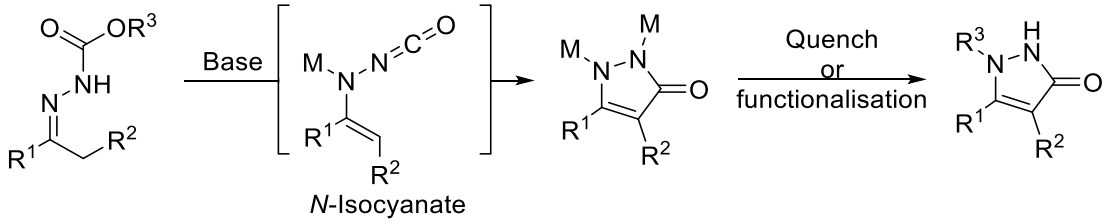


Synthesis of Pyrazolones by Cyclisation of *N*-Isocyanate Precursors

A. Mohamed,† F. Vuillermet,† M. A. Gill, A. M. Beauchemin*
Dept of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, ON, K1N 6N5
fvuiller@uottawa.ca

Nitrogen-substituted isocyanates are seldom used in organic synthesis due to their propensity for side reactions. However, when generated *in-situ* they enable new approaches to heterocyclic compounds.[1] Pyrazolones are privileged bioactive subunits, as in analgesics phenazone and edaravone. However, their synthesis can be challenging due to the difficulty in accessing β-dicarbonyl reagents required for condensation chemistry. The discovery of a reaction forming 1,2-dihydro-3*H*-pyrazol-3-ones from related hydrazones will be presented. The approach relies on formation of a metal complex, deprotonation, followed by formation of the *N*-isocyanate and cyclisation. Selected optimization efforts, reaction scope and mechanistic insights will be presented.

References

1. Vincent-Rocan, J. F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjani, J.; Beauchemin, A. M. *Chem*. *Sci*. **2016**, 7, 315

Strategic use of gold(I)-catalysis for the concise synthesis of polycyclic indole motifs

Ali Mansour, David F. León Rayo, Wenbin Wu, Benjamin N. Bhawal, and Fabien Gagosz*
University of Ottawa, Ottawa, Ontario, Canada
E-mail: amans092@uottawa.ca

Catalysis by electrophilic gold complexes represents an increasingly specific and powerful tool for the generation of molecular complexity and diversity.[1] The Lewis acidic and electron donating properties of electrophilic gold complexes provide an excellent opportunity for the efficient functionalization of carbon π-systems, particularly for alkynes and allenes by π-acid catalysis.[1-3] This reactivity mode is highlighted in the formal transfer of nitrene species onto gold(I)-activated carbon π-systems, where a key α-imino gold carbene intermediate is generated. Owing to the high reactivity of the α-imino gold carbene, the addition of nucleophiles to trap this species has been thoroughly studied.[4] We leverage this unique mode of reactivity by demonstrating the efficient and rapid access to polycyclic indole motifs that can be derived into structures relevant to natural products by the intermediate α-imino gold carbene (Figure 1).[5] This will be showcased through a concise approach to the natural product (±)-brevianamide A.[6]

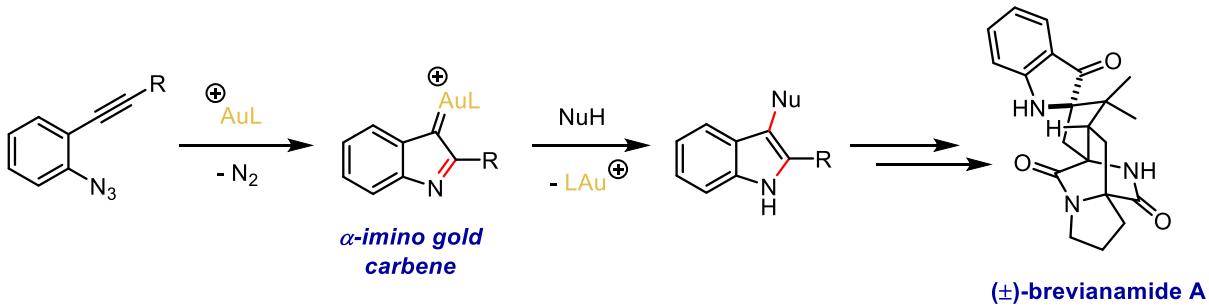


Figure 1. Synthesis of indole scaffolds using gold(I)-catalysis

References

1. Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.
2. Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.
3. Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482–486.
4. Wetzel, A.; Gagosz, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7354–7358.
5. León Rayo, D. F.; Mansour, A.; Wu, W.; Bhawal, B. N.; Gagosz, F. *Angew. Chem. Int. Ed.* **2023**, *62*, e202212893.
6. Mansour, A.; Gagosz, F. *Org. Lett.* **2022**, *24*, 7200–7204.

Poster Information

Title: Approaches to Enable Medicinal Chemistry in Hit-to-Lead Optimization

Authors: Shima Rezaeian, Simon Woo, Steven R. LaPlante

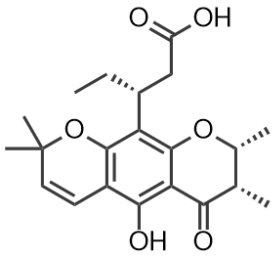
Institution: INRS - Armand-Frappier Health and Biotechnology Research Center

Abstract: Fragment-Based Lead Discovery (FBLD) has emerged as a valuable technique in drug discovery, aiming to identify fragment hits with relatively weak affinities (K_D in the μM–mM range) and low molecular weights. Potent leads are then developed from these fragments, presenting the main challenge of optimizing low-affinity compounds into high-affinity (nM) potential drugs. Additionally, we encountered issues during biophysical and bioassay methods such as compound solubility and aggregation. This poster emphasizes the crucial role of medicinal chemistry in enabling hit-to-lead optimization, addressing the challenges encountered in the FBLD process. We illustrate this with examples from both the literature and our research group. Our research team employs a combination of NMR biophysical experiments with medicinal chemistry to monitor compound behavior, rank affinities, and generate structure-activity relationships (SAR) to guide the transformation of hits into lead-like compounds.

Synthetic Efforts Toward Calofolic Acid A

Roxann Forget, Princeton Luong, Mathew Piotrowski, Jakob Magolan*

Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada



calofolic acid A

Calofolic acid A is a phenolic natural product isolated in 2017 from the bark of the *Calophyllum Scriblitifolium* tree [1]. It exhibits vasorelaxant activity in rats, which is indicative of its potential as a lead for the development of therapeutics for cerebrovascular diseases like aneurysms or strokes [2].

The aim of this project is to develop an efficient synthesis of calofolic acid A and thereby enable further biomedical investigations. This presentation will disclose our proposed nine-step synthetic route and describe our progress to date.

References

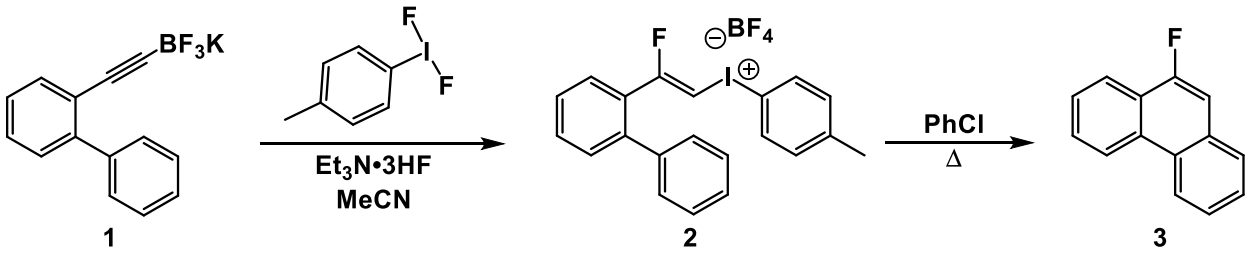
1. Nugroho, A. E., Sasaki, T., Kaneda, T., Hadi, A.H.A. *Bioorg. Med. Chem. Lett.* **2017**, 27(*10*), 2124-2128.
2. Kaneda, T., Ifadotunnikmah, F., Nugroho, A. E., Koshikawa, S., Tadahiro, S., Hirasawa, Y., & Morita, H. *J. Nat. Prod.* **2022**, 85(*9*), 2192-2198.

Umpolung Cyclizations of Alkynes in the Synthesis of Fluorinated Polycyclic Aromatic Hydrocarbons

Fabio Cuzzucoli[a], Liam H. Britt[a], Julie Dang[a], Tess Fortier[a] and Graham K. Murphy[a].
University of Waterloo, Waterloo, Ontario, Canada

Email: Fcuzzuco@uwaterloo.ca

Numerous industries employ fluorine and fluorinated motifs in their small-molecule design strategies to engineer and modulate their molecule's physical properties.[1, 2] In recent years there has been increased interest in fluorinated polycyclic aromatic hydrocarbons (PAHs) and conjugated polymers due to their applications in organic-based electronics. This research exploits the reactivity of hypervalent iodine reagents to develop a fluorination/tandem cyclization strategy for the synthesis of novel fluorine-substituted PAHs. (Difluoroiodo)toluene ($TolIF_2$) is a versatile hypervalent iodine-based fluorinating agent that can be made on large scale using 48% aqueous HF.[3] Ethynyl trifluoroborates have been shown in the literature to undergo ligand exchange with hypervalent iodine reagents to displace suitable apical nucleofuges (e.g. OTs, OAc, Cl).[4] Using $TolIF_2$, these ethynyl trifluoroborates (**1**) can be converted to isolatable fluorovinylaryl iodoniums (**2**) through conjugate addition of HF. Biarylfluorovinylaryl iodoniums synthesized this way can cyclize to give 9-fluorophenanthrenes (**3**) through a suspected vinylic S_N2 process. This research seeks to address a critical scientific need, by developing novel reactivity to incorporate fluorine into valuable PAHs directly, using inexpensive feedstock metal or hydrogen fluorides. Bypassing the multistep preparation of fluorinating agents, it could be an invaluable tool for researchers who use site-specific fluorination as a tool in molecular engineering.



References

1. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H., Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014,** *114* (4), 2432-2506.
2. Fujiwara, T.; O'Hagan, D., Successful fluorine-containing herbicide agrochemicals. *J. Fluorine Chem*. **2014,** *167*, 16-29.
3. Tao, J.; Murphy, G. K., A Practical, Large-Scale Synthesis of p-(Difluoroiodo)toluene (p-TolIF2). *Synthesis* **2019,** *51* (16), 3055-3059.
4. Borrel, J.; Waser, J., Tosyloxybenziodoxolone: A Platform for Performing the Umpolung of Alkynes in One-Pot Transformations. *Org. Lett.* **2022,** *24* (1), 142-146.

Theoretical assessment of the binding modes of VHL-recruiting PROTAC designed for oncogenic KRas^{G12C}

Tanos C. C. Franca[a], Eleonore Delaire[a], Steven R. LaPlante[a]

[a]INRS-Centre Armand Frappier Santé et Biotechnologie, Laval, QC, Canada.

Recently VHL-recruiting PROTACs designed for oncogenic KRAS^{G12C} were reported in the literature by Bond and co-workers[1]. They synthesized and performed cell assays of six PROTACs with five different linkers by combining the KRAS^{G12C} covalent ligand MRTX849[3] and a VHL 3 ligase ligand[2]. According to the authors, one of the compounds (LC2) induced the highest levels of endogenous KRAS^{G12C} degradation in a panel of cancer cells at relatively low concentrations, ranging between 0.25 and 0.59 μM, when compared to the others. To provide a theoretical explanation for this and better understand the engaging mechanism of the KRAS^{G12C}-PROTAC-VHL ternary complexes, we employed the conformational searching and scoring protein-linker-protein tool of the MOE® package (https://www.chemcomp.com/Products.htm). We used this tool to predict the possible ternary complexes formed by each of the six compounds and further validated them through 200 ns of molecular dynamics simulations[4]. Our results, revealed a predominant binding mode and the solvent exposure of the amide groups close to MRTX849 in LC1, LC3 and LC6 during the MD simulations. This supports the authors' hypothesis that the hydrolysis of these amides might be responsible for the lowest degradation rates observed for these PROTACs.

References

1. Bond et al. Targeted degradation of oncogenic KRAS^{G12C} by VHL-recruiting PROTACs. *ACS Cent. Sci.* **2020**, 6, 1367-1375. DOI: https://doi.org/10.1021/acscentsci.0c00411
2. Hallin et al. The KRAS^{G12C} inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. *Cancer discovery* **2020**, 10, 54-71. DOI: https://doi.org/10.1158/2159-8290.CD-19-1167
3. Buckley et al. Targeting the von Hippel–Lindau E3 Ubiquitin Ligase Using Small Molecules To Disrupt the VHL/HIF-1α Interaction. *JACS* **2012**, 134, 4465-4468. DOI: https://doi.org/10.1021/ja209924v
4. Hansson et al. Molecular dynamics simulations. *Curr. Op. in Struc. Biol.* **2002**, 12, 190-196. DOI: https://doi.org/10.1016/S0959-440X(02)00308-1

Dual Covalent Proximity Induction Strategy for Synthetic Immunotherapy

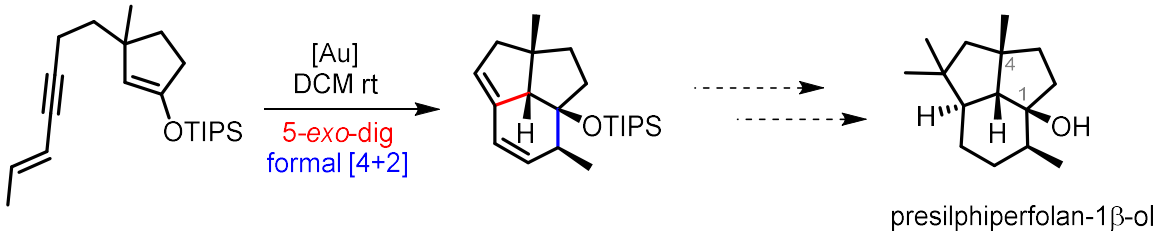
Eden Kapcan, Anthony F. Rullo

Synthetic 'Proximity Inducing' molecules represent a growing class of novel therapeutic. Previously, our lab created Covalent Immune Recruiters (CIRs), which can covalently label and redirect endogenous serum antibodies towards cancer antigens. CIRs has demonstrated that covalent engagement within an immune synapse leads to enhanced immunotherapeutic function. Since current CIRs only stabilize one of the two terminal proteins in the immune complex, we hypothesized greater immune activation can be achieved by developing dual covalent molecules that covalently engage both terminal proteins in the immune complex, i.e. tumor antigen and antibody. This approach uniquely "locks" the immune complex. Towards this end, we developed novel molecules called Dual Covalent Immune Recruiters (DCIRs), with the goal of covalently engaging both anti-DNP IgG and the urokinase plasminogen activating receptor (uPAR) tumor antigen. DCIRs were shown to efficiently out-compete a high affinity endogenous ligand for uPAR (i.e. urokinase), whose binding drives cancer metastasis. We demonstrate for the first time that optimal placement of two electrophiles on a single bi-functional molecule can affect selective covalent crosslinking of the two proteins in a functional ternary complex. In models of macrophage and NK cell activation, we observe 'locking' of the ternary complexes via DCIRs enables additional functional enhancements compared to covalent engagement of either terminus. However, in engineered CAR-T cell systems, covalent engagement of the tumor antigen is sufficient to maximize function, suggesting intrinsic differences in receptor pharmacology and biophysics of receptor signaling. This work represents the first example of dual covalent proximity inducing molecules with therapeutic potential.

Towards the synthesis of presilphiperfolan-1β-ol

Chris Wicks, Prof. Louis Barriault, University of Ottawa.

Presilphiperfolanols constitute a family of biosynthetically important sesquiterpenes which can rearrange to a diverse array of terpenoid skeletons owing to the considerable ring strain found within their framework. This structurally complex family of natural products is distinguished by their uncommon and highly compact tricyclo[5.3.1.$0^{4,11}$]undecane sesquiterpene skeleton, bearing five contiguous stereocenters, two all-carbon quaternary centers, and a tertiary hydroxy group. To date, only three natural presilphiperfolanols have been isolated: presilphiperfolan-1β-ol, presilphiperfolan-8α-ol, and presilphiperfolan-9α-ol. Of most interest to our group is presilphiperfolan-1β-ol which has been previously prepared by Stoltz in the first asymmetric synthesis of any presilphiperfolanol,[1] and by Tiefenbacher in a semi-synthesis involving supramolecular catalysis.[2] Herein, we will describe our efforts towards presilphiperfolan-1β-ol involving a highly efficient tandem [Au^{I}] 5-*exo*-dig and formal [4+2] cyclization to rapidly afford the tricyclic core of our target. In this way, we generate 3 of the 5 stereocentres found within our target in a single transformation, having previously installed the requisite methyl substituent at C_4. Ongoing efforts towards the completion of this project will be discussed as well as our end-game strategy.



1 Y. Hong,B. M. Stoltz, *Angew. Chem. Int. Ed.* **2012**, *51*, 9674 9678.

2. L.-D. Syntrivanis, I. Némethová, D. Schmid, S. Levi, A. Prescimone, F.Bissegger, D. T. Major, K. Tiefenbacher, *J. Am. Chem. Soc.* **2020**, *142*, 5894–5900.

Title: Incorporation of Loratadine-Cyclodextrin Complexes in Oral Thin Films for Rapid Drug Delivery

Complete Authorship: Annika Yardy,[†] Kirsten Entz,[†] Dayna Bennett,[†] Benjamin Macphail,[‡] and Alex Adronov[†]

Institutions: [†]Department of Chemistry and Chemical Biology and the Brockhouse Institute for Materials Research, McMaster University, Hamilton, Ontario, Canada

[‡]Rapid Dose Therapeutics, Corp., Burlington, Ontario, Canada

Poster Abstract: Rapidly dissolving polymer thin films, or oral thin films (OTFs), have recently emerged as an improved oral drug delivery vehicle with its ability to bypass liver first pass metabolism, longer shelf-life, and simpler transport and distribution requirements, compared to traditional tablets and liquid formulations. Loratadine (LOR), an antihistamine commonly used to treat allergic rhinitis, undergoes liver first pass metabolism and is a prime candidate for incorporation within an OTF. However, loratadine is a BCS II drug with low aqueous solubility. Herein, the solubility of loratadine was improved by complexation with methyl β-cyclodextrin (MBCD) by co-evaporation in the molar preparations of 2:1, 1:1, and 1:2 LOR:MBCD and incorporation into a pullulan-based OTF at 4 wt% by solvent casting at 50 °C for 30 – 35 minutes. A therapeutically relevant 10 mg LOR dose could be prepared in a 3 cm by 3 cm OTF. The feasibility of complexation was observed with a B_s-type phase solubility diagram, and complexation itself was confirmed via differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), ^{1}H NMR spectroscopy and via diffusion-ordered spectroscopy. LOR:MBCD could be incorporated homogeneously throughout an OTF, and LOR:MBCD OTFs exhibited reasonable mechanical strength and endured 12 ± 3 folds before breaking. LOR:MBCD OTFs disintegrated within 38 ± 10 s. The cumulative *in vitro* release of LOR in LOR:MBCD OTFs peaked at 80% within 3-4 minutes of dissolution, and LOR in LOR:MBCD OTFs demonstrated permeability across a 0.22 μm nitrocellulose membrane, indicating its applicability as a rapid drug delivery vehicle.

Ni-Catalyzed Reductive Arylation of Electronically Biased NHP Esters Enabled by a Chlorosilane Additive

Alexis L. Gabbey,[1] Nicholas W. M. Michel,[1] Michael S. West,[1] Raquel Edjoc,[1] Emmanuel Fagbola,[1] Malcolm P. Huestis,[2] Jonathan M. E. Hughes,[3] L.-C. Campeau,[3] and Sophie A. L. Rousseaux[1]

[1]*Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 2H6, Canada*
[2]*Discovery Chemistry, Genentech Inc., 1 DNA Way, South San Francisco, California 94080, USA*
[3]*Department of Process of Process Research and Development, Merck & Co. Inc., Rahway, USA*

Email: alex.gabbey@mail.utoronto.ca

Ni-catalyzed cross-couplings of *N*-hydroxyphthalimide (NHP) esters have emerged as a powerful strategy to form a variety of C–C bonds.[1] NHP esters are redox-active and can undergo single electron transfer (SET) reduction and decarboxylation under mild conditions to yield radical intermediates, which are then captured by a nickel catalyst and subsequently functionalized. NHP esters also readily participate in reductive cross-electrophile coupling reactions, which avoid the use of harsh organometallic reagents. Bench stability, as well as their accessibility from inexpensive carboxylic acids, renders these substrates extremely attractive cross-coupling partners.

To date, our research group has leveraged Ni-catalyzed reductive cross-coupling (RCC) of electronically biased NHP esters with aryl halides to synthesize several classes of molecules which are difficult to access using traditional methods (Figure 1). α-Arylation of both nitriles[2] and secondary amides[3] has proven possible under this manifold. α-Arylation of secondary amides is particularly noteworthy, as Pd-catalyzed alpha-arylation strategies typically require strong base and are not compatible with the amide N–H.[4] Synthesis of 1-arylcyclopropylamines, a common bioisostere for benzylamines,[5] has also been achieved using this strategy.[6] Both (hetero)aryl bromides and iodides may be employed in this transformation, and the reaction is also compatible with other α-amino strained rings. Mechanistic studies of these RCC reactions reveal that reduction and decarboxylation of the NHP ester to the radical intermediate is accomplished by the combination of a key chlorosilane additive and zinc. This poster will detail reaction optimization, scope, and substrate synthesis. Mechanistic hypotheses will also be discussed.

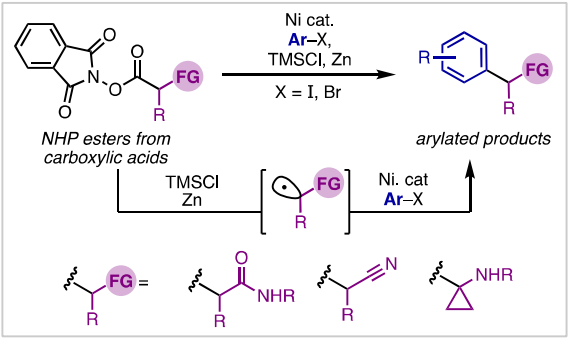


Figure 1: Ni-catalyzed reductive cross-coupling of electronically biased NHP esters with aryl halides.

References

[1] Muraruka, S. *Adv. Synth. Catal*. **2018**, *360*, 1735–1753.
[2] Michel, N. W. M.; Gabbey, A. L.; Edjoc, R. K.; Fagbola, E.; Hughes, J. M. E.; Campeau, L.-C.; Rousseaux, S. A. L. *ChemRxiv Preprint: 10.26434/chemrxiv.14450007.v2.*
[3] Gabbey, A. L.; Michel, N. W. M.; Hughes, J. M. E.; Campeau, L.-C.; Rousseaux, S. A. L. *Org. Lett.* **2022**, *24*, 3173–3178.
[4] (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146; (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res*. **2003**, *36*, 234–245.
[5] Talele, T. T. *J. Med. Chem*. **2016**, *59*, 8712–8756.
[6] West, M. S.; Gabbey, A. L.; Huestis, M. P.; Rousseaux, S. A. L. *Org. Lett.* **2022**, 24, 8441–8446.

Covalent Peptides to Chemically Program Immunity for Cancer Therapy

Karolina Krygier, Dr. Anthony Rullo
McMaster University

Antibodies recognize and target foreign substances for immune-mediated clearance. IgG mediated degradation proceeds through antibody dependent cellular cytotoxicity (ADCC) and/or antibody dependent cellular phagocytosis (ADCP) through various Fc receptor interactions. Due to the highly specific nature of antibodies, their use as a host protein in bioconjugation protocols remains of considerable interest for the development of novel targeted therapeutics and diagnostic probes. For example, the development of covalent antibody recruiting molecules (cARMs) remains a powerful strategy to employ for cancer immunotherapy. Bifunctional cARMs contain an antibody-binding domain (ABD) and a target-binding domain (TBD) to bridge a “ternary complex” at the tumor cell surface. By templating these complexes, cARMs allow for immune recognition and clearance via Fc:FcR interactions. However, cARMs are limited in their efficacy with low antigen expressing tumors and are limited in their ability to target only one endogenous antibody source, and thus the titers of said antibody. Using our covalent immune proximity-inducing strategy, we propose to explore how a pan IgG binding peptide incorporated into a covalent immune recruiter (CIR) mediates immune recognition of tumors and can employ natural antibodies against a target of interest.

