriptase (RT) is essential for HIV replication. We identified novel chemical classes of RT inhibitors that target specifically the pre-translocational conformation of the RT-DNA/DNA complex. Foscarnet (**1**) and the mesoxalic acid derivative **2** have been shown to trap the pre-translocational state, presumably by binding in close proximity to the active site *via* metal-mediated interactions. The synthesis of bioisosteres with improved "drug-like" properties and their biochemical evaluation will be described. These novel HIV-1 RT inhibitors have the potential to be developed into compounds that show antiviral activity against HIV strains that are resistant to current drugs targeting the RT enzyme.



OR6 Palladium(II)-catalyzed enantioselective synthesis of α-(trifluoromethyl)arylmethylamines

Thomas Johnson and Mark Lautens* Department of Chemistry, University of Toronto, Toronto, Ontario, M5S 3H6, mlautens@chem.utoronto.ca

Trifluoromethylated amines have generated increasing interest in medicinal chemistry, both as amide bond isosteres and as more lipophilic versions of the non-fluorinated analogues. We have developed an enantioselective synthesis of α-(trifluoromethyl)arylmethylamines, by a palladium(II)-catalyzed addition of boroxines to trifluoromethylaldimines, generated *in situ* from the corresponding *N,*O-acetals. Notably, the reaction tolerates ambient air and moisture and generally high enantiomeric ratios are obtained, with the use of a pyridine-oxazoline (PyOx) ligand.[1]

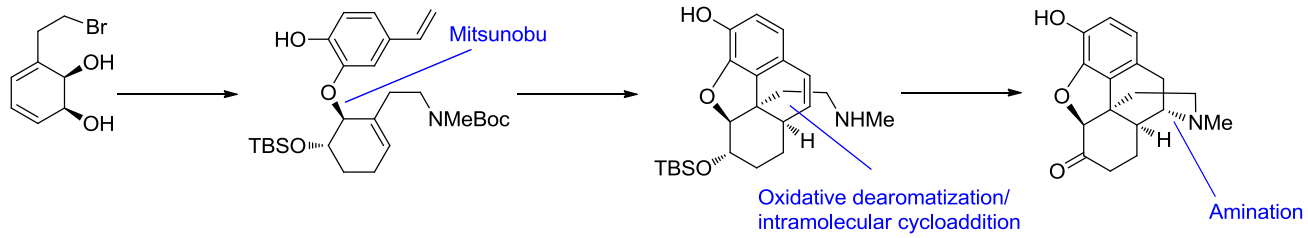


(1) Johnson, T.; Lautens, M. *Org. Lett.* **2013,** *15*, 4043.

OR7 Short chemoenzymatic total synthesis of *ent*- hydromorphone by oxidative dearomatization/intramolecular [4+2] cycloaddition/ amination sequence

Vimal Varghese and Tomas Hudlicky* Department of Chemistry, Brock University, 500 Glenridge Ave., St. Catharines, ON, L2S 3A1, thudlicky@brocku.ca

The application of biocatalytic methods to target-oriented synthesis has resulted in short, enantioselective syntheses of a number of natural products.[1] Enzymatic dihydroxylation of β-bromoethylbenzene generates the corresponding *cis*-diene diol,[2] which is utilized as starting material for the synthesis of *ent*-hydromorphone. We will describe the most efficient route towards hydromorphone, which involves a Mitsunobu reaction to tether A and C rings, an oxidative dearomatization/intramolecular cycloaddition to furnish the tetracyclic core and an amination/oxidation sequence to complete the synthesis in 12 steps. Details of the synthesis will be presented.



Hudlicky, T.; Reed, J. W. *Chem. Soc. Rev*. **2009**, *38*, 3117-3132.
Hudlicky, T.; Reed, J. W. *Synlett* **2009**, 685-703.

OR8 Combining computational, synthetic and biophysical tools for the development of covalent prolyl oligopeptidase (POP) inhibitors

Stéphane De Cesco*, Anthony Mittermaier and Nicolas Moitessier Chemistry department, McGill University, Montreal, Quebec, H3A 0B8, stephane.decesco@mail.mcgill.ca

POP is a serine endoprotease linked to neurodegenerative (e.g. Alzheimer's disease) disorders. Using our computational tools and evaluation of synthetic feasibility, a first series of constrained **covalent inhibitors** exhibiting activity and selectivity for POP was developed. In practice, following its computational design, a virtual hit molecule together with analogues were selected for synthesis and then evaluated for their inhibitory potency. As predicted by our software, this new chemical series shows not only activity in the nanomolar range in intact cells but also acceptable metabolic stability[1]. In order to further understand the covalent aspect of binding, in vitro and biophysical assays have then been developed.

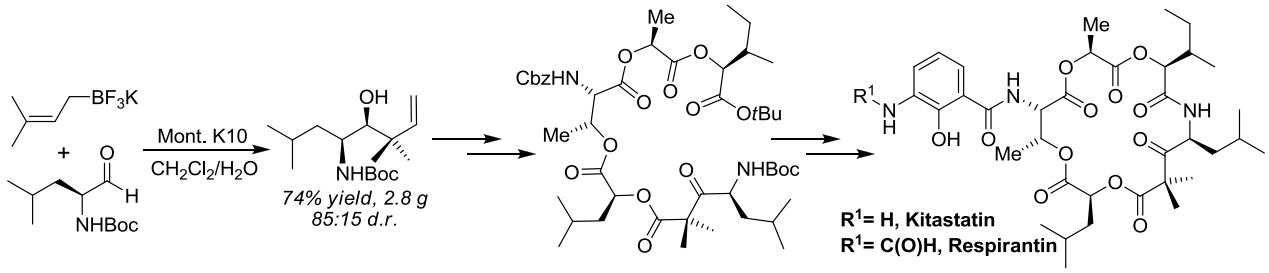
We will describe the design and development of a novel molecular scaffold that led to inhibitors with improved drug-like profile compared to our first developed inhibitor. a study of their kinetic of binding as well as their pharmacokinetic and thermodynamic profile (through Isothermal Titration Calorimetry) is currently ongoing.

1. De Cesco, S.; Deslandes, S.; Therrien, E.; Levan, D.; Cueto, M.; Schmidt, R.; Cantin, L.-D.; Mittermaier, A.; Juillerat-Jeanneret, L.; Moitessier, N. *J. Med. Chem.* **2012**, *55*, 6306–6315.

OR9 Convergent total synthesis of the potent cancer cell growth inhibitory depsipeptide natural products kitastatin and respirantin

Ramsay E. Beveridge, Robert A. Batey*, Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6, rbatey@chem.utoronto.ca

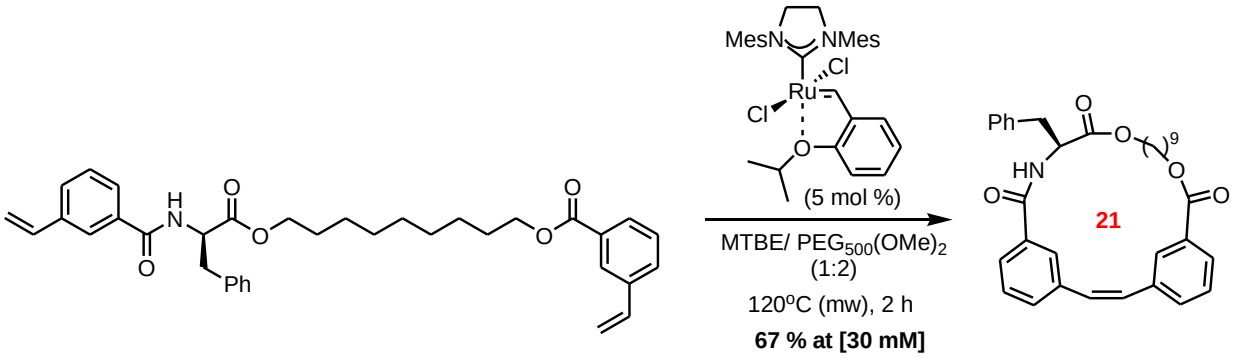
Kitastatin and respirantin are two recently discovered neo-antimycin macrocyclic depsipeptides with clinically attractive ng/mL cytotoxic activity and structurally interesting ester-rich 18-membered macrocycles containing a unique gem-dimethyl-β-keto-ester unit. Currently, pre-clinical development of these compounds as cancer treatment agents is restricted by the small quantities that can be obtained from the natural bacteria source (e.g., 380 L of fermentation broth is required to obtain 2.6 mg of kitastatin) which we sought to address by targeting these natural products for synthesis. In this talk, we outline a non-linear and scaleable total synthesis of kitastatin and respirantin utilizing an efficient C and N-terminus bis-deprotection/macrolactamization sequence to convergently secure the core macrocycle. In addition, a diastereoselective multi-gram scale prenyltrifluoroborate addition to N-Boc-L-Leucinal is featured as a strategy to install the structurally unique gem-dimethyl-β-keto-ester fragment.



OR10 Macrocyclic Olefin Metathesis at High Concentrations Employing a Phase Separation Strategy.

Raymond, Michaël, Holtz-Mulholland, M., Collins, S. K.*, Département de Chimie, Center for Green Chemistry and Catalysis, Université de Montréal, Montréal, Québec, H3T 1J4

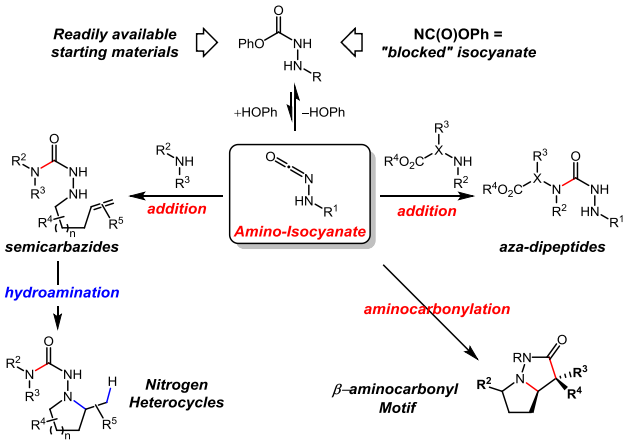
Olefin metathesis has emerged as a "go-to" method for the preparation of macrocycles. Despite the wealth of applications, macrocyclic olefin metathesis typically exploits high dilution/slow addition type strategies to promote efficient macrocyclization. The tedious reaction set-up and extremely dilute reaction media is cumbersome and environmentally damaging. Herein, the development of a macrocyclic olefin metathesis protocol is described which can be conducted at relatively high concentrations via a phase separation strategy. Ru-based olefin metathesis catalysts were applied to macrocyclization reactions of pharmaceutically relevant motifs such as rigidified macrocyclic peptides and cyclophanes.



OR11 Exploration of Amino-Isocyanate Reactivity

Jean-François Vincent-Rocan, Christian Clavette and André Beauchemin, Department of Chemistry, University of Ottawa, Ottawa, ON, K1N 6N5, andre.beauchemin@uottawa.ca

Hydrazine derivatives are useful in heterocyclic synthesis, peptidomimetics, and present as subunits in many pharmaceuticals and agrochemicals. Despite the importance of these motifs, inclusion of hydrazine subunits in molecular scaffolds can quite problematic due to inherent chemoselectivity issues: often each nitrogen atoms can react, which would lead to different products. Recently, we have shown that hydrazides can react with alkenes to afford either hydroamination or amino-carbonylation products.[1] Selected reagents act as precursors of amino-isocyanates, which are rare, reactive intermediates. We will report on the controlled generation and use of such amphoteric intermediates to form complex hydrazine derivatives via cascade reactions.



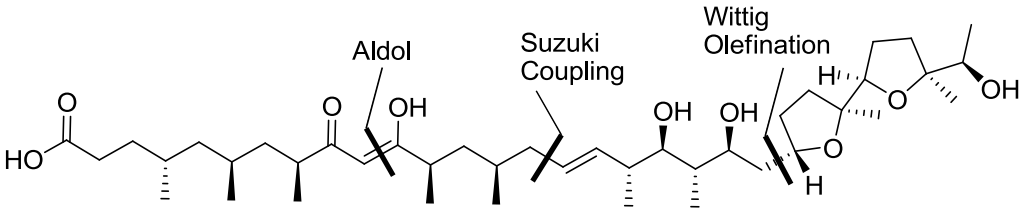
1) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Whipp, C. J.; Gorelski, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

OR12 Progress towards the total synthesis of ionomycin

Pascal Léveillé, Martin Allan, Marc-André Joly and Claude Spino, Département de chimie, Université de Sherbrooke, Sherbrooke, QC, J1K 2R1, Claude.Spino@usherbrooke.ca

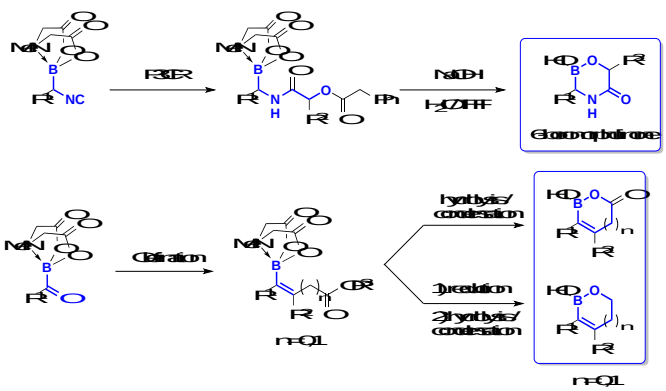
Ionomycin, an ionophore isolated from the bacteria Streptomyces conglobatus, is often used for its remarkable ability to selectively complex Ca^{2+} cations in a 1:1 ratio. A total synthesis of the natural enantiomer is currently being completed using a convergent strategy, taking advantage of the hidden pseudosymmetry.

The 1,3-relationship structural pattern encompassing the methyls is created using a SN2'-type displacement of menthol-derived allylic carbonates by cuprates. The isolated chiral alkenes are obtained with great diastereoselectivity. They are then cleaved by ozone and the obtained alcohols can be used directly towards the synthesis or used in iteration to add another propyl unit. These compounds are used to prepare three of the four fragments of ionomycin. The bis-tetrahydrofuran fragment is obtained using a polycyclisation of a chiral diepoxyde, starting from geraniol. The planned synthesis takes about 50 steps, 22 for the longest linear sequence.



OR13 Amphoteric boron-transfer agents in the preparation of biologically-active boron-containing heterocycles

Adam Zajdlik and Andrei K. Yudin*; Department of Chemistry, University of Toronto, Toronto, ON, M5S3H6, ayudin@chem.utoronto.ca



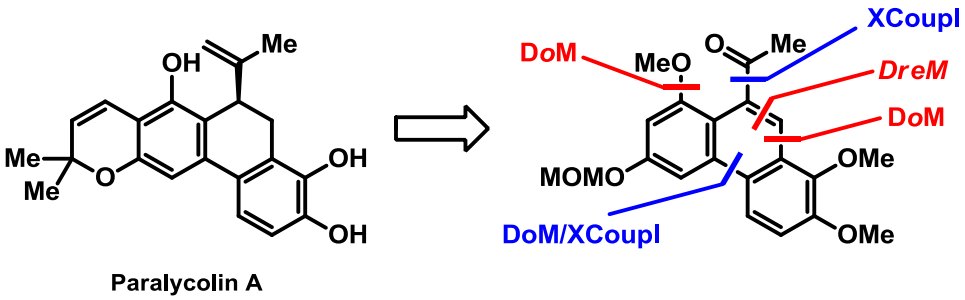
Boron-containing heterocycles are known to exhibit a wide range of desirable biological activity and have significant potential for interesting synthetic applications. 6-Boromorpholinones are demonstrated to be potent and selective 20S protease inhibitors (IC_{50} value of 19 nM for chymotrypsin-like enzymes) with improved epithelial cell permeability (CACO-2) over the leading boron-containing drug bortezomib. Our research aims to tune these biological properties by altering ring size and endocyclic carbon hybridization. Access to these previously unreported heterocycles is enabled by amphoteric boron-transfer agents including acyl boronates[1] and α-boryl isocyanides.[2]

[1] He, Z.; Trinchera, P.; Adachi, S.; St Denis, J. D.; Yudin, A. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 11092–11096. [2] Zajdlik, A.; Wang, Z.; Hickey, J. L.; Aman, A.; Schimmer, A. D.; Yudin, A. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 8411–8415.

OR14 Towards the total synthesis of (±)-Paralycolin A

Keller G. Guimarães,[1,2] C.-H. Frank Lee,[2] Timothy E. Hurst,[2] Matthew O. Kitching, [2] Alcides J. M. da Silva,[3] and Victor Snieckus[2]*
1 Departamento de Química do Instituto de Ciências Exatas (DQ/ICEx), Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil; 2 Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, Ontario, K7L 3N6, Canada; 3 Laboratório de Química Bioorgânica (LQB), Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, Bloco H, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ 21941-590, Brazil, Snieckus@chem.queensu.ca

Our efforts towards the total synthesis of the polycyclic natural product Paralycolin A will be discussed. Key features of our route are: a) the preparation of starting materials by directed *ortho* metalation (DoM) which provides unique substitution patterns, b) the powerful combination of this methodology with the Suzuki-Miyaura cross-coupling reaction to synthesize sterically conjested biaryls and c) the synthetic utility of Directed remote metalation (DreM) affording synthetically elaborate phenanthrols. In addition, methodology developed to effect chromene ring synthesis and its application to Paralycolin A will also be presented.

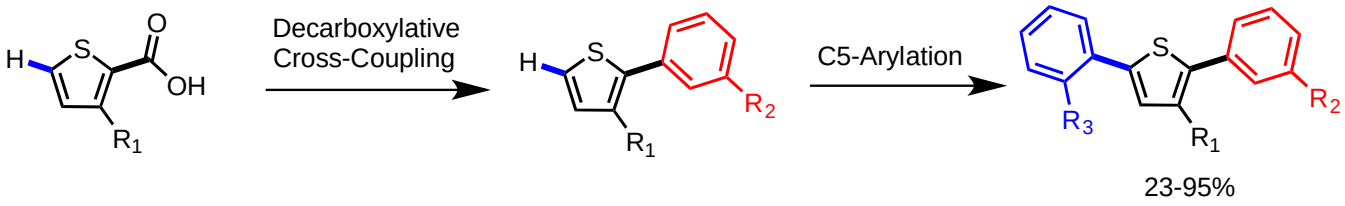


Paralycolin A

OR15 Synthesis of 2,5-diaryl substituted thiophenes towards the modulation of islet amyloid polypeptide (IAPP) amyloid fibril formation

Avid Hassanpour[a], Carole Anne De Carufel[b], Steve Bourgault[b] and Pat Forgione*[a]
[a]Department of Chemistry & Biochemistry, Concordia University, Montréal, Québec, H4B 1R6
[b]Department of Chemistry, Pharmaqam Université du Québec à Montréal, Montréal, Québec, H3C 3P8, *pat.forgione@concordia.ca*

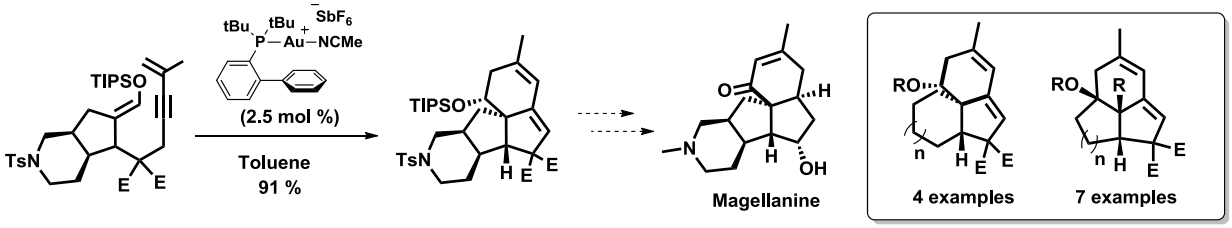
A range of 2,5-diarylated thiophenes has been synthesized as small molecule mimetics of the α-helix to modulate the amyloidogenesis and the cytotoxic effect of islet amyloid polypeptide (IAPP). 3-Substituted thiophene-2-carboxylic acids have been used as key intermediates and functionalized via palladium decarboxylative cross coupling and direct C-H activation successively with overall yields ranging from 23 to 95%. The effect of the ligands on IAPP amyloid fibril formation has been evaluated by the thioflavin T (ThT) fluorescence-based assay. Furthermore, the capacity of these compounds to inhibit the cytotoxic effect of IAPP has been assessed using β-pancreatic cells.