We have synthesized a CIR that consists of a covalent IgG binding peptide equipped with a reactive electrophile and a TBD that targets urokinase-type plasminogen activator receptor (uPAR) on cancer cells. Initial validation of anti-tumor function in ADCP assays have been investigated using uPAR+/- cancer cell lines. Furthermore, tumor growth kinetics, mouse survival, and immune cell tumor infiltration will be measured using xenograft mouse breast tumor models. Using our CIR technology, we demonstrate a broadly applicable technique to covalently reprogram endogenous antibodies for targeted tumor immunotherapy.

Abstract for poster presentation QOMSBOC 2023

Title : Continuous Flow Synthesis of Amine Derivatives by Mesylate Substitution : Application to the Synthesis of Active Pharmaceutical Ingredients

Authors (first author is the presenter) : Corentin Charbonnier,[a] Gary Mathieu,[a] Hélène Lebel[a]

Institution : [a] Université de Montréal, Département de Chimie and Centre in Green Chemistry and Catalysis (CGCC)

Poster abstract : Amines are among the most widely used functional groups in medicinal chemistry, due to their ability to form very specific interactions in the human body. As such, methods for the synthesis of functionalized amines are of great interest to both organic and medicinal chemists. With the emergence of continuous flow chemistry as a technique for developing chemical reactions, new methodologies are being explored to build complex molecules. Our group focused on the development of continuous flow nucleophilic substitution to form C-N bonds from alkyl mesylates. These mesylates were easily obtained from the corresponding alcohol prior to reaction with an aqueous amine solution. The method provided primary, secondary and tertiary amines with very good yields and productivities. In addition, a significantly lower excess of amine was used compared to the previously described method. Differently substituted amines were also used. Interestingly, no polyalkylated by-products are formed during the reaction, which solves a common problem when performing this type of reaction in batch. An optimized synthesis of diphenhydramine was also developed.

Investigation of enzymes involved in fluorination during nucleocidin biosynthesis

Dr. Cunha, Luana and Dr. Zechel, David

Institution: Queen's University

Poster abstract: Organofluorine compounds constitute around 25% of all pharmaceuticals that have been licensed since the development of modern medicinal chemistry. Nucleocidin is a 4’-fluoronucleoside and is one of the very few natural products known to contain fluorine (Lowe and O’Hagan, 2023). Nucleocidin is also notable for containing a rarely seen 5’-O-sulfamoyl substituent (Awakawa et al., 2021). The biosynthetic gene cluster (Zhu et al., 2015) in *Streptomyces* strains associated with the biosynthesis of nucleocidin have been studied by gene knockouts (Pasternak et al., 2022; Wojnowska et al., 2022). The genes orf(-3), orf2 and orf3 encodes enzymes that are essential for fluorination (Wojnowska et al., 2022). However, the specific reactions catalyzed by the encoded enzymes are unknown. To investigate the functions of orf(-3), orf2 and orf3, we aim to heterologously overexpress the encoded enzymes in *E. coli* and characterize their functions in vitro. Recent progress will be presented.

Chemical Programming of Macrophages through Direct Covalent Immune Receptor Engagement for Targeted Tumour Immunotherapy

Zi (Sissi) Yang[1,2,3], and Anthony F. Rullo[1,2,3]

[1]Department of Chemistry and Chemical Biology, McMaster University, Hamilton, ON, Canada
[2]Department of Medicine, McMaster University, Hamilton, ON, Canada
[3]Centre for Discovery in Cancer Research, McMaster University, Hamilton, ON, Canada

Macrophages play a very important role in cancer progression and patient outcome. They have been promising therapeutic targets for cancer treatment due to their functional plasticity and role as immune effectors. Our project focuses on the chemical programming of macrophages for targeted tumour immunotherapy through direct covalent immune receptor engagement. These chemically programmed macrophages will recognize tumour specific antigens to target and destroy tumour cells. To program macrophages, we have developed and characterized covalent immune programmers (CIPs), which are molecules that contain a macrophage targeting domain and a tumour targeting domain (Figure 1). The macrophage targeting domain is a peptide that binds an activating receptor on the macrophage surface. It also contains a proximity-induced sulfonyl-fluoride exchange chemistry (SuFEx) covalent warhead that irreversibly labels the receptor once bound. Once attached to the activating receptor, the tumour targeting molecule can promote macrophage tumour engagement and stimulate tumoricidal function by binding a tumour-specific antigen on the tumour surface.

We have successfully synthesized the immune binding peptide with the SuFEx chemical warhead installed using solid-phase peptide synthesis. To optimize CIP design, we synthesized analogs with SuFEx installed at different positions within the peptide to determine if SuFEx position affects reaction kinetics and aqueous stability. Flow cytometry experiments have shown that CIPS are able to bind Fc receptors specifically and effectively on the surface of macrophage cell lines. Further, CIPs were able to induce macrophage activation and promote antibody-dependent cellular phagocytosis. These experiments have also shown that direct engagement of the receptor by the CIP is more effective than antibody-mediated engagement at inducing an immune response. Therapeutically, this shows that our platform could outperform current antibody treatments found in the clinic. These results point to the development of a novel immunotherapeutic that is more versatile, accessible, and effective.

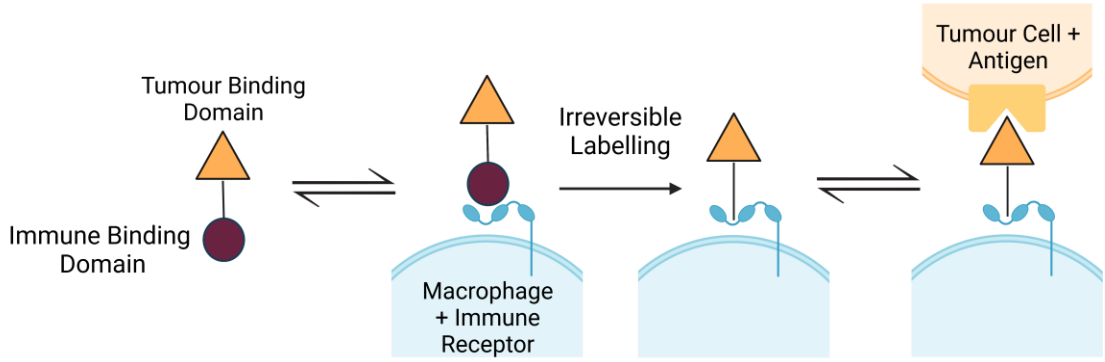


Figure 1. Schematic showing how CIPs can be used to program immune cells for cancer treatment.

Title: ***Synthesis of O^6-Cross-Linked Deoxyguanosine for the Optimization of hAGT Repair Assays on DNA Tetrahedra***

Authors: **Tyler Rutherford**, William Copp and Christopher J. Wilds
Department of Chemistry & Biochemistry, Concordia University, Montreal, QC

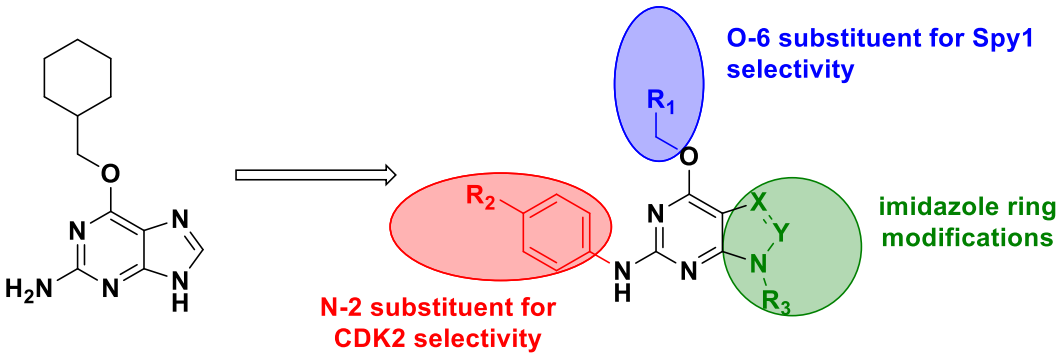
Abstract: O6-Alkylguanine DNA alkyltransferase (hAGT) is a DNA repair protein proficient at removing alkyl lesions from the O6-atom of 2'-deoxyguanosine (dG). Our lab has demonstrated that hAGT can unhook O6-alkylene interstrand and intrastrand cross-links (IaCL) between dG residues in DNA duplexes. This inspired our interest in exploring hAGT activity towards this IaCL in other DNA structures. One example is the DNA tetrahedron (TDN), a promising platform for cell permeable cargo delivery systems. Recently, our laboratory reported the preparation of a DNA TDN containing butylene and heptylene IaCL located at the vertices. hAGT demonstrated the ability to unhook this IaCL leading to TDN disassembly. However, differences in hAGT activity towards the IaCL at the vertices was observed. To optimize the design of the IaCL containing DNA TDN for efficient hAGT triggered disassembly, we are exploring the influence of incorporating longer alkylene linkers into this structure. This is achieved through the preparation of dG dimer phosphoramidites via a consice synthetic approach, followed by bilateral chain extention during solid phase synthesis to prepare three-way junction (TWJ) oligonucleotides. With these TWJ oligonucleotides, formation of the DNA TDN and its susceptibility towards hAGT based disassembly will be evaluated, providing a new approach for DNA based nanostructures to serve as a delivery platform with intracellular release triggered by endogenous factors.

SYNTHESIS OF SELECTIVE TARGETING CDK2-SPY1 INHIBITORS BY THREE DIFFERENT APPROACHES TO ACHIEVE BIG CHEMICAL SCOPE.

AUTHORS: Silva-Nigenda, Ezequiel; Meister, Daniel; Homon, Anton; Merk, Lukas; Prasad, Pavithra; Hayward, John J.; Trant, John F.;

Department of Chemistry & Biochemistry, University of Windsor. Windsor, Ontario, Canada.

Cyclin-dependent kinases (CDKs) are phosphorylating enzymes involved in cell division that promote transitions through the cell cycle by activation by cyclins.(1) If their activity is not regulated then this can result in uncontrolled cell proliferation which can, in turn, lead to different cancers.(2) In healthy cells the CDK activity is regulated by inhibitory proteins known as CKIs. However, it has previously been found that the overexpression of cyclin-like proteins, in particular Spy1, results in activation of CDK2 that is not affected by endogenous or synthetic CKIs.(3) Our computational team has proposed a series of promising compounds based on a purine core with selectivity towards the CDK2-Spy1 complex vs the CDK2-Cyclin complex. In this work, I will discuss the current progress towards the synthesis of a library of these small molecule inhibitors that aims to provide a lead compound with a novel mechanism of action against these cancers.



1. Malumbres M. Cyclin-dependent kinases. *Genome Biol*. **2014**;*15*(6), 122.
2. Ortega S, Malumbres M, Barbacid M. Cyclin D-dependent kinases, INK4 inhibitors and cancer. *Biochimica et Biophysica Acta*. **2002;** 1602 (1), 73-87.
3. Meister D, Hayward J, Fifield B-A, Porter L, Trant J. Spy1-activated Cyclin Dependent Kinase 2 Shows Reduced Affinity for Current Synthetic Small Molecule Inhibitors of the CDK2-Cyclin Complex . *ChemRxiv*. **2023**; This content is a preprint and has not been peer-reviewed. https://doi.org/10.26434/chemrxiv-2023-kzgfbORCID:https://orcid.org/0000-0002-4780

Exploring Macrolactamization Towards the Total Synthesis of a Novel Fungal Hybrid Polyketide-Non Ribosomal Peptide Natural Product

Claudia Natola, Samuel W. Shields, Dave Overy, Christopher N. Boddy

Polyketide synthase-nonribosomal peptide synthetases (PKS-NRPS) have emerged as an important resource for the biosynthesis of diverse and complex molecular scaffolds necessary in the discovery of novel drug candidates. Common to this class of natural products, is the macrocyclic ring structure that is formed through a condensation of the PKS fragment onto the amino acid backbone. Although conformational rigidity is a common feature across bioactive small molecules with site selective target interactions, the construction of the macrocycle is synthetically challenging and often the bottleneck of most synthetic attempts. In this study, we explored ring-closure through macrolactamization of a novel fungal PKS-NRPS hybrid natural product. With the goal of exploring the feasibility of its total synthesis, as well as confirming the connectivity and stereochemical arrangement of its multiple stereogenic centers, two routes to ring-closure were evaluated. A strained 12-memebered macrocycle composed of a pipecolic acid-aromatic amino acid dipeptide backbone and a short model fragment of the polyketide portion was constructed to resemble the macrocyclic core of our target fungal natural product. A reaction profile of amide bond ring-closure at two positions with in-situ formation of various activated esters was tested on the basis of product conversion and diastereomeric outcomes. The implications of this work on the viability of the synthesis of the macrocyclic core in the context of the natural product will be discussed, as well as our results of an early-stage pharmacophoric evaluation of our model system.

Asymmetric total syntheses of proaporphine alkaloids enabled by a dearomative radical cyclization strategy

Aromatic compounds (benzene derivatives) are produced on a large scale by the petrochemical and coal industries. These compounds serve as the primary raw materials in the production of agrochemicals and pharmaceuticals. Traditional synthetic approaches have focused on the use of robust aromatic substitution chemistry for the core functionalization of arenes. This approach has been proven useful in the past allowing the rapid diversification of these readily available feedstocks. However, with this strategy only relatively simple, flat, and sp^2-rich scaffolds can be accessed. This creates a significant gap between this easily synthesized compounds and the more complex structures found in natural products and modern drug-candidates, which typically possess three-dimensional topology with several stereocenters.[1] To close this gap, the implementation of dearomatization chemistry for the synthesis of complex molecules has recently become an integral part of the synthetic toolbox.[2] Dearomatization reactions enable the transformation of relatively inexpensive aromatic substrates into more complex scaffolds with an increased number of sp^3 carbons and stereocenters (Fig1. 1a). Within this particular research context, the objective of my study is to establish a dearomative cyclization strategy for the synthesis of proaporphine alkaloids. Notably, these alkaloids possess significant therapeutic potential and exhibit a broad range of bioactivities.[3]

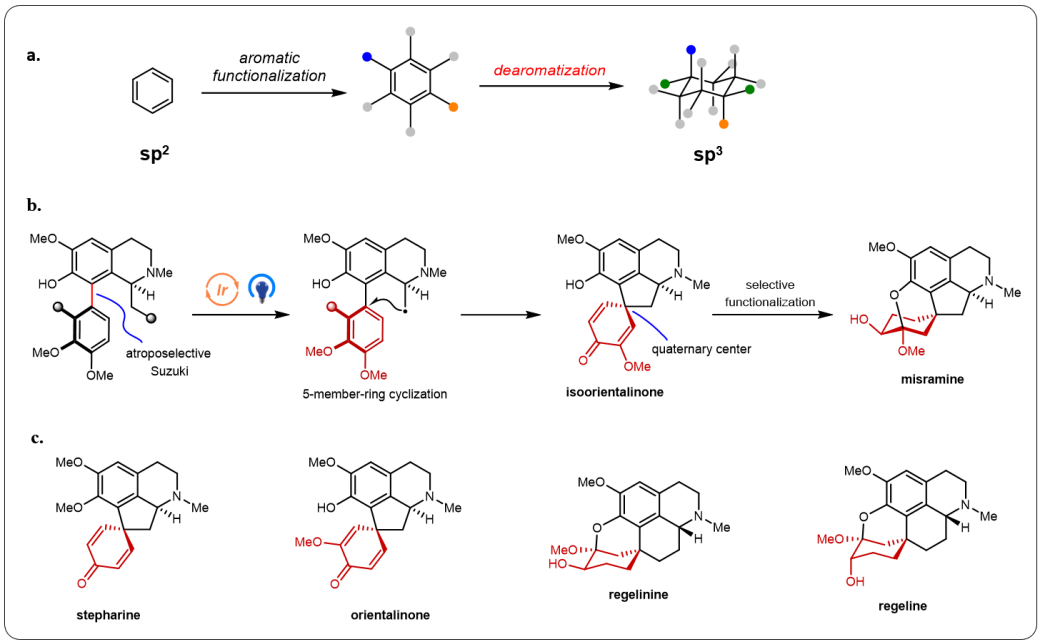


Figure 1: (a)-(c) *Overall strategy and plan*

The first part of our strategy (Fig. 1b) involves the synthesis of a key biaryl substrate employing an atroposelective Suzuki reaction (Aim 1). Of note, this biaryl intermediate already possess all the carbon atoms required in the target natural product, however not with the required complexity. As such, the next stage of the synthesis focuses on drastically increasing the stereochemical complexity of the molecules via the key dearomatization step (Aim 2). This would enable the construction of a quaternary stereocenter and directly provide the 5-member spirocyclic natural product isoorientalinone.[4] Further selective hydrogenation and functionalization of the dearomatized ring would then afford the more complex alkaloid misramine. Finally, we will further expand the applications of this dearomative cyclization strategy to other different important proaporphine alkaloids (Aim 3), including stepharine, orientalinone, regelinine and regeline (Fig. 1c). All together, these total syntheses will demonstrate the advantages of dearomative cyclizations for the rapid construction of highly complex scaffolds while also offering valuable natural products for biochemical investigations.

Title: Red light harvesting complexes for photocatalysis

Authors: Noémie Beaucage, Corentin Cruché, Jérémie Bourdon and Shawn K. Collins*

Institution: Département de Chimie, Université de Montréal, 1375 Avenue Thérèse-Lavoie-Roux, Montréal, QC H2V 0B3 Canada

Abstract:
Photocatalysis has had a transformative effect on molecular synthesis. The majority of modern photocatalysis makes use of visible light, typically between 390 and 550 nm. Typically, photocatalysis using lower energy light (red light) requires absorption of more than one photon. Disappointingly, there are little to no examples of complexes bearing abundant transition metals that can promote low energy photocatalysis. We have developed copper complexes used designed “extended” ligands to promote two-photo absorption in photocatalysis under red light. Eight new catalysts have been prepared, studied according to their photophysical data and evaluated in the dimerization of benzylamine with yields as high as 90%.

Structure-Activity Relationship Study of a New Potentiator of Gram-Positive Antibiotics Against Gram-Negative Bacteria

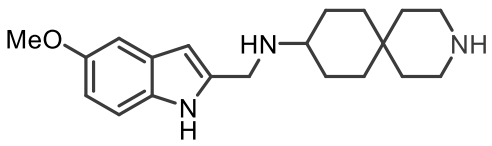
Keaton Peterson, Nikki Ritchie, Kristina Klobucar, My Cao, Jarrod Johnson, Eric Brown, Jakob Magolan*

Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada

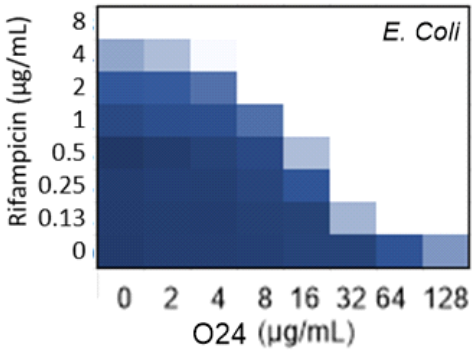
Antimicrobial resistance (AMR) occurs when antibiotics create selective pressure driving bacterial evolution that leads to decreases in antibiotic efficacy. AMR has been described by the World Health Organization as one of the biggest threats to global health, food security and development today.

One method to combat AMR is the synthesis of antibiotic potentiators which are small molecules that do not possess intrinsic antibiotic activity but rather increase the susceptibility of bacteria to existing antibiotics. Antibiotic potentiators are especially useful for extending the spectrum of Gram-positive antibiotics to Gram-negative bacteria. In this case, potentiators often perturb the outer membrane of Gram-negative bacteria to enable antibiotics enter these cells.

A unique high-throughput screen developed to identify potentiators led to the discovery of **Compound O24** that potentiates the activity of the antibiotic rifampicin in the Gram-negative pathogen *E. coli.* Here we present our ongoing investigation of the structure-activity relationship of Compound O24 that includes the synthesis and evaluation of focused library of analogues including novel compounds with enhanced potentiation ability.



Compound O24

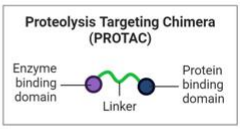


Exploiting Fragment-Based Lead Discovery in the Design and Synthesis of PROTACs for HRAS G12V

Eleonore K. Delaire, Tanos C.C. Franca, Steven R. LaPlante

Institut National de Recherche Scientifique -

To aim undruggable targets, fragment-based drug discovery enters on small, low molecular weight fragments used as foundational elements to construct more intricate molecules. In this context, the screening process usually relies on biophysical techniques to assess the affinity of these fragments rather than their inherent activity. The correlation between molecular structure and functional activity remains a time-intensive phase, demanding meticulous effort in the aim to obtain a candidate compound. In our laboratory, we have conceived an innovative strategy aimed at developing promising compounds with a pronounced affinity for the target protein. This approach entails integrating them with a current focal point in drug discovery, namely PROteolysis TArgeting Chimeras PROTACs). PROTACs represent hetero-bimolecular entities, featuring the ligand for the protein of interest and a ligand for an E3 ligase protein, interconnected by a linker. Their synthesis necessitates thoughtful consideration in terms of linker choice, including aspects like length and rigidity, which, in turn, offer a range of prospective synthesis techniques such as PEGylation, click-chemistry, amidation, and more. The selection of these PROTACS primarily hinges on the practicality of binding each constituent through straightforward chemical reactions. Furthermore, the choice of the E3 ligase is rendered more accessible due to the knowledge of the proteins capable of rendering the PROTAC effective. Additionally, ligands for these ligases have been determined through the Fragment-Based Drug Discovery method. This approach collectively enables the design of novel compounds tailored to target specific protein segments and thereby enhances the drug discovery process by mitigating time-consuming aspects.



TITLE : Chemoenzymatic Dynamic Kinetic Resolution of Secondary Alcohols and Amines Employing Copper-Based Photocatalysis.

AUTHORS : Clémentine Minozzi, Nicolas Dowe, Noémie Beaucage and Shawn K. Collins

INSTITUTION : Université de Montréal

ABSTRACT :

A tandem photo- and biocatalytic dynamic kinetic resolution of secondary alcohols and amines has been achieved employing a commercially available lipase CALB, and a heteroleptic copper complex. The process is an example of using copper-based photocatalysis to promote HAT processes employing thiyl radicals. A screening of 48 complexes and 5 disulfides identified Cu(**dtbbpy**)(**DPEPhos**)BF_4 and $(Ph_3SiS)_2$ as an optimal catalyst system to promote the HAT process. The catalytic system represents a general system for radical-mediated racemization applicable to both aliphatic and aromatic alcohols and amines (18 examples, 60→97 % yield, 76→99 % *ee*).

KEYWORDS : *Copper, photocatalysis, dynamic kinetic resolution, secondary alcohols, biocatalysis*

TPDYs: Strained Macrocyclic Diynes for Bioconjugation Processes

Corentin Cruché, Adem Hadjabdelhafid-Parisien, Bernard D'Onofrio, Joelle N. Pelletier,* Radu Iftimie,* and Shawn K. Collins*

Département de Chimie, Center for Green Chemistry and Catalysis, Université de Montréal, 1375 Ave.Thérèse-Lavoie-Roux, Montréal, QC H2V 0B3

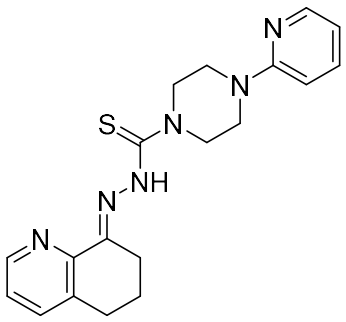
ABSTRACT: Ter**p**henyl **d**i**y**ne (TPDY) macrocycles have been developed for bioligation. The reagents incorporate highly bent 1,3-diynes that are active in SPAAC processes affording atropoisomeric triazole products. In particular, the 3,5-TPDY derivative was found to be bench stable and easily accessible via a streamlined two-pot synthesis. Experimental evidence and computation support SPAAC rates that rival typical cyclooctyne reagents. TPDYs can also exploit the 1,3-diyne in a strain-promoted diyne/hydrazine hydroamination. The cycloadduct obtained exhibited a novel fused hexacyclic pyrazole. A pendant amine allowed bioconjugation of TPDY to two proteins in a microbial transglutaminase-catalyzed reaction. The resulting TPDY-conjugated crystallizable fragment of IgG1 antibody (hFc) and B domain of protein G (GB1) were subsequently labelled with a fluorophore via SPAAC.

COTI-2: Towards new probes for investigating the mechanism of action

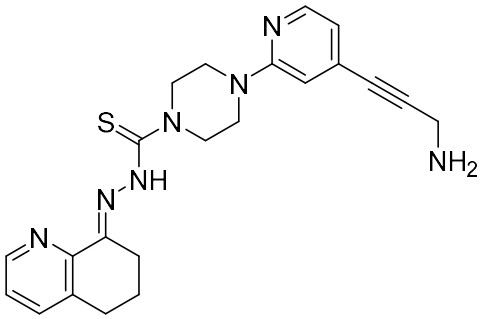
P. Xu, İ. Şimşek, J. J. Hayward, F. S. Raz & J. F. Trant*
University of Windsor, Windsor, Ontario
xupeiha@uwindsor.ca

COTI-2 is a cancer drug developed by COTINGA pharmaceutics thought to target p53. It has shown promise during phase 1 clinical trials but its mechanism of action remains unclear. Our in vitro tests have shown that Zn-COTI-2 complex is the key to its cytotoxicity, but the same cytotoxicity observed in p53-null cell lines as well as the lack of evidence of COTI-2 binding to p53 puts a question mark on the p53-targeting theory. In order to study the targeting of this drug, we have synthesized functionalised analogue of COTI2 that can be tagged with fluorophores and biotin for microscopy and pulldown assays.

In this poster, the synthesis of functionalised COTI2 will be presented, alongside the modifications that were required to incorporate the functional handle and our mechanistic study results.



COTI-2



COTI-2 analogue

Regioselective gold-catalyzed addition of oxygen-based nucleophiles to 2,2,2-trifluoroethyl-substituted alkynes

Raphaël Pronovost,[1] Raphaël Gauthier,[1] Steve P. Nolan,[2] Jean-François Paquin[1,*]

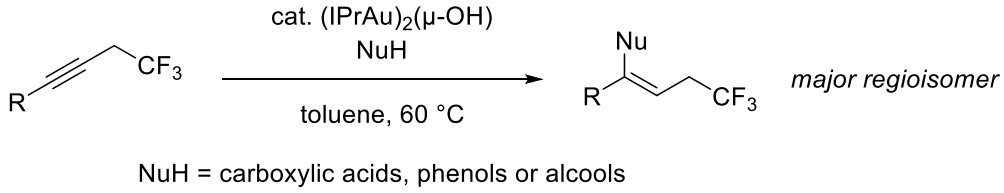
[1] *CCVC, PROTEO, Département de chimie, Université Laval, Québec, Canada, G1V 0A6*

[2] *Department of Chemistry and Centre for Sustainable Chemistry, Ghent University, Ghent 900, Belgium*

**e-mail: jean-francois.paquin@chm.ulaval.ca*

Fluorine being the most electronegative element, it often changes the reactivity of adjacent functional groups [1]. Over the years, we have exploited this effect to control the regioselectivity in the gold-catalyzed hydration of alkynes bearing a fluorinated group at the propargylic position [2,3]. Recently, we have also shown that the regioselectivity for the hydration reaction was maintained even if the fluorinated group (a CF_3 in this case) was pushed one carbon away (*i.e.*, with a 2,2,2-trifluoroethyl group at the propargylic position) [4].

Herein, we report our studies on the gold-catalyzed addition of other oxygen-based nucleophiles to 2,2,2-trifluoroethyl-substituted alkynes. The optimization and the current scope will be presented.



References

[1] Ni, C.; Hu, J. *Chem. Soc. Rev.* **2016**, *45*, 5441.

[2] (a) Hamel, J.-D.; Hayashi, T.; Cloutier, M.; Savoie, P. R.; Thibeault, O.; Beaudoin, M.; Paquin, J.-F. *Org. Biomol. Chem.* **2017**, *15*, 9830. (b) Cloutier, M.; Roudias, M.; Paquin, J.-F. *Org. Lett.* **2019**, *21*, 3866. (c) Cloutier, M.; Mamone, M.; Paquin, J.-F. *Chem. Commun.* **2020**, *56*, 5969.

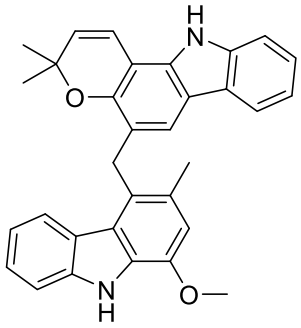
[3] This effect was also obtained in the gold-catalyzed hydrofluorination reaction, see: (a) Gauthier, R.; Mamone, M.; Paquin, J.-F. *Org. Lett.* **2019**, *21*, 9024. (b) Gauthier, R.; Tzouras, N. V.; Zhang, Z.; Bédard, S.; Saab, M.; Falivene, L.; Van Hecke, K.; Cavallo, L.; Nolan, S. P.; Paquin, J.-F. *Chem. Eur. J.* **2022**, *28*, e202103886.

[4] Gauthier, R.; Tzouras, N. V.; Nolan, S. P.; Paquin, J.-F. *Chem. Commun.* **2023**, *59*, 9138.

Total Synthesis of Clausanisumine

Princeton Luong, Valeria Vergine, Mathew Piotrowski, Jakob Magolan*

Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada



Clausanisumine

Clausanisumine is a natural product found in the fruits of *Clausena anisum-olens* [1]. Isolated and characterized in 2021 by Li and coworkers, this compound is comprised of two unique carbazole scaffolds linked by a methylene unit. Clausanisumine is an inhibitor of HIV-1 reverse transcriptase with an EC_{50} value of 18.58 nM [1]. This presentation will disclose our recently completed first total synthesis of clausanisumine in seven steps (*unpublished*).

References:

1. Yan-Ping Liu, Jia-Ming Guo, Zhen Xie, Xin-Yuan Suo, Ze-Yu Liu, Ze-Hua Qiao, Ruo-Qing Guan, Yuan Bian, Lei Qiang, and Yan-Hui Fu. *J. Org. Chem.* **2021** *86* (24), 17722-17726.

Development of a Linchpin Reagent for Direct Preparation of Amides

*M. A. Aubry, B. Uppalapati, Q. Wang, A. M. Beauchemin**
maubr010@uottawa.ca
University of Ottawa

Amides are one of the most common subunits in pharmaceuticals and agrochemicals.[1] While their synthesis often involves construction of the N-(C=O) bond, an efficient alternative synthetic route involves the use of isocyanates. Previous work in the Beauchemin group enabled the development of bench-stable masked (blocked) *O*-isocyanates, which allow for the slow release of free isocyanates *in situ*, allowing for the control of their concentration and reactivity.[2] This work focuses on the use of masked *O*-isocyanate **1** as a *linchpin reagent* (**Figure 1**), a building block designed to be chemoselectively functionalized via sequential reactions. To our knowledge, a linchpin reagent has not yet been reported for the formation of amides. We have achieved chemoselectivity for both the C-OPh and N-OBz bonds and applied these conditions to form various amides. New conditions for N-OBz bond functionalization through rhodium-catalyzed amination of masked *O*-isocyanates will be presented. Both catalytic and stoichiometric conditions for the derivatization of masked *C*-isocyanates **2** into amides **3** will also be presented.

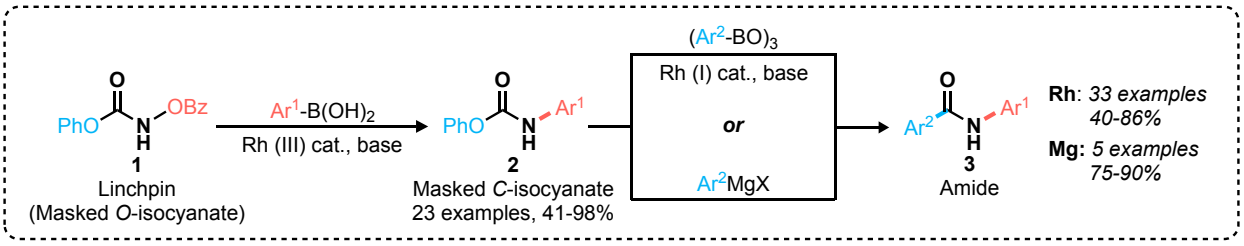


Figure 1. Amide linchpin strategy to generate amides from masked *O*-isocyanates

(1) Massolo, E.; Pirola, M.; Benaglia, M. *Eur. J. Org. Chem*. **2020**, 4641.
(2) (a) Ivanovich, R. I.; Polat, D. E.; Beauchemin, A. M. *Adv. Synth. Catal*. **2017**, *359*, 4289; (b) Derasp, J. S.; Beauchemin, A. M. *ACS Catal*. **2019**, *9*, 8104.

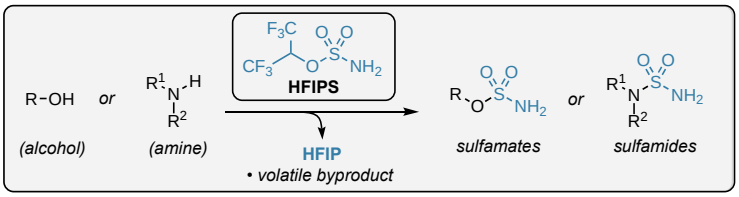
Hexafluoroisopropyl sulfamate as a reagent for the synthesis of sulfamates and sulfamides

Matthew A. Sguazzin[1], Jarrod W. Johnson, and Jakob Magolan
[1]*McMaster University, Hamilton, Canada*

E-mail: sguazzm@mcmaster.ca

The synthesis of sulfamates and sulfamides from alcohols and amines is often problematic due to the instability of sulfamoyl chloride which is the most common reagent used for this transformation. We have developed a bench-stable reagent, hexafluoroisopropyl sulfamate (HFIPS), to prepare sulfamates and sulfamides under mild reaction conditions from the corresponding alcohols and amines [1]. The only byproduct, hexafluoroisopropyl alcohol (HFIP), is volatile and easily removed by rotary evaporation. The reaction products can be isolated in high purity following an aqueous workup. This presentation will detail the discovery, development, and scope of this chemistry and highlight related research that is ongoing in our lab.

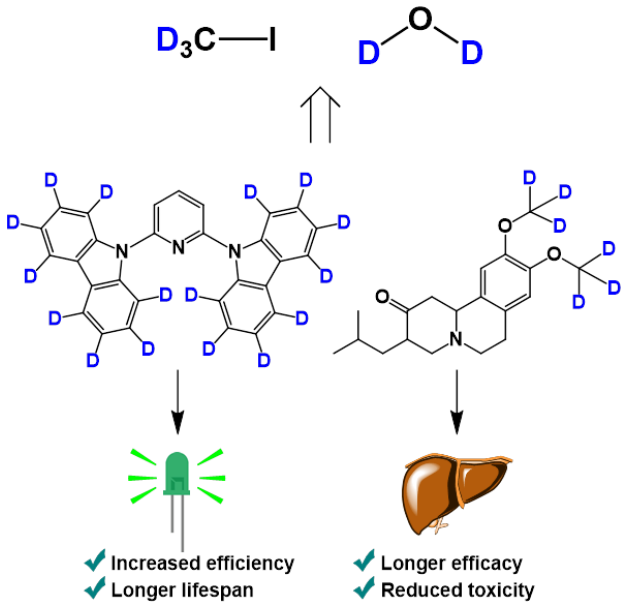
Figure:



1. Sguazzin, M. A.; Johnson, J. W.; Magolan, J., Hexafluoroisopropyl Sulfamate: A Useful Reagent for the Synthesis of Sulfamates and Sulfamides. *Organic Letters* **2021,** *23* (9), 3373-3378

deutraMedTM and the Murphy Group: A 1-year Collaborative Retrospect

Ben Kappheim*, Graham K. Murphy* and Pavel Gris†
*Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1
†deutraMedTM, Collingwood, Ontario, Canada L9Y 4V7
E-mail: bjkapphe@uwaterloo.ca



Recent investigations into the effects of deuterium reveal significant benefits to the pharmaceutical and electronics industries. Exchanging hydrogen with its heavier isotope deuterium imparts greater stability to relevant compounds in these industries, greatly reducing their tendency to undergo unwanted decomposition. PAHs are commonly used in the production of devices such as organic light-emitting diodes (OLEDs),[1–3] and organic solar cells (OSCs).[4,5] The incorporation deuterium into these scaffolds has shown to reduce minimum operating voltages and increase high voltage stability, greatly improving the lifespan of OLED devices.[1–3,6] The investigation of site-specific deuteration within drug development has already yielded commercial success, allowing for longer therapeutic window and decreased dosages.[7–9] To support and better facilitate similar new discoveries in deuterium science, the Murphy group is involved in a 5-year collaboration with deutraMed Inc., an emerging Canadian retailer of deuterated small organic molecules. This poster will provide an overview of the accomplishments made to date during the collaboration, including the syntheses of deuterated caffeine, benzene and carbazole.

References

(1) Chun, C. T.; Kuo, C. H. *J. Phys. Chem. C* 2007, *111* (8), 3490–3494.

(2) Wang, P., et al. *J. Mater. Chem. C. Mater.* 2013, *1* (32), 4821–4825.

(3) Tsuji, H.; Mitsui, C.; Nakamura, E. *Chem. Comm.* 2014, *50* (94), 14870–14872.

(4) Wang, Y., et al. *Adv. Energy. Mater.* 2019, *9* (24), 1803976.

(5) Li, Q., et al. *J. Mater. Chem. C. Mater.* 2022, *10* (7), 2411–2430.

(6) Luo, Y.; Aziz, H.; Xu, G.; Popovic, Z. D. *Chem. Mater.* 2007, *19* (8), 2079–2083.

(7) Schmidt, C. *Nat. Biotechnol.* 2017, *35* (6), 493–494.

(8) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. *Angew. Chem., Int. Ed.* 2018, *57* (7), 1758–1784.

(9) Niemann, N.; Jimenez-Shahed, *J. Neurodegener. Dis. Manag.* 2019, *9* (2), 59–71.

Cope-type hydroamination enabled by selective osmium-catalyzed reduction

*Huy M. Ly, Monica A. Gill, André M. Beauchemin**
Mly024@uOttawa.ca
Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, ON

Intramolecular hydroamination of alkenes is a well-known method for the formation of C-N bonds, especially for synthesis of pyrrolidines and piperidines, which are common moieties in numerous natural compounds and commercially available medications. Hydroamination reactions in the presence of transition metal catalysts have been employed efficiently for decades for this purpose. However, requirements on the structure of the substrates, such as Thorpe-Ingold bias, and extreme conditions, often hindered the applicability of this approach.[1]

Inspired from our recent discovery of the redox-enabled strategy for Cope-type hydroamination,[2] a one-pot, catalytic process has been developed that uses mild reaction conditions and enables novel reactivity. Specifically, hydroxylamines are easily prepared by a mild oxidation of secondary amines, cyclized to form *N*-oxides (in equilibrium), and are then reduced selectively and catalytically to obtain pyrrolidines or piperidines. The selectivity of the osmium reduction enables the shift in equilibrium towards the cyclized products, even when the K_{Eq} is as low as 0.07. We will demonstrate that selective osmium-catalyzed reduction of *N*-oxides over hydroxylamines enables challenging, thermodynamically unfavourable cyclizations to yield unprecedented nitrogen-containing scaffolds.

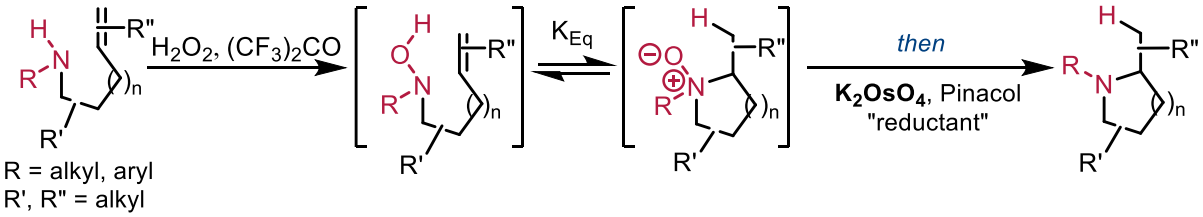


Figure 1. Cope-type hydroamination enabled by selective osmium-catalyzed reduction

[1] Bernoud, E.; Lepori, C.; Mellah, M.; Schulz, E.; Hannedouche, J. *Catal. Sci. Technol*. **2015**, *5*, 2017–2037.
[2] Allen, M. A.; Ly, H. M.; O'Keefe, G. F.; Beauchemin, A. M. *Chem. Sci*., **2022**, *13*, 7264-7268.

Valorisation of phenols to coumarins through one-pot palladium-catalysed double C–H functionalizations

Benedetta Di Erasmo,[a,b] Giulia Brufani,[a] Federica Valentini,[a] Flavio Sabatelli,[a] Anastasiia Afanasenko,[b] Chao-Jun Li,[b] Luigi Vaccaro[a]

[a] *Laboratory of Green S.O.C. – Dipartimento di Chimica, Biologia e Biotecnologie, Università degli Studi di Perugia, Via Elce di Sotto 8, 06123 – Perugia – Italy*

[b] *Department of Chemistry, and FQRNT Centre for Green Chemistry and Catalysis – McGill University, 801 Sherbrooke Street West, Montreal, QC H3A0B8, Canada*

benedetta.dierasmo@mail.mcgill.ca

Phenols are key intermediates in chemical industries since they can undergo to several transformations to give different value-added chemicals. Moreover, phenols are sustainable starting materials in synthesis because they can be formed from the controlled depolymerisation of lignin in the presence of formic acid and heat. Lignin is, indeed, one of the three components of lignocellulosic biomass, a carbon-neutral renewable feedstock alternative to fossil fuels. In this context, the design of sustainable strategies to synthesize value-added chemicals from phenols is gaining a lot of attention. Our research is mainly dedicated to the green C–H functionalizations: these reactions are very promising since they have a high step economy, they generate a small amount of waste, they have a high regioselectivity and not-prefunctionalized substrates are used. An example of this reaction is the formation of coumarins from phenols.[1] We selected Pd/C as the most efficient heterogeneous catalyst and we chose HCOOH as reaction medium that also plays the role of H-source. As the base co-catalyst, NaOAc was necessary to recover the catalyst since it preserves Pd catalyst from degradation. With this optimized reaction conditions in hand, a broad substrate scope starting from electron-rich phenols was obtained. Several APIs such as Citropten, Ayapin, Aesculetin and Scoparon were synthesized. Moreover, a double C–H activation of phenols was achieved by a first *ortho*-alkylation of electron-rich phenols with primary alcohols in solvent-free conditions followed by the formation of pharmaceutically-relevant prenylated coumarins (**Figure 1**).

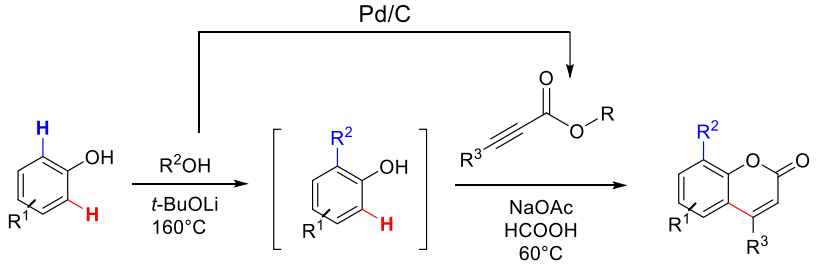


Figure 1: Double C–H activation of phenols to access prenylated coumarins.

References

1. G. Brufani, F. Valentini, F. Sabatelli, B. Di Erasmo, A. Afanasenko, C.-J. Li, L. Vaccaro, Valorisation of phenols to coumarins through one-pot palladium-catalysed double C–H functionalizations. *Green Chem.*, **2022**, *24*, 9094-9100

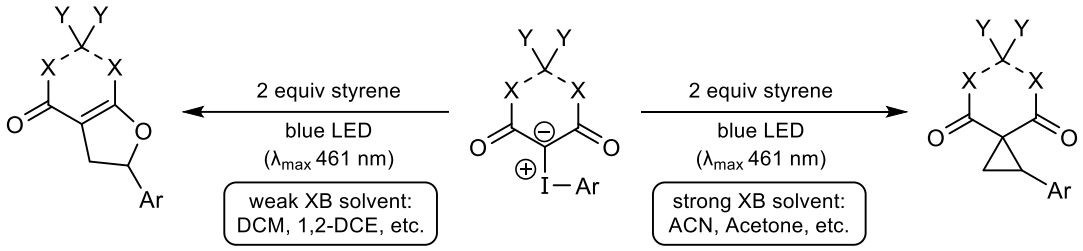
Chemoselective Reaction of Iodonium Ylides under Blue LED Irradiation: Exploring the Influence of Halogen Bonding

Carlee A. Montgomery, Eleanor Wong, Tristan Chidley, Richard D. Pham, Sarah Meston, Graham K. Murphy

Department of Chemistry, University of Waterloo, Canada

Email: camontgo@uwaterloo.ca

In 2019, the Murphy group introduced a protocol for synthesizing cyclopropanes through blue LED irradiation of iodonium ylides with styrenes, a reaction believed to proceed via a halogen bond adduct.[1] Upon further investigation of the solvent used, the unexpected generation of the dihydrofuran isomer was instead observed with dichloromethane. However, the chemoselective behavior of this solvent proved inconsistent across repeated experiments producing different product ratios. The role of solvent, temperature, oxygen, and styrene equivalent are being explored aiming to understand how chemoselective control is accomplished. Previous reports of halogen bonding induced reaction selectivity in iodonium ylides led to our suspicion of a solvent-participating halogen bonding interaction.[2] This probed our examination of different iodonium ylide derivatives with varying halogen bonding potential, inspired by other reports of suspected intramolecular halogen bonding derivatives,[3-6] comparing their effects on rate, yield, and chemoselectivity.



References

1. Chidley, T.; Jameel, I.; Rizwan, S.; Peixoto, P. A.; Pouységu, L.; Quideau, S.; Hopkins, W. S.; Murphy, G. K. Blue LED Irradiation of Iodonium Ylides Gives Diradical Intermediates for Efficient Metal-free Cyclopropanation with Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58* (47), 16959-16965.
(2) Montgomery, C. A.; Murphy, G. K. Exploring the role of halogen bonding in iodonium ylides: insights into unexpected reactivity and reaction control. *Beilstein J. Org. Chem.* **2023**, *19*, 1171-1190.
(3) Kimura, T.; Hamada, S.; Furuta, T.; Takemoto, Y.; Kobayashi, Y. Synthesis and Properties of ortho-t-BuSO2C6H4-Substituted Iodonium Ylides. *Crystals* **2021**, *11* (9), 1085.
(4) Saito, M.; Kobayashi, Y.; Takemoto, Y. Divergent and Chemoselective Transformations of Thioamides with Designed Carbene Equivalents. *Chem. – Eur. J.* **2019**, *25* (44), 10314-10318.
(5) Zhu, C.; Yoshimura, A.; Ji, L.; Wei, Y.; Nemykin, V. N.; Zhdankin, V. V. Design, Preparation, X-ray Crystal Structure, and Reactivity of o-Alkoxyphenyliodonium Bis(methoxycarbonyl)methanide, a Highly Soluble Carbene Precursor. *Org. Lett.* **2012**, *14* (12), 3170-3173.
(6) Wang, L.; Jacobson, O.; Avdic, D.; Rotstein, B. H.; Weiss, I. D.; Collier, L.; Chen, X.; Vasdev, N.; Liang, S. H. Ortho-Stabilized 18F-Azido Click Agents and their Application in PET Imaging with Single-Stranded DNA Aptamers. *Angew. Chem., Int. Ed.* **2015**, *54* (43), 12777-12781.

Structure-Activity Relationship Studies of a New Antibiotic Targeting *Acinetobacter baumannii*

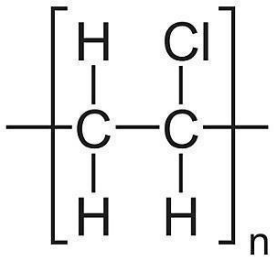
Marissa MacIver, Meghan Fragis, Denise Catacutan, Jonathan Stokes, Jakob Magolan*

Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada

Acinetobacter baumannii (*A. baumannii*) is an opportunistic nosocomial Gram-negative bacterium responsible for multiple health care associated infections amongst hospitalized patients. Listed as a critical concern by the WHO, *A. baumannii* has a propensity for resistance against many modern antibiotics due to its robust outer membrane, opposition to desiccation, and ability to retain extracellular DNA. A robust drug-discovery campaign, aided by machine learning identified compound RS-102895 as a potential narrow-spectrum antibiotic specifically targeting *A. baumannii*. To probe the structure-activity relationship (SAR) of RS-102895 analogues, two different synthetic routes were used to access variations of the spirocyclic core, incorporating electron-withdrawing groups and modifying the ring size of the molecule. These changes provided insight into how sensitive the core of the molecule is for maintaining *in vitro* activity. Changes to the alkyl linker on the tertiary amine using phenethyl, phenylpropyl, and benzylic bromide derivatives highlighted the sensitivity of the SAR while providing an opportunity to examine both steric and electronic influences on compound activity.