OR16 Synthesis of angular fused polycyclic molecules with Au(I) catalyst

Philippe McGee, Geneviève Bétournay and Louis Barriault*, Department of Chemistry, University of Ottawa, Ottawa, Ontario, K1N 6N5, pmcge031@uottawa.ca

The development of new synthetic methods for the formation of carbon-carbon bonds is of paramount importance for the efficient synthesis of molecules having applications in medicine, material science, biofuels, etc. The high affinity of Au(I/III) salts to alkyne and allene in the presence of many other functional groups and combined by its ability to stabilize cationic charges provide tremendous opportunities for the discovery of novel and useful reactions. We are currently investigating the potential of gold(I) catalysis to construct angular fused polycyclic cores by using the unique selectivity of Au(I) combined with a Prins cyclization. This will give access to functionalized polycyclic cores embedded in many complex bioactive natural products. We herein report a substrate scope for the 5-exo-dig/Prins carbocyclization as well as the total synthesis of the Magellanine.



OR17 Palladium-catalyzed direct arylation of cyclopropanes: facile access to spiro 3,3'-cyclopropyl oxindoles

Carolyn L. Ladd, Daniela Sustac Roman, André B. Charette* Département de Chimie, Université de Montréal, Montréal, H3C 3J7, andre.charette@umontreal.ca

Palladium-catalyzed, Ag(I)-mediated intramolecular direct arylation of cyclopropane C–H bonds is described.[1] Various spiro 3,3'-cyclopropyl oxindoles can be obtained in good to excellent yields from easily accessible 2-bromoanilides. The kinetic isotope effect was determined and epimerization studies were conducted, suggesting that the formation of a putative Pd-enolate is not operative and that the reaction proceeds via a C–H arylation pathway. Related direct arylation reactions targeting cyclopropanes to produce other classes of bio-relevant compounds will also be discussed.

1. Ladd, C. L.; Sustac Roman, D.; Charette, A. B. *Org. Lett.* **2013**, *15*, 1350.

OR18 Diastereoselective synthesis of nucleoside analogues via cyclization of acyclic precursors

Starr Dostie Michel Prévost, Yvan Guindon*, Chemistry, McGill University, Montreal, Quebec, H3A 0G4, yvan.guindon@ircm.qc.ca

In spite of intensive efforts over the past decades aimed at the development of preventive and therapeutic treatments, cancer and viral infections (HIV, HCV or HBV) remain leading causes of mortality and morbidity worldwide. Effective treatments involve the administration of nucleosides analogues (NAs) that act as inhibitors (antimetabolites) of tumor growth and progression. A novel approach to NA synthesis from chiral acyclic thioaminals, bearing the nucleobase, is described. We developed a kinetically-controlled cyclization of an acyclic precursor already containing the nucleobase to synthesize these sterically encumbered molecules. Such cyclizations involve a stereogenic center (at C1') bearing the nucleobase and a thioether, which may serve as a leaving group (Path A) or alternatively as a nucleophile (Path B). In order to take advantage of the stereochemistry of the thioaminal at C1', both types of cyclizations involve S_N2-like nucleophilic displacements. As well, a new series of NAs bearing a C3'-quaternary center and a C2'-F atom has been investigated as potential antimetabolites.

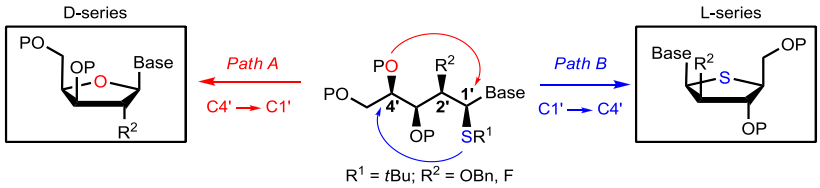
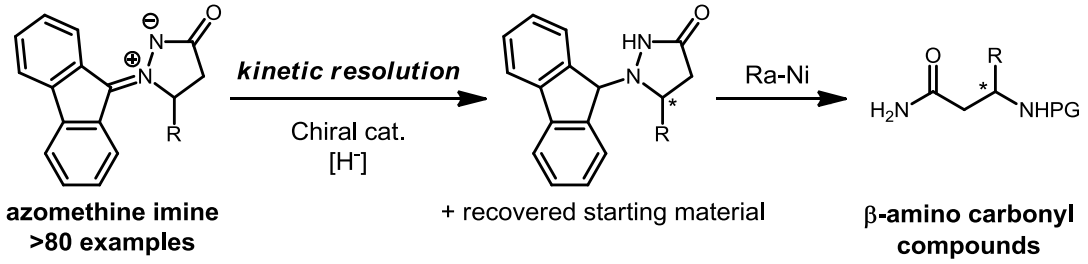


Figure 1: Synthesis of Nucleoside Analogues via Cyclization of Acyclic Precursors.

P1 Accessing β-Aminocarbonyl Compounds from Azomethine Imines

Amanda Bongers, André Beauchemin*, Department of Chemistry, Centre for Catalysis Research and Innovation, University of Ottawa, Ottawa, ON, K1N 6N5. *andre.beauchemin@uottawa.ca

Azomethine imines are valuable sources of β-aminocarbonyl compounds, a key motif in peptidomimetics and drug discovery. Our group has reported new aminocarbonylation reactivity of hydrazones and alkenes to form a variety of functionalized azomethine imines (*JACS* **2012**, 16111). Derivatization of these dipolar compounds gives access to pyrazolidinones and racemic β-amino amides, esters, and acids. Existing procedures for the kinetic resolution of azomethine imines have limited scope and low utility for our new substrates. I will present recent progress in the kinetic resolution of our azomethine imines using chiral Brønsted acid catalysts to supply enantio-enriched β-amino carbonyls.



P2 Investigation of a new family of anionic *N*-heterocyclic carbene ligands based on *N*-sulfonyliminoimidazolium ylides.

Alain Ménard, Hannah Guernon, Claude Y. Legault*, Département de chimie, Université de Sherbrooke, Sherbrooke, QC, J1K 2R1, Claude.Legault@USherbrooke.ca

A new family of *N*-heterocyclic carbene (NHC) ligands based on *N*-sulfonyliminoimidazolium ylides has been developed and are currently under investigation. The ylides are stable and are easily obtained in two steps. Following deprotonation, they form anionic NHC ligands. The synthesis of silver(I) complexes was explored. Different complex structures have been obtained, depending on the steric and electronic properties of the starting ylide proligands. Trimeric structures were usually obtained, but a tetrameric structure was observed under certain conditions. The electronic properties of the complexes can be modified by the choice of the electron-withdrawing group attached to the anionic tether. Those silver complexes could be used for insertion reaction, cycloadditions or as ligand transfer agent.

P3 DESIGN and synthesis of poly-Guanidines peptidomimetics as potential Cell-penetrating agent.

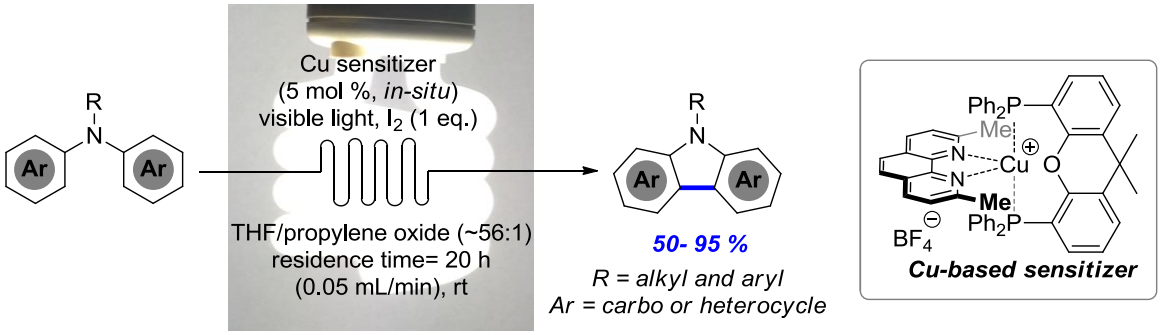
Albane NECKEBROECK, Antoine LE ROUX, Eric MARSAULT*, Laboratoire de chimie médicinale, Institut de Pharmacologie de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, J1H 5N4, eric.marsault@usherbrooke.ca

A number of biological targets are intra-cellular (e.g. RNA, transcription factors …). Usually, small and lipophilic molecules cross readily the membrane but number of biologically active molecules are unable to cross it. These molecules need efficacious transporters for cellular penetration, which ideally would also possess cell specificity. Cell penetrating peptides, often composed of poly(Arg) motifs, have the ability to penetrate cells and deliver large cargos. In order to better understand the relationship between structure and penetration as well as optimize transporters possessing cellular selectivity, we embarked on the synthesis of synthetic scaffolds displaying multiple guanidine residues in topologically rigid orientations. In this poster, we present the first steps toward the synthesis of two aryl-based artificial templates capable to display guanidine residues, for their subsequent incorporation in a solid phase synthesis scheme for the preparation of new molecular transporters.

P4 A Visible-Light-Mediated Synthesis of Carbazoles

Augusto C. Hernandez-Perez and Shawn K. Collins*, Département de Chimie, Center for Green Chemistry and Catalysis, Université de Montréal, Montréal, Qc, H3T 1J4, shawn.collins@umontreal.ca

The photosynthetic preparation of *N*-aryl- and *N*-alkyl-bearing carbazoles utilizes continuous flow, visible light, and an in situ formed Cu-based sensitizer (see picture). The method is mild and efficient, and allows the straightforward synthesis of a variety of carbazoles with different substituents, heterocycles, and complex carbon architectures.

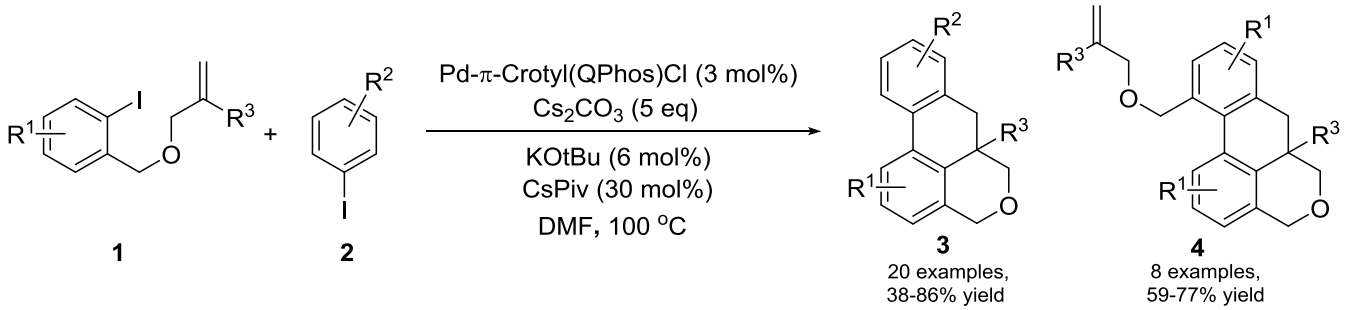


1. A.C. Hernandez-Perez, S. K. Collins *Angew. Chem., Int. Ed.* **2013**, *52*, *Early View.*

P5 3,2,1: 3 New C-C bonds, 2 C-H activations, 1 pot; a highly efficient palladium-catalyzed domino reaction

Brendan Peters, M. Sickert, H. Weinstabl, M. Lautens*, Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6, mlautens@chem.utoronto.ca

Domino reactions involve a series of transformations in which the product of one transformation is immediately consumed in the subsequent transformation. These one-pot processes are more efficient than ones requiring multiple vessels as less solvent and fewer synthetic agents are consumed. We have designed a domino process that involves the activation of two C-H bonds and the formation of three new C-C bonds to form compounds of generalized structure **3** and **4**. Similar reactions have been reported but feature fewer transformations through more facile intramolecular routes.[1]

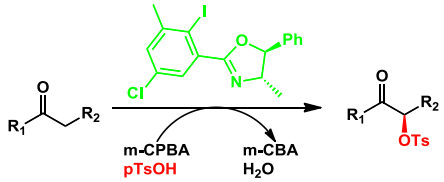


R. C. Larock, et al, *J. Am. Chem. Soc.* **2004**, *126*, 7460–7461.

P6 Catalytic enantioselective iodine(III)-mediated alpha-tosyloxylation of ketones : Recent progress

Benoit Basdevant, Audrey-Anne Guilbault, Vincent Wanie, Claude Legault*, Department de chimie, Université de Sherbrooke, Sherbrooke, QC, J1K 2R1, Claude.Legault@ushebrooke.ca

Iodine(III) reagents are of interest as they are polyvalent electrophiles and mild oxidants. They are a great alternative to toxic transition metals often used to effect similar transformations. A particularly interesting iodine(III)-mediated reaction is the α-oxidation of carbonyl compounds. The traditional method to functionalize ketones relies on the generation of an enol or enolate intermediate followed by reaction with an electrophile. Using iodine(III) reagents, it is possible to introduce nucleophiles at the same position. This type of reaction can even be rendered catalytic and enantioselective by the use of chiral iodine(I)-based catalysts. With the goal to improve enantioselectivities we developed a new class of catalysts based on iodoaryloxazolines and we evaluated their activity and selectivity. A comprehensive survey of the electronic and steric properties of the iodoaryloxazolines was accomplished and will be discussed.[1]

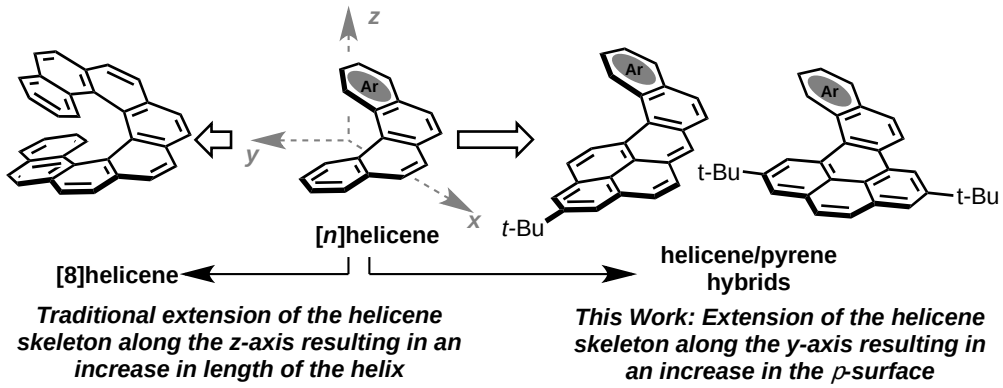


1. Legault, C. Y.; Guilbault, A.-A.; Basdevant, B.; Wanie, V. *J. Org. Chem.* **2012**, *77*, 11283-11295.

P7 Synthesis, Crystal Structure and Photophysical Properties of Novel Pyrene/Helicene Hybrids

Bédard, A.-C.; Vlassova, A.; Hernandez-Perez, A. C.; Bessette, A.; Hanan, G. S.; Heuft, M. D.; Collins, S. K.* Department of Chemistry, Center for Green Chemistry and Catalysis, University of Montreal, Montreal, QC, H3T 1J4, shawn.collins@umontreal.ca

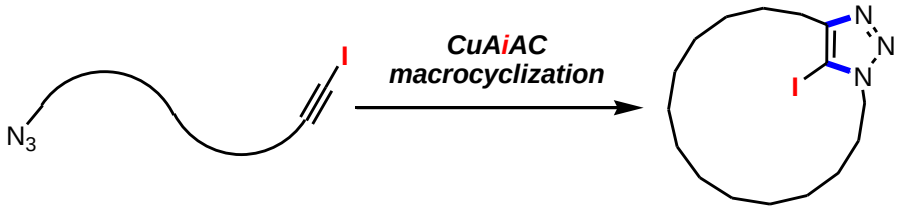
Synthesis of helically chiral aromatics resulting from fusion of pyrene and [4]- or [5]helicene has been accomplished using photoredox catalysis employing a Cu-based sensitizer as the key step. Photocyclization experiments for the synthesis of the target compounds were carried out in batch and using continuous flow strategies. The solid-state structures, UV/Vis absorption spectra and fluorescence spectra of the pyrene–helicene hybrids were investigated and compared to that of the parent [5]helicene to discern the effects of merging a pyrene moiety within a helicene skeleton.



P8 Efficient Macrocyclic Cu(I)-Catalyzed Cycloaddition of Iodoalkynes and Azides via a Phase Separation Strategy

Bédard, A.-C. and Collins, S. K.,* Department of Chemistry, Center for Green Chemistry and Catalysis, University of Montreal, Montreal, QC, H3T 1J4, shawn.collins@umontreal.ca

The copper-catalyzed azide–alkyne cycloaddition reaction has become an important synthetic strategy for the preparation of macrocycles, particularly in medicinal chemistry, where the triazole can act as an amide isostere. Despite the wealth of applications, most macrocyclic CuAAC reactions still suffer from the slow rate of ring closing associated with conventional macrocyclization reactions. Consequently, long reaction times and high catalyst loadings can be required to obtain practical and efficient macrocyclization. We report the development of an efficient macrocyclic Cu(I)-catalyzed azide-iodoalkyne cycloaddition process that can be performed at relatively high concentrations using a phase separation strategy.