Enzymes: The Natural Solution to PVC pollution

Sahar Shokrgozar, David Zechel
Department of Chemistry, Queen's University



Polyvinyl chloride (PVC)

Plastic pollution is found globally from deserts to farms, mountaintops to the deep ocean, tropical landfills, and Arctic snow[1]. Billions of pounds of plastic can be found in swirling convergences that makeup about 40 percent of the world's ocean surfaces. At current rates plastic is expected to outweigh all the fish in the sea by 2050[2]. Polyvinyl chloride (PVC) is the world's third-most widely produced synthetic polymer of plastic, and about 40 MMT of PVC are produced each year[3,4]. PVC is the most environmentally damaging plastic. The PVC lifecycle, its production, use, and disposal, results in the release of toxic, chlorine-based chemicals. These toxins are building up in the water, air, and food chain[5]. Recently enzymatic degradation of plastics such as polyethylene terephthalate (PET) has shown promise as an approach for the sustainable treatment of plastic waste[6]. However, PVC biodegradation lags that of the biodegradation of PET. This project aims to find enzymatic solutions for the degradation of PVC. In this project, we will examine the potential of dehalogenating enzymes and laccases enzymes for PVC biodegradation.

[1] M. MacLeod, H. Peter H. Arp, M. B. Tekman, Annika Jahnke, The global threat from plastic pollution, 2 Jul 2021, Vol 373, Issue 6550, pp. 61-65, DOI: 10.1126/science.abg5433
[2] https://www.biologicaldiversity.org/campaigns/ocean_plastics/
[3] D. Danso, J. Chow, W. R. Streit, Plastics: Environmental and Biotechnological Perspectives on Microbial Degradation, Applied and Environmental Microbiology, October 2019, Volume 85, Issue 19, https://doi.org/10.1128/AEM.01095-19
[4] Global Polyvinyl Chloride (PVC) Market - by End-Use Industries, Products, and Region - Market Size, Demand Forecasts, Industry Trends and Updates (2018-2025), published by ResearchAndMarkets.com
[5] https://www.greenpeace.org/usa/wp-content/uploads/legacy/Global/usa/report/2009/4/pvc-the-poison-plastic.html
[6] Z. Zhang, H. Peng, D. Yang, G. Zhang, J. Zhang & F. Ju, Polyvinyl chloride degradation by a bacterium isolated from the gut of insect larvae, Nature Communications, 2022, Vol 13, no. 5360, https://doi.org/10.1038/s41467-022-32903-y

Synthesis of a reversible fluorescent sensor based on frustrated Lewis pair for the detection of nitric oxide (NO) in solution

Lara Harter[1,2], Frédéric-Georges Fontaine*[1], Guillaume Bélanger-Chabot*[1], Denis Boudreau*[1,2]

1 : Département de Chimie, Université Laval, Pavillon Alexandre-Vachon, 1045 Avenue de la Médecine, Québec (Québec) G1V 0A6

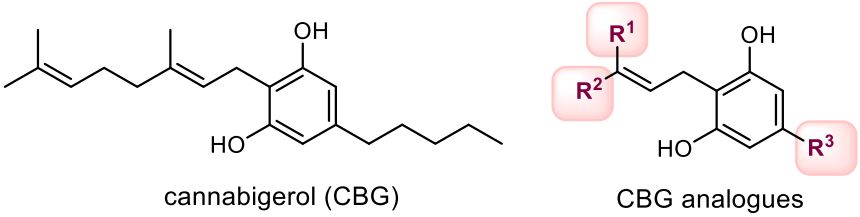
2 : Centre d'optique, photonique et laser, 2375 Rue de la Terrasse, Québec, QC G1V 0A6

Nitric oxide is present in various biological and environmental media. Excess NO can lead to respiratory problems as well as serious illnesses such as strokes and heart diseases. Therefore, quantifying this molecule is crucial to detecting the risk of diseases. The project's main objective is to develop a sensor to quantify NO in cells. The sensor consists of two parts; a frustrated Lewis pair (FLP) to trap nitric oxide and a fluorophore that turns on upon NO interaction with the Lewis pair. The purpose of this study is to synthesize such a sensor to test and optimize its analytical performance. In this presentation, density functional theory results, as well as reactions of different FLPs, phosphines and boranes with NO, will be discussed.

Synthesis and Evaluation of Cannabigerol-Inspired Antimicrobial Compounds

Eleanor Wong, Nicholas Jentsch, Xiong Zhang, Omar El-Halfawy, Eric Brown, Jakob Magolan*
Department of Biochemistry and Biomedical Sciences, McMaster University, Canada

Cannabigerol (CBG) and other cannabinoid natural products demonstrate potent antimicrobial activity.[1,2] Here we report the chemical synthesis and antimicrobial evaluation for more than forty novel synthetic derivatives of the cannabigerol scaffold. As a key step in the synthesis of these compounds we employed a newly-discovered alumina-mediated phenol geranylation reaction. This presentation will include a discussion of this chemistry and the results of the evaluation of our novel CBG-inspired compounds against methicillin-resistant *Staphylococcus aureus* (MRSA).



cannabigerol (CBG) CBG analogues

References

1. Farha, M. A.; El-Halfawy O. M., Gale, R. T.; MacNair, C. R.; Carfrae, L. A.; Zhang, X; Jentsch, N. G.; Magolan, J; Brown, E. D., Uncovering the Hidden Antibiotic Potential of Cannabis. *J. Infect. Dis.* **2020**, 6(*3*), 338-46.

2. Appendino, G.; Gibbons, S.; Giana, A.; Pagani, A.; Grassi, G.; Stavri, M.; Smith, E.; Rahman, M. M.; Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. *J. Nat. Prod*. **2008**, 71(*8*), 1427-30.

Synthesis of Optically Pure α-Methyl Amino Acids with Heteroaryl-Functionalized Sidechains: Progress Toward a General Synthetic Approach

Kyle D. Passley,[‡] Michael G. Organ.[‡]

[‡]Centre for Catalysis Research and Innovation (CCRI), Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada.

Abstract:

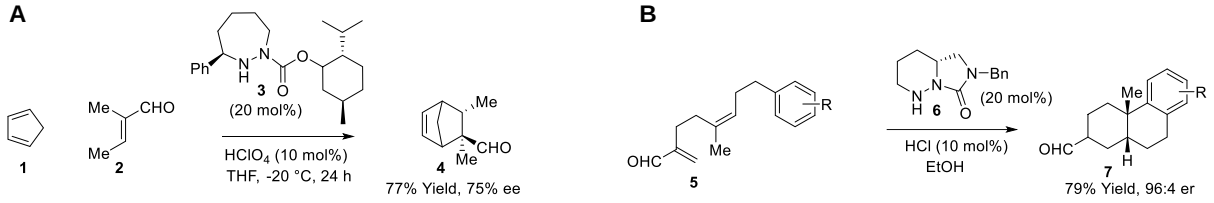
Since the introduction of insulin into clinical use in the 1920s, peptides have been explored as possible therapeutics. However, development of peptide therapeutics is often hindered by their poor *in vivo* stability due to rapid hydrolysis by proteases. Multiple structural modifications have been developed to address this limitation, with the inclusion of α-methylated amino acids being one of the most effective modifications at reducing the rate of proteolysis. Despite the interest, few α-methylated amino acids are commercially available, particularly those with non-canonical side chains. A general strategy for the synthesis of a wide variety of α-methyl non-natural amino acids is proposed, allowing for the production of optically pure alkyl- and (hetero)aryl-amino acids from suitably protected amino acid building blocks. One such amino acid building block was synthesized as a single enantiomer in four steps from Cbz-D-alanine, which was used to produce the corresponding organozinc. Using Negishi coupling, the PEPPSI iHept^{Cl} catalyst was utilized to functionalize the organozinc with a diverse selection of heteroaryl electrophiles to produce ten optically pure α-methyl amino acids with heteroaryl-functionalized n-propyl side chains. A representative tripeptide incorporating an α-methyl non-natural amino acid was prepared in a good yield using standard peptide coupling methods. Synthesized amino acids demonstrate the ability of this strategy to incorporate diverse heteroaryl functionalities into amino acids, with the goal of expanding the strategy to include a wider variety of side chain lengths and functionalities.

A Platform of Chiral 1,2,4-Triazinane Organocatalysts for Application in the Cope Rearrangement and Diels Alder Cycloaddition

Vanessa Watts and Prof. James L. Gleason

McGill University

Abstract. The Gleason group have a well-established programme of cyclic hydrazide organocatalysts with application in several transformations, including Cope, Diels-Alder and polyene cyclizations.[1,2,3] Several examples have featured chiral hydrazide catalysts such as the examples shown in Scheme 1. However, the catalyst synthesis was sometimes lengthy and, more importantly, not easily tuned to improve reactivity and selectivity.



Scheme 1. Selected examples of the previously established organocatalyst frameworks developed by the Gleason group.

This project will create a platform of 1,2,4-triazinane catalysts that can be synthesised in a modular fashion and have multiple sites for optimizing the catalytic activity. Catalyst framework **8** contains three sites where the catalyst can be easily tuned (Figure 1). The R^1 group can be easily set through condensation of the acyclic hydrazide or sulfamido with aldehydes and can be used to control the positioning of the adjacent EWG. The normal EWG is a carbamate, but we are investigating the use of chiral sulfinamides, (e.g. **9**) adding an additional stereocentre adjacent to the site of iminium formation. These catalysts will be screened in Cope rearrangements to assess reactivity and Diels-Alder cycloadditions to assess enantioselectivity. Ultimately these catalysts will be applied to more complex reactions such as polyene and Nazarov cyclizations.

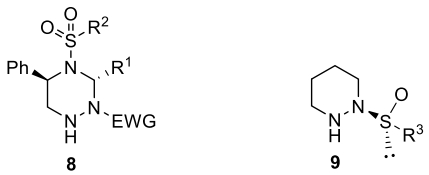


Figure 1. The organocatalysts of interest that can be made via modular syntheses.

References.

[1] D. Kaldre, J. L. Gleason, *Angew. Chem. Int. Ed.* **2016**, *55*, 11557; *Angew.Chem*. **2016**, *128*, 11729. [2] N. O. Häggman, B. Zank, H. Jun, D. Kaldre, and J. L. Gleason, *Eur. J. Org. Chem*. **2018**, 5412–5416. [3] S. J. Plamondon, J. M. Warnica, D. Kaldre, and J. L. Gleason, *Angew. Chem. Int. Ed*. **2020**, *59*, 253–258.

Synthesis of 2-(pentafluoro-λ^6-sulfanyl)ethane-1-sulfo compounds

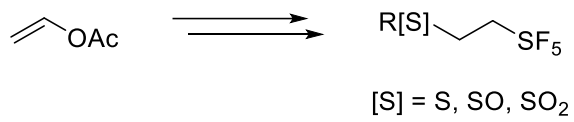
Laurianne Verret, Antoine Marchi, Jean-François Paquin*

CCVC, PROTEO, Université Laval, 1045 av. de la Médecine, Québec (Québec), G1V 0A6, Canada

**e-mail: jean-francois.paquin@chm.ulaval.ca*

The trifluoromethylthio group (–SCF_3), its oxidated analogues (–$SOCF_3$ and –SO_2CF_3) as well as the corresponding substituents bearing carbon spacers (*e.g.*, –SCH_2SCF_3 or –$SCH_2CH_2SCF_3$) have been of interest for the pharmaceutical and agrochemical industries given their unique properties (lipophilicity, electron-withdrawing capacity, etc.) [1]. Likewise, the pentafluorosulfanyl group (–SF_5), also called the "super CF_3", possesses remarkable features of importance for applications in various fields [2].

Given our interest in the synthesis of pentafluorosulfanylated compounds [3], we decided to explore hybrids bearing both a sulfur atom and a SF_5 group. We initially targeted 2-(pentafluoro-λ^6-sulfanyl)ethane-1-sulfo compounds as we have already explored the nitrogen equivalent [3b]. Herein, we will describe our preliminary results toward their synthesis (Scheme 1).



Scheme 1. General approach to 2-(pentafluoro-λ^6-sulfanyl)ethane-1-sulfo compounds

References

[1] (a) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (b) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765.

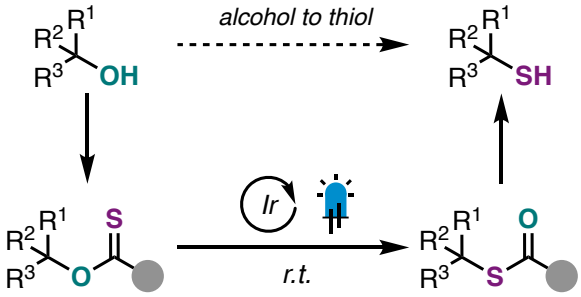
[2] (a) Sowaileh, M. F.; Hazlitt, R. A.; Colby, D. A. *ChemMedChem* **2017**, *12*, 1481. (b) Chan, J. M. W. *J. Mater. Chem. C*. **2019**, *7*, 12822. (c) Sani, M.; Zanda, M. *Synthesis* **2022**, *54*, 4184. (d) Kordnezhadian, R.; Li, B.-Y.; Zogu, A.; Demaerel, J.; De Borggraeve, W. M.; Ismalaj, E. *Chem. Eur. J.* **2022**, *28*, e202201491.

[3] For recent examples, see: (a) Birepinte, M.; Champagne, P. A.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2022**, *61*, e202112575. (b) Gilbert, A.; Langowski, P.; Paquin, J.-F. *Tetrahedron* **2021**, *98*, 132424. (c) Roudias, M.; Gilbert, A.; Paquin, J.-F. *Eur. J. Org. Chem.* **2019**, 6655. (d) Cloutier, M.; Roudias, M.; Paquin, J.-F. *Org. Lett.* **2019**, *21*, 3866. (e) Gilbert, A.; Bertrand, X.; Paquin, J.-F. *Org. Lett.* **2018**, *20*, 7257.

Photocatalytic *O*- to *S*-Rearrangement of Aliphatic Alcohols

J. J. Monteith, J. Pearson, S. A. L. Rousseaux*
University of Toronto, Toronto, ON, Canada
E-mail: johnj.monteith@mail.utoronto.ca

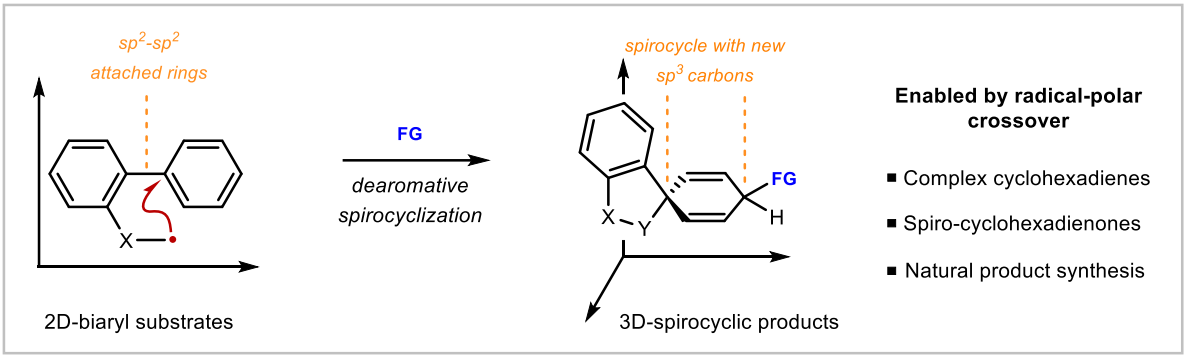
The Newman-Kwart rearrangement, which thermally converts *O*-aryl thiocarbamates to *S*-aryl thiocarbamates, is a powerful transformation that formally provides access to thiophenols from abundant phenol feedstocks. Despite recent advances that have lowered the high reaction temperatures typically required for efficient rearrangement, an aliphatic variant of this transformation, which would formally convert aliphatic alcohols to aliphatic thiols, is critically underexplored. Herein, we report the development of a novel reductive photocatalytic approach for an efficient ambient temperature aliphatic *O*- to *S*-rearrangement. After demonstrating that a range of difficult to access cyclopropanethiol derivatives can be obtained with this strategy, we show that these rearranged products can be easily hydrolyzed and further derivatized. We conclude this study with mechanistic findings that enabled an initial extension of this approach toward other classes of aliphatic alcohols.



Dearomatization of Biaryls: A Spirocyclization/Functionalization Approach Enabled by Radical-Polar Crossover

Carlos R. Azpilcueta-Nicolas, Derek Meng, Simon Edelmann, Xiaobo Zhao, Glen Loo, & Jean-Philip Lumb

Department of Chemistry, McGill University, Montreal, Quebec H3A 0B8, Canada



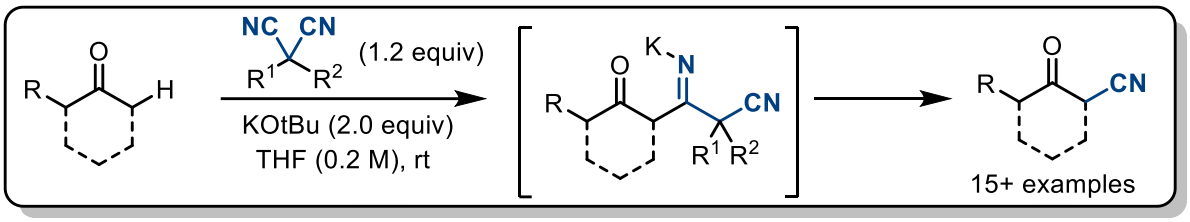
Abstract: Despite the development of novel chemical transformations during the last two decades, the medicinal chemistry synthetic toolbox relies on only few synthetic methods that mainly employ aromatic building blocks. One of the most widely used is the Suzuki-Miyaura cross-coupling of aryl-halides and aryl-boronic acids to produce biaryl compounds. Biaryls are prevalent in agrochemical and pharmaceutical collections, however, the structural diversity of molecules containing the biaryl motif is surprisingly limited, with most compounds covering a narrow region of chemical space characterized by high aromatic content and low stereochemical complexity. Dearomatization reactions involving radical cyclizations can facilitate the synthesis of complex polycyclic systems that find applications in medicinal chemistry and natural product synthesis. This poster will describe the dearomatization of biaryl compounds through a radical-polar crossover mechanism under redox-neutral photocatalytic conditions. Our method provides an efficient means of creating quaternary spirocenters, that we use to diversify biaryls into complex natural products and functionalized spirocyclic compounds.

For more information see:

1. C. R. Azpilcueta-Nicolas, D. Meng, S. Edelmann and J-P. Lumb., *Angew. Chem. Int. Ed.* **2023**, *62* e202215422.
2. Z. Huang and J.-P Lumb., *Nat. Chem* **2021**, *13*, 24.

α-Cyanation of Ketones using Simple Malononitriles

J. M. Graham, J. D. Pingol, S. A. L. Rousseaux
Department of Chemistry, University of Toronto, Toronto, Canada
...
E-mail: joshm.graham@mail.utoronto.ca



The α-cyano ketone motif is a useful building block in the construction of heterocyclic scaffolds. This motif often appears early in synthetic sequences, which necessitates methodology that is simple to perform, proceeds in high yields and utilizes readily available reagents. In addition, cyclic α-cyano ketones are challenging to access with existing methodologies. To this end, we have developed a method allowing for the direct α-cyanation of ketones using both dimethylmalononitrile (DMMN) and 2-methyl 2-phenyl malononitrile (MPMN) as electrophilic cyanating reagents. A range of ketones can be α-cyanated in good to quantitative yield with both reagents, allowing for a comparison of malononitrile reactivity that allows the user to select the most appropriate reagent for their own work. This presentation will describe the optimization and scope of this transformation, followed by derivatization of some α-cyano ketone products.

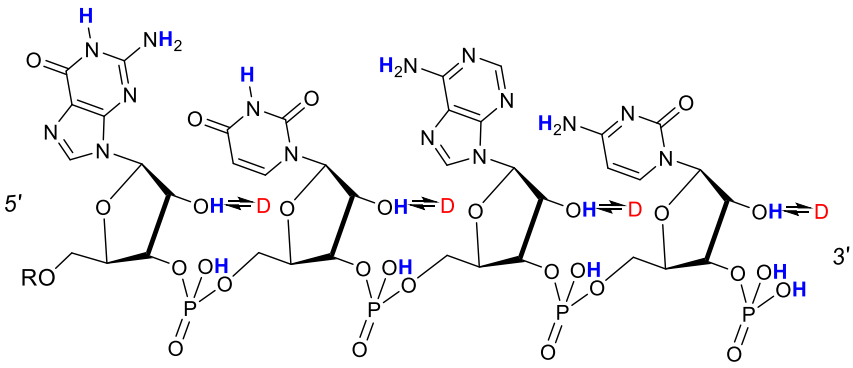
Hydrogen/deuterium exchange coupled to mass spectrometry as an approach to studying mRNA stabilization in heavy water

Yulia A. Vlasenko[1], Ashwini Rajasekaran[2], Denis Gris[2], Pavel Gris[1,3], Graham K. Murphy[1]
[1]*Department of Chemistry, University of Waterloo, Waterloo, ON, Canada*
[2]*Department of Physiology and Pharmacology, FMSS, CRCHUS, University of Sherbrooke, QC, Canada*
[3]*deutraMed, 40 Sandford Fleming Drive, Collingwood, ON, Canada*

E-mail: iuliiav@uwaterloo.ca

One of the greatest challenges in mRNA production is its inherent instability.[1] mRNA-based therapeutics[2-5] are sensitive to temperature fluctuations, which can accelerate their degradation. A small degradation reaction anywhere along a mRNA strand can result in loss of translation or synthesis of aberrant proteins. The incorporation of a stable isotope of hydrogen - Deuterium (D, H2) - into the structure causes an isotope-kinetic effect (IKE) and protects it from degradation. It was shown that synthesis and storage of mRNA in D_2O increases mRNA stability and reduces its susceptibility to enzymatic and thermal hydrolysis, leading to a patented invention called D-Lock™. This poster will discuss the role of deuterium IKE in mRNA stabilization, through assessment of the completeness of deuteration of mRNA building blocks, as well as the tendency of easily exchanged protons to reverse exchange.

mRNA Backbones



- Extended stability at room temperature & at 4 °C
- Improved the efficiency of the polymerase
- Increase of translational efficiency

References

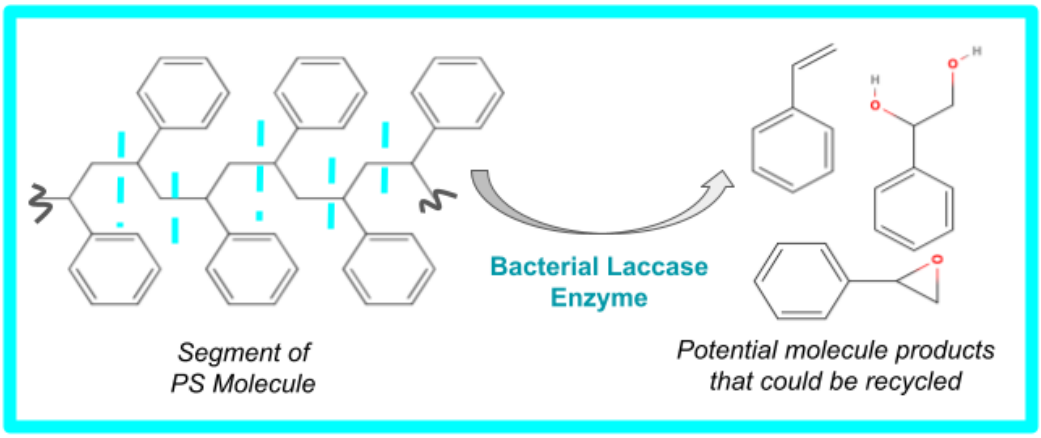
1. Wayment-Steele, H. K. et al. *Nucleic acids research*, **2021**, 10604.
2. Sheridan, C. *Nat Biotechnol*, *30*, **2012**, 909.
3. Burnett, J. C. & Rossi, J. J. *Chem. Biol*. *19*, **2012**, 60.
4. Kole, R., Krainer, A. R. & Altman, S. *Nat. Rev. Drug Discov*. *11*, **2012**, 125.
5. Crooke, S. T., Witztum, J. L., Bennett, C. F. & Baker, B. F. *Cell Metabolism*, *27*, **2018**, 714.