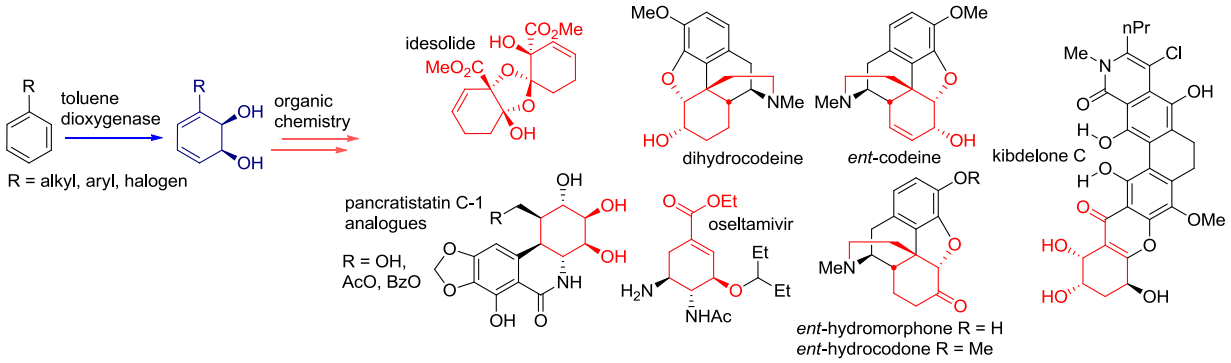


First demonstration of a macrocyclic CuAiAC process
Retained wide functional group tolerance, Catalytic copper
Simple experimental set-up/Relatively high concentrations
New sites for further functionalization

P9 Enzymatic dihydroxylation in enantioselective synthesis of complex natural products. Update from the Hudlicky Group

Brennan Murphy, Tomas Hudlicky,* Department of Chemistry and Centre for Biotechnology, Brock University, St. Catharines, ON, L2S 3A1, thudlicky@brocku.ca

A summary of recent synthetic endeavors from the Hudlicky laboratories will be presented. Projects involving the total synthesis of C-1 analogues of pancratistatin, morphine alkaloids, oseltamivir, and idesolide and kibdelone congeners will be discussed. Enzymatic dihydroxylation of aromatic compounds by a recombinant strain of *E. Coli* JM 109 (pDTG601A), which overexpresses toluene dioxygenase, leads to enantiomerically pure starting materials for natural product synthesis. Details of recent total syntheses will be provided.[1]



1. Hudlicky, T.; Reed, J. W. *Synlett* **2009**, *5*, 685-703.

P10 Synthesis of chiral diamines and their utilization in asymmetric synthesis

Christopher Bérubé, Sébastien Cardinal and Normand Voyer, Département de chimie, Université Laval, Québec, QC, G1V 0A6, christopher.berube.1@ulaval.ca

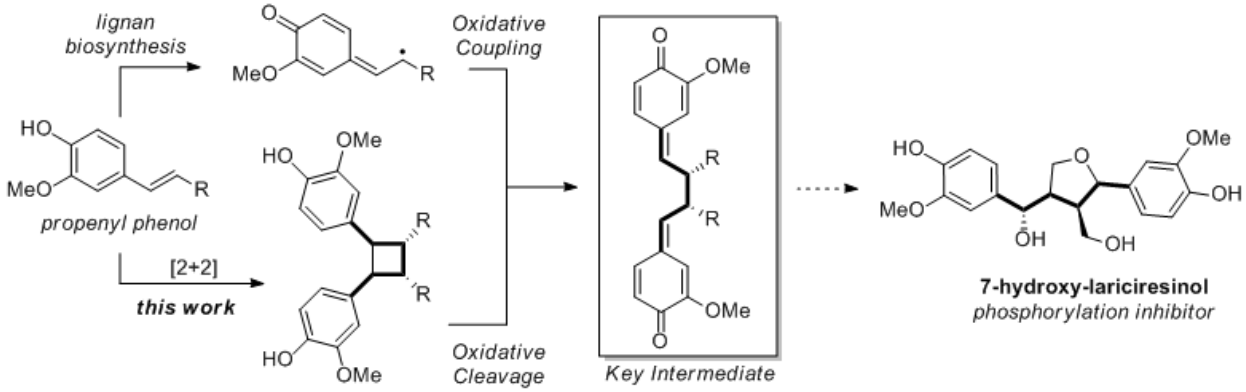
The use of chiral ligands is a useful strategy for efficient enantioselective synthesis. (-)-Sparteine, a natural chiral diamine, has been used successfully in asymmetric synthesis, but has important limitations. With the objective of developing novel chiral ligands, our group has explored a strategy to prepare chiral N,N'-dimethylpiperazines, six-member heterocyclic molecules that possess features of sparteine. Such diamines could potentially be used as source of chirality in various enantioselective chemical reactions.

To obtain chiral N,N'-dimethylpiperazines, a strategy using solid-phase peptide synthesis on oxime resin was developed with natural and non-natural amino acids. Cyclization-cleaveage of dipeptides from the resin leads to the formation of diketopiperazines, which were then transformed into the desired diamines ligands. Considering that the synthetic strategy uses amino acids, a library of various chiral diamines can thus be created easily. We will report our results on the development of the strategy and present applications of the newly prepared diamines ligands in enantioselective synthesis.

P11 A biomimetic approach to lignan natural products using an oxidative cyclobutane opening

Anna K.F. Albertson; Jean-Philip Lumb* Department of Chemistry, McGill University, Montreal, QC, H3A 2K6, jean-philip.lumb@mcgill.ca

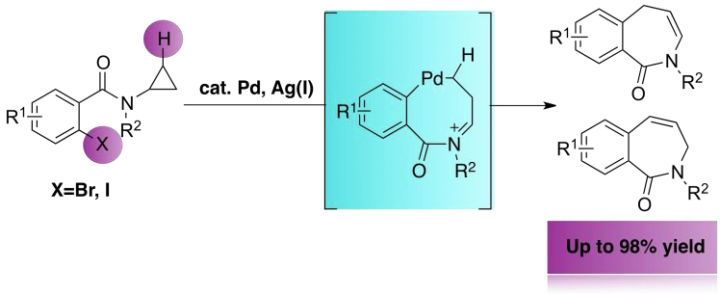
Lignans comprise a vast array of highly oxygenated, polyaromatic natural products. Despite their structural diversity, lignan biosynthesis starts from simple propenyl phenols. Attempts to mimic the biosynthetic oxidative coupling of these phenols have suffered from poor regio- and chemoselectivity, precluding their application in synthesis. Here we report a novel biomimetic approach that relies on an oxidative cyclobutane opening to intercept a biosynthetic intermediate. We demonstrate the utility of this strategy for the synthesis of numerous lignan natural products, including the phosphorylation inhibitor 7-hydroxy-lariciresinol.



P12 Synthesis of benzo[c]azepine-1-ones via palladium-catalyzed, silver-mediated intramolecular direct arylation of cyclopropyl benzamides

Carolyn L. Ladd, Daniela Sustac Roman, André B. Charette* Département de Chimie, Université de Montréal, Montréal, H3C 3J7, andre.charette@umontreal.ca

A collection of benzo[*c*]azepine-1-ones were synthesized via palladium-catalyzed, Ag(I)-promoted intramolecular cyclization of cyclopropyl benzamides.[1] Both aryl bromides and iodides were effective substrates. A range of functional groups was well tolerated, furnishing the desired products in good to excellent yields. Mechanistic studies indicate that the reaction proceeds via a carboxylate-promoted cyclopropyl C(sp^3)-H cleavage that occurs prior to ring-opening.

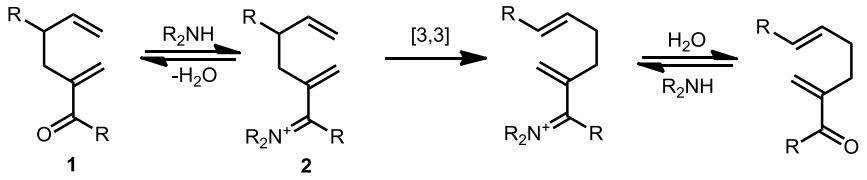


1. Ladd, C. L.; Sustac Roman, D.; Charette, A. B. *Tetrahedron* **2013**, *69*, 4479-4487.

P13 Iminium accelerated Cope rearrangements

Dainis Kaldre*, James L. Gleason, Department of Chemistry, McGill University, Montreal, Quebec, H3A 2K6, dainis.kaldre@mail.mcgill.ca

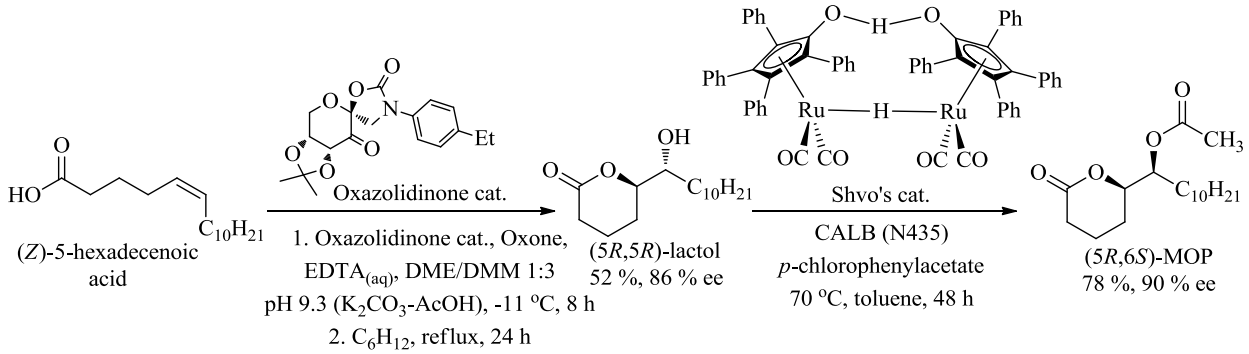
Iminium organocatalysis has found widespread use in cycloaddition and Michael addition chemistry. In contrast to wide application in cycloadditions, organcatalysts have seen only sporadic use in other pericyclic processes such as sigmatropic shifts and electrocyclic reactions. In the case of the Cope rearrangement, the only reports of catalysis use transition metals and only a single asymmetric Cope rearrangement has been reported. Preliminary computations using DFT at the B3LYP/6-31G* level suggested that the Cope reaction could be accelerated by iminium catalysis at the 2-position of a 1,5-hexadiene. Indeed, we have found that a number of secondary amines, in combination with an acid co-catalyst, do indeed catalyze the Cope rearrangement of diene **1**. In particular, N-acylhydrazines afford the greatest level of rate acceleration with reactions proceeding at room temperature with as little as 10 mol% catalyst. Catalyst optimization, substrate scope and efforts to extend to an enantioselective reaction will be discussed.



P14 Total Synthesis of Mosquito Oviposition Pheromone from a Fatty Acid Precursor

David Hurem, Travis Dudding*, Department of Chemistry, Brock University, St. Catharines, ON, L2S 3A1, tdudding@brocku.ca

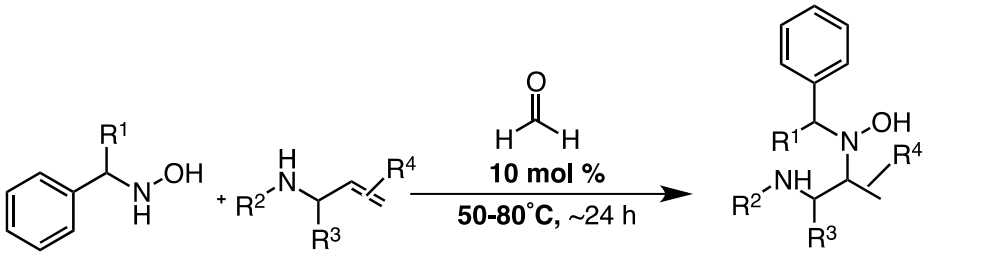
Mosquito Oviposition Pheromone (MOP) is a potent oviposition attractant of gravid *Culex sp*. mosquitos. As part of our focus on asymmetric catalysis for the synthesis of natural products, we have developed a synthetic route to MOP from (*Z*)-5-hexadecenoic acid. The key lactol intermediate was accessed *via* Shi's epoxidation, employing a chiral oxazolidinone catalyst. The requisite (*S*)-stereochemistry at C(6) of the target was obtained from dynamic kinetic resolution by lipase mediated esterification to yield (5*R*,6*S*)-MOP.



P15 Organocatalytic tether formation: a strategy enabling directed intermolecular amination reactions

D. Bilodeau, M. J. MacDonald, C. R. Hesp, S. Zhao and A.M. Beauchemin* Department of Chemistry, CCRI, University of Ottawa, Ottawa, ON, K1N 6N5, andre.beauchemin@uottawa.ca

The use of temporary intramolecularity in directed or tethered reactions is a common strategy to achieve increased reactivity in synthesis, often leading to increases in the rate, regioselectivity and stereoselectivity of intermolecular reactions. Unfortunately, approaches relying on temporary tethers are typically stepwise. As part of work toward challenging intermolecular hydroaminations, we showed that several achiral and chiral aldehydes can be efficient tethering organocatalysts, enabling a room temperature directed Cope-type hydroamination route for the synthesis of diamines. Optimization of this reactivity, increased scope, and stereoselective approaches will be presented.

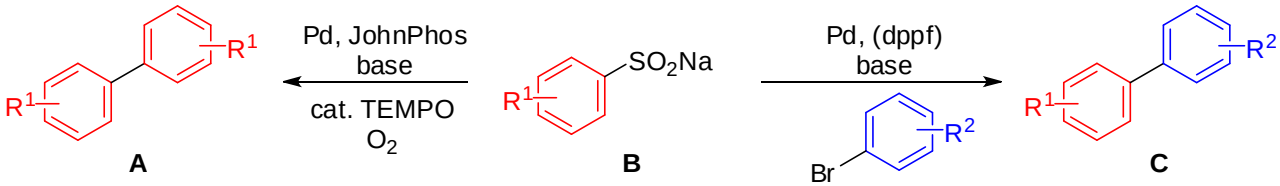


20 Examples up to 99% yield, and 20:1 *dr*

P16 Aryl sulfinates provide an alternative to organometallic reagents in palladium-catalyzed coupling reactions

Dirk Ortgies and Pat Forgione*, Department of Chemistry & Biochemistry, Concordia University, Montréal, QC, H4B 1R6 and Centre in Green Chemistry and Catalysis, Montreal, QC pat.forgione@concordia.ca

Biphenyls (**A**, **C**) are an important motif in multiple pharmacophores. Their synthesis is generally achieved via palladium-catalyzed carbon-carbon bond formation of organometallic reagents with aryl halides. Preparation of the organometallic coupling partner often requires multiple reactions, expensive reagents, and moisture-sensitive transformations. One alternative to overcome these limitations are decarboxylative cross-couplings. By analogy, a range of desulfinative processes have recently been developed. We disclosed the scope of a palladium-catalyzed coupling of aryl sulfinates (**B**) with aryl bromides, as well as a ligand-free version ([1] and references therein). Further efforts led to the development of a catalytic homo-coupling reaction of arylsulfinates under oxidative conditions. Research aimed at expanding the scope to other aryl halides and employing more sustainable conditions will also be presented.



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P17 Lewis-acid tethered imine ligands: synthesis and coordination to Pd. Designing metal-catalyzed imine/CO co-polymerization.

Fabio Lorenzini, Bruce Arndtsen*, Department of Chemistry, McGill University, Montreal, Québec, H3A 2K6, bruce.arndtsen@mcgill.ca

We are aiming at a shortcut synthetic method for polypeptides that employs, instead of amino acids as starting materials, imines and carbon monoxide as inexpensive, readily available building blocks that undergo metal-catalyzed alternating copolymerization to directly form polypeptides.

In 1998, our and Sen's group reported independently the first observation of imine insertion into acyl C–palladium bonds. This achievement constitutes a critical step toward metal-catalyzed copolymerization of imines and CO. However, desired subsequent insertion of CO into the resulting carbon–metal bond failed to occur. Tuning the ligands on palladium could solve the problem, helping CO insertion to produce a single amino acid unit, and therefore allowing continuous insertion of imines and CO.

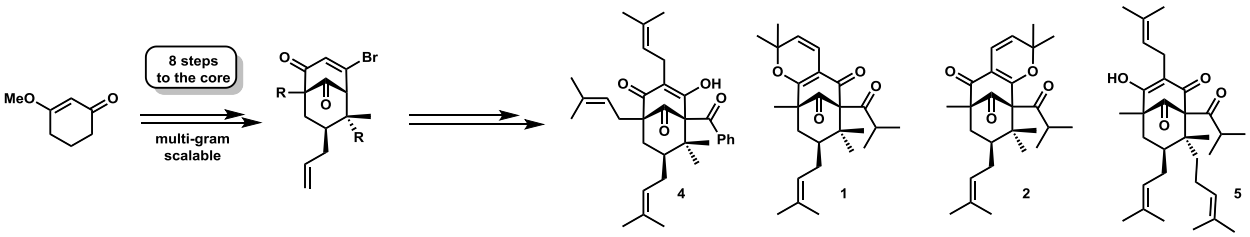
We address this issue by employing, as the ligands, Lewis-Acid tethered imine bearing further donor atoms such as N and P. The synthesis of the ligands so far investigated and their coordination to Pd are hereby discussed.

1. Dghaym, R. D.; Yaccato, K. J.; Arndtsen, B. A. *Organometallics* **1998**, *17*, 4–6. 2. Kacker, S.; Kim, J. S.; Sen, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 1251 – 1253.

P18 Unveiling Polycyclic Polyprenylated Acylphloroglucinols (PPAPs)

Gabriel Bellavance and Louis Barriault* Center for catalysis and innovation, University of Ottawa, department of chemistry, 10 Marie Curie, Ottawa, On, K1N6N5

Our group demonstrated that gold(I) catalyzed cyclization of enynes gave the corresponding bicyclo[3.3.1]alkenone which provides a direct route to the core of PPAPs natural products.[1] In the past decades, more than 100 PPAPs exhibiting a wide variety of interesting biological activities (antibiotic, anti-HIV, anti-oxidant, etc.) have been isolated from *Guttiferrea* plants. Their complex densely oxygenated, heavily substituted cores and numerous beneficial therapeutic properties have stimulated research from several groups. One can easily recognize that a general and efficient route to PPAPs would be a major breakthrough in the field of organic synthesis and medicinal chemistry. This poster will focus on the development of a new divergent synthetic pathway enabling the total synthesis of papuaforin A (**1**), papuaforin B (**2**), papuaforin C, nemorosone (**4**) and hyperforin (**5**).



[1] Barabé F., Bétournay G., Bellavance G. and Barriault L.; *Org. Lett.* **2009**, *11*, 4236–4238 b) Sow B., Bellavance G., Barabé F. and Barriault L.; *Beilstein J. Org. Chem*. **2011**, *7*, 1007–1013

P19 Exploring the chemical space of GPR40 and GPR120 with small molecules

Hugo Tremblay[1], Takafumi Hara[2], Akira Hirasawa[2], Gozoh Tsujimoto[2], Eric Marsault*[1]
1-Institut de Pharmacologie de Sherbrooke, Université de Sherbrooke, Sherbrooke, Quebec J1H 5N4; 2-School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan; eric.marsault@usherbrooke.ca

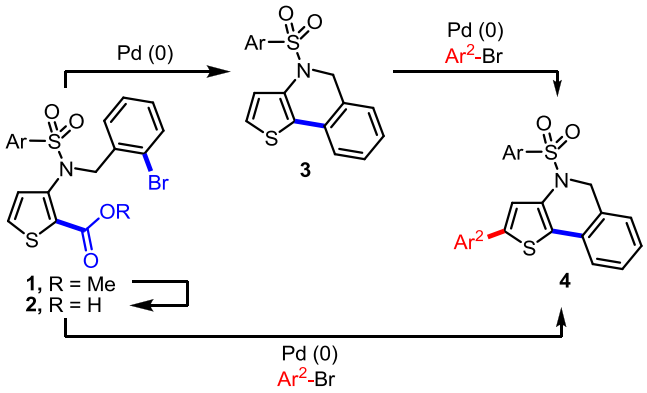
GPR40 (FFAR1) and GPR120 are both G protein-coupled receptors activated by long chain fatty acids. While GPR40 is predominantly expressed on the beta cells of the pancreas, GPR120 is expressed on intestinal L cells, adipocytes and macrophages. While the main role of GPR40 is to elicit fatty acid-mediated potentiation of insulin in the presence of glucose, the roles of GPR120 are broader and involve the release of the incretin GLP-1 as well as key steps in adipocyte inflammation. Collectively, the activation of GPR40 and GPR120 has the potential to address the two main deficiencies of type 2 diabetes deficient insulin secretion and insulin resistance.

GPR40 and GPR120 share very little homology, yet they are both activated by long chain fatty acids and so far, synthetic ligands bear some similarities. In this presentation, we will present our efforts in the optimization of small molecules to better understand the ligand-receptor interactions between the two receptors, with the goal to optimize bi-functional agonists of GPR40 and GPR120.