Evaluating the Potential for Degradation of Polystyrene and Other Non-Hydrolyzable Plastics with *Rhodococcus* Laccases

Liwah Keller*, Maria Cleveland, Kennedy Quigg, David L. Zechel

Department of Chemistry, Queen's University

Due to the inefficiency of current methods of recycling plastics, only 10 to 20% of plastic waste is recycled.[1,2] More effective pathways are needed, as hundreds of millions of tonnes of plastic waste is accumulating and harming our environment. One possibility is using enzymatic catalysis, since enzymatic reactions require more moderate conditions than the reactions currently used in industry to break down plastics. Additionally, scientists have found enzymes in microbes that can degrade certain kinds of plastics or have the potential to do so.[1] This project concerns using laccases, a type of multi-copper oxidase enzyme, to degrade polystyrene (PS), a plastic commonly used for packaging. PS is one of the most difficult plastics to decompose, as its wholly carbon molecular backbone makes it non-hydrolyzable.[3] Research has shown that there is increased laccase expression in bacteria that can consume non-hydrolyzable plastics, such as in the genus *Rhodococcus*.[4,5] In nature laccases degrade a class of polymers called lignins, which resemble polystyrene in containing phenyl moieties. Using *E. coli*, we have heterologously expressed laccases from *Rhodococcus opacus* R7 that have been implicated in plastic degradation.[5] Recent progress in characterizing the activity of these enzymes in vitro will be presented.



Liwah Keller, Zechel Lab, Queen's University

(1) Zhu, B.; Wang, D.; Wei, N. Enzyme Discovery and Engineering for Sustainable Plastic Recycling. *Trends Biotechnol.* **2022**, *40* (1), 22–37. https://doi.org/10.1016/j.tibtech.2021.02.008.

(2) Geyer, R.; Jambeck, J. R.; Law, K. L. Production, Use, and Fate of All Plastics Ever Made. *Sci. Adv.* **2017**, *3* (7), e1700782. https://doi.org/10.1126/sciadv.1700782.

(3) Inderthal, H.; Tai, S. L.; Harrison, S. T. L. Non-Hydrolyzable Plastics – An Interdisciplinary Look at Plastic Bio-Oxidation. *Trends Biotechnol.* **2021**, *39* (1), 12–23. https://doi.org/10.1016/j.tibtech.2020.05.004.

(4) Santo, M.; Weitsman, R.; Sivan, A. The Role of the Copper-Binding Enzyme – Laccase – in the Biodegradation of Polyethylene by the Actinomycete Rhodococcus Ruber. *Int. Biodeterior. Biodegrad.* **2013**, *84*, 204–210. https://doi.org/10.1016/j.ibiod.2012.03.001.

(5) Zampolli, J.; Orro, A.; Manconi, A.; Ami, D.; Natalello, A.; Di Gennaro, P. Transcriptomic Analysis of Rhodococcus Opacus R7 Grown on Polyethylene by RNA-Seq. *Sci. Rep.* **2021**, *11* (1), 21311. https://doi.org/10.1038/s41598-021-00525-x.

LIGHT-ACTIVATION OF SF_5Cl FOR THE ATOM TRANSFER RADICAL ADDITION ONTO ALKENES AND ALKYNES

Marie-Rose Ouellet-Du Berger, Maxim Boucher, Jean-François Paquin*

CCVC, PROTEO, Département de chimie, Université Laval, 1045 avenue de la Médecine, Québec, Canada

*e-mail: jean-francois.paquin@chm.ulaval.ca

Due to its unique characteristics such as a high lipophilicity and a strong electron withdrawing capacity [1], the pentafluorosulfanyl group (SF_5) is of great interest in various fields [2]. For the preparation of pentafluorosulfanylated molecules containing either a C(sp^3)–SF_5 or a C(sp^2)–SF_5 bond, an atom transfer radical addition of SF_5Cl onto alkenes and alkynes is the main approach. The most versatile activation method remains the use of Et_3B/O_2 as reported by Dolbier [3] although a few practical drawbacks are associated with the use of Et_3B, an air-unstable and pyrophoric reagent [4]. Herein, we document the use of a readily available 20 W compact fluorescent lamp (CFL) blacklight as a reagent-free approach to activate SF_5Cl (Scheme 1). This method represents a complementary, yet oxygen-free alternative, to the most common SF_5Cl addition reaction conditions [5].

Scheme 1. Alkenes and alkynes scope for the light-activated SF_5Cl addition.

References

[1] Savoie, P. R.; Welch, J. T. *Chem. Rev.* **2015**, *115*, 1130-1190.

[2] Reviews: a) Sowaileh, M. F.; Hazlitt, R. A.; Colby, D. A. *ChemMedChem* **2017**, *12*, 1481-1490. b) Chan, J. M. W. *J. Mater. Chem. C* **2019**, *7*, 12822-12834. c) Sani, M.; Zanda, M. *Synthesis* **2022**, *54*, 4184-4209. d) Kordnezhadian, R.; Li, B.-Y.; Zogu, A.; Demaerel, J.; De Borggraeve, W. M.; Ismalaj, E. *Chem. Eur. J.* **2022**, *28*, e202201491.

[3] a) Aït-Mohand, S.; Dolbier, W. R.; *Org. Lett.* **2002**, *4*, 3013-3015. b) Dolbier, W. R.; Aït-Mohand, S.; Schertz, T. D.; Sergeeva, T. A.; Cradlebaugh, J. A.; Mitani, A.; Gard, G. L.; Winter, R. W.; Thrasher, J. S. *J. Fluorine Chem.* **2006**, *127*, 1302-1310.

[4] For alternative protocols, see: a) Gilbert, A.; Langowski, P.; Delgado, M.; Chabaud, L.; Pucheault, M.; Paquin, J.-F., *Beilstein J. Org. Chem.* **2020**, *16*, 3069-3077. b) Gilbert, A.; Langowski, P.; Delgado, M.; Chabaud, L.; Pucheault, M.; Paquin, J.-F., *Beilstein J. Org. Chem.* **2021**, *17*, 1725-1726. c) Gilbert, A.; Birepinte, M.; Paquin, J.-F., *J. Fluorine Chem.* **2021**, *243*, 109734.

[5] Ouellet-Du Berger, M.-R.; Boucher, M.; Paquin, J.-F. *J. Fluorine Chem.* **2023**, *268*, 1110131.

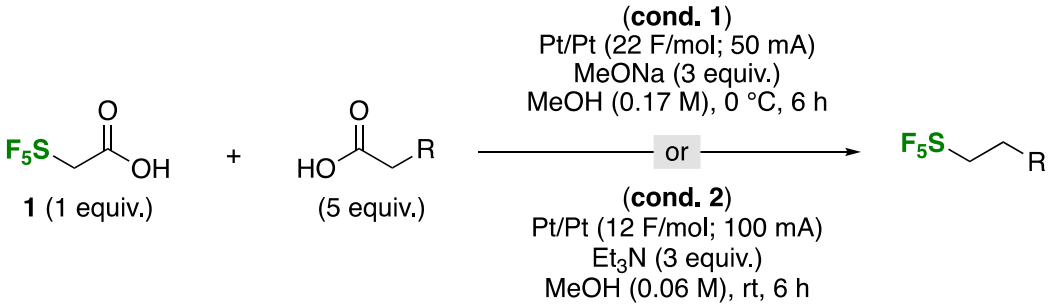
Synthesis of pentafluorosulfanylated organic compounds by Kolbe-type decarboxylative electrochemical cross-coupling

Vincent Mastalerz,[1] Kevin Lam,[2] Jean-François Paquin[1*]

[1] *CCVC, PROTEO, Département de chimie, Université Laval, Québec (Québec), Canada*
[2] *Department of Pharmaceutical, Chemical and Environmental Sciences, University of Greenwich, Chatham Maritime, Kent, UK*

**e-mail: jean-francois.paquin@chm.ulaval.ca*

The pentafluorosulfanyl (SF_5) group, first described in 1950 and known as a "super CF_3", presents "extreme" properties that make it attractive in many fields [1]. Methods to synthesize aliphatic-type compounds containing this group are still minimal. To fill this gap, we explored an electrochemical approach based on a Kolbe-type decarboxylative electrochemical cross-coupling since this reaction allows sp^3-sp^3 asymmetric radical cross-coupling [2,3]. We chose 2-(pentafluoro-λ^6-sulfanyl)acetic acid (**1**) as the source of the CH_2SF_5 group. This presentation will describe the optimization and the scope and limitations of the reaction [4].



1. (a) Sheppard, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 4751. (b) Duda, B.; Lentz, D. *Org. Biomol. Chem.* **2015**, *13*, 5625. (c) Huang, Y.; Xing, J.; Gong, Q.; Chen, L.-C.; Liu, G.; Yao, C.; Wang, Z.; Zhang, H.-L.; Chen, Z.; Zhang, Q. *Nat. Commun.* **2019**, *10*, 169. (d) Chan, J. M. W. *J. Mater. Chem. C*. **2019**, *7*, 12822.
2. (a) Hayrapetyan, D.; Shkepu, V.; Seilkhanov, O. T.; Zhanabil, Z.; Lam, K. *Chem. Commun.* **2017**, *53*, 8451. (b) Petti, A.; Leech, M. C.; Garcia, A. D.; Goodall, I. C. A.; Dobbs, A. P.; Lam, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 16115. (c) Quertenmont, M.; Goodall, I.; Lam, K.; Markó, I.; Riant, O. *Org. Lett.* **2020**, *22*, 1771.
3. Kurihara, H.; Tajima, T.; Fuchigami, T. *Electrochem.* **2006**, *74*, 615.
4. Mastalerz, V.; Lam, K.; Paquin, J.-F. *J. Fluorine Chem.* **2023**, *268*, 110113.

Characterizing the P450-Catalyzed Tailoring of Seongsanamide B through Chemoenzymatic Total Synthesis and Derivatization

Jason Ma, Andre Paquette, Jordan Brazeau-Henrie, Christopher N. Boddy

University of Ottawa,

Microorganisms produce a wide variety of bioactive secondary metabolites, often used as leads for drug development with varied biological activities. However, often the biosynthetic assembly of these molecules involve complex enzymatic steps that can be difficult to replicate through organic synthesis. A chemoenzymatic approach maintains the synthetic flexibility of organic synthesis while accomplishing complex reactions with high selectivity through enzyme catalysis.

In this study, we present the chemoenzymatic total synthesis and derivatization of the bicyclic depsipeptide, seongsanamide B. The antiallergic seongsanamides, isolated from *Bacillus safensis*, are produced by nonribosomal peptide synthetases. Following its assembly, the linear intermediate undergoes a thioesterase catalyzed macrocyclization to produce the macrocyclic depsipeptide precursor, seongsanamide E. A subsequent cytochrome p450-catalyzed oxidative phenolic coupling yields seongsanamide B.

We have previously established a synthetic route to synthesize the linear thioester intermediate using solid-phase peptide synthesis strategies. Treating the linear peptide with the native thioesterase produces the precursor, seongsanamide E. The bicyclic seongsanamide B contains an additional biaryl ether linkage between two tyrosine residues, catalyzed by a cytochrome p450 enzyme. While most p450 require a protein-linked substrate, seongsanamide B catalysis occurs after cleavage from the peptidyl carrier protein, allowing for the possibilities of more diverse applications of this p450 enzyme. Treatment of the linear intermediate with native thioesterase and p450 can provide a one-pot chemoenzymatic synthesis of seongsanamide B. The capabilities of this enzymatic coupling will be probed using novel synthetic analogs of seongsanamide B. This oxidative phenolic coupling may be expanded for future chemoenzymatic applications to produce novel molecules beyond seongsanamide B, as it can be used on non-carrier protein linked substrates.

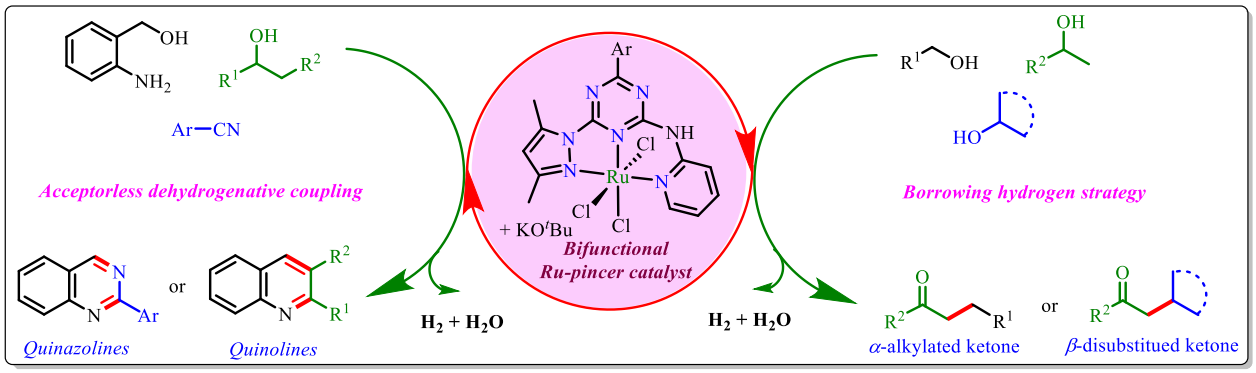
Catalytic Synthesis of Branched Ketones, and N-Heteroaromatic Compounds Using Acceptorless Dehydrogenative Coupling and Borrowing Hydrogen Strategies

Dipanjan Bhattacharyya, Animesh Das*

Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India

Email ID: dipanjan.bhattacharyya@concordia.ca, adas@iitg.ac.in

Carbon–carbon bond formation is pivotal to the synthesis of pharmaceuticals, agrochemicals, and natural products. In this context, transition metal catalyzed transformation of alcohols to other fine chemicals is an attractive approach since alcohol is found as a cheap, abundant in nature, and bio renewable substrate produced from a diverse range of sustainable resources.[1] Herein, a novel phosphine-free pincer ruthenium (III) catalyzed synthesis of branched ketones[2-3] and *N*- heteroaromatic compounds is reported.[4] This strategy explored the synthesis and catalytic activity of a bench-stable ruthenium (III) pre-catalyst, without the use of stoichiometric base, aerobic reaction condition and high selectivity. This catalytic method was well tolerated toward various substrates, with diverse functionality and even for functionalization of complex vitamin-E and (±) cholesterol derivatives efficiently. Interestingly, this reaction produces H_2 and H_2O as the only byproducts making the protocol, atom economical, and relatively environmentally benign. DFT calculations further sheds light on the mechanistic finding demonstrating the dehydrogenation of alcohols and the overall catalytic cycle.



References

1. Crabtree, R. H. *Chem. Rev.*, **2017**, *117*, 9228–9246.
2. Bhattacharyya, D.; Sarmah, B. K.; Nandi, S.; Srivastava, H. K.; Das, A. *Org. Lett.* **2021**, *23*, 3, 869–875.
3. Bhattacharyya, D.; Adhikari, P.; Hazarika, N.; Sarmah, B. K.; Das, A. *ChemCatChem*, **2023**, *15*, e202300542.
4. Bhattacharyya, D.; Adhikari, P.; Deori, K.; Das, A. *Catal. Sci. Technol*., **2022**, *12*, 5695–5702

Synthesis of a hexasaccharide epitope towards a vaccine against Group B Streptococcus

S. Bahadori, D. Giguère*
Département de chimie, Université Laval, Québec, Canada

E-mail: sam.bahadori.1@ulaval.ca

Streptococcus agalactiae is a Gram-positive bacteria known as Group B Streptococcus (GBS). Type III of GBS bacteria is dangerous because pregnant women can infect new-born during childbirth. The WHO and the London School of Hygiene and Tropical Medicine urging the development of a vaccine as a matter of urgency after conducting a new study published in November 2021. According to the report, it would be 91,000 deaths from newborn, 46,000 stillbirths and 40,000 infants with neurological disorders due to GBS worldwide in 2020 [1].

The surface of the bacteria is made of a thick layer of Poly-Sialylated Capsular (PSC) which one unit can be defined as a serotype. Moreover, the PSC is a key for immune response because of its virulence factor [2]. PSC gives generally weak immune response, so combining PSC to an immunogenic protein provides a long-lasting memory response.

The capsular is a saccharide polymer consisting of a sequence of five sugars. The recent identification of a hexasaccharide **1** that binds to specific monoclonal antibodies of interest inspired us [3].

The synthesis of target **1** was achieved by a convergent 3 + 3 strategy. In addition, we avoided benzyl protecting groups to increase the yield of the deprotections steps (from **2**). The protected hexasaccharide was synthetized from two trisaccharides, namely north (**3**) and south (**4**). The trisaccharides were formed from a dimer and a monomer and all these building blocks were synthetized from inexpensive starting materials.

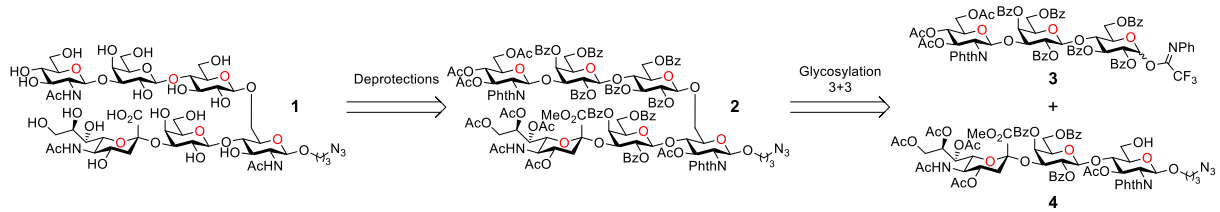


Figure 1. Retrosynthetic analysis of target **1**

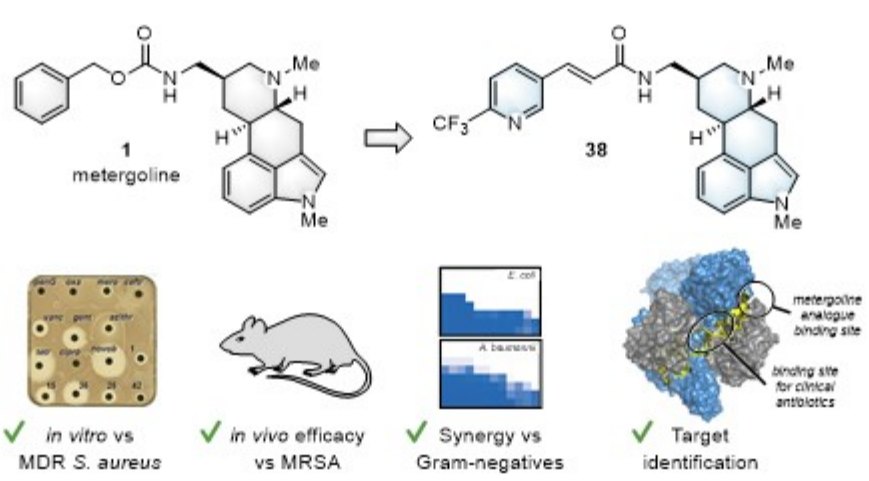
References

1. Group B streptococcus vaccine: full value of vaccine assessment. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
2. Calzas, C.; Taillardet, M.; Fourati, I.S.; Roy, D.; Gottschalk, M.; Soudeyns, H.; Defrance, T.; Segura, M. *Pathogens*, **2017**. *6*, 16.
3. Oldrini, D.; Del Bino, L; Arda, A.; Carboni, F.; Henriques, P.; Angiolini, F .; Quintana, J.I.; Calloni, I.; Romano, M.R.; Berti, F.; Jimenez-Barbero, J.; Margarit, I.; Adamo, R. *Chem. Eur. J.*, **2020**. *26*, 7018-7025

Antibacterial Activity of Metergoline Analogues and Investigations into Their Mechanisms of Action

Ella Harness, Jarrod W. Johnson, Shawn French, Michael J. Ellis, Zoë A. Piquette, Eric D. Brown, and Jakob Magolan*

Department of Biochemistry and Biomedical Sciences and the Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, Ontario, Canada



Metergoline is a semisynthetic ergot alkaloid unknown to have antibacterial activity until recently, when it was identified in a screen for inhibitors of intracellular growth of *Salmonella* Typhimurium.[1] We synthesized a series of carbamate, amine, and amide analogues and found that cinnamides (*e.g.*, **38**) showed improved activity against strains of MRSA, *B. subtilis*, and *E. coli*, and showed synergistic activity with outer-membrane permeabilizer SPR741 against *E. coli*, *A. baumannii*, and *B. cenocepacia*. Cinnamide analogues also retained activity against a MDR strain of *S. aureus*, and compound **38** was efficacious *in vivo* in an MRSA skin infection model.[2] To investigate the mechanism of action, we generated mutants of *S. aureus* resistant to a metergoline analogue and mapped the mutations to binding sites on a validated protein target. Separately, we also used transcriptional profiling with fluorescence imaging to independently identify gyrase as the same protein target in *E. coli*.[3]

References:

1. Ellis, M. J.; Tsai, C. N.; Johnson, J. W.; French, S.; Elhenawy, W.; Porwollik, S.; Andrews-Polymenis, H.; McClelland, M.; Magolan, J.; Coombes, B. K.; Brown, E. D. A macrophage-based screen identifies antibacterial compounds selective for intracellular Salmonella Typhimurium. *Nat. Commun.* **2019**, *10*, 197 (doi: 10.1038/s41467-018-08190-x).
2. Johnson, J. W.; Ellis, M. J.; Piquette, Z. A.; MacNair, C.; Carfrae, L.; Bhando, T.; Ritchie, N. E.; Saliba, P.; Brown, E. D.; Magolan, J. Antibacterial activity of metergoline analogues: Revisiting the ergot alkaloid scaffold for antibiotic discovery. *ACS Med. Chem. Lett.* **2022**, *13*, 284–291 (doi: 10.1021/acsmedchemlett.1c00648)
3. French, S.; Guo, A. B. Y.; Ellis, M. J.; Johnson, J. W.; Rachwalski, K.; Piquette, Z. A.; Lluka, T.; Zary, M.; Gamage, S.; Magolan, J.; Brown, E. D. *Manuscript under review.*

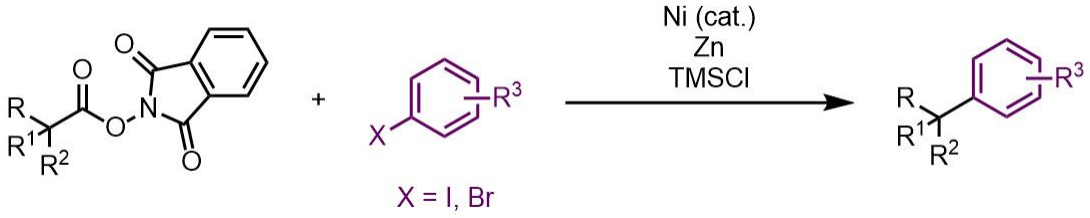
Development of a Generalized Nickel-Catalyzed Reductive Cross-Coupling between *N*-Hydroxyphthalimide Esters and Aryl Halides

By: Dudra, S.L., Gabbey, A.L., Scotchburn, K., Martone, V., Rousseaux, S.A.L.*

University of Toronto, Toronto, ON, Canada

E-mail: sam.dudra@mail.utoronto.ca

The formation of C(sp^2)-C(sp^3) bonds is an area of interest due to its utility in the pharmaceutical and agrochemical industries. In recent years, nickel-catalyzed reductive cross-couplings using *N*-hydroxyphthalimide (NHP) esters and aryl halides has been established to be a powerful method to generate these C(sp^2)-C(sp^3) bonds with excellent yields, mild conditions, and functional group tolerance. These NHP esters are attractive started materials due to their facile one step synthesis from carboxylic acids which are readily available starting materials. However, with previously developed methods, the conditions are often tailored to a specific substrate class and the potential breadth of reactivity is not fully demonstrated. In order to address this, we have taken a wide variety of substrates and subjected them to three generalized methods to determine which set of conditions is best for representative substrate groups. Here, we present how the couplings of a wide variety of NHP esters and aryl halide substrates perform in these different conditions.