P20 Applying Palladium-catalyzed cross-couplings with non-organometallic precursors towards the synthesis of thiophene scaffolds

Fei Chen, Nicolas Wong and Pat Forgione*, Department of Chemistry & Biochemistry, Concordia University, Montréal, QC, H4B 1R6 and Centre in Green Chemistry and Catalysis, Montreal, QC
pat.forgione@concordia.ca

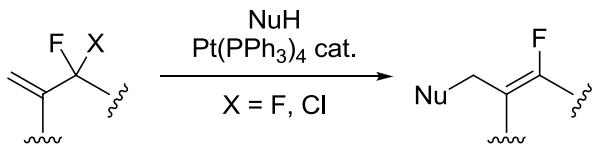
Thiophene is one of the most abundant heteroarenes in fields such as medicinal chemistry and organic semiconductors. In order to gain access to these desired compounds, Pd-mediated reactions that do not require stoichiometric amounts of organometallic reagents can be employed as key steps to functionalize thiophenes. The biologically active thienoisoquinoline scaffold (**4**) was discovered by Wyeth as a potential therapeutic for breast cancer. We have developed a route that accesses this scaffold through a 5-step synthetic pathway involving two palladium-catalyzed reactions, an intramolecular decarboxylative cross-coupling (**2** → **3**) and a direct C-H arylation (**3** → **4**). To further increase the efficiency of this route, the combination of the two palladium-mediated reactions as a one-pot, one step transformation (**2** → **4**) was investigated.



P21 Synthesis of monofluoroalkenes via Pt-catalyzed allylic substitution of 3-fluoro-3-halopropenes

Jean-Denys Hamel, Myriam Drouin and Jean-François Paquin*, CCVC, Département de chimie, Université Laval, Québec, QC, G1V 0A6, jean-francois.paquin@chm.ulaval.ca

Owing to their strong structural and electronic similarity with amide bonds, monofluoroalkenes (**2**) are used as non-hydrolyzable isosteres in drug discovery. However, to date, few satisfying methods are available for their stereocontrolled synthesis. In this context, the Pt-catalyzed allylic amination of 3-fluoro-3-halopropenes (**1**) was explored. The reaction uses easily-accessed $Pt(PPh_3)_4$ as a catalyst and proceeds under mild conditions. Optimization data, scope of the reaction as well as preliminary results towards the use of other nucleophiles will be presented.

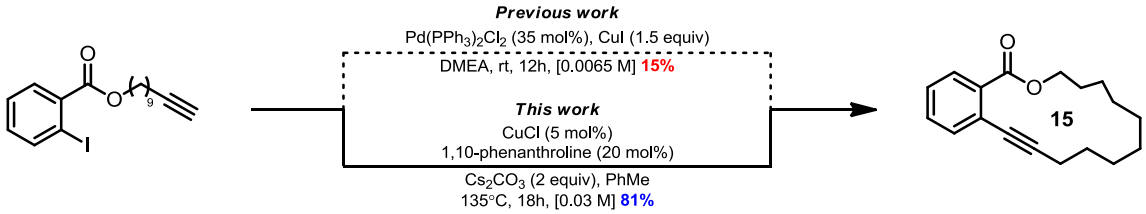


1 **2**

P22 Development of a copper-catalyzed Sonogashira macrocyclization protocol

Jeffrey Santandrea and Shawn K. Collins*, Département de Chimie, CGCC, Université de Montréal, Montréal, Québec, H3T 1J4, shawn.collins@umontreal.ca

Macrocyclic products are usually synthesized from a handful of known macrocyclization methods such as the olefin metathesis reaction, the Suzuki coupling and the Yamaguchi macrolactonization. Surprisingly, the Sonogashira coupling has yet to be a commonly used method to accomplish macrocyclizations, despite relatively mild reaction conditions. Recent examples highlight the lack of practicality and effectiveness of this reaction on a large scale since significant amounts of palladium and stoichiometric amounts of copper in a dilute media are needed to afford benzolactones in poor yields.[1] The development of a copper-catalyzed Sonogashira protocol performed at high-concentrations is described as an alternative to Pd-catalyzed methods to access a wider range of compounds and pharmaceutically relevant motifs such as polyketide-derived resorcyclic acid lactones.



1. Krauss, J *et al*. *Arch. Pharm. Chem. Life Sci.* **2005**, *338*, 605-608.

P23 Palladium Catalyzed Synthesis of Münchnones: From Mechanistic Studies to a New Active Catalyst

Jevgenijs Tjutrins, Bruce A. Arndtsen*, Chemistry Department, McGill University, Montreal, Quebec, H3A 2K6, Corresponding Author's email

Previously we have reported palladium catalyzed multicomponent approach to construct a range of biologically relevant core structures.[1] A common feature of these syntheses involves catalytic generation of 1,3-oxazolium-5-oxide (Münchnone) intermediate via a palladium catalyzed coupling of imines, acid chlorides and CO. These intermediates can be trapped via a 1,3-dipolar cycloaddition to form various heterocycles, as well as they demonstrate ketene reactivity.

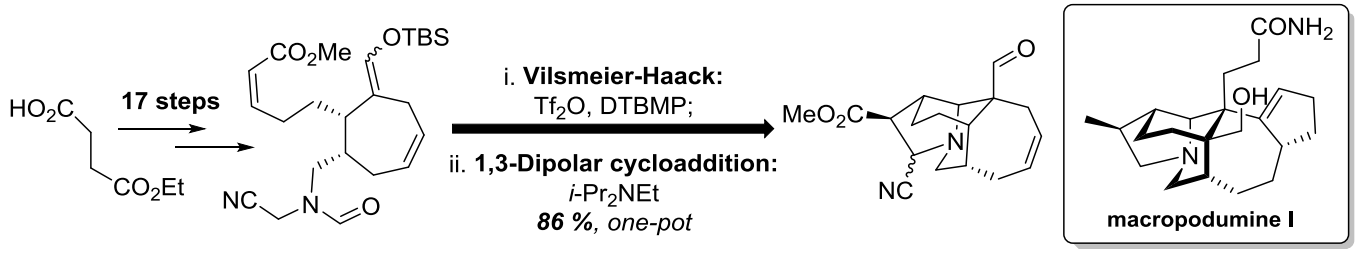
In order to understand the factors that control catalytic formation of Münchnones, we have undertaken a study of the mechanism of this reaction. These suggest not only the route by which Münchnones are formed, but also the importance of balancing the factors that favor the various steps in this catalytic process (e.g. oxidative addition, carbonylation, and Pd(0) stabilization) in facilitating efficient catalysis. Employing these insights, a new and more active catalyst for the efficient synthesis of Münchnones is described.

1. Arndtsen,* B., *Chem. Eur. J.* **2009***, 15*, 302-313

P24 Toward the Total Synthesis of Macropodumine I Using a One-Pot Sequence of Intramolecular Vilsmeier-Haack and Azomethine Ylide 1,3-Dipolar Cycloaddition

Jonathan Boudreault and Guillaume Bélanger* Département de chimie, Université de Sherbrooke, Sherbrooke, QC, J1K 2R1, Guillaume.Belanger@USherbrooke.ca

Natural alkaloid compounds frequently show interesting pharmacologic properties but syntheses are often long and challenging. One-pot sequential cyclizations are well known to be an efficient strategy for a rapid access to the cores of architecturally complex natural products. Our research group has developed a new sequence of intramolecular Vilsmeier-Haack cyclization and 1,3-dipolar cycloaddition. This methodology was successfully applied to the synthesis of the core of macropodumine I and allowed for the formation of three C-C bonds with perfect control of four stereocenters.[1] The advanced tetracyclic core was obtained in only 18 steps. Strategy and progress towards a non-racemic synthesis will be presented to demonstrate the effectiveness of our sequential cyclizations.

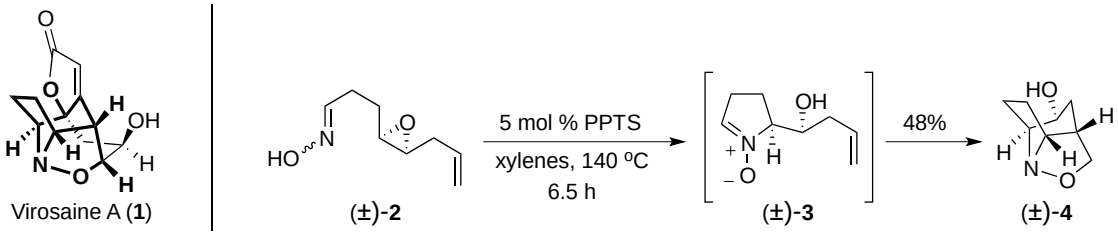


1. Bélanger,* G.; Boudreault, J; Lévesque F. *Org. Lett.* **2011***, 13,* 6204-6207.

P25 Progress towards the total synthesis of virosaine A

Jonathan M. E. Hughes, James L. Gleason* Department of Chemistry, McGill University, Montreal, QC, H3A 2K6, Jim.Gleason@mcgill.ca

Securinega alkaloids are a small but varied class of natural products that have been associated with a number of biological activities. Virosaine A (**1**), which was isolated in 2012, contains the most highly caged skeleton of all the *Securinega* alkaloids. We report preliminary work directed towards the total synthesis of virosaine A. Our proposed route includes a cascade oxime *N*-alkylation to open an epoxide, followed by a [2+3]-dipolar cycloaddition to allow rapid access to the complex skeleton. The feasibility of this cascade was confirmed by converting an acyclic model system into a simplified virosaine core ((±)-**2** to (±)-**4**), which is highlighted in bold in **1**.

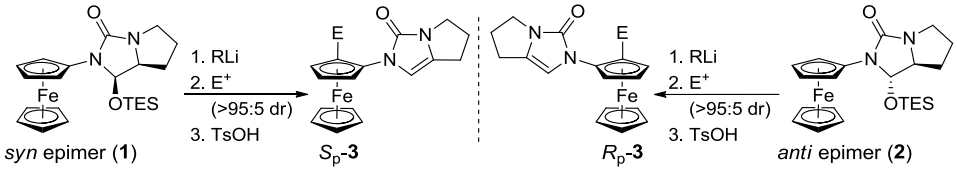


Virosaine A (**1**) (±)-**2** (±)-**3** (±)-**4**

P26 Diastereoselective synthesis & applications of planar chiral *N*-substituted ferrocenes derived from epimeric imidazolones

Joshni John, Cody Wilson-Konderka and Costa Metallinos* Department of Chemistry, Brock University, 500 Glenridge Ave., St. Catharines, ON L2S 3A1, cmetallinos@brocku.ca

We have developed nitrogen based chiral auxiliaries, derived from L-proline hydantoin, for the highly diastereoselective synthesis of planar chiral *N*-substituted ferrocenes (>95:5 dr).[1] The directing groups permit manipulation of the products with simple reagents by virtue of labile triethylsilyloxy moieties. The *syn*- (**1**) and *anti*-epimers (**2**) induce lithiation of the pro-S_p and pro-R_p, position of the cyclopentadienyl ring, respectively.[2] This behavior obviates the need to prepare the more expensive D-proline derived starting materials for the synthesis of planar chiral antipodes (e.g., **3**). In this talk, we will discuss investigations into the origin of lithiation stereoselectivity in both epimers, and the synthesis of unusual iridium complexes derived from these ferrocenes that catalyze asymmetric reduction of substituted quinolines at much lower pressures than previous analogous complexes.[3]



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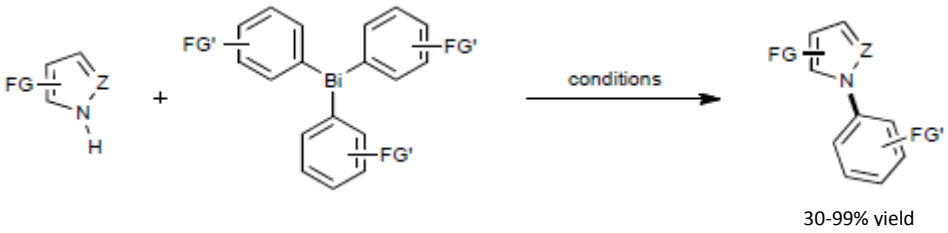
2. Metallinos, C.; John, J. Nelson, J.; Dudding, T. Belding, L., *Adv. Synth. Catal*. **2013**, *355*, 1211.

P27 Copper-catalyzed N-arylation of azoles using highly functionalized organobismuth reagents

Julien Dansereau, Pauline Petiot, Alexandre Gagnon*, Département de chimie, Université du Québec à Montréal, Montréal, QC, H3C 3P8, gagnon.alexandre@uqam.ca

Indoles and pyrroles are privileged scaffolds which are frequently used in medicinal chemistry to project pharmacophores in different vectors inside the binding pocket of a biological target. The *N*-arylation of these compounds allows the modification of the biophysical properties of the molecule and enables the search for new interactions with the target. Classical methods for the *N*-arylation of azoles include the copper-catalyzed coupling using arylmetals and with aryl halides. However, these methods either involve excess of arylating agents or excess catalyst. Furthermore, their tolerance to functional groups is, in some cases, relatively low. New methods that tolerate a higher diversity of functional groups are thus still needed. The results of our laboratory in the development of a general method for the synthesis of highly functionalized *N*-aryl azoles using air-stable triarylbismuthanes and substoichiometric amount of copper acetate catalyst will be presented.

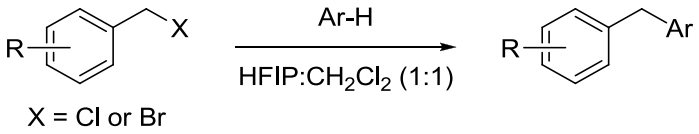


30-99% vield

P28 Friedel-Crafts reaction of benzyl alcohols and benzyl halides promoted by hydrogen-bond donation

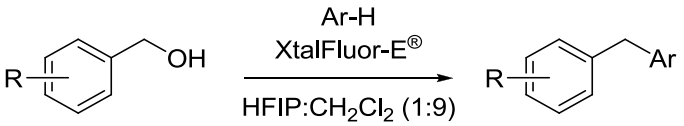
Justine Desroches, Samuel Caron, Jean-François Paquin*, Département de chimie, CCVC, Université Laval, Québec, Québec, G1V 0A6, jean-francois.paquin@chm.ulaval.ca

Benzylic C-X (X = Cl or Br) bond activation for S_N1 type reaction has been largely studied in the literature and often uses strong Lewis or Brønsted acids. Herein, we document the Friedel-Crafts reaction of benzyl halides using HFIP as a hydrogen-bond donor in almost neutral conditions.



X = Cl or Br

As the benzylic halides are generally prepared from the corresponding alcohol, we have developed a similar reaction starting directly from the alcohol using *in situ* activation by XtalFluor-E®. The scope and the optimisation of the reaction conditions will be presented.



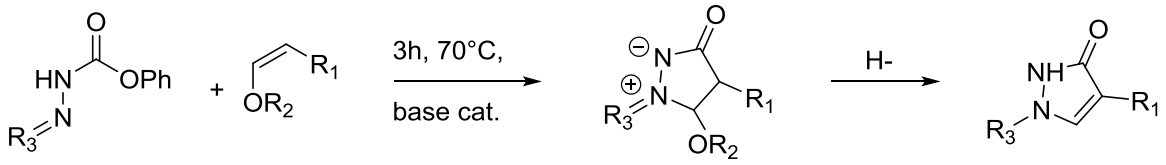
P29 Investigation into Catalytic Aminocarbonylation of Alkenes with Imino-iscocyanates and Derivatization into Pyrazolones

Kaitlyn Lavergne, Amanda Bongers, André M. Beauchemin* Department of Chemistry, CCRI, University of Ottawa, Ottawa, Ontario, K1N 6N5, abeauche@uottawa.ca

Recently, our group discovered that cyclic β-aminocarbonyl motifs are accessible through metal free alkene aminocarbonylation approaches. We embarked on the development of catalytic variants of this reactivity hoping to achieve milder conditions. Effects of additives were investigated with several alkenes. Basic additives proved useful with reactive alkenes: aminocarbonylation products are observed under conditions where the reported procedure would not afford any desired product.

We also discovered that aromatization of azomethine imines synthesized from vinyl ethers allows a new modular route to useful pyrazolones.

Development efforts, reaction scope and our rationale for the improved reactivity will be discussed.



Clavette, C.; Gan,W.; Bongers,A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc*. **2012**, *134*, 16111

P30 Investigation of P450 3A4 for stereoselective epoxidation using a chemical auxiliary

Kin Jack Cheong; Vanja Polic; Aaron Larsen; Karine Auclair*, Department of Chemistry, McGill University, Montreal, Quebec, H3A 0B8, kin.cheong@mail.mcgill.ca

Selective C-H functionalization of inactivated carbon in the presence of similar groups is one of the most challenging transformations in synthetic chemistry. In nature, enzymes of the cytochrome P450 (CYP) family can catalyze these difficult chemical transformations in both a regio- and stereoselective manner under ambient reaction conditions.

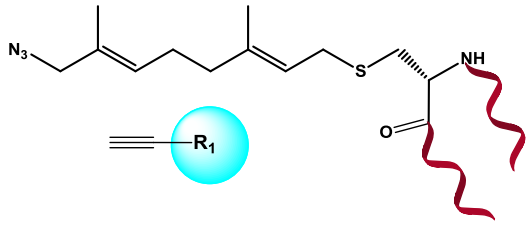
Given the highly diverse and useful suite of reactions catalyzed by P450s in nature, our group envisions harnessing the power of this biocatalyst for synthetic purposes. A chemical auxiliary approach described previously was explored to control the selectivity of hydroxylation reactions by the human P450 3A4[1]. Reaction with a series of theobromine linked alkane and alkene substituents produced hydroxylation or epoxidation at the fourth carbon position relative to theobromine with *pro-R* facial selectivity. Interestingly, epoxidation of terminal C-4/5 alkene generated enantiopure (>99%) product. As an extension to this work, we have constructed a series of theobromine linked alkene compounds to further investigate the use of our auxiliary system in hopes of controlling epoxidation selectivity.

[1] Larsen *et al. J. Am. Chem. Soc.*, **2011**, 133 (20), 7853–7858

P31 ZMPSTE24 inhibitors in cancer treatment: A model to quantify the activity of ZMPSTE24 by fluorescence measurement

Kristina Wolf,[1] Gerardo Ferbeyre,[2] Youla S. Tsantrizos*[1]. [1]Department of Chemistry, McGill University, Montreal, Quebec; [2]Université de Montréal, Département de biochimie, Montréal, Québec, youla.tsantrizos@mcgill.ca

A new strategy in cancer treatment is associated with cellular senescence; the aging of cells and arrest of cell proliferation.[1] Inhibition of the human ZMPSTE24, an inner nuclear membrane zinc metalloproteinase, is involved in the induction of senescence. ZMPSTE24 plays a key role in the maturation of lamin A, by cleaving the prenylated C-terminal peptide of pre-lamin A. Inhibition of ZMPSTE24 leads to accumulation of pre-lamin A at the nuclear rim, resulting in shape abnormalities and cell cycle arrest. We are developing a novel assay for *in vitro* testing of ZMPSTE24 inhibitors. We are synthesizing the C-terminal peptide (substrate for ZMPSTE24) with a modified prenylated cysteine residue of the CaaX motif. This prenylated cysteine will be used to cross-link a chromophore during in vitro testing of the catalytic turnover and quantification of enzyme inhibition.



[1] Cairney, C. J.; Bilsland, A. E.; Evans, T. R. J.; Roffey, J.; Bennett, D. C.; Narita M.; Torrance C. J.; Keith W. N., *Drug Discovery Today*, **2012**, 17, 5/6

P32 Novel Pyrimidine Analogs Targeting Guanine Riboswitch in Clostridium difficile.