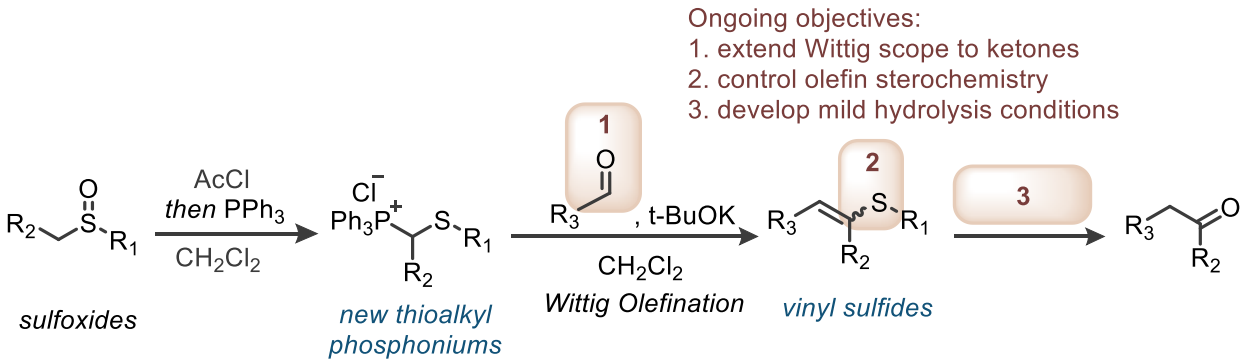


Expanding the Versatility of Wittig-Derived Vinyl Sulfides

Lara Lima, Meghan Fragis, Nikkie Ritchie, Jakob Magolan*

Biochemistry and Biomedical Sciences, McMaster University, Hamilton, ON

Vinyl sulfides, or enol thioethers, are valuable synthetic intermediates in organic chemistry. Our group recently developed a facile Pummerer-like synthesis of thioalkyl phosphonium salts from sulfoxides which facilitates the preparation of a wide range of vinyl sulfides via Wittig olefination [1]. This poster review this work and present our ongoing related investigations that include: 1) efforts to extend the scope of Wittig substrates to include ketones, 2) developing strategies to control olefin stereochemistry in this vinyl sulfide synthesis, and 3) developing new strategies for hydrolysis of vinyl sulfides to carbonyls under mild conditions.



References

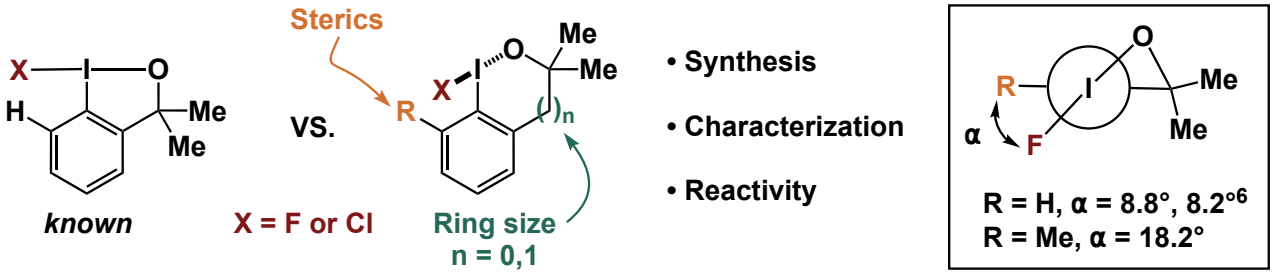
1. M. Fragis, J. L. Deobald, S. Dharavath, J. Scott, J. Magolan *Org. Lett.* **2021**, 23(*12*), 4548-4452.

The hypervalent twist in fluoro- and chlorobenzoiodoxoles/ines

Avery J. To, Graham K. Murphy
Department of Chemistry, University of Waterloo, Waterloo, Canada

E-mail: ajto@uwaterloo.ca

The idea of introducing steric bulk at the position *ortho* to the hypervalent iodine was first reported by Su and Goddard when studying the oxidation of alcohols with IBX.[1] This idea has been successfully translated into the design of novel λ^3-hypervalent iodine reagents or precursors for the oxidative dearomatization of phenols and α-tosylation of carbonyls.[2-4] Hypervalent iodine(III) reagents with an increased torsion angle between the plane of the aryl ring and the hypervalent iodine bond have shown increased reactivity, and at times selectivity, when compared to the parent reagent. Given the utility of both fluoro- and chlorobenzoiodoxoles as fluorination and chlorination reagents,[5] we sought to synthesize variants with *ortho*-substituents (R = H vs. Me vs. *t*-Bu) to probe the limits of the induced torsion angle and assess their reactivity. As such, this poster will discuss the design, synthesis, characterization, and preliminary reactivity of twisted fluoro- and chlorobenzoiodoxoles/ines.



References

1. Su, J. T.; Goddard, W. A., *J. Am. Chem. Soc.* **2005**, *127*, 14146-14147.
2. Guilbault, A.-A.; Legault, C. Y., *ACS Catal.* **2012**, *2*, 219-222.
3. Abazid, A. H.; Nachtsheim, B. J., *Angew. Chem. Int. Ed.* **2020**, *59*, 1479-1484.
4. Parida, K. N.; Moorthy, J. N., *Chem. - Eur. J.* **2023**, *29*, e202203997.
5. Robidas, R.; Legault, C. Y., *Helv. Chim. Acta* **2021**, *104*, e2100111.
6. Legault, C. Y.; Prevost, J., *Acta Crystallogr., Sect. E Struct. Rep. Online* **2012**, *68*, o1238.

Alexanne Bisson
M. Sc. student under the supervision of Anne Marinier and Guy Sauvageau

Institution : Institute for Research in Immunology and Cancer (IRIC), Université de Montréal

Title : UM171 TARGET DETERMINATION STUDIES USING PHOTOREACTIVE PROBES

Authors : Alexanne BISSON[1], Stéphane GINGRAS[2], Simon GIRARD[3], Houssam ISMAIL[3], Haithem BARBOUR[3], Rodrigo MENDOZA-SÁNCHEZ[2], Cédric DICAIRE-LEDUC[2], Réjean RUEL[2], Guy SAUVAGEAU[3,4,5], Anne MARINIER[1,2,6]

Authors affiliations :
[1] Department of Pharmacology and Physiology, Faculty of Medecine, Université de Montréal, Institute for Research in Immunology and Cancer (IRIC)
[2] Medicinal Chemistry, Université de Montréal, Institute for Research in Immunology and Cancer (IRIC)
[3] Molecular Genetics of Stem Cells, Université de Montréal, Institute for Research in Immunology and Cancer (IRIC)
[4] Department of Hematology, Maisonneuve-Rosemont Hospital, Montréal, Canada
[5] Medecine Department, Faculty of Medecine, Université de Montréal
[6] Chemistry Department, Faculty of Arts and Science, Université de Montréal

Abstract:

Blood cancer patients can be treated with hematopoietic stem cell transplants. Stem cells derived from umbilical cord blood are highly compatible and cause few complications. However, these stem cells are not abundant per umbilical cord.

Remarkably, the UM171 molecule enables self-renewal of hematopoietic stem cells contained in these umbilical cord bloods. This molecule, developed at the Université de Montréal, is currently in clinical trials with more than 100 patients already treated.

Although our group recently elucidated the biological mode of action of UM171, the target protein to which UM171 directly binds is still unknown. Determining this target protein would provide a better understanding of UM171 mechanism of action at the molecular level, and would represent a major advance in the overall understanding of the fundamental mechanism governing stem cell self-renewal.

In order to identify this target protein, we synthesize a photochemical probe based on the structure of UM171. This photochemical probe includes a photoreactive group, covalently binding to the target protein, and a reporter group, enabling the target protein-photochemical probe complex to be bound to a solid support. This enables the identification of the target protein by mass spectrometry.

In this project, the photoreactive moiety will be a tetrazole, an innovative approach enabling greater selectivity in the formation of the covalent bond by targeting carboxylic acids. The first steps in the synthesis of this new photochemical probe, as well as the structure-activity relationship studies in cells justifying this approach, will be presented.

I do not want my abstract evaluated by the organizing comitee for an oral presentation.

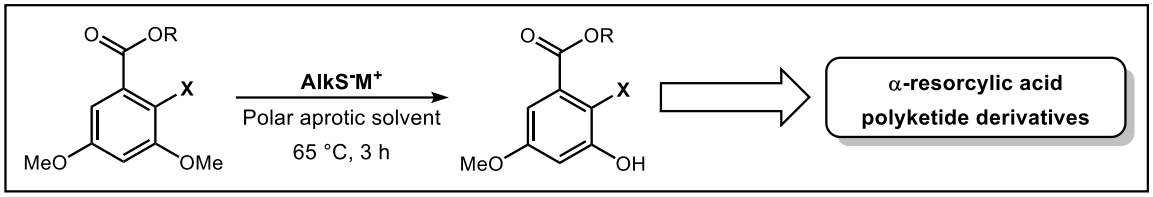
Chemo- and regioselective demethylation of α-resorcylic acid derivatives using alkylthiolates

T. Fraser[1,2], Z. Harbour[1], S. Cardinal[2], N. Voyer[1]
[1]*Département de chimie, Université Laval, Québec, Canada*
[2]*Département de biologie, chimie et géographie, UQAR, Rimouski, Canada*

tommy.fraser.1@ulaval.ca

Natural products are an endless source of highly useful medicines.[1] However, these compounds are often difficult to extract or to biosynthesize in sufficient from their natural sources, hence requiring access by chemical synthesis.[2] This is the case for an interesting class of molecules mainly biosynthesized by lichens and fungi : α-resorcylic acid type polyketide derivatives. In the course of our investigation towards the total synthesis of natural products identified from a Nunavik sample of S. paschale, we envisioned using a regioselective demethylation as one of the key steps.[3]

This presentation will feature our recent results to develop and to optimize a demethylation reaction using alkylthiolates to generate 2-halogeno-3-hydroxy-5-methoxybenzoate derivatives. Using a variety of substrates, we investigated the impact of a combination of electronic and steric factors involved in chemo- and regio-selective demethylation.



References

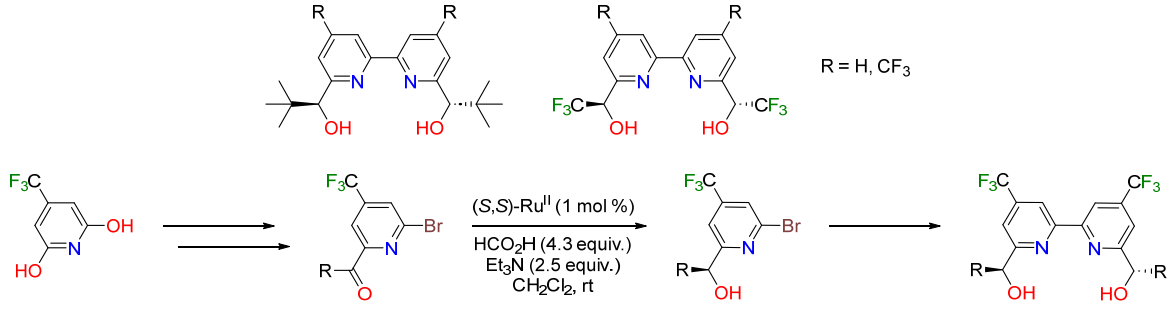
1. Atanasov, A.G.; Zotchez, S.B.; *et al. Nat. Rev. Drug Discov.* **2021**, *20*, 200.
2. Beutler, J.A. *Curr. Protoc. Pharmacol.* **2009**, *46*, 9.11.1.
3. Carpentier, C.; Queiroz, E.F.; Marcourt, L.; Wolfender, J.-L.; Azelmat, J.; Grenier, D.; Boudreau, S.; Voyer, N. *J. Nat. Prod.* **2017**, *80*, 210.

Ref # (to be added)	**Design of 2,2'-bipyridinediol chiral ligands and their use in asymmetric catalysis**

Antony Marcoux, Thierry Ollevier*

Département de chimie, Université Laval, 1045 avenue de la Médecine, Québec (Québec) G1V 0A6. E-mail: thierry.ollevier@chm.ulaval.ca

Chirality and stereoselectivity are among the most crucial factors in the preparation of biologically active compounds. In our investigations in iron-catalyzed asymmetric catalysis,[1] we demonstrated that C_2 symmetrical 2,2'-bipyridinediol derivatives, used as chiral ligands, were effective when used with FeX_2 in selected organic transformations. These ligands proved to be highly efficient in promoting asymmetric reactions across a wide range of substrates. The introduction of a trifluoromethyl group to the structure of the ligand is expected to enhance the Lewis acid properties of the catalyst and to potentially exert a significant influence on selectivity.



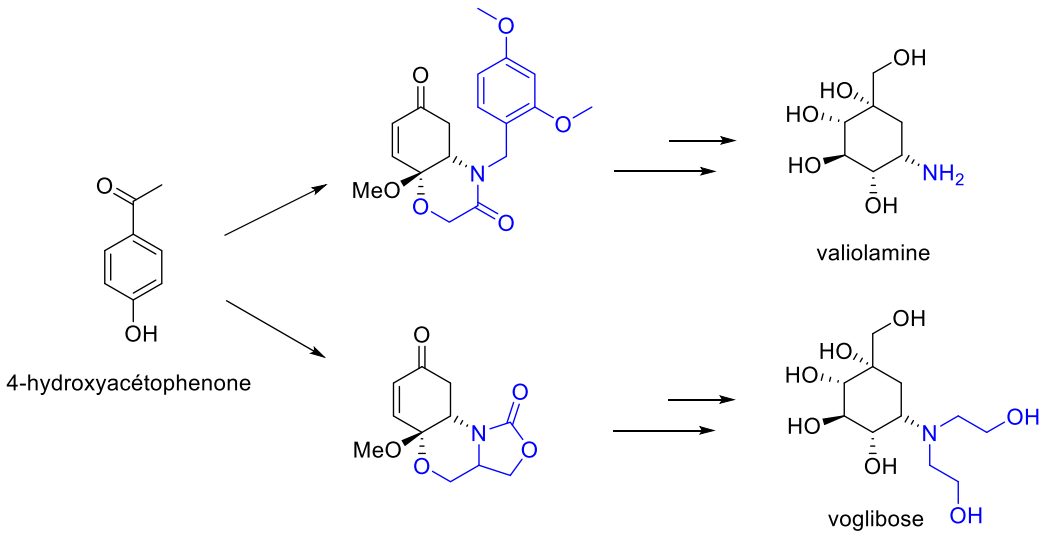
[1] a) S. Lauzon, H. Keipour, V. Gandon, T. Ollevier, *Org. Lett.* **2017**, *19*, 6324-6327. b) S. Lauzon, T. Ollevier, *Chem. Comm.* **2021**, *57*, 11025-11028. c) S. Lauzon, L. Caron, T. Ollevier, *Org. Chem. Front.* **2021**, *8*, 2242-2249. d) S. Lauzon, L. Schouwey, T. Ollevier, *Org. Lett.* **2022**, *24*, 1116-1120.

Towards the total synthesis of the natural molecule valiolamine and its main derivative, voglibose

*Camille Rocq, Vincent Hamel, Sylvain Canesi**

Laboratoire de Méthodologie et Synthèse de Produits Naturels – Université du Québec à Montréal (UQAM)

The first objective of that project is to develop a rapid and efficient synthesis method for valiolamine, a natural molecule that has already demonstrated interesting biological properties, notably for the treatment of type 2 diabetes. This molecule has 5 contiguous stereogenic centers, which represents a major challenge in organic chemistry. In parallel, voglibose, the main derivative of valiolamine, has also shown remarkable bioactive activities. For that synthesis, the aim is to rely on the use of a functional chiral auxiliary. The auxiliary group permits to induce stereoselectivity but also be part of the final target molecule.



Nickel-Catalyzed Deoxygenative Suzuki-Miyaura Cross-Coupling of Ketones

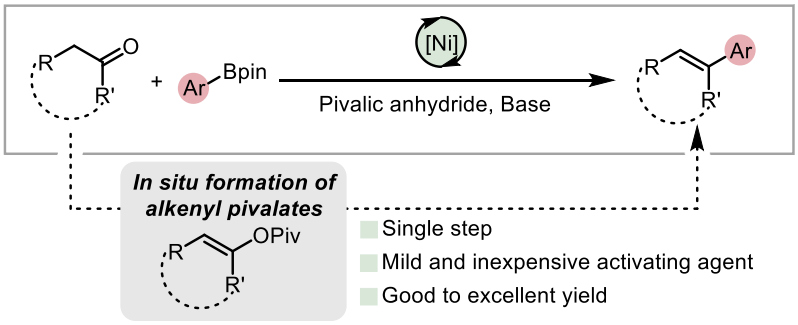
Aref Vaezghaemi, Shajia I. Khan, Stephen G. Newman*

Centre for Catalysis Research and Innovation, Department of Chemistry and Biomolecular Sciences, University of Ottawa, 10 Marie Curie, Ottawa, Ontario K1N 6N5, Canada

Email: Avaez028@uOttawa.ca; Stephen.newman@uOttawa.ca

The Suzuki-Miyaura cross-coupling is among the most frequently used methods to forge new C–C bonds.[1] Organohalides are recognized as the classical electrophilic coupling partner in Suzuki-Miyaura cross-coupling. However, given the abundance of C–O bonds in common feedstock molecules like phenols, carboxylic acids, and alcohols, these have emerged as attractive alternatives to organohalide.[2] Ketones are particularly common precursors in cross-coupling chemistry, which are commonly converted to vinyl triflates first to enable activation by Pd or Ni catalysis.[3] While there has been a strong push in the recent literature to enable oxygen-containing substrates to be directly grouped without requiring isolation of an activated 'pseudohalide' intermediate,[4-6] such chemistry has not yet been identified for ketone activation.

Aiming to fill this void, we sought to identify mild and inexpensive activating agents that could enable in situ activation and cleavage of the C–O bond of ketones via Suzuki-Miyaura cross-coupling. This requires compatibility between base, activating agent, and low valent metal catalyst. A high throughput screening campaign led us to a Ni-catalyzed, pivalic anhydride-mediated set of reaction conditions that enables the direct transformation of ketones into vinyl arenes, avoiding the need to form and isolate sensitive vinyl triflate intermediates. The discovery, development, and application of this new reaction will be described.



References

1. Brown, D.G., Boström J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443–4458.
2. Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. Nickel-catalyzed cross-couplings involving carbon-oxygen bonds. *Chem. Rev.* **2011**, *111*, 1346–1416.
3. Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483.
4. Liu, X.; Xu, B.; Su, W. Ni-Catalyzed Deoxygenative Borylation of Phenols Via O-Phenyl-uronium Activation. *ACS Catal.* **2022**, *12*, 8904–8910.
5. Cook, A.; St. Onge, P.; Newman, S. G. Deoxygenative Suzuki–Miyaura arylation of tertiary alcohols through silyl ethers. *Nat. Synth.* **2023**, *2*, 663–669.
6. Toupalas, G.; Thomann, G.; Schlemper, L.; Rivero-Crespo, M. A.; Schmitt, H. L.; Morandi, B. Pd-Catalyzed Direct Deoxygenative Arylation of Non-π-Extended Benzyl Alcohols with Boronic Acids via Transient Formation of Non-Innocent Isoureas. *ACS Catal.* **2022**, *12*, 8147 –8154.

Nickel-Catalyzed Kumada-Corriu Coupling of Silyl Ketene Acetals

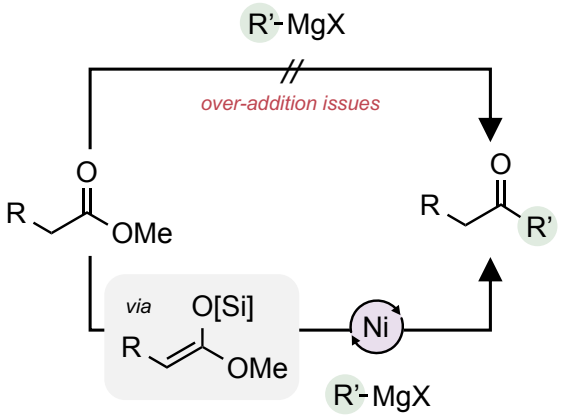
Shajia I. Khan, Aref Vaezghaemi, Stephen G. Newman*

Centre for Catalysis Research and Innovation, Department of Chemistry and Biomolecular Sciences, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, K1N 6N5, Canada

Email: skhan275@uottawa.ca; stephen.newman@uottawa.ca

Transition metal-catalyzed cross-coupling reactions are a commonly used strategy to synthesize new carbon-carbon bonds. [1] Traditionally, aryl halides have been used as electrophiles in many cross-coupling reactions. However, extensive research has been dedicated to increasing the scope of electrophilic coupling partners, with esters being one substrate of interest. [2-4] Nevertheless, converting simple aliphatic esters into ketones and related species remains an ongoing challenge.

As a result, we aimed to develop a nickel-catalyzed strategy to transform aliphatic esters into ketones. The preliminary protocol is a Kumada-Corriu-type coupling, which first converts the ester to a silyl ketene acetal. This conversion is used as both an activation strategy and to circumvent the over-addition issues that occur when using Grignard reagents with carbonyl substrates.



References

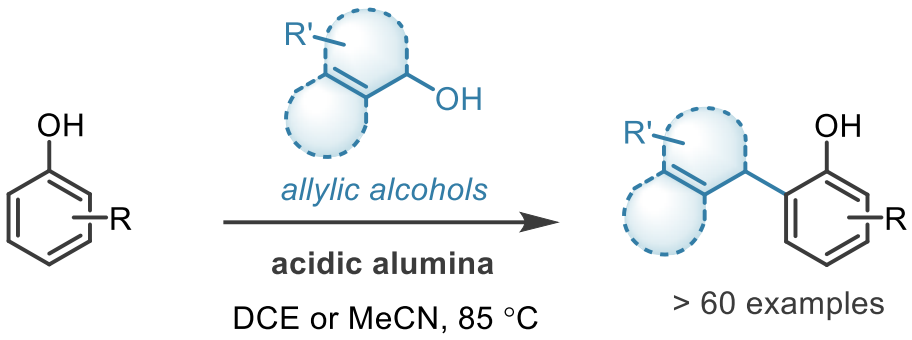
[1] Ayogu, J. I.; Onoabedje, E. A. *Catal. Sci. Technol.* **2019**, *9* (19), 5233–5255.
[2] Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6* (20), 3597–3599.
[3] Ben Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Newman, S. G. *J. Am. Chem. Soc.* **2017**, *139* (3), 1311–1318.
[4] Hie, L.; Fine Nathel, N. F.; Hong, X.; Yang, Y. F.; Houk, K. N.; Garg, N. K. *Angew. Chem. Int. Ed.* **2016**, *55* (8), 2810–2814.

Selective *ortho*-Allylation of Phenols using Acidic Alumina

Philip Samokhin, Mathew Piotrowski, Lauren Irwin, Patrick Darveau, Xiong Zhang, Jarrod Johnson, Jakob Magolan*

Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada

Existing approaches to the assembly of *ortho*-allyl phenols include [3,3]-sigmatropic rearrangements of *O*-allyl substrates, directed-*ortho*-metalation, and Friedel-Crafts allylations. For the past two years our lab has been engaged in an expansive development effort focused on a versatile new methodology for *ortho*-allylation of phenols with allylic alcohols enabled by acidic alumina (*unpublished work*). We hypothesize that the alumina surface coordinates to both phenol and allyl alcohol substrates and chaperones an *ortho*-selective C-C bond formation. This presentation will summarize our methodology development effort. One limitation of this chemistry is a lack reactivity of phenolic substrates that contain amides or basic nitrogen atoms. This presentation will disclose our ongoing efforts to explore the compatibility of N-protecting groups with our reaction conditions.



Poster Abstract for QOMSBOC, 2023

Rose G. Boivin, Charette Group, Faculty of Sciences, Department of Chemistry, Université de Montréal, Campus MIL, rose.boivin@umontreal.com

Title : Efficient synthesis of allylic ester bromide organozinc synthesis under continuous flow by a regiocontrolled γ– or α–addition to carbonyls derivatives.

Complete authorship : Rose G. Boivin and André B. Charette

Institution : Université de Montréal

Poster abstract : The *Reformatsky* reaction is one of the most practical reaction for the synthesis of β-hydroxyesters, a prevalent pattern observed in various natural compounds. This transformation involves the reaction of zinc powder with an α-bromoester in an anhydrous solvent to produce the zinc enolate that adds to carbonyls. This reaction efficiently produce β-hydroxyesters.[1] One downside is the important exothermicity of the reaction during both the zinc activation step and the carbonyl addition. This leads to scale-up and reproducibility issues. Conditions for a continuous *Reformatsky* reaction have already been reported and flow chemistry is a powerful technique for carrying out safer and more efficient reactions.[2] Indeed, zinc dust is packed in an Omnifit® glass column. The usual TMSCl activation can be performed directly in the column before the *in-situ* zinc enolate formation and the subsequent addition to produce the corresponding β-hydroxyester (**7**). An interesting variation of this reaction was first suggested in 1946 by Arens and van Dorp where they used γ-bromocrotonic ester **2** instead of the traditional α-bromoester **6** as the reactant to synthesize a more complex product. However, only a 27% yield was observed.[3] As suggested by Hudlicky, two reaction pathways could lead to two different regioisomers known as the γ **4** and α adduct **5**.[4] Because of the lack or regiocontrol, this *Reformatsky* variation has never been extensively utilized in synthesis. In this work, the parameters to better control the regioselectivity of this reaction were studied. The optimized conditions were tested on different substrates to obtain selectively the γ or α alkylation product under different reaction conditions.