Kumaraswamy Boyapelly,[a] Antoine Le Roux,[a] Lok-Hang Yan,[a] Anne-Marie Lamontagne,[b] David Lalonde-Séguin,[c] Louis-Charles Fortier,[c] Daniel Lafontaine,[b] and Eric Marsault[a]
[a]Institut de Pharmacologie de Sherbrooke, [b]Department of Biology, [c]Department of Microbiology and Infectiology, Université de Sherbrooke, Sherbrooke (QC), Canada, Eric.Marsault@USherbrooke.ca

Clostridium difficile (C. difficile) is a major causative pathogen among hospital acquired infections, and in recent years has become a major cause of morbidity and mortality. The problem has been compounded with the emergence of drug resistance against frontline antibiotics. The recent advancement in understanding of riboswitches (RWS) opens up new opportunities to develop narrow spectrum antibiotics that target the pathogen via a new mechanism of action.

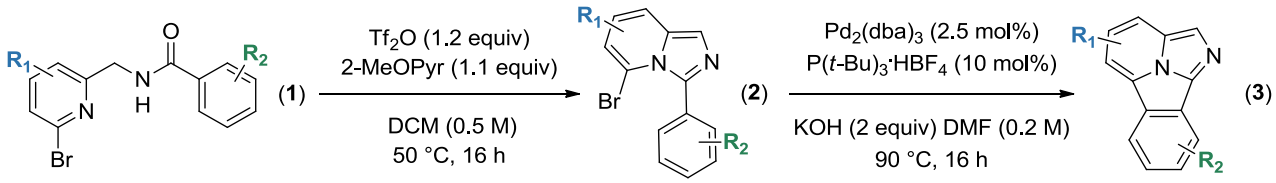
Guanine riboswitch is a major regulatory element found in the 5'-UTR of mRNA coding for genes involved in guanine transport and biosynthesis (pbuG, xpt, uraA, guaA) in C. difficile. Based on this we have synthesised few novel pyrimidine analogs and screened them to determine their ability to bind the various guanine riboswitches in vitro and inhibit the growth of C. difficile.

These compounds were screened primarily by in-line probing of RWS coding for four genes (pbuG, xpt, uraA, guaA), which confirms the binding of synthesised compounds. After primary screening we tested these compounds on C. difficile & Escherichia coli (E. coli) to determine their minimum inhibitory concentration (MIC). The synthesis of compounds, their structure-activity relationships on the four RWS and their MICs will be presented.

P33 Practical Synthesis of Benzo[*a*]imidazo[2,1,5 c,d]indolizines via a Palladium

Léa Contstantoneau-Forget, Guillaume Pelletier, and André B. Charette* Centre in Green Chemistry and Catalysis, Department of Chemistry, Université de Montréal, Montréal, Québec, Canada, H3C 3J7.

Our research efforts recently focused on the activation of amide derivatives with triflic anhydride (Tf_2O) in presence of a 2-halopyridine buffer. As such, some of our new results in that field imply the formation of imidazo[1,5-*a*]pyridines from *N*-(2-pyridinylmethyl)amide using a mild cyclodehydratation-aromatization in presence of 2-methoxypyridne (2-MeOPyr).[1] Following our studies on the cyclodehydration-dehydration step, we've identified the 5-bromo-3-phenylimidazo[1,5-*a*]pyridine (**2**), synthesized from *N*-[(6-bromo-2-pyridinyl)methyl] benzamide (**1**), as a potential starting point for further diversification. At first, a Suzuki-Miyaura reaction was conducted under classic conditions, and to our surprise the intramolecular direct arylation product **3** was obtain as the major product (see Figure 1). Since this catalytic approach represent a facile way to access a new functionalizable class of molecules, by this project, we decided to elaborate further on the mechanism and the scope of different derivatives of 3.



1. Pelletier, G.; Charette, A. B. *Org. Lett.* **2013**, *15*, 2290.

P34 New guanine-riboswitch inhibitors as potential antibiotics targeting *Clostridium difficile*

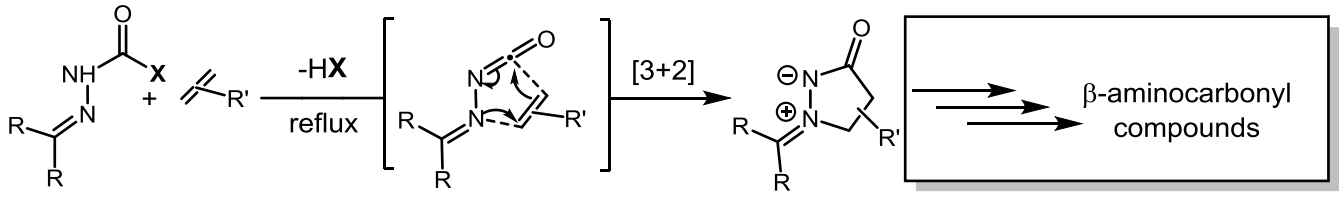
Lok-Hang YAN,[a] Antoine Le-Roux, [a] Kumaraswamy Boyapelly, [a] Anne-Marie Lamontagne,[b] David Lalonde-Seguin,[c] Louis-Charles Fortier,[c] Daniel Lafontaine[b] and Éric Marsault[a*].
[a] Institut de Pharmacologie de Sherbrooke; [b] Department of biology; [c] Department of microbiology; Université de Sherbrooke, Sherbrooke (QC), Canada J1H 5N4, eric.marsault@usherbrooke.ca

Clostridium difficile is one of the leading causes of nosocomial infections, inducing moderate to fulminant diarrhea which can lead to fatal pseudomembranous colitis. The increase of infection frequency, severity and mortality worldwide is linked to the emergence of hypervirulent and multidrug resistant strains. Riboswitches are structured RNA domains that can bind directly to specific ligands and regulate gene expression involved in fundamental metabolic pathways. In this context, the riboswitches appear to be a new potential target for narrow-spectrum antibiotics against *Clostridium difficile*. Our team has demonstrated recently the potential of the guanine riboswitch as a new target against several gram-positive bacteria, among which *C. difficile*. The structure-activity relationships of purine derivatives, with an emphasis on modifications at positions 2 and 6 of the guanine ring, will be described. Their activity on the four guanine riboswitches of *C. difficile* and their minimum inhibitory concentrations against *C. difficile* will be also presented.

P35 Derivatization of alkene-derived azomethine imines into β-aminocarbonyl motifs

Lyanne Betit, C. Clavette, A. Bongers, K. Tanveer, A. M. Beauchemin*, Department of Chemistry, CCRI, University of Ottawa, Ottawa, ON, K1N 6N5, abeauche@uottawa.ca

β-Aminocarbonyl motifs are a privileged substructure in medicinal chemistry and peptidomimetics.[1] As part of our efforts toward metal free aminations, we developed a method for intermolecular amino-carbonylation of alkenes using hydrazones.[1] This method provides access to cyclic azomethine imines containing a β-aminocarbonyl motif. Conceptually, these dipoles can be derivatized into many bioactive compounds, such as 1,3-diamines, β-aminoamides and β-aminoacids. Herein we will provide our results on the derivatization of our aminocarbonylation products into various nitrogen-containing molecules, such as β-aminoamides and β-aminoacids.

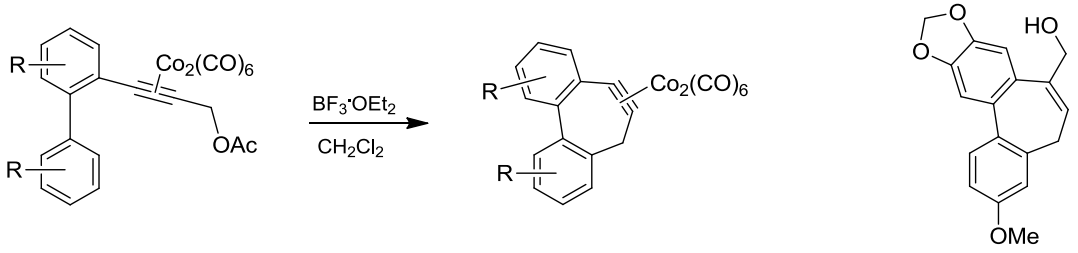


1. Karlsson; Pomerantz; Neilsen; Gellman; Palecek *ACS Chem. Biol.* **2009,** *4*, 567. **2.** Clavette; Gan; Bongers; Markiewicz; Toderian; Beauchemin *JACS* **2012,** *134***,** 16111.

P36 Synthesis of tenuifolin via dibenzocycloheptynedicobalt complexes

Mariam Mehdi, Sinisa Djurdjevic and James R. Green*, Department of Chemistry and Biochemistry, University of Windsor, Windsor, ON, N9B 3P4, jgreen@uwindsor.ca

We have developed a method for the synthesis of dibenzocycloheptenes by way of Nicholas reactions on biaryls bearing propargyl acetate substituents, as their $Co_2(CO)_6$ complexes, followed by reductive decomplexation of the resultant cycloheptynedicobalt adducts. The application of this chemistry to the total synthesis of the sesquiterpenoid tenuifolin will be discussed.

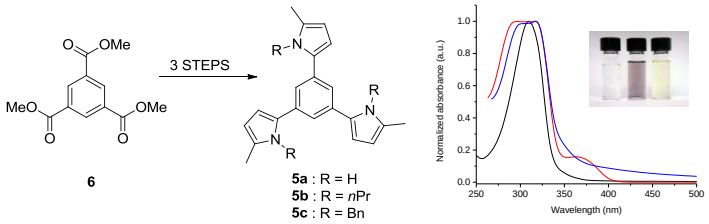


Tenuifolin

P37 Conjugated C_3 symmetric aryl tripyrroles and aryl bipyrroles : synthesis, optical and electronic properties

M. S. Mbyas Saroukou,[†] Thomas Skalski, [‡] W. G. Skene,[‡]* , William D. Lubell[†]*, Département de Chimie, Pavillon Roger Gaudry, and [‡]Laboratoire de caractérisation photophysique des matériaux conjugués, Département de Chimie, Pavillon J. A. Bombardier, Université de Montréal, CP 6128, succ. Centre-ville, Montréal, Québec, Canada H3C 3J7, w.skene@umontreal.ca; lubell@chimie.umontreal.ca

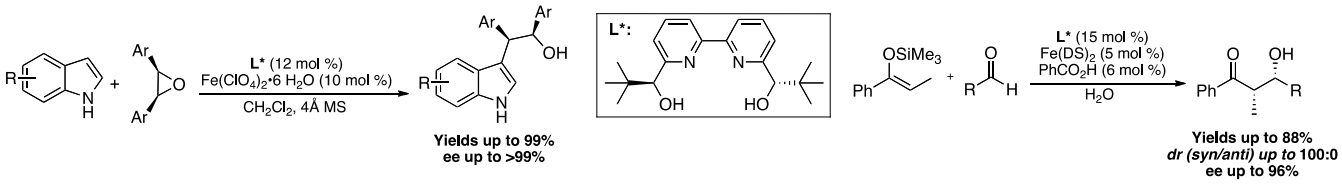
Towards the development of molecules with interesting electronic and electrochromic properties, we have been pursued conjugated C3 symmetric aryl tri-pyrroles. Our presentation describes a novel three step synthesis of 1,3,5-tripyrrolobenzenes from trimethyl 1,3,5-benzenetricarboxylate, featuring copper catalyzed cascade addition of vinyl magnesium bromide to convert the esters to homoallylic ketones, Tsuji-Wacker olefin oxidations to form tris-(1,4-diones), and Paal-Knorr condensation with ammonia and different amines to furnish the final tripyrroles. In addition, partial reaction of vinyl magnesium bromide to 1,3,5-benzenetricarboxylate provided entry to 3,5-dipyrrolylbenzoates by a similar pathway. These synthetic approaches as well as preliminary data on the electronic and electrochromic properties of the conjugated C3 symmetric aryl tripyrroles will be discussed.



P38 Chiral iron(II) catalysts for highly enantioselective epoxide-opening and Mukaiyama aldol reactions

Mathieu Lafantaisie, Baptiste Plancq and Thierry Ollevier* Département de chimie, Université Laval, Québec, QC, G1V 0A6, thierry.ollevier@chm.ulaval.ca

Iron(II) is one of the greenest Lewis acid used in organic chemistry. Combined with a chiral bipyridine type ligand it was used as catalyst for selected organic reactions.[1,2] In the desymmetrization of aromatic *meso* epoxides, excellent yields and enantioselectivities were obtained (up to >99% ee).[1] Iron(II) was also used as a Lewis-acid-surfactant-combined catalyst for Mukaiyama aldol reaction in pure water. Using this method, good yields and high enantioselectivities were obtained (up to 96% ee). A quick centrifugation could replace the common work-up procedure without the need of any organic solvent.

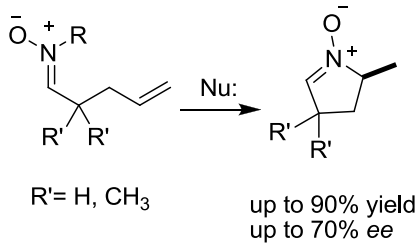


1. Plancq, B.; Lafantaisie, M.; Companys, S.; Maroun, C.; Ollevier, T., *Org. Biomol. Chem.* **2013**, *11*, 7463-7466. 2. Ollevier, T.; Plancq., B., *Chem. Commun.* **2012**, *48*, 2289–2291.

P39 Development of hydroamination approach for the synthesis of enantiomerically enriched chiral nitrones

Mohammad M. Zahedi, André M. Beauchemin*, Department of chemistry, CCRI, University of Ottawa, Ottawa, ON, K1N 6N5, andre.beauchemin@uottawa.ca

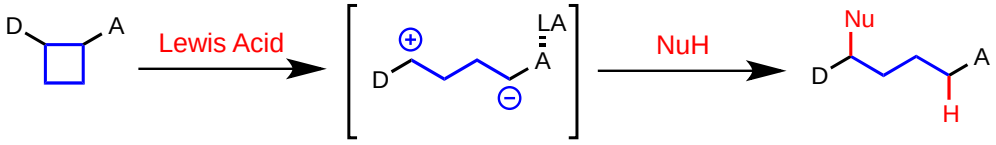
Nitrones are fascinating and useful nitrogen containing molecules. For example, nitrones are used to trap free radicals in biochemical systems and their reactions with dipolarophiles produce functionalized five-membered heterocycles. Our group has been interested in the synthesis and reactivity of nitrones for several years. However, hydroamination methods leading to nitrone formation are quite rare, and asymmetric variants have not been reported. In a current project, simple nitrones are used as substrates for the formation of more complex nitrones through intramolecular Cope-type hydroamination of alkenes. The details of this ongoing study and investigations towards formation of enantiomerically enriched products will be discussed.



P40 Nucleophilic additions to the donor - acceptor cyclobutanes

Nahed O. Bawakid, Naresh Vemula and Brian L. Pagenkopf* Department of Chemistry, Western University, London, ON, Canada, N6A 5B7. bpagenko@uwo.ca

Manipulation of ring strain as a driving force in cycloaddition chemistry is a powerful strategy in modern organic synthesis. Among the strained carbocycles, cyclobutanes are particularly interesting because they provide a bridge between very reactive cyclopropanes and less reactive cyclopentanes. It is well demonstrated that in presence of Lewis acid catalyst, donor-acceptor (DA) cyclobutanes can form 1,4-zwitterionic intermediates that can be used as 1,4-dipole equivalents in cycloaddition chemistry. In this regard our group reported reactivity of (DA) cyclobutanes with various dipolarophiles, such as aldehydes, nitrones, imines, and terminal alkynes. When we furthered this study, only alkylation was observed with certain dipolarophiles instead of annulation. We are currently investigating this type of reactivity with a variety of nucleophiles and preliminary results will be presented.

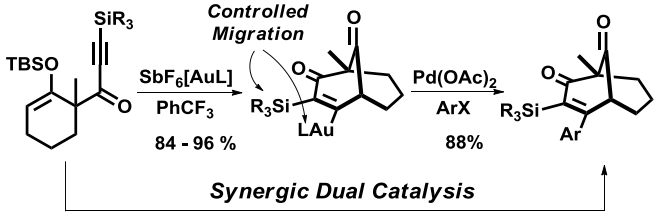


D= Electron donar
A= Electron acceptor

P41 Efforts towards a novel synergic dual-catalyzed reaction with Au(I) and Pd(0)

Philippe McGee, Gabriel Bellavance and Louis Barriault*, Department of Chemistry, University of Ottawa, Ottawa, Ontario, K1N 6N5, pmcge031@uottawa.ca

Gold(I/III) complexe are soft Lewis acid and have the interesting characteristic to activate alkynes, allenes and alkenes under mild conditions with stereoselective outcome. In general, gold-catalyzed reactions usually undergo a fast protodeauration to regenerate the initial active catalyst. It was reported that in particular cases it was possible to isolate the vinyl gold intermediate. We recently isolated new organogold complexes. To our surprise, these complexes resulted from a *1,2 migration* of the gold with the tertbutyldimethylsilane. Moreover, we observed that the migration can be inhibited by the use of triphenylsilane groups on the terminal alkyne. Our research focused on merging of the unique selectivity of the gold-catalyzed process with palladium reactivity in order to develop a *synergic dual-catalysis*.

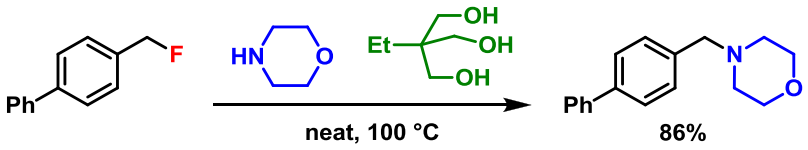


P42 Activation of C-F bonds using hydrogen-bond donors: nucleophilic substitution of activated alkyl fluorides

Pier Alexandre Champagne, Alexandre Saint-Martin, Mélina Drouin and Jean-François Paquin*
CCVC, Département de chimie, Université Laval, Québec, QC, G1V 0A6, jean-francois.paquin@chm.ulaval.ca

Simple alkyl fluorides are generally regarded as poor electrophiles in nucleophilic substitution reactions, mainly because of the strength of the carbon-fluorine bond. Examples of this transformation in the literature rely on strongly basic or acidic conditions, or on the use of transition metals.

We have shown that water can be used as a hydrogen-bond donor to activate C-F bonds under neutral conditions.[1] Using insight we had gathered by DFT calculations during that study, we conceived that a triol could replace water and activate C-F bonds with careful positioning of its three hydroxyl groups. Herein, we report the applicability of this concept to the nucleophilic substitution of benzylic fluorides under highly concentrated conditions.[2]



(1) Champagne, P. A.; Pomarole, J.; Thérien, M.-È.; Benhassine, Y.; Beaulieu, S.; Legault, C. Y.; Paquin, J.-F. *Org. Lett.* **2013**, *15*, 2210. (2) Champagne, P. A.; Saint-Martin, A.; Drouin, M.; Paquin, J.-F. *Beilstein J. Org. Chem.* **2013**, *accepted for publication*.

P43 Design and synthesis of an artificial fluorinated ion channel

Raphaël Godbout, Claudia Carpentier, François Otis, Normand Voyer* Département de chimie, Université de Laval, Québec, G1R 1X9, Normand.Voyer@chm.ulaval.ca

Nature is constantly innovating to develop new molecules to defend herself. Ion channels are essential components to sustain life and defend it against bacteria. By forming amphiphilic coiled-coil nanostructures, they can penetrate lipid bilayers and permeabilize them to ions, leading to cellular death.

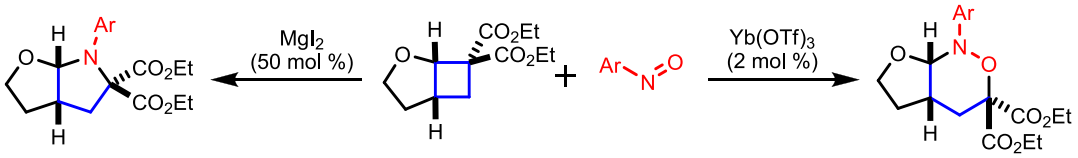
Exploring new structures for artificial ion channels is a major research axis of Voyer's lab. By conceiving peptides integrating artificial amino acids and forming coiled-coil nanostructures when inserted in lipid bilayer, insights have been gained on ion transport.