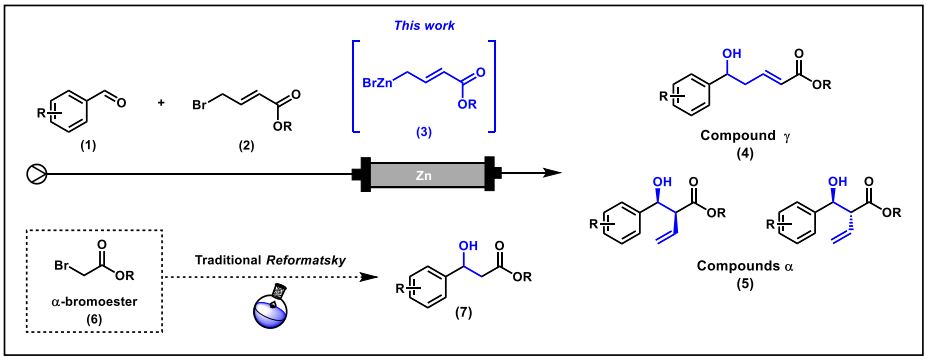


Figure 1. *In-situ* organozinc reactant for *Reformatsky* variation reaction in continuous flow.

(1) Saeed, S.; Zahoor, A. F.; Ahmad, S.; Akhtar, R.; Sikandar, S. *Synth. Commun.* **2022**, *52* (3), 317-345. DOI: 10.1080/00397911.2021.2008447.
(2) Huck, L.; Berton, M.; de la Hoz, A.; Díaz-Ortiz, A.; Alcázar, J. *Green Chem.* **2017**, *19* (6), 1420-1424. DOI: 10.1039/C6GC02619B.
(3) van Dorp, D. A.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1946**, *65* (5), 338-345. DOI: https://doi.org/10.1002/recl.19460650505.
(4) Rice, L. E.; Boston, M. C.; Finklea, H. O.; Suder, B. J.; Frazier, J. O.; Hudlicky, T. *J. Org. Chem.* **1984**, *49* (10), 1845-1848. DOI: 10.1021/jo00184a042.

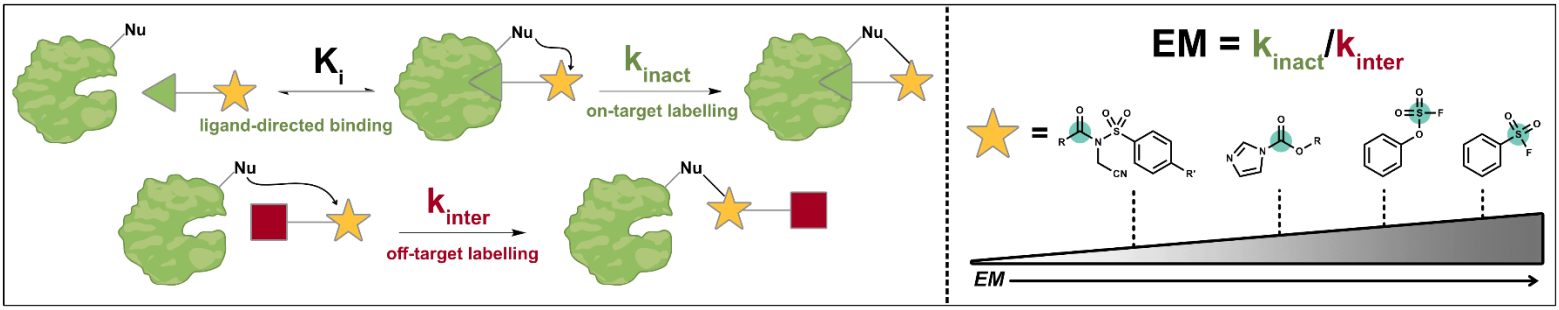
Electrophiles used in targeted covalent inhibitors are associated with intrinsically distinct kinetic effective molarities

Tomas V. Frankovich[*1, 2], Harrison M. McCann*[1, 2], Anthony F. Rullo[1, 2]

[1] Centre for Discovery in Cancer Research, McMaster University

[2] Department of Chemistry and Chemical Biology, McMaster University

Small molecules that form irreversible covalent bonds to proteins are widely used as chemical probes and targeted inhibitors. Covalent probes possess an electrophilic moiety that reacts with nucleophilic residues on a target protein. Selective labelling is a key trait for covalent probes, and “latent” electrophiles that only become sufficiently reactive upon binding target protein are highly desirable. We envisioned that the selectivity and “turn-on” reactivity of latent electrophiles could be quantitatively characterized by applying the concept of kinetic effective molarity (kEM). kEM is the ratio of selective (intramolecular) to off-target (intermolecular) reaction rate constants. We synthesized a range of sulfonylating, acylating, and alkylating probes, linked to a hapten affinity handle, that target lysine, serine, and tyrosine residues in the binding pocket of a monoclonal antibody. We also synthesized complementary probes lacking an affinity handle to measure off-target labelling. Using this library of probes, we calculated kEMs for each electrophile. Interestingly, we observed that probes with mechanistically distinct electrophiles are associated with significantly different kEM values, despite equal binding affinities and comparable distance between electrophile and affinity handle. Within the series of electrophiles evaluated, we identified sulfonyl fluorides as uniquely latent. We optimized a sulfonyl fluoride probe and obtained selective, ultra-fast labelling rates with second-order rate constant ~ 9.6 * 10^5 M^{-1} s^{-1}. To better understand the relationship between kEM and electrophile mechanism, we measured the transition state parameters associated with intra- and intermolecular reaction kinetics. We find that kEM depends on transition state stabilization through electrophile pre-organization in the binding pocket, and this enzyme-like transition state stabilization is sensitive to electrophile labeling mechanism. These results will aid in the development of highly selective covalent probes and inhibitors capable of latent, “turn-on” reactivity.



Chemical and electrochemical transformation of substituted phenolic derivatives

Tyra Lewis, Stephanie Gao, Dr. Sanela Martic
Trent University, Department of Forensic Science, Environmental and Life Sciences, Peterborough, ON, Canada

Phenolic compounds are natural molecules with applications in biotechnology, agriculture, and industry which may ultimately contribute to the movement of phenolic contaminants into the environment. The chemical transformation of phenolic compounds is of interest which may be achieved by traditional chemical means. However, sustainable transformation of phenolic compounds into new functional molecules can also be achieved through selective electrosynthesis.[1] Electro-oxidation of a phenol, via formation of reactive radicals, may result in variety of products, including quinones, polymers and new carbon-carbon bond formation, resulting in new value-added chemicals which are of industrial interest. Herein, the electrochemical and chemical transformation of 2,6-di-*tert*-butylphenol (DTBP), 2,6-diphenylphenol (DPP), and 5-chloro-2-(2,4-dichlorophenoxy)phenol (triclosan) were evaluated. All compounds underwent oxidation following cyclic voltammetry or by addition of an oxidizing agent resulting in significant colour changes. The product formation was monitored by UV-vis spectroscopy and characterized by X-ray single crystal diffraction and gas chromatography-mass spectrometry (GC-MS). The electrochemical oxidation of phenolics resulted in a carbon-carbon bond formation into products with extended conjugation, and an absorbance within the visible range. Overall, the data suggest that the yield and selectivity of electrochemical transformations are dependent on the parameters used, and that electrosynthesis may allow for the generation of products that may not be achievable by chemical means.

References

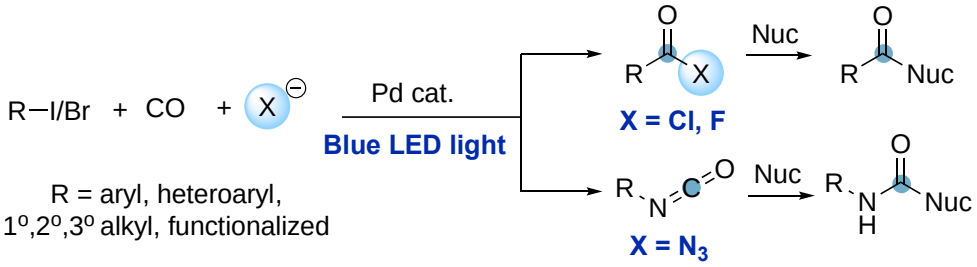
[1] Zabik, N. L.; Virca, C. N.; McCormick, T. M.; Martic-Milne, S. Selective Electrochemical versus Chemical Oxidation of Bulky Phenol. *J. Phys. Chem. B* **2016**, 120 (34), 8914–8924. https://doi.org/10.1021/acs.jpcb.6b06135.

Versatile Visible-Light Driven Palladium-Catalyzed Approach towards Various Carbonyl-Containing Products via Acyl Electrophiles

Cuihan Zhou[1], Bruce A. Arndtsen[1]
[1] *Department of Chemistry at McGill University, Montreal, Canada*

E-mail: cuihan.zhou@mail.mcgill.ca

Transition metal–catalyzed coupling reactions have become one of the most important tools in modern synthesis. However, an inherent limitation to these reactions is the need to balance operations, as the factors that favor bond cleavage via oxidative addition ultimately inhibit bond formation via reductive elimination. Here, we describe an alternative strategy that exploits simple visible-light excitation of palladium to drive oxidative addition with low barriers. This create a unidirectional catalytic cycle that is uninhibited by the classical effect of carbon monoxide(CO) coordination. Palladium-catalyzed carbonylations can thereby proceed under ambient conditions, with challenging aryl or alkyl halides and difficult nucleophiles, and generate valuable carbonyl derivatives of acid chlorides, fluorides, isocyannates, and eventually convert to more stable esters, amides, thioesters, ketones, ureas, or carbomate in assembly of highly functionalized carbonyl-containing products and drug-liked molecules.



✓ Broadly applicable ✓ Stable reagents ✓ Ambient temperature

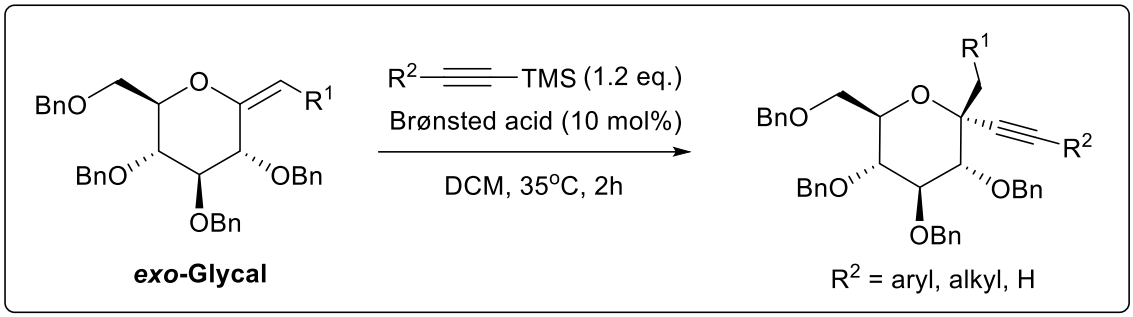
Title: Synthesis of *C,C*-Glycosides *via* Brønsted Acid-Catalyzed Alkynylation of *exo*-Glycals

Rony Gantous and Yuri Bolshan
Ontario Tech University, Oshawa, Ontario

Abstract:

The synthesis of *C*-glycosides is of importance due to their inherent resilience against in *vivo* hydrolytic enzymes, thus establishing them as optimal substitutes for the native *O*-, *N*-, and *S*-glycosides[1]. Among these, *C,C*-glycosides, possessing a quaternary pseudoanomeric center within carbohydrate framework, hold special interest given their occurrence in natural products and bioactive substances such as Thyrsiferol, Sphydrofuran, and Secosyrin. [2-3] However, current literature methods for the preparation of *C*-alkynyl glycosidation compounds often use hazardous reagents and exhibit a limited substrate scope.[4]

Our research is focused on the derivatization of *exo*-glycals. Recently, we developed a Brønsted acid-catalyzed alkynylation of *exo*-glycals. The formation of quaternary anomeric centers occurs in a diastereoselective manner under mild conditions. A broad range of commercially available alkynyltrimethylsilanes were submitted to the developed conditions to afford the desired *C,C*glycosides in good to excellent yields.



References:

1. Yang, Y.; Yu, B. *Chemical Reviews* **2017**, *117* (19), 12281-12356.
2. Wong, H. Eur. *J. Org. Chem.* **1999**, 1757-1765.
3. Gonzalez, I.; Forsyth, C. *J. Am. Chem. Soc.* **2000**, 122, 9099
4. Liao, H.; Ma, J.; Yao, H.; Liu, X.-W. *Organic & Biomolecular Chemistry* **2018**, *16* (11), 1791-1806.

Further investigation in solid phase syntheses of oligonucleotides

Q Li, T. Yan*

Department of Chemistry, Brock University, 1812 Sir Isaac Brock Way, St. Catharines, ON L2S 3A1, E-mail: ql05qt@brocku.ca (QL); hyan@brocku.ca (TY)

While solid phase syntheses by the phosphoramidite chemistry have enabled ready access to oligonucleotides on laboratory scales, significant challenges still remain for their industrial production. There is currently demand for improved detritylation reactions to reduce solvent use and to address swelling of polymeric solid support during this reaction. This work examined common solvents for their use in detritylation reactions. In this respect, solvents that interact with dichloroacetic and trichloroacetic acid are unsuitable for the detritylation reaction, leading to poor overall yields of full-length products.[1] This work also examined the overall yields of full-length products of different sequences in order to identify patterns in the synthesis of DNA sequences. It was shown that syntheses of purine-rich sequences tend to be more challenging, likely due to their higher propensity to undergo depurination. In addition, certain dinucleotide repeat sequences, such as d(CG) and d(GC), were also identified as difficult in their syntheses.

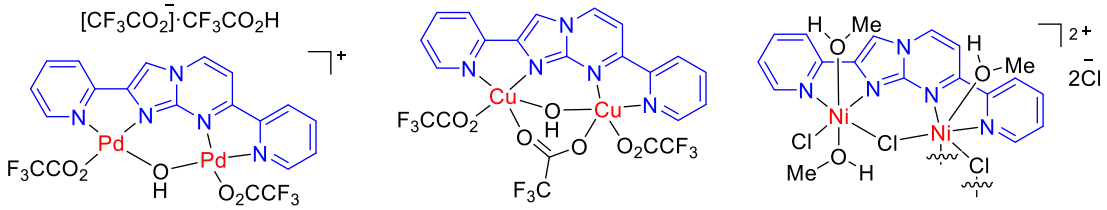
(1) Li, Q.; Sanghvi, Y.; Yan, H. Solvent Selection in the Detritylation Reaction for the Solid-Phase Synthesis of Oligonucleotides. *SynLett* **2023**, in press.

(2) Li, Q.; Yan, H. “Difficult” deoxyribonucleotide sequences in the solid-phase synthesis by the phosphoramidite chemistry. **2023**, revised manuscript submitted.

Mila Abaeva, Christian Ieritano, W. Scott Hopkins, Derek Schipper.*
Department of Chemistry, University of Waterloo, Waterloo, ON N2L 3G1, Canada
* derek.schipper@uwaterloo.ca

Unsymmetrical Imidazopyrimidine-based Bimetallic Catalysts

Bimetallic catalysts have become increasingly studied due to their unique reactivity over their analogous monometallic counterparts, owing to the synergistic effects that arise from the enforced proximity of the two metals.[1] The synthesis of many bimetallic complexes is limited by the difficult synthesis of the ligand, with many overall ligand syntheses being low yielding, requiring costly reagents, or requiring a significant number of synthetic steps.[2,3] Additionally, there is a significant lack of structurally and electronically diverse ligands, with especial emphasis on the lack of unsymmetrical ligands, which are necessary to selectively bind two different metals.[4] To further the widespread use of bimetallic complexes the ease of synthesis and scalability of the synthesis, in addition to straightforward bis-ligation to a wide variety of metals, is a priority. Here we describe the synthesis of unsymmetric ligand 2,7-di(pyridin-2-yl)imidazo[1,2-a]pyrimidine (**dpip**) that is achieved in four steps on a multi-gram scale in an overall 54% yield.[5] The ability of **dpip** to act as a scaffold for the formation of bimetallic complexes is demonstrated with the one-step syntheses of several bimetallic complexes in good yields (79-92%). The potential of **dpip** to selectively bind two different metals is discussed and preliminary data of the catalytic properties of the dicopper complex is discussed.



References
1. *Acc. Chem. Res.* **2020**, *53*, 9, 1944–1956.
2. *Inorg. Chem.* **2014**, *53*, 21, 11770–11777.
3. *Chem. Eur. J.* **2019**, *25*, 58, 13280–13284.
4. *Chem. Eur. J.* **2018**, *24*, 41, 10329 – 10333.
5. ChemRxiv Preprint DOI: 10.26434/chemrxiv-2023-rrs7z.

Revealing potential thermostable biocatalysts as both poly (ethylene terephthalate) hydrolases and polyurethane hydrolases

Zhenyu Hu*, Dr. Sheng Li, Dr. Graeme Howe Department of Chemistry, Queen's University

Current PET recycling methods result in significant material and energy losses. Most of the PET waste is improperly treated, leading to its deposition in the ecosystem. However, enzymes have been discovered in several microorganisms that enable the hydrolysis of PET into small molecules, such as ethylene glycol and terephthalic acid, for reuse. These enzymes have inspired efforts to use biocatalysts to establish a circular PET economy, which reduces or eliminates the detrimental environmental effects of this plastic while maximizing PET utilization.

We employed genome mining to search for more thermostable PETases in thermophilic microorganisms. Sequence similarity networks were used to identify ten candidate enzymes with potential PETase activity. Following the overexpression and purification of these proteins from E. coli, we initially used p-nitrophenyl butyrate as a model substrate to test our enzymes for esterase activity. We also synthesized bis(benzoyloxyethyl) terephthalate (3PET) as a small molecule mimic of authentic PET polymer substrate. Kinetic studies with both 3PET and authentic PET emulsions have yielded promising results as PETases. Additionally, we synthesized a novel compound to mimic polyurethane substrates. Several candidates were tested against this substrate, and they exhibited favorable responses as determined by a fluorescence assay. This poster will provide a detailed account of our efforts to evaluate the enzymatic activities of nine novel biocatalysts through UV-Vis, turbidity, and fluorescence assays at various temperatures. We will also present our preliminary proposal on the mechanisms of these biocatalysts as PETases and PUases using AutoDock

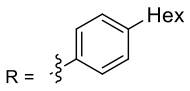
EXCITON BINDING ENERGY OF BITHIAZOLE N-OXIDE CONJUGATED ORGANIC MATERIALS

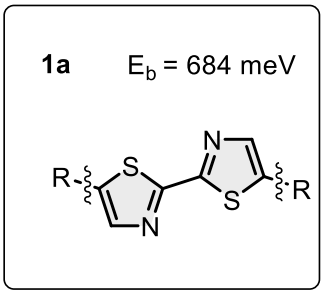
Eduarda Omena, Scott McNeil, Franklin Frasca, Jean Duhamel, Derek Schipper*
Department of Chemistry, University of Waterloo, Waterloo, ON N2L 3G1, Canada
*derek.schipper@uwaterloo.ca

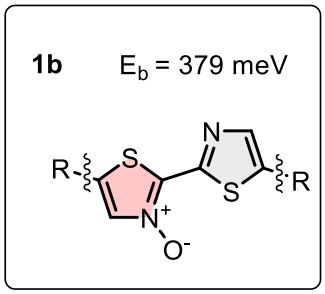
Organic conjugated materials have made a great impact in modern technology, especially in the development of OLEDs, organic solar cells (OSCs), and field effect transistors. Compared to inorganic semiconductors, these materials present advantages in their flexibility and tunability, but drastic disadvantages in power conversion efficiency (PCE).[1] One of the shortcomings of OSCs is its high exciton binding energy, E_b (500-1000 meV), which prevents proper charge separation and requires a p-type and n-type junction as a driving force for this to occur. On the other hand, while single material perovskites present low E_b (50-100 meV) and high PCE, they present toxicity and long-term stability issues. In this study we aimed to overcome high E_b in OSCs, as well as considering the advantages of true single-semiconductor materials.[2] According to Equation (a), by increasing the dielectric constant, which is directly proportional to polarity, we can decrease the exciton binding energy.[3] In previous work from our group, a series of thiazole *N*-oxide molecules with increasing polarity was synthesized.[4] Encouraged by promising computational studies results, we decided to further investigate their E_b through a different approach. We performed variable temperature photoluminescence measurements and fitted the resulting integrated intensities to the Arrhenius Equation.[5] E_b values obtained for compounds **1a**, **1b,** and **1c** were respectively 684 meV, 379 meV and an impressive 65 meV, a result comparable with perovskites.[6] Thus, our studies showed that by increasing the polarity of the molecule, we do decrease their exciton binding energy. Due to their electrical neutrality, molecules containing thiazole *N*-oxide motif can also act as charge transport for both electrons and holes.[7] Thus, thiazole *N*-oxide conjugated materials show great potential for producing low-exciton binding conjugated materials, possibly leading to true single-semiconductor OSCs.

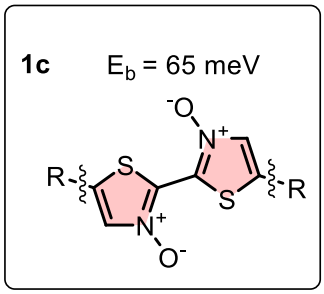
(a) $E_b = \frac{R_0 \mu}{m_e \varepsilon_r^2}$

$\varepsilon_r \propto polarity$









References

[1] Optical Properties of Materials and Their Applications. Edited by Jai Singh. Second edition. JohnWiley & Sons, **2020**.
[2] Zhu, Y. et al. *Adv. Energy Sustainability Res.* **2022**, 3, 2100184.
[3] Niedzwiedzki, D. M. et al. *The Journal of Physical Chemistry C* **2022**, *126* (2), 1046–1054.
[4] Sinclair, G. S. et al. *Chemical Science* **2021**, *12* (6), 2304–2312.
[5] Wang, W. et al. *Chemical Science* **2022**,13, 8679-8685.
[6] Kim, J. Y. et al. *Chemical Reviews* **2020**, 120, 7867−7918.
[7] Coropceanu, V. et al. *Chemical Reviews* **2007**, 107, 4, 926–952.

Metal-catalyzed (3+2) cycloadditions between alkynyl sulfides and alkynes

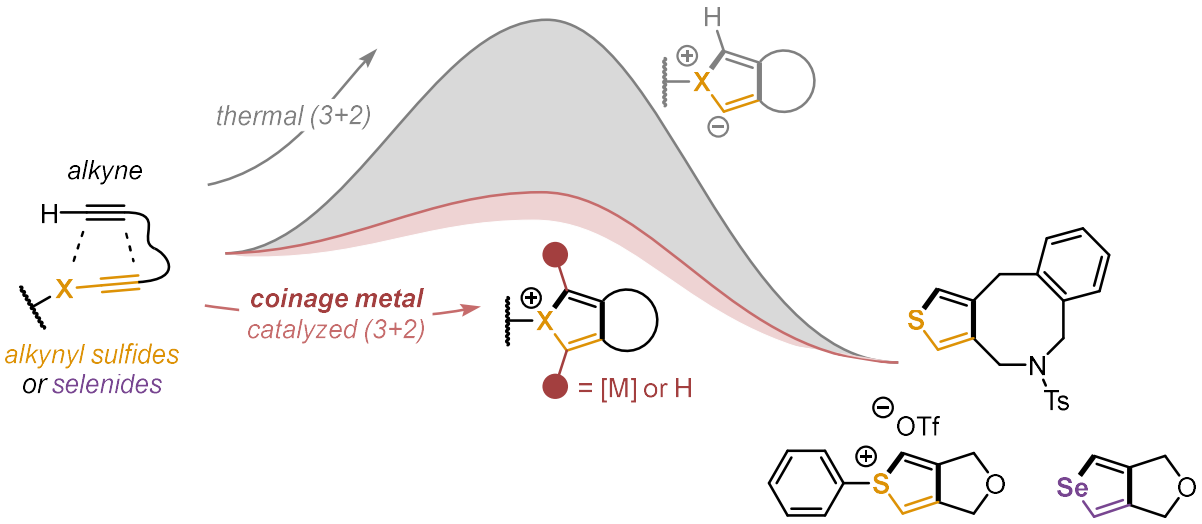
D. Campeau, A. Pommainville, M. Gorodnichy, F. Gagosz
University of Ottawa, Ottawa, Canada

E-mail: dcamp028@uottawa.ca

Metal catalysis plays a crucial role in expanding the applicability of traditional (3+2) cycloadditions by providing milder conditions and wider structural tolerance. The participation of terminal alkynes in cycloadditions is often accelerated by the presence of copper salts; this is best exemplified by the Kinugasa reaction [1] and the copper-catalyzed azide-alkyne coupling (CuAAC).[2]

Recently, our group has reported that fused thiophenes can result from an intramolecular (3+2) cycloaddition between alkynes and alkynyl sulfides.[3] Alkynyl sulfides are neutral three-atom components (TACs): a linear three-atom sequence – complimentary to classical 1,3-dipoles – that can participate in (3+2) cycloadditions.[4]

We have now found that (3+2) cycloadditions between terminal alkynes and alkynyl sulfides can be greatly accelerated by coinage metal salts (Cu, Ag or Au).[5] Mechanistic studies were coupled with careful experimental observations to rationally optimize this novel reaction. Under these mild new conditions, the scope of accessible fused thiophenes has been significantly increased. In some cases, intermediate thiophenium salts can even be isolated with slightly modified conditions.



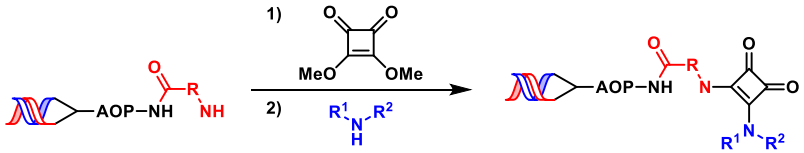
[1] *Tetrahedron* **2014**, *70* (43), 7817-7844.
[2] *https://www.nobelprize.org/uploads/2022/10/advanced-chemistryprize2022.pdf*
[3] *Angew. Chem. Int. Ed.* **2022,** *61,* e202205963.
[4] *Cell Rep. Phys. Sci.* **2023**, *4* (1), 101212.
[5] *J. Am. Chem. Soc.* **2023**, *145* (34), 19018.

Squaramide formation for DNA-Encoded Library Synthesis.

Antoine Douchez, **Julien Poupart**, Gaoqiang Yang, Louis Vaillancourt, Bruno Simoneau, Anne Marinier*

Drug Discovery Unit, Institute of Research in Immunology and Cancer, Université de Montréal, Montréal, QC H3C 3J7, Canada

ABSTRACT: DNA-encoded libraries (DEL) can be considered has one of the most powerful tools for the discovery of small molecules of biological interest. However, the ability to access large DEL is contingent upon having robust conditions for chemical transformations, causing minimal DNA alterations and on the availability of numerous building block compatible with on-DNA chemistry. In addition, accessing scaffolds of interest to medicinal chemist can be challenging in a DEL setting due to inherent limitations of DNA-supported chemistry. In this context, a squaramide formation reaction was developed using a two-step process. The mild, and high yielding reaction tolerates a wide array of functional groups and was shown to be safe for DNA.



This methodology is ideal for the elaboration of drug-like DEL, and development of pilot libraries is ongoing.

Rapid access to cyclopropane scaffolds via photochemically induced ring contraction

J. Parent, A. Mansour, L. Rochez, F. Gagosz*

Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Canada

E-mail: jpare071@uottawa.ca

The cyclopropane motif is very sought after in medicinal chemistry. It is commonly found in drugs and in natural products. It is used to improve potency, metabolic stability, brain permeability and binding to the desired active site. [1,2] Due to its common use, a variety of methods to access the cyclopropane scaffold exist. However, ring contractions are an uncommon way to access the cyclopropane scaffold.[3] Using this unusual path, our goal is to develop a method that would allow easy access to a variety of functionalized cyclopropane motifs. Our strategy relies on the extrusion of sulfur dioxide from a 2,3-disubstituted thietane dioxide under photochemical conditions.[4] The corresponding 2,3-disubstituted thietane dioxide can be easily synthesized from the 1,1 thiete dioxide which is commercially available. Various 2,3-disubstituted thietane dioxide can participate in this reaction, yielding a variety of trans-substituted cyclopropane scaffolds allowing for their use as building block.

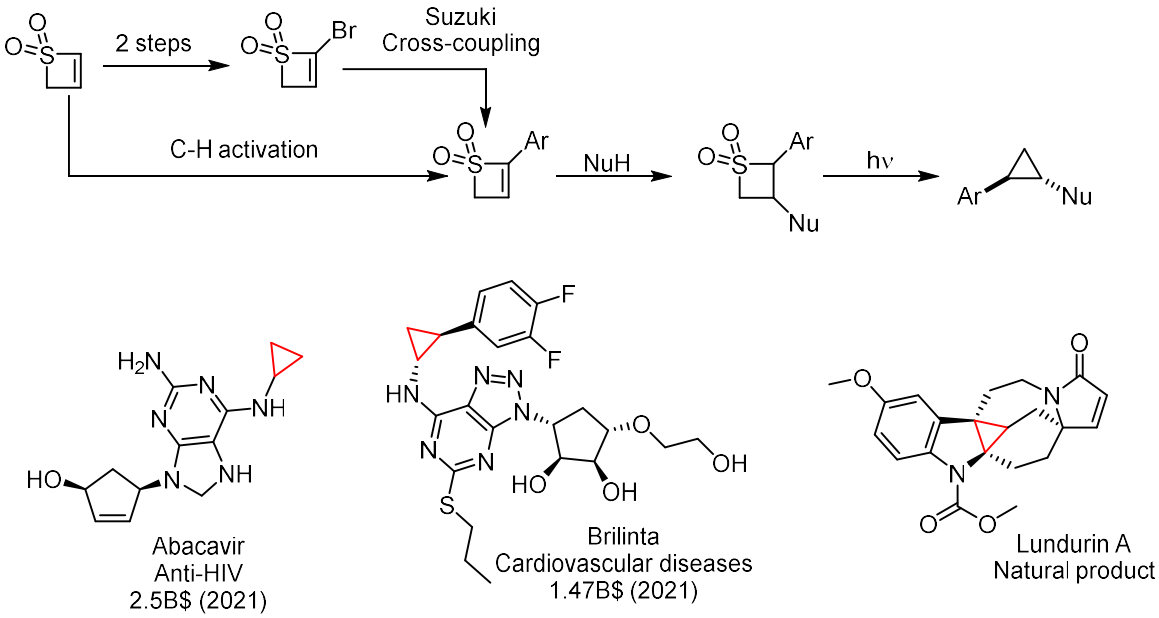


Figure 1. Photochemical synthesis of cyclopropanes from 1,1 thietane dioxide.

1- McGrath, N. A.; Brichacek, M.; Njardarson, J. T. J. Chem. Ed. 2010, 87, 1348.
2- Talele, T. T.. Am. Chem. Soc. 2016, 138, 8328-8348. DOI: 10.1021/jacs.6b03852
3- Ebner, C.; Carreira, E. M. Chem. Rev. 2017, 117, 11, 11651–11679.
4- Durst, T.; Finlay, J. M.; Smith, D. W. J. Am. Chem. Soc. 1973, 95 (3), 849-851. DOI: 10.1021/ja00783a045.

Alkylidene Dihydropyridines as Versatile Intermediates for Functionalization of 4-Alkylpyridines

Jiaqi Shi[1], Faizan Rasheed[1], Arturo Orellana[1], Dan Fishlock[2]
[1]*York University, Toronto, Canada*
[2]*F. Hoffmann - La Roche Ltd., Basel, Switzerland*

E-mail: shijiaqi@yorku.ca

With the importance of pyridines in drug discovery [1], it becomes of great interest to develop new methods that facilitate their synthesis which will likely bring significant impact on drug development process. There is also a demand for mild functionalization to accomplish functional group tolerance as well as selectivity. Our group is dedicated to developing mild and selective functionalizations of 4-alkylpyridines. Through a "soft-enolization" approach, 4-alkyl pyridines can be readily converted to corresponding alkylidene dihydropyridines (Figure 1), enabling various chemical transformations under mild conditions. Here we first describe the addition of alkylidene dihydropyridine to activated *α,β*-unsaturated ketones and as well as pyridine hydrochlorides. We then introduce the reaction between alkylidene dihydropyridines and Selectfluor® to achieve mild and selective fluorination of 4-alkylpyridines. Finally, we will present a simple and practical method to perform oxidation of 4-alkylpyridines to generate their corresponding ketones.

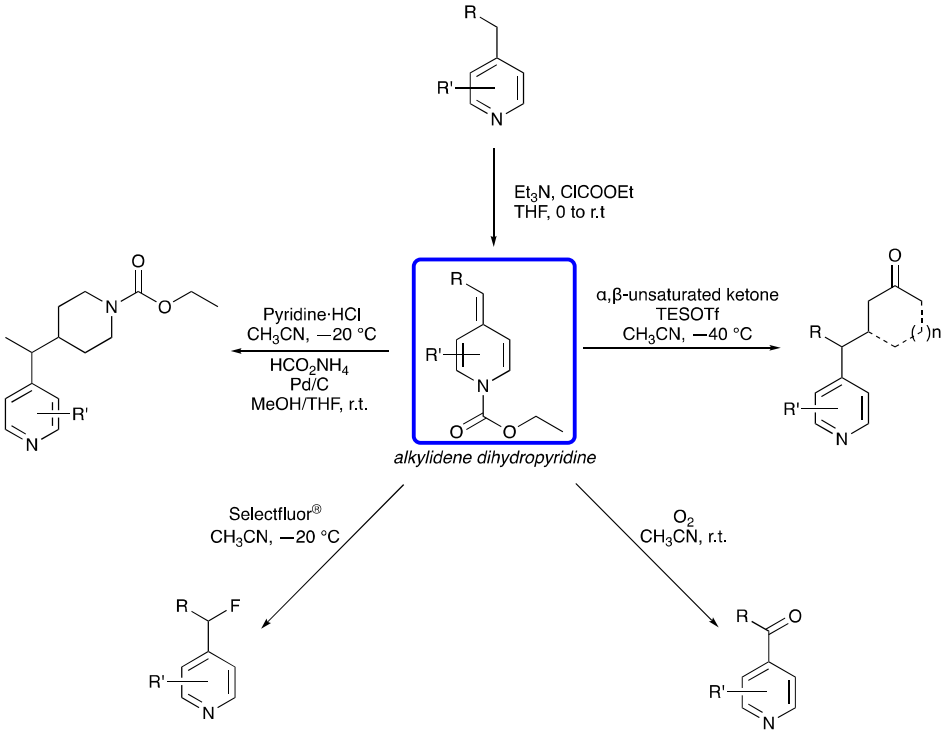


Figure 1: Alkylidene dihydropyridines as intermediates for functionalizing 4-alkylpyridines

References

1. Njardason, J. T.; Vitaku, E.; Smith, D. T., *J. Med. Chem.*, **2014**, *57*, 10257-10274.

Title: Synthesis and Antiviral Activity of Fucose-Containing Saponins

Presenter: Sheida Moghadasi[1]
Supervisor: Charles Gauthier[1]*

[1]*Unité mixte de recherche (UMR) INRS-UQAC, Centre Armand-Frappier Santé Biotechnologie, Institut national de la recherche scientifique, 555, boulevard de l'Université, Chicoutimi, Québec, Canada, G7H 2B1*

Poster abstract: In the current era, viruses have emerged as a paramount subject. Upon infecting host cells, viruses compel rapid reproduction, leading to human illnesses. To address this issue, we aim to develop novel antiviral agents through the synthesis of a library of fucose-containing saponins bearing triterpenoid moieties as non-toxic and readily available naturally-occurring aglycons, which possess intrinsic biological activities. We envision that these chimeric compounds could act as potential entry inhibitors of several viruses, including coronaviruses, dengue virus, human immunodeficiency virus-1 (HIV-1), herpes simplex virus (HSV-1), and Ebola virus by interacting with the dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) receptor found on the surface of dendritic cells, which is one of the main entry accesses for these viruses.

We have planned that the saponins could be synthesized through glycosylation reactions between a library of triterpenoid acceptors (*i.e.*, betulin, betulinic acid, and echinocystic acid) and a thiofucoside donor, either at position C-3 or C-28. By using the promoter system $CuBr_2/Bu_4NBr$, we have envisioned that these glycosylations could be performed with full 1,2-*trans*-*α* stereoselectivity. Moreover, it is worth noting that L-fucose was chosen as the glycosidic moiety because it is known to play a pivotal role in the activation of DC-SIGN receptors *in vivo*. This donor was synthesized through a four-step sequence involving (1) acetylation; (2) anomeric thiolation; (3) Zemplén deacetylation; and (4) *para*-methoxybenzylation of positions C2, C3, and C4. The resulting thiofucosyl donor, accessed in an overall yield of 42%, was then employed for the glycosylation of betulin, yielding a fully protected saponin intermediate with complete α-stereoselectivity. Based on the success of this coupling, we plan on capitalizing on this same strategy to access a library of saponins by using various triterpenoid acceptors, including 28-acetoxybetulin, 3-acetoxybetulin, allyl betulinate, and allyl echinocystinate. After completing these syntheses, our future work will involve investigating the potential of these compounds as primary entry inhibitors against a range of viruses, including coronaviruses, Dengue virus, HIV-1, HSV-1, and Ebola virus. We will assess their antiviral activity against OC43 (a coronavirus) and HSV-1, conduct *in vitro* anti-HIV-1 assays, evaluate cytotoxicity on human normal skin fibroblasts (WS1), and perform a hemolytic assay on sheep red blood cells. Ultimately, we envision that this project could give access to a new class of antiviral agents to prevent infections caused by DC-SIGN-interacting viruses. The project will also provide new fundamental insights into how the sugar moieties affect the capacity of saponins to self-assemble and how these synthetic structures could be used to probe and block the interaction of microbial pathogens with DC-SIGN.

Title: Synthesis of degradable poly(azomethine)s inspired by nature

Authors: Azalea Uva[1], Angela Lin[1], Helen Tran[1,2]

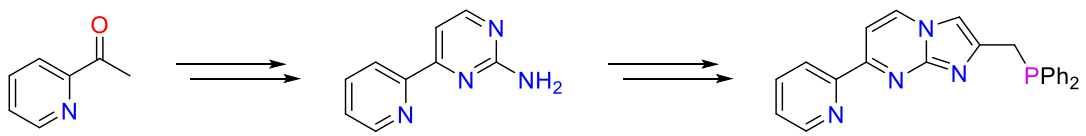
Affiliations:
[1]Department of Chemistry, University of Toronto, 80 St. George Street LM 514, Toronto, ON, M5S 3H6, Canada
[2]Department of Chemical Engineering, University of Toronto, 200 College St, Toronto, Toronto, ON, M5S 3E5, Canada

Biobased compounds, such as carotenoids, vanillin, and eumelanin, are natural candidates to be incorporated into pi-conjugated polymer systems due to their intrinsic aromaticity or conjugation, leading to opportunities to create conductive materials with site-specific degradable linkages. The majority of reported biobased compounds for degradable electronics center on directly using the small molecule or readily available derivatives. Compared to their small molecule counterparts, polymers offer extended conjugation lengths, a variety of molecular architectures, tunable morphologies, and tailored degradation sites. Herein, we present the use of a carotenoid monomer, C10 dialdehyde, in the synthesis of degradable poly(azomethine)s. To impart on-demand acid hydrolysis of this new class of conjugated polymers, imine bonds are introduced into the polymer backbone, leading to depolymerization within minutes. Since carotenoids are capable of degrading via UV oxidation, and enzymatic oxidation, we explored sunlight-mediated oxidation as an alternative degradation strategy. This poster presentation will primarily focus on the synthesis of this new class of polymers, as well as the degradation characterization.

DEVELOPMENTS IN THE SYNTHESIS OF A PYRIDINE-PHOSPHINE BASED HOMOGENEOUS BIMETALLIC LIGAND PPIP

Ryan Scott, Mila Abeava, Derek Schipper*
Department of Chemistry, University of Waterloo, Waterloo, ON N2L 3G1, Canada
*derek.schipper@uwaterloo.ca

Bimetallic catalysis, a key area in coordination chemistry, is primarily led by homobimetallics over heterobimetallics.[1] Heterobimetallic catalysts can outperform monometallic ones in reactivity as they can facilitate unique synergy between metal centers.[1,2] However, the production of unsymmetric bimetallic catalysts, is challenging.[1] Our work addresses this by using the imidazo[1,2-a]pyrimidine ring as an unsymmetrical backbone for our bimetallic ligand, enabling simpler synthesis and stronger binding regions.[3] This asymmetry should allow selective binding to two different metals, with the phosphine arm preferentially binding softer metals like palladium.[4] We report the synthesis of the unsymmetric ligand 2-((diphenylphosphaneyl)methyl)-7-(pyridin-2-yl)imidazo[1,2-a]pyrimidine (**ppip**) using basic straightforward synthetic methods. We developed two synthesis routes for **ppip**: one using a nucleophilic phosphanide and the other an electrophilic chlorophosphine. This research serves to diversify heterobimetallic catalysis by designing a ligand with different binding sites.



ppip

References

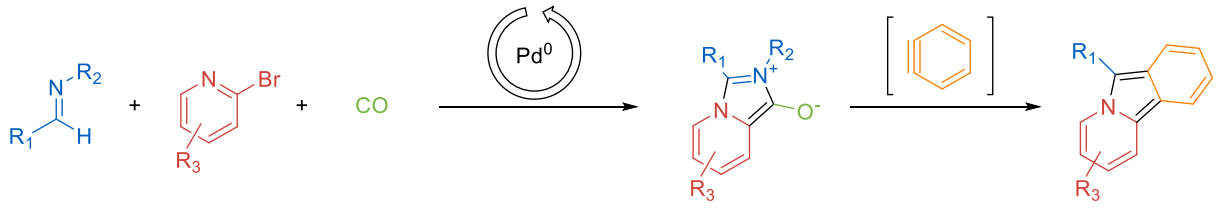
[1] *Accounts of Chemical Research* **2020**, *53* (9), 1944–1956.
[2] *Chemistry – A European Journal* **2018**, *24* (41), 10329–10333.
[3] ChemRxiv Preprint DOI: 10.26434/chemrxiv-2023-rrs7z.
[4] *Organometallics* **1990**, *9* (4), 1206–1210.

Palladium-Catalyzed Carbonylative Synthesis of 1,3-Dipoles Towards Pyrido[2,1-α]Isoindoles

Karina S. Wong[1]; Bruce A. Arndtsen[1*]

[1]McGill University, Montréal, Québec

Chemistry encapsulates all aspects of our society; hence, the development of chemical processes towards greater efficiency is in constant demand. Unlike conventional stepwise synthesis, metal-catalyzed multicomponent reactions (MCRs) involve the combination of three or more starting materials at the same time or subsequently within the same reaction solution to form multiple bonds in one sequence.[1] In addition to addressing several Green Chemistry principles, the employment of multiple starting materials allows for greater structural diversification of complex products, making MCRs highly modular. Described herein is a multicomponent carbonylative route to access pyridine-based 1,3-dipoles that undergo cycloaddition with benzyne towards pyrido[2,1-α]isoindoles. This one-pot, two-step process begins with the formation of the 1,3-dipole from the combination of imines, 2-bromopyridines, and carbon monoxide – all of which are commercially available and/or diversifiable reagents, followed by a 1,3-dipolar cycloaddition with an *in-situ* generated benzyne from *ortho*-silyl aryl triflates.[2,3] Overall, this approach demonstrates a more convergent and modular route toward heterocycles to their conventional stepwise syntheses.



References

(1) Quesnel, J. S.; Arndtsen, B. A. Metal-Catalyzed Multicomponent Reactions. In *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Four Volumes*; Cornils, B., Herrmann, W. A., Beller, M., Paciello, R., Eds.; 2017; pp 1195–1220.

(2) Roy, S. A.; Zgheib, J.; Zhou, C.; Arndtsen, B. A. Palladium Catalyzed Synthesis of Indolizines via the Carbonylative Coupling of Bromopyridines, Imines and Alkynes. *Chem Sci* **2021**, *12* (6), 2251–2256. https://doi.org/10.1039/d0sc03977b.

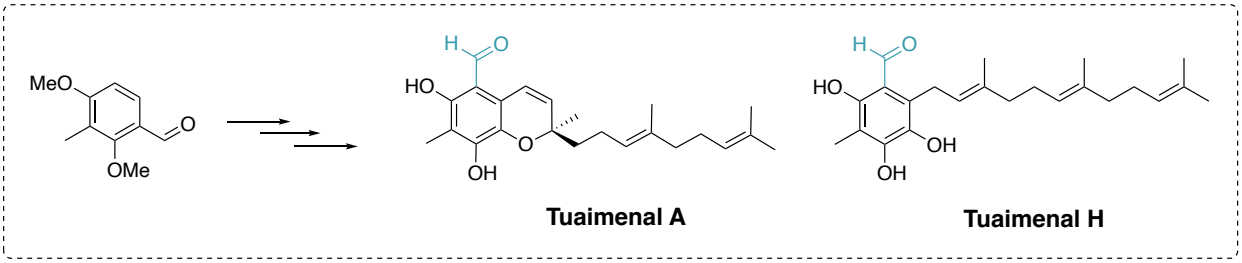
(3) Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-Induced 1,2-Elimination of o-Trimethylsilylphenyl Triflate to Benzyne Under Mild Conditions. *Chem Lett* **1983**, *12* (8), 1211–1214. https://doi.org/10.1246/CL.1983.1211.

Total Syntheses of Tuaimenals A & H

Elizabeth Lach, Mathew Piotrowski, Dr. Jakob Magolan*

Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada

Deep sea sponges remain a rich treasure trove of unique bioactive natural products. Approximately 75% of sponge-derived natural products are bioactive towards human disease targets [1]. Natural products Tuaimenal A and H were isolated from the *Duva florida* sponge in 2022 [1]. Preliminary bioactivity screening showed that both compounds have modest cytotoxicity in cervical cancer cell lines (EC_{50} 46 µM, 23 µM; CaSki) [2]. Cervical cancer is fourth most common cancer affecting women worldwide. Additionally, tuaimenal A is a moderate viral protease inhibitor (EC_{50} 21 µM; SARS-CoV-2 3CLpro) and thus a potential anti-viral lead [1]. A novel methodology from our research group allows selective *ortho*-allylation of phenols with allylic alcohols using alumina. Use of this approach enables access to tuaimenal A and H natural products in an atom-efficient and concise manner. This poster presentation will detail a five- and six-step divergent routes to these natural products.



References:

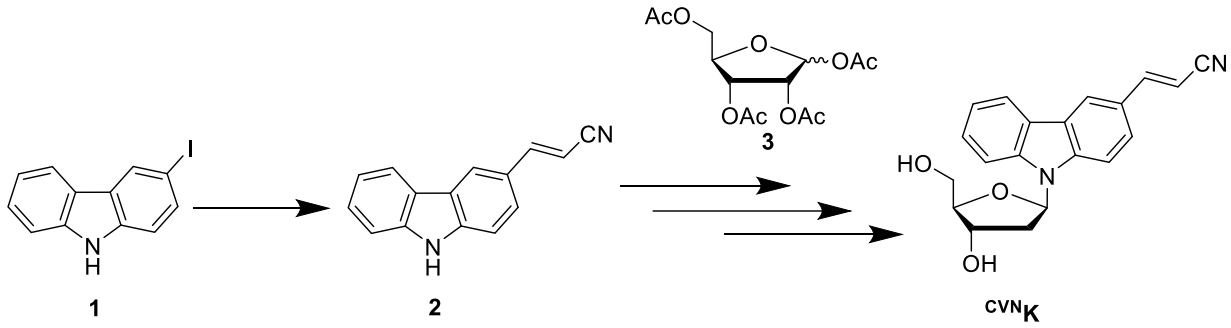
[1] Avalon, N. E.; Nafie, J.; Verissimo, C. M.; Warrensford, L. C.; Dietrick, S. G.; Pittman, A. R.; Young, R. M.; Kearns, F. L.; Smalley, T.; Binning, J. M.; Dalton, J. P.; Johnson, M. P.; Woodcock, H. L.; Allcock, A. L.; Baker, B. J. *J. Nat. Prod.* **2022**, *85*, 1315−1323.
[2] Welsch, J. T.; Smalley, T. B.; Matlack, J. K.; Avalon, N. E.; Binning, J. M.; Johnson, M. P.; Allcock, A. L.; Baker, B. J. *J. Nat. Prod.* **2023**, *86*, 182−190.

Synthesis of a Carbazole Nucleoside for Incorporation into Oligonucleotides to Study of Z-DNA Structures

Matteo Iacucci, Tony Yan

Department of Chemistry, Brock University, hyan@brocku.ca

DNA is known to exist in different forms such as A-, B-, and Z-duplex. Under biological conditions, DNA is found predominantly in the B-form, though it has been shown that DNA can take the Z-form under certain conditions. Although Z-DNA structures have been known for over four decades, the biological roles