We will present our newest approach towards the design of new artificial ion channels. It is inspired by the general structure of amphiphilic coiled-coil peptides made only of leucines and serines able to self-assemble in superstructures. To promote self-assembly and to increase enzymatic degradation resistance, we substituted serines for a fluorinated analog, L-4,4,4-trifluoro-2-butyric acid. Conception, characterisation and preliminary results of ion transport through membranes will be presented thoroughly.

P44 Divergent synthesis of tetrahydro-1,2-oxazines and pyrrolidines via cycloadditions of donor-acceptor cyclobutanes and nitrosoarenes

Naresh Vemula, Andrew C. Stevens, Tyler B. Schon, and Brian L. Pagenkopf* Department of Chemistry, Western University, London, ON, N6A 5B7, bpagenko@uwo.ca

Strained carbocyclic donor-acceptor (DA) cyclobutanes have recently been reported to undergo efficient cycloadditions with a variety of dipolarophiles.[1] We have most recently examined the reaction of alkoxy-activated 1,1-cyclobutanediesters with nitrosoarenes under Lewis acid catalyzed conditions. The cycloaddition between DA cyclobutanes and nitrosoarenes provides facile access to the tetrahydro-1,2-oxazines in excellent to moderate yield. Additionally, when electron-rich nitrosoarenes were employed with 50 mol % of MgI_2 as a Lewis acid, an unexpected deoxygenation occurred, resulting in the formation of pyrrolidine products. A detailed discussion of the results will be presented.

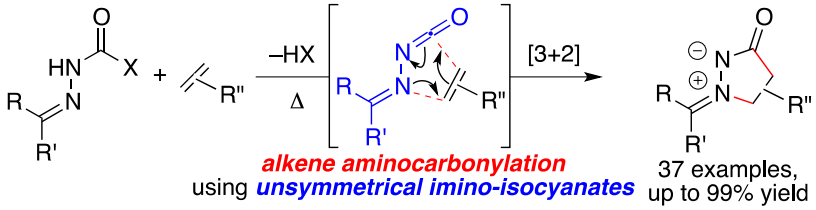


(a) Moustafa, M. M. A. R.; Stevens, A. C.; Machin, B. P.; Pagenkopf*, B. L. *Org. Lett.* **2010**, *12*, 4736. (b) Moustafa, M. M. A. R.; Pagenkopf*, B. L. *Org. Lett.* **2010**, *12*, 4732. (c) Stevens, A. C.; Palmer, C.; Pagenkopf*, B. L. *Org. Lett.* **2011**, *13*, 1528.

P45 Synthesis of β-aminocarbonyls from alkenes and hydrazones, and efforts towards kinetic resolutions of complex azomethine imines

Moon, P.J.; Gan, W.; Bongers, A; Clavette, C.; Beauchemin*, A.M., Department of Chemistry, University of Ottawa, Ottawa, Ontario, K1N 6N5, andre.beauchemin@uottawa.ca

In recent years, peptidomimetics assembled with unnatural aminoacids, including β-aminoacids, have shown tremendous potential in medicinal chemistry. The β-aminocarbonyl subunit is also very common in small-molecule pharmaceuticals and natural products. As part of efforts toward novel amination methodologies, our group developed an efficient method to synthesize azomethine imines and β-aminocarbonyl compounds via the direct aminocarbonylation of alkenes.[1] Recent advances on the synthesis and reactivity of unsymmetrical azomethine imines will be presented.[2] Recent progress on kinetic resolutions of these azomethine imines, which is targeted to access enantioenriched derivatives, will also be discussed.

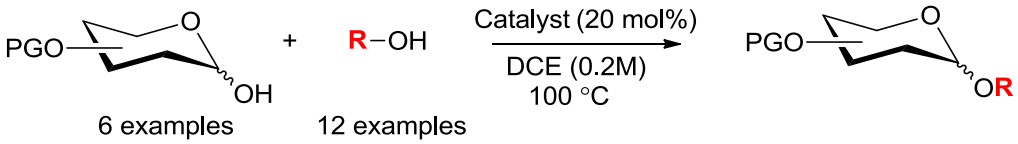


1. Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.B.; Gorelsky, S.I.; Beauchemin*, A.M. *J. Am. Chem. Soc*., **2012**, *134* (39), pp 16111–16114. 2. Gan, W.; Moon, P.J.; Clavette, C.; Das Neves, N.; Markiewicz, T.; Toderian, A.B.; Beauchemin*, A.M. *Org. Lett*., **2013**, *15* (8), pp 1890–1893.

P46 Dehydrative glycosylations catalyzed by boronic esters

Sanjay Manhas, Mark S.Taylor* Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6, mtaylor@chem.utoronto.ca

The synthesis of an *O*-glycosidic bond usually involves the displacement of a leaving group on the glycosyl donor by a nucleophilic hydroxyl group on the glycosyl acceptor. Commonly employed leaving groups for such reactions include halides, trichloroacetimidates and sulfoxides, along with a suitable activator [1]. A less developed approach using free glycosidic hemiacetals activated through in situ leaving group formation is of interest. Previously our group has been successful in using borinic acid catalysts for activation of glycosyl acceptors[2]. The current work explores a distinct activation mode in which electron-deficient boronic esters activate unprotected 2-deoxyglycosyl donors towards nucleophilic attack.



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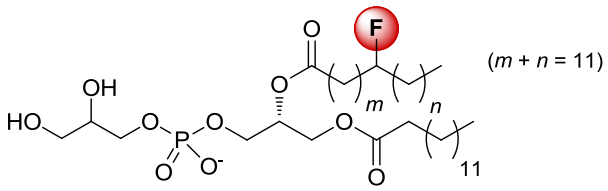
P47 Synthesis of monofluorinated phosphatidylglycerol: potential probes for the study of membrane topology

Sébastien Dautrey, Marie-Claude Gagnon, Michèle Auger*, Jean-François Paquin* PROTEO, Département de chimie, Université Laval, Québec, QC, Canada, jean-francois.paquin@chm.ulaval.ca

Understanding the interactions between lipid membranes and drugs, peptides or proteins is of primary importance to determine their mechanism of action. Due to the great complexity of natural lipid membranes, simpler model are used for these studies. For instance, dimyristoylphosphatidylcholine (DMPC) is often utilized to mimic human cell membranes whereas dimyristoylphosphatidylglycerol (DMPG) is used for bacterial cell membranes. We have recently developed a strategy to access monofluorinated DMPC analogues as potential probes for ^{19}F-solid state NMR studies.[1] However, a similar synthetic strategy is not possible for DMPG derivatives. As such, a new route for the preparation of DMPG and monofluorinated DMPG derivatives was investigated and will be the subject of this presentation.



Monofluorinated dimyristoylphosphatidylglycerol derivatives (F-DMPG)

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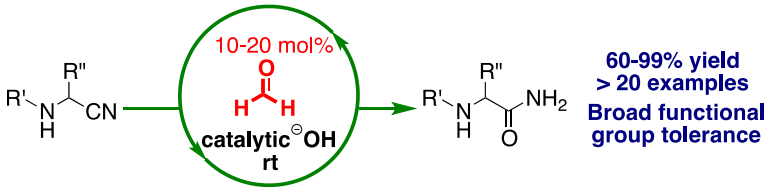
P48 Catalysis via Induced Intramolecularity: Mimicking Nature's Approach to Intermolecular Reactivity

Sampada Chitale, Bashir Hussain, Kashif Tanveer, André Beauchemin* Centre for Catalysis Research & Innovation Department of Chemistry, University of Ottawa, 10 Marie Curie Pvt., Ottawa, ON K1N 6N5, abeauche@uottawa.ca

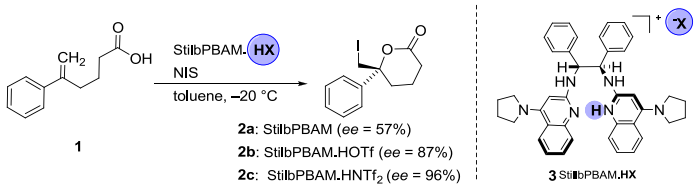
As part of our program to develop simple catalysts exploiting temporary intramolecularity, we are optimizing the catalytic activity of inexpensive carbonyl compounds to mimic one of the basic types of enzymatic reactions: hydrolysis! We have successfully optimized a highly efficient and mild carbonyl catalyzed hydrolysis of α-amino nitriles to synthesize α-amino amides. Formaldehyde is a very effective carbonyl catalyst for this transformation. The reaction is proposed to go through an *N,O*-acetal intermediate, which under basic condition releases α-amino amide and regenerates formaldehyde. This methodology can be further extended to the hydrolysis of α-amino amides and β-amino nitriles to access natural and unnatural α and β amino acids. Finally, the implications of these findings in the prebiotic chemistry (origin of life) debate will be discussed.



P49 A Theoretical Study of Achiral Counterion Effects on Enantioselective H-Bond Catalyzed Iodolactonizations

Seyedeh Maryamdokht Taimoory and Travis Dudding* Department of Chemistry, Brock University, St. Catharines, ON, L2S 3A1, tdudding@brocku.ca

A number of experimental studies have demonstrated the effects of counterions on organocatalyzed asymmetric reactions. However, the exact role of the counterion in these processess is still under developed. Recently, Johnston *et al.* reported a catalytic enantioselective iodolactonization that showed a marked dependence upon the achiral counterion used in terms of selectivity and reactivity.[1] We report herein a theoretical study using Density Functional Theory calculations (DFT) that provides insight into the steric and electronic factors contributing to enantioselection in this iodolactonization reaction. As well, a detailed knowledge of the role played by the achiral counterion in this reaction and the importance of polar ionic hydrogen bonding is discussed.



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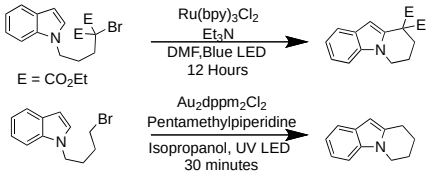
P50 Gold (I) photoredox catalyst for 5/6-exo-trig cyclizations onto Indole cores

Sherif Kaldas, Stéphanie Lanoix, and Prof. Louis Barriault* Centre for Catalysis Research and Innovation, University of Ottawa, Ottawa, Ontario, K1N 6N5, lbarriau@uottawa.ca

Photoredox chemistry has been dominated in recent years by such catalysts as $[Ru(bpy)_3]Cl_2$ and $[Ir(ppy)_2(dtbbpy)]PF_6$ [2]. Such catalysts remove the need for expensive and dangerous radical initiators by exploiting visible light, a cheap and renewable resource.[1] Although these catalysts offer low loadings and excellent yields, they suffer from low reduction potentials, resulting in the inability to cleave inactivated alkyl, alkenyl and aryl bromide bonds.[2] Our group has recently reported a method for cleaving inactivated substrates with the use of dimeric gold(I) catalyst, $[Au_2dppm_2]Cl_2$, which has an inherently higher reduction potential . Herein, we demonstrate the cleavage of primary alkyl-bromides resulting in the 5/6-exo-trig cyclizations onto the C2 position of substituted indoles. Reaction optimization has so far lead to an isolated yield of 76% of the basic tricylic indole.



[1] Prier, C.K.; Rankic, D.A.; MacMillan, D.W.C. *Chem. Review.,* **2013**, 113, 7, 5322-5363. [2] Tucker, J.W.; Narayanam, J.M.R.; Krabbe, S.W.; Stephenson, C.R.J. *Org. Lett.,* **2010** 12, 2, 368-371. [3] Revol, G.; McCallum, T.; Morin, M.; Gagosz, F.; Barriault, L. *Angew. Chem. Int. Ed.*, **2013**, 52, in press.

P51 Synthesis of N-Substituted Muramyl Dipeptides and Prelimina on Its Role in NOD2-Mediated Innate Immune Response

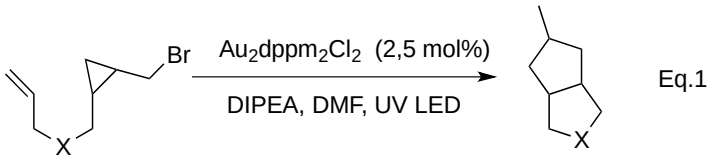
Shuo Xing, Marcel Behr, James L. Gleason*, Department of Chemistry, McGill University, Montreal, QC, H3A08B, jim.gleason@mcgill.ca

An improper innate immune response to bacterial infection underlies many chronic inflammatory diseases such as asthma or rheumatoid arthritis. Nod2 is a mammalian cytosolic signaling protein that responds to bacterial invasion by interacting with muramyl dipeptide (MDP) present in the peptidoglycan of the bacterial cell wall. Hyperactivity of Nod2 is linked to the development of Crohn's disease and Blau syndrome. Previous research has shown that a more severe Nod2-mediated immune response is triggered when the more common N-acetyl MDP is oxidized *in situ* to N-glycolyl MDP, as seen in mycobacteria and actinomycetes. Nevertheless, the exact mode of interaction between Nod2 and its ligands has not been clarified. Our present studies investigate the Nod2-N-glycolyl MDP interaction and its response on a molecular level through synthetically modified N-glycolyl MDP. The challenges and different approaches toward an efficient and versatile synthesis of N-glycolyl MDP are presented.

P52 Pushing radical chemistry to new boundaries: Gold(I) photocatalyzed cascade cyclizations

Stéphanie Lanoix and Prof. Louis Barriault* Centre for Catalysis Research and Innovation, University of Ottawa, Ottawa, Ontario, K1N 6N5, lbarriau@uottawa.ca

Radical chemistry is a crucial asset to organic chemists, however these methods usually require toxic organometallic compounds as hydrogen donors, potentially explosive and expensive initiators. Recent trends in the field have been directed towards the development of photocatalysts generating a radical by a single electron transfer through a renewable source like sunlight. Amongst the most efficient we find *fac*−$Ir(ppy)_3$ and $Ru(bpy)_3Cl_2$. Although these catalysts eliminate the use of hazardous reagents their substrate scope remains limited to activated C-X. We have recently developed a method using a dinuclear gold(I) catalyst, $Au_2dppm_2Cl_2$, having a stronger reducing potential, thus allowing for expansion of the reactivity.[2] On another note, fused carbocycles are frequently encountered scaffolds in diterpenoid natural products. The use of radical cyclization to synthesize these fused-carbocycles has been reported, however employing hazardous reagents. Herein, we combine advantages of photochemistry and radical cyclizations to access carbocyclic compounds in a facile and efficient way.



Eq.1

[1] Revol, G., McCallum,T., Morin, M., Gagosz, F. and Barriault, L., *Angew. Chem.,* **2013***, 52*, in press

P53 Tetraarylphosphoniums salts as soluble molecular support in peptide synthesis

Sylvain Taillemaud, Jeremy Zimbron, Frederica Stazi, David Marcoux, Jean-Christophe Poupon, Daniel Latassa and André B. Charette* Departement de Chimie, Université de Montréal, Montréal, QC, H3C 3J7, andre.charette@umontreal.ca

Peptides are nowadays made in industry using resins as supports, the purification of the growing peptides being easy at each step of the synthesis. However, this methodology has some drawbacks: the heterogeneous mixture slows down the reaction; a lot of equivalents of each reagent are needed; a huge quantity of resin is essential if a large amount has to be synthetized. In the past few years, our group demonstrated the use of tetraarylphosphonium salts as soluble support for organic reagents[1], allowing to recover them or their byproducts by a simple precipitation/filtration sequence. This strategy was then employed for the synthesis of small peptides by anchoring a Wang linker onto the TAP salt[2]. Today, a much simpler support has been elaborated and tested in view to adapt it to automatized peptide synthesis.

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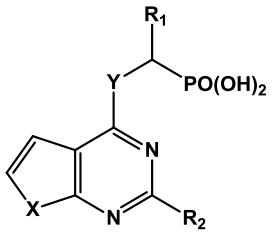
P54 Design of hGGPPS inhibitor for prevention of Alzheimer's disease

Viviane C-Y Ta,[1] Chun Yuen Leung,[1] J. Poirier,[1,2] Youla S. Tsantrizos,*[1]
[1]Department of Chemistry, McGill University, Montreal, Quebec; [2]Douglas Mental Health University Institute, Montréal, Québec, Canada, youla.tsantrizos@mcgill.ca

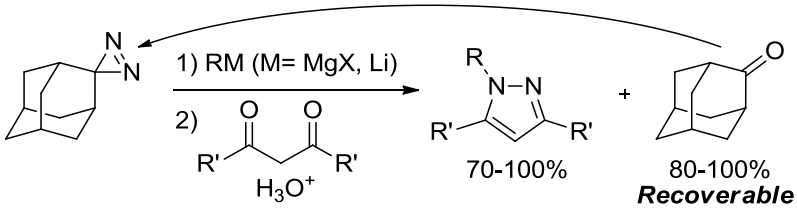
Human GGPPS catalyzes the biosynthesis of GGPP, an essential metabolite for the prenylation of small G-proteins involved in cell signaling. Current literature strongly suggests that GGPP is involved in the accumulation of the phospho-Tau (P-Tau) protein in the aging brain *via* the prenylation cascade from GGPP → RhoA-cdc42 → GSK3-beta → P-Tau. Accumulation of P-Tau leads to neurodegeneration and the progression of the Alzheimer's disease (AD). Consistent with this hypothesis, high intracellular levels of GGPP are present in the brains of aging mice (compared to young mice), with accumulation of P-Tau and neurofibrillary tangles, mimicking the early symptoms of AD. The focus of our research is to design inhibitors of the human GGPPS that can be used to investigate *ex-vivo* and *in vivo* the role of GGPP in neurodegeneration. We have identified thienopyrimidine-based hits which we are currently optimizing into potent inhibitor for GGPPS.



P55 Study of the electrophilic potential of diazirines and application to the synthesis of pyrazoles

Yoann Schneider and Claude Y. Legault* Département de chimie, Université de Sherbrooke, Sherbrooke, QC, J1K 2R1, Claude.Legault@USherbrooke.ca

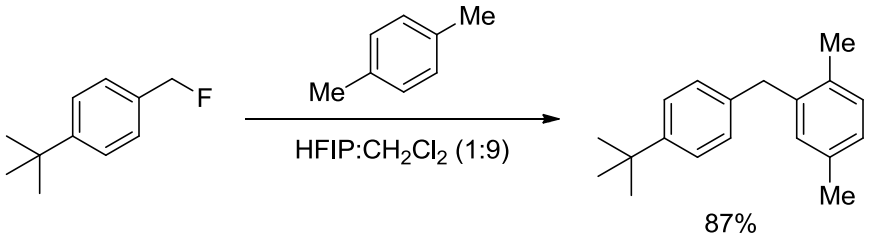
Diazirines are well-known molecules often used as carbene precursors. They are also a potential source of electrophilic nitrogen. This property, although studied, was never truly exploited. We demonstrate that the diazirine derived from adamantanone can circumvent the issues that prevented its wide use and resolve this longstanding limitation. By addition of nucleophilic compounds, such as organolithium or magnesium reagents, the corresponding *N*-monosubstituted diaziridines or hydrazones are obtained. Under hydrolysis conditions, they liberate in situ the monosubstituted hydrazines and adamantanone. The hydrazines are converted to numerous pyrazoles in high yields. The adamantanone can be recovered in 80-100% yields. This proof of concept demonstrates the potential of diazirines as proficient and environmentally friendly electrophilic nitrogen sources.



P56 Friedel-Crafts reaction of benzyl fluorides promoted by hydrogen-bond donation

Yasmine Benhassine, Pier Alexandre Champagne and Jean-François Paquin* Département de chimie, CCVC, Université Laval, Québec, QC, G1V 0A6, jean-francois.paquin@chm.ulaval.ca

Simple alkyl fluorides are generally regarded as poor electrophiles in nucleophilic substitution reactions, mainly because of the strength of the carbon-fluorine bond and the low leaving group ability of fluoride compared to the other halides. Nevertheless, some examples of C-F activation for S_N1 type reactions have been described using strong Lewis or Brönsted acids. Herein, we document the Friedel-Crafts reaction of benzylic fluorides under almost neutral conditions. This transformation is promoted by a strong hydrogen-bond donor, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and uses aromatic compounds as nucleophiles. The optimization of the reaction conditions, the scope of the reaction and preliminary mechanistic studies will be presented.

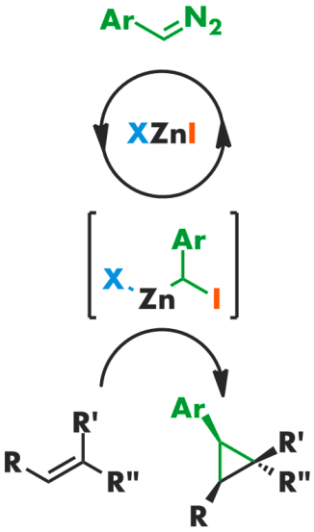


(1) Champagne, P. A.; Benhassine, Y.; Legault, C. Y. Paquin, J.-F. *In preparation*.

P57 Zinc-Catalyzed Simmons-Smith Reaction: Access to Various 1,2,3-Trisubstituted Cyclopropanes

Éric Lévesque, Sébastien R. Goudreau and André B. Charette*, Département de Chimie, Université de Montréal, Montréal, Québec, H3C 3J7, andre.charette@umontreal.ca

The Simmons-Smith reaction of zinc carbenoids with alkenes is a powerful method to access cyclopropanes containing various substitution patterns. The typical procedure involves generating an excess of the desired zinc carbenoid from an alkylzinc reagent and an organic dihalide before introducing the substrate alkene. The drawbacks of such a procedure include solubility issues, handling of air-sensitive organozinc compounds in large amounts and the generation of metal-containing waste.

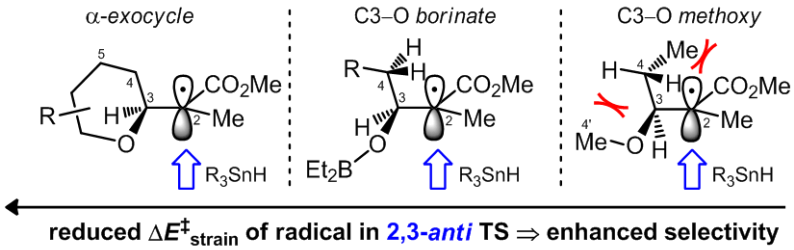


This work exploits the high reactivity of aryldiazomethanes towards zinc halides to generate aryl-substituted zinc carbenoids *in-situ*. The procedure allows the use of a catalytic amount of zinc reagent to arylcyclopropanate various alkenes, including unactivated styrene derivatives and hindered trisubstituted allylic ethers. The zinc catalyst can be modified via the introduction of an anionic ligand, such as a phenolate or a phosphate, to enable the use of free alcohols as substrates.

P58 The influence of conformational factors on diastereoselective hydrogen transfer reactions: the *exocyclic effect* revisited

F. Godin, M. Prévost, F. Viens, P. Mochirian, S.I. Gorelsky and Y. Guindon*, Institut de recherches cliniques de Montréal, 110, av. des Pins Ouest, Montréal, QC, H2W 1R7, yvan.guindon@ircm.qc.ca

Radical reductions of halogenated precursors vicinal to an ester and bearing a heterocycle exo (α) to the carbon-centered radical proceed with enhanced 2,3-*anti* selectivity, a phenomenon termed the *exocyclic effect*. Lately, we have demonstrated using DFT calculations that it is linked to the strain energy required for a radical intermediate to reach its reactive conformation at the transition state ($\Delta E^{\ddagger}_{strain}$).[1] Furthermore, the analysis performed on substituted tetrahydropyrans, found in numerous ionophores, as well as on various acyclic substrates bearing a borinate at C3 enabled us to assess the importance of steric repulsion with the incoming hydride to rationalize the levels of diastereoselection observed experimentally.[2]

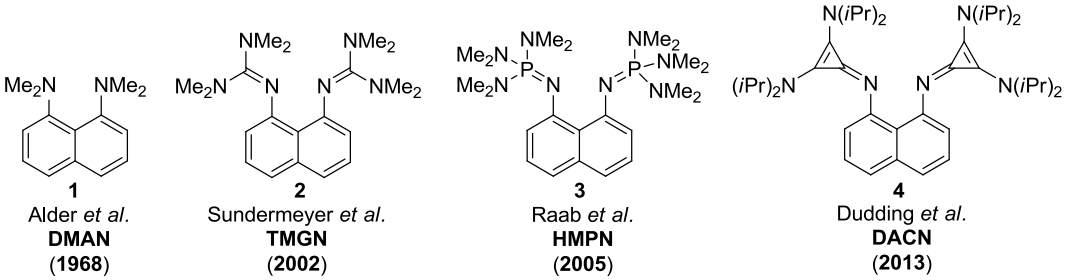


1) Godin, F.; Prévost, M.; Gorelsky, S. I.; Mochirian, P.; Nguyen, M.; Viens, F.; Guindon, Y., *Chem. Eur. J.* **2013**, *19*, 9308. 2) Godin, F.; Prévost, M.; Viens, F.; Mochirian, P.; Brazeau, J.-F.; Gorelsky, S. I.; Guindon, Y., *J. Org. Chem.* **2013**, *78*, 6075.

P59 Synthesis and Theoretical Investigation of 1,8-Bis(bis(diisopropylamino)cyclopropeniminyl)naphthalene, a new Proton Sponge Derivative

Lee Belding and Travis Dudding* Department of chemistry, Brock University, St. Catharines, ON, L2S 3A1, tdudding@brocku.ca

Alder's prototypical 'proton sponge' (**1**) was first discovered in 1968. Since this seminal publication modified proton sponges (*e.g.*, **2** and **3**) with substantially increased proton affinities (PA) have been reported. Recently we designed a new proton sponge that introduces an additional influence on the PA of proton sponges, the generation of aromaticity. By functionalizing 1,8-diaminonaphthalene with bis(dialkylamino)cyclopropenimines, protonation leads to formation of the aromatic cyclopropenylium cation.[1] The synthesis and theoretical investigation of **4** is presented, as are current results in applying **4** as an organocatalyst.



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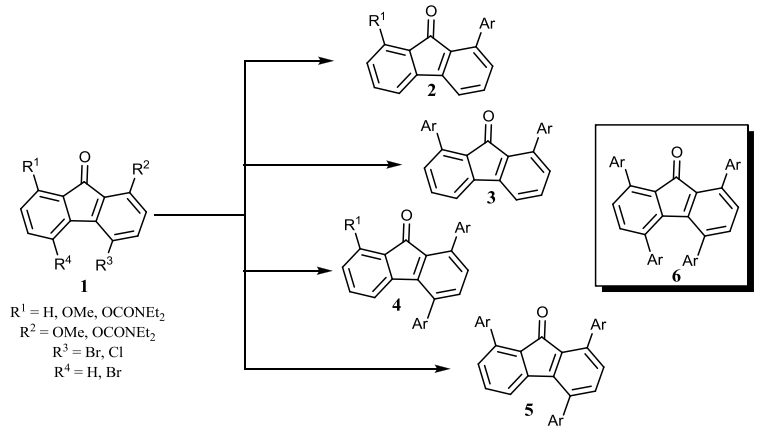
P60 Regioselective arylation of fluorenone skeleton via combined Ru- and Pd-catalyzed Suzuki cross coupling reactions

Lívia Cristina Frota, Alcides J. M. da Silva, Cédric Schneider and Victor Snieckus*, Department of Chemistry, Queens University, Kingston, ON, K7L 2S7,victor.snieckus@chem.queensu.ca vicus@chem.queensu

The fluoren-9-one skeleton is found in antitumor antibiotic natural products[1,2] and material science areas.[3] We present a route to polyaryl fluorenones based on our previous Directed remote metalation (DreM) chemistry followed by combination of $RuH_2(CO)(PPh_3)_3$ catalyzed C-O activation and Suzuki cross coupling reactions of **1** to afford 1-aryl-substituted (**2**), 1,8 diaryl- substituted (**3**) and 1,4-diaryl-substituted (**4**) 1,4,8-triaryl- substituted fluorenones (**5**). The synthesis of the tetraaryl-substituted fluorenones (**6**) will be presented as progress allows.



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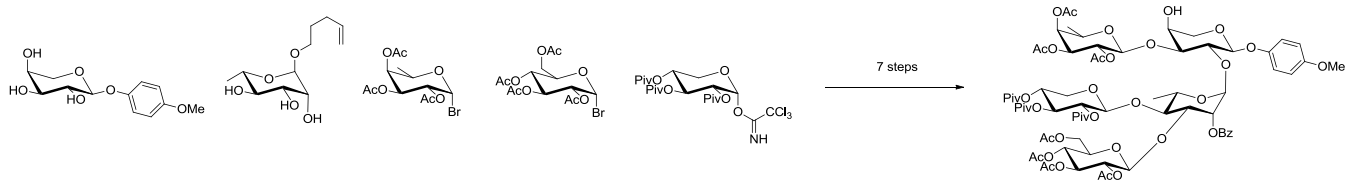
P61 Organoboron-promoted selective glycosylation reactions in the synthesis of a pentasaccharide natural product

Ross Mancini, Stefi Anthonipillai, Mark S. Taylor*, Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6, mtaylor@chem.utoronto.ca

Protective groups are used extensively in oligosaccharide synthesis to enforce regioselectivity in glycosylation reactions. Methods for selective glycosylation of unprotected or minimally protected acceptors could significantly streamline the synthesis of such targets.[1] Our lab has developed protocols that exploit the selective complexation of sugars by organoboron compounds to achieve site-selective glycosylation of pyranoside-derived di- and triol substrates.[2] Applications of this methodology to the preparation of a saponin-derived pentasaccharide natural product will be discussed, highlighting the role of organoboron-promoted selective glycosylations in simplifying the synthetic route.



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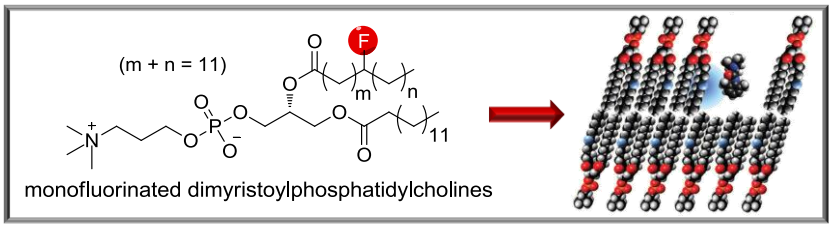
P62 Synthesis and characterization of monofluorinated DMPC, potential NMR probes for the study of membrane topology

Marie-Claude Gagnon, Jonathan Guimond-Tremblay, Michèle Auger* and Jean-François Paquin*
PROTEO, CQMF, CERMA, Département de chimie, Université Laval, Québec, QC, G1V 0A6, marie-claude.gagnon.24@ulaval.ca

Understanding the interactions between lipid membranes and drugs, peptides or proteins is of primary importance to determine their mechanism of action. In this context, nuclear magnetic resonance (NMR) is a method of choice to study their effects on model membranes. The incorporation of ^{19}F in membranes offers several advantages for NMR studies (high sensitivity, 100% natural abundance, etc.). The synthesis of a variety of monofluorinated dimyristoylphosphatidylcholine derivatives (F-DMPC) will be described.[1] FTIR and preliminary solid-state NMR studies suggest that the presence of the fluorine atom does not significantly perturb the properties of the lipid bilayers and that these fluorinated lipids could be used as probes for the study of membrane topology.

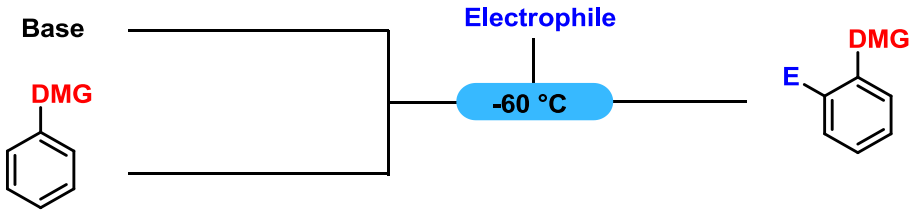


1. Guimond-Tremblay, J.; Gagnon,* M.-C.; Pineault-Maltais, J.-A.; Turcotte, V.; Auger, M.; Paquin, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 1145-1148.

P63 Directed ortho metalation in flow

Ondrej Kysilka, Mathew Kitching, Victor Snieckus*, Department of chemistry, Queen's University, Kingston, Ontario, K7L 3N6, snieckus@chem.queensu.ca

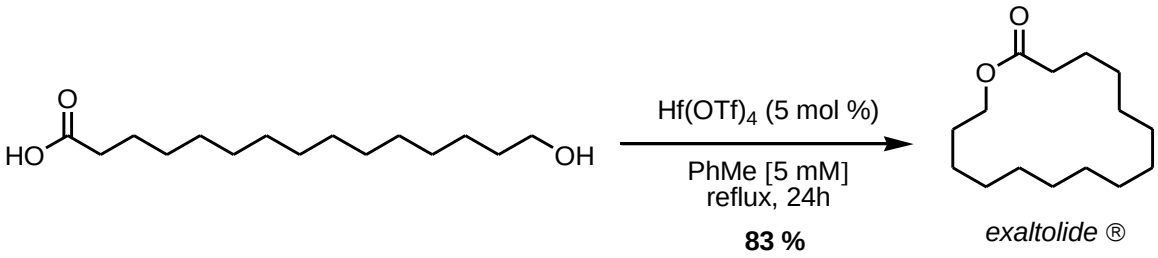
Directed ortho metalation (D*o*M) is a term coined for the functionalization of the aromatic ring with an electrophile, *ortho* to a directed metalation group (DMG). It allows the construction of densely substituted aromatic systems, where other methods of the aromatic functionalization are usually difficult or fail. The highly exothermic features of this reaction and nature of the reagents make it a perfect candidate for the flow chemistry. Due to the small volumes involved, the heat generated at cryogenic temperatures by any exotherm can be rapidly removed. Moreover, since the material is rapidly pumped away from the reaction zone, the products of the reaction have limited contact with the reagents and therefore side reactions to the D*o*M process are minimized. A new enabling technology for the safe and efficient pumping of organometallic reagents such as *n*-butyllithium through the Vapourtec R2+ microflow system will be presented and the first successful cases of D*o*M in flow will be reported.



P64 Towards a Hafnium-Catalyzed Direct Macrolactonization Protocol

Mylène de Léséleuc and Shawn K. Collins*, Département de Chimie, Center for Green Chemistry and Catalysis, Université de Montréal, Montréal, Qc, H3T 1J4, shawn.collins@umontreal.ca

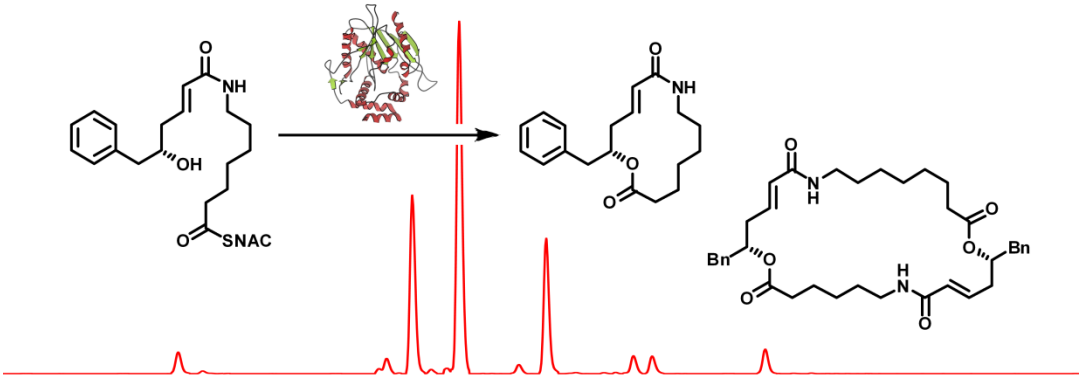
Macrolactones are important structural motifs in numerous chemical industries, in particular the pharmaceutical and cosmetic markets. However, the traditional strategy for the preparation of macrolactones remains cumbersome, often requiring stoichiometric or excess amounts of activating reagents. Consequently, stoichiometric quantities of by-products are generated. These are often toxic, environmentally damaging, and/or require tedious purification methods to remove them. Herein, we describe efforts to develop an efficient Hafnium-catalyzed direct macrolactonization between carboxylic acid and alcohol functionalities, generating only water as a by-product. Application towards the synthesis of industrially relevant macrolactones, such as Exaltolide®, as well bis-macrolactones will be reported.



P65 6-Deoxyerythronolide B synthase thioesterase-catalyzes stereoselective macrolide and macrodiolide formation

Taylor P.A. Hari & Christopher N. Boddy*, Department of Chemistry, University of Ottawa, Ottawa, ON, K1N 6N5, cboddy@uottawa.ca

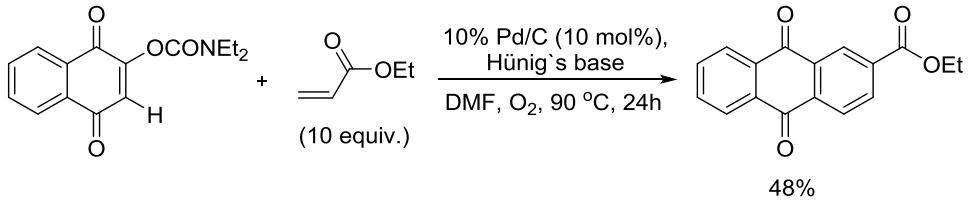
Macrocyclic polyketide natural products are a requisite source of therapeutic agents. The final stage of their biosynthesis, macrocyclization, is catalyzed regio- and stereoselectively by a thioesterase. A series of substrates were synthesized to test their specificity for macrocylzation by the erythromycin polyketide synthase TE (DEBS TE) *in vitro*. It was shown that DEBS TE is highly stereospecific, successfully macrocyclizing a 14-member ring substrate with an *S* configured *O*-nucleophile, and unprecedented generation of a 28-member macrolide ring substrate.



P66 Pd-catalyzed cross-coupling reactions of Naphthoquinone O-Carbamates with Acrylates.

Sara Gomes, Alcides da Silva, Victor Snieckus* Department of Chemistry, Queen`s University, Kingston, ON, K7L 3N6, victor.snieckus@chem.queensu.ca

Transition metal catalyzed reactions constitute the new wave of synthetic tools for the construction of C-C bonds. In this presentation, we present the reaction between 2-*N*,*N*-diethyl *O*-carbamate of lawsone (1) and ethyl acrylate under Heck conditions, which, surprisingly, provided the anthraquinone (2) as the major product. The scope of the reaction and the mechanism are under study, results of which will be presented as achieve. The current reaction represent the first Pd-catalyzed C-O activation involving the *O*-carbamate as the leaving group.



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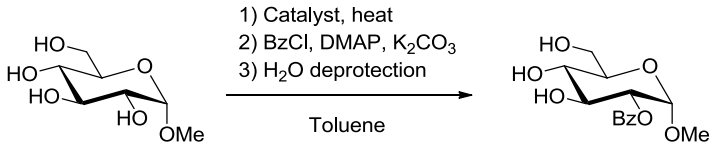
P67 Development of a new glycosylation strategy based on directing-protecting groups.

Sylvain Rocheleau* and Nicolas Moitessier, Chemistry Department, McGill University, Montréal, Québec, H3A 0B8, sylvain.rocheleau@mail.mcgill.ca

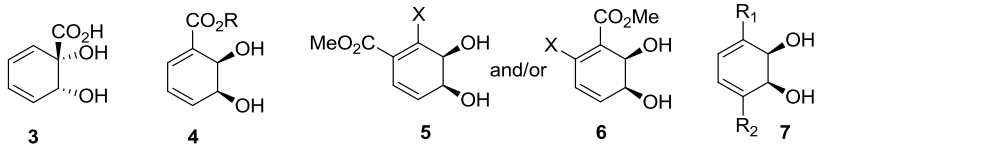
Currently, synthetic strategies towards oligosaccharides are based upon numerous time-consuming, cost-inefficient and not environmentally friendly protection and deprotection steps. We develop a novel synthetic strategy to prepare oligosaccharides in a concise, scalable and green way. We designed directing-protecting groups (DPGs) which, when attached to the primary 6-hydroxyl group of glucopyranosides, influence the regioselectivity of a variety of chemical reactions (e.g., acetylation, benzoylation, pivaloylation, silylation and glycosylation) on one of the three other unprotected hydroxyl groups. As an application, glycosylating glucose using this methodology led to a single disaccharide over six possible, significantly improving the regio- and stereoselectivity of this reaction. We then moved on to developing directing-protecting catalysts (DPCs) such as boronic acids which form labile bonds with the carbohydrate unit and activates a given hydroxyl group for functionalization, in a one-pot process. With such a group, there is no need for protection and deprotection steps.



P68 Processing of *o*-halobenzoates by toluene dioxygenase. The role of the nature of alkoxide in the regioselectivity of the enzymatic dihydroxylation.

Jordan Froese, Mary Ann Endoma-Arias, and Tomas Hudlicky*. Department of Chemistry, Brock University, St. Catharines, Ontario, L2S 3A1, thudlicky@brocku.ca

The enzymatic *cis*-dihydroxylation performed by toluene dioxygenase has yielded many diverse metabolites which have provided useful chiral scaffolds for organic synthesis. In order to investigate the relationship between the size of substituents on the aromatic substrate and their directing effect on the dihydroxylation, a series of various alkyl 2-halobenzoates was synthesized and subjected to the whole cell fermentation with toluene dioxygenase (TDO) overexpressed in E. coli JM109 (pDTG601A). A significant correlation was observed between the size of the substituents and their directing effect on the dihydroxylation.

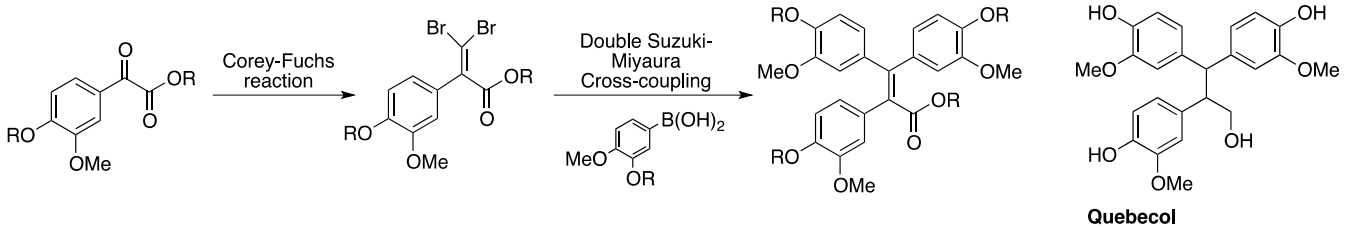


Furthermore, significant increases in yield and regioselectivity were observed using propargylic esters, relative to any other ester substituent. *Para*-disubstituted aromatic substrates have also been tested in dihydroxylations with TDO to provide further insight into the directing effects of halogen and alkyne substituents. Absolute stereochemistry was determined for all new metabolites.

P69 Synthesis of a new polyphenolic compound found in maple syrup

Sébastien Cardinal, Normand Voyer*, Département de chimie and PROTEO, Université Laval, Québec, QC, G1V 0A6, Normand.Voyer@chm.ulaval.ca

A new polyphenolic compound formed during maple syrup processing from *acer saccharum's* sap has been recently reported[1]. Its structural similarity with common bioactive agents and its potential antioxidant properties lead our group to work on the total synthesis of this compound, which was named quebecol. Our synthetic approach involves two key steps. The first one consists of a Corey-Fuchs type reaction on an α-ketoester to produce the dibromoalkene analog. This product is used in the second key step: a double Suzuki-Miyaura cross-coupling with the appropriate arylboronic acid using conditions optimised for hindered systems. This efficient and convenient strategy has led us to prepare quebecol on a large scale[2]. Moreover, this convergent synthetic route could allow us to produce a library of analogs.



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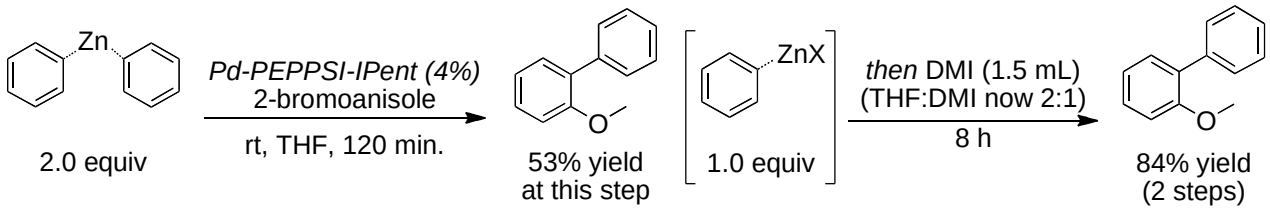
P70 From alkyl-alkyl to aryl-aryl bond formation: the vastly different role of salts in Negishi cross-coupling

Lucas McCann, Michael G. Organ* Department of Chemistry, York University, Toronto, ON, M3J1P3, Organ@YorkU.ca

Organozincs are used frequently in Negishi cross-coupling with organohalides. The mechanism and identification of the active transmetalating species has been under intense investigation.[1] Alkylzinc halides can be prepared salt-free and, in alkyl-alkyl couplings, additive salts (e.g. LiX, X = halide) are required to form $RZnX_2^-$ and subsequently, $RZnX_3^{2-}$ before transmetalation to Pd^{II} will occur. Though sp^2-hybridized organozincs are thought to transmetalate more readily than their sp^3 counterparts, preparation is almost exclusively from the corresponding organolithium or Grignard reagent, thus the study of salt-free arylzinc species is challenging. Once isolated, diarylzincs were found to directly transmetalate to *Pd-PEPPSI-IPent* without the need of salt-additive *or* polar co-solvent. The coupled by-product, arylzinc halide, remains inactive unless the solution reaches a high enough dielectric (by polar co-solvent or salt addtive) before a second transmetalation will occur.



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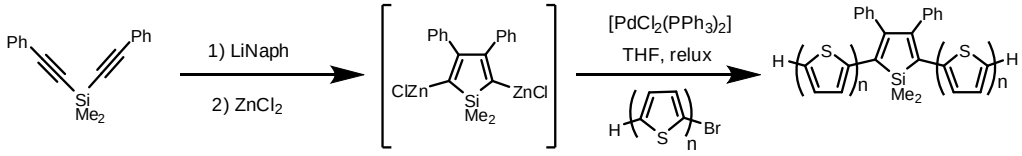
P71 Silole chemistry lights our life: synthesis and electrochemical properties of new silole based lumiphores

Tyler Day, Mahmoud Moustafa, Chris Na, Brian Pagenkopf, and Zhifeng Ding. Western University, Ontario, ON, N6A 5B7, bpagenko@uwo.ca

Our group has recently developed a practical synthesis of oligomeric siloles using a one pot, two step reductive cyclization[1], followed by Negishi cross-coupling[2]. These siloles are being studied because of their low lying LUMOs compared to cyclopentadiene, which gives them great Electrogenerated Chemiluminesenc (ECL) properties. ECL, when coupled with biological probes, is a remarkably powerful method for detecting trace materials in biological samples, and is used in hospitals universally to help diagnose disease[3]. Future research would involve the synthesis of new benzosiloles due to inconsistencies in the performance of the lithium metal. These benzosiloles will be synthesized via rhodium catalyzed cyclization[4], to determine their ECL efficiency though collaboration with the Ding group



Where n=1,2,3

1. S. Yamaguchi, T. Goto, K. Tamao, *Angew. Chem. Int. Ed.* **2000,** 39, 1695. 2. A. O. King, N, Okukado, E. Negishi, *J. Chem. Soc,. Chem. Commun.,* **1977,** 683.

P72 Development of a new scaffold for catalytic acyl transfer reactions

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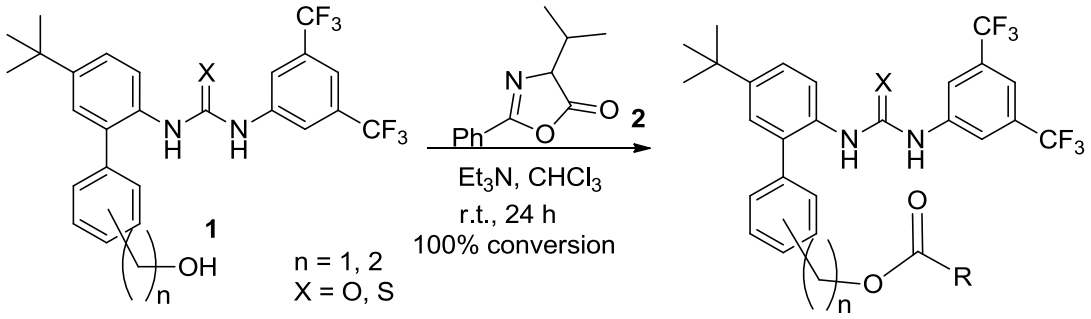
The amination of carboxylic acid derivatives is a vital chemical transformation, both in nature and in the laboratory. However, it is plagued by several shortcomings (stoichiometric coupling reagents, costly metals and/or high temperatures). A new scaffold for catalytic amidation of carboxylic acids would provide a solution to these issues. We are examining a dual hydrogen bonding urea-based acyl receptor (**1**) with a proximally positioned nucleophile. While the ultimate goal will be activation of carboxylic acids, oxazolone (**2**) was chosen as acylation reagent for preliminary evaluation of the design. Optimization, including the location and nature of the nucleophilic group and the tuning of the electronics of the hydrogen bonding group has yielded several urea based scaffolds capable of undergoing acylation at room temperature.



P73 Progress towards the total synthesis of (+)-bovidic acid via a diastereoselective alkylation and Mukaiyama oxidative cyclization

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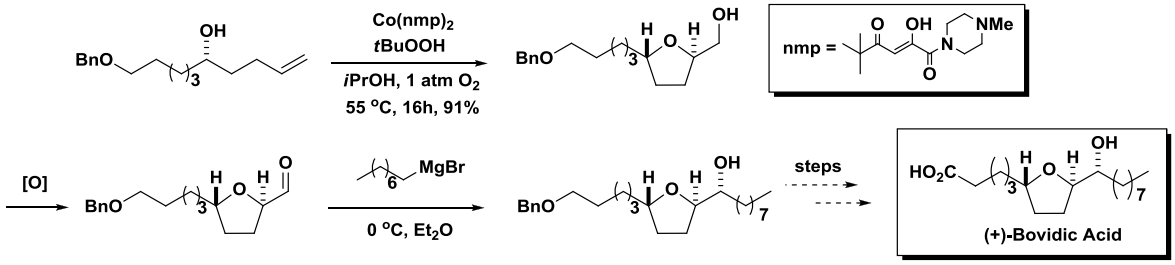
The *trans*-2,5-tetrahydrofuran(THF) structure is abundant in natural products, one such example is (+)-bovidic acid, which was first isolated in 2004 in the wool of domestic sheep.[1] The *trans*-THF of the molecule was efficiently achieved *via* oxidative cyclization of the corresponding pentenol derivative, using the 2nd generation cobalt catalyst developed in our lab.[2] Next, the required side chain was installed via a diastereoselective alkylation. Current progress and future directions towards (+)-bovidic acid will be presented.



References. [1] Ishii et al., *J. Nat. Prod.* **2004**, *67*, 1426. [2] Palmer et al., *Org. Lett.* **2009**, *11*, 5614.

P74 Straightforward synthesis of propargyl ketones from acyl chlorides and trifluoroborates.

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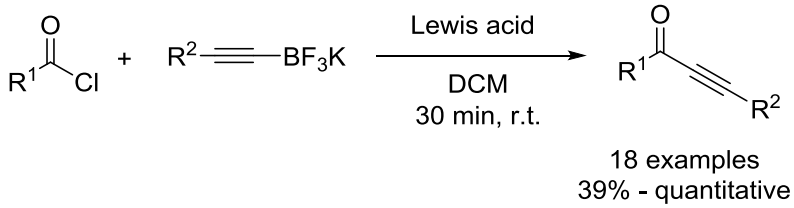
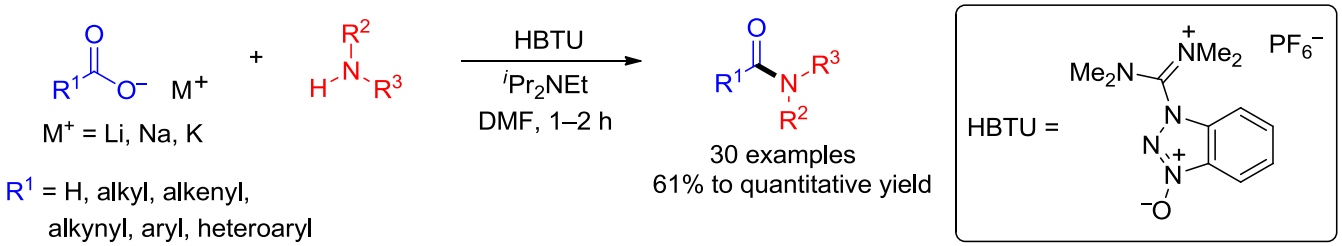
Propargyl ketones are important building blocks in organic chemistry. Traditionally, propargyl ketones have been prepared via two step procedures using either Weinreb amides or addition-oxidation chemistry. More recently, transition-metal-catalyzed reactions have emerged as an alternative approach. As a part of our research program focused on the investigation of transition-metal-free reactions of organoboranes, we have developed a novel method for the preparation of propargyl ketones from acyl chlorides and alkynyl trifluoroborate salts. This one-pot reaction proceeds rapidly in the presence of the Lewis acid without exclusion of air and moisture. The value of this approach lies in the operational simplicity of the method. Under the developed reaction conditions, propargyl ketones were obtained in modest to excellent yields from a variety of acyl chlorides and alkynyl trifluoroborate salts in the presence of a Lewis acid.



P75 AMIDATION Reactions from the Direct Coupling of Metal Carboxylate Salts with Amines

Jordan Goodreid, Petar A. Duspara, Caroline Bosch, Robert A. Batey*, Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6, rbatey@chem.utoronto.ca

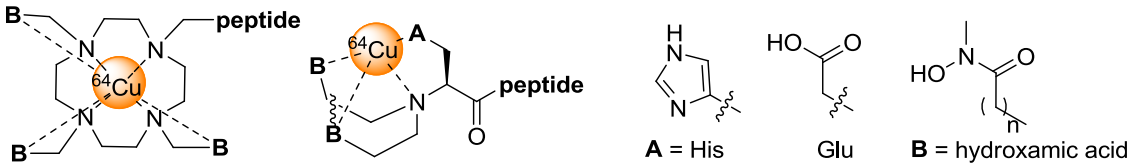
A general method for the synthesis of amides involving the direct coupling of alkali metal carboxylate salts with amines is described. Amidation of a wide variety of carboxylate salts with either free amines or their ammonium hydrochloride salts can be achieved using HBTU as a coupling agent in combination with Hünig's base. The reaction is highly efficient and is generally complete in as little as 1–2 h, giving the products in good to excellent yields. The protocol is valuable for the coupling of carboxylates for which the corresponding carboxylic acids or acyl chlorides are unstable, less conveniently manipulated/isolated or are not commercially available. The protocol can be combined with other reactions in a sequenced fashion, as exemplified by the synthesis of acetylenic amides, in a one-pot procedure, via the coupling of a lithium carboxylate salt formed initially by the addition of carbon dioxide to a lithiated terminal alkyne.



P76 Development and evaluation of bifunctionnal chelating agents for peptide labeling with ^{64}Cu.

Céline Denis, Geneviève Tremblay, Samia Ait-Mohand, Brigitte Guérin*, Département de Médecine Nucléaire et Radiobiologie, Université de Sherbrooke, Sherbrooke, QC, J1K 2R1, Brigitte.Guerin2@usherbrooke.ca

The tremendous interest of peptides for positron emission tomography (PET) imaging and tumour targeting is due to the many advantages including small size, easy preparation, low toxicity and low immunogenicity. Among others, the ability to attach bifunctional chelates (BFC) to peptides can extremely simplify their labeling with radiometal to the point where kit formulations are possible. Currently available BFC are limited by either harsh and/or slow radiolabeling chemistry that may cause radiolysis of natural peptides. With the goal of identifying improved BFC that stably complex with fast kinetics ^{64}Cu ($T_{1/2}$= 12.7h), a radiometal of interest for PET imaging, we developed cyclic and acyclic BFC derived from polyazacycles and amino acids (His, Glu) functionalized with methyl-hydroxamic acid as pendant arms. Each chelate has been compared to currently used BFC with respect to radiolabeling efficiency under mild conditions and stability.



P77 Unraveling the structure-activity relationship of tomatidine, a steroidal alkaloid with antibiotic properties against persistant forms of *Staphylococcus aureus*

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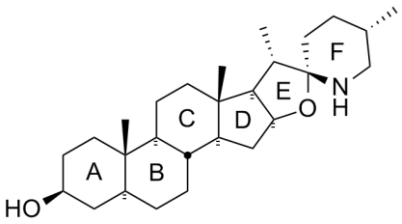

Staphylococcus aureus (*S. aureus*) is a pathogen presenting a wide range of adaptations to known treatments. Small colony variants (SCVs) represent a phenotypic adaptation that occurs in a wide variety of bacteria. *S. aureus* SCVs produce large amounts of biofilm, can reside within host cells, show a reduced susceptibility to aminoglycoside antibiotics and are consequently often associated with persistent infections. Previous works have shown that tomatidine (TO), a steroidal alkaloid has growth inhibitory activity against SCVs (MIC of 0.06-0.12µg/mL). Despite its lack of antibacterial activity against the normal phenotype of *S. aureus* (MIC > 16 µg/mL), TO acts both as an antivirulent and as a potentiator for aminoglycoside antibiotics. For example, the presence of TO increases the activity of gentamicin against normal *S. aureus* strains by 8-16 fold. Although TO treatment was shown to impact protein biosynthesis and the expression of virulence factors, biological targets have yet to be identified. In order to further our understanding of its antibacterial mode of action, analogs of TO have been generated bearing modifications on the hydroxyl function on cycle A and on the spiroaminoketal of cycle E and F. Such analogs managed to replicate the activity of TO, both on normal strains and SCVs of *S. aureus*.

Conférences plénières / Plenary speakers

Présentation orales / Oral presentations

Affiches / Posters

Albertson, Anna, McGill University
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Bawakid, Nahed, University of Western Ontario
Beauchemin, Sophie, Université de Sherbrooke
Bédard, Anne-Catherine, Université de Montréal
Bélanger, Étienne, OmegaChem Inc.
Bélanger, Guillaume, Université de Sherbrooke
Belding, Lee, Brock University
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Betit, Lyanne, University of Ottawa
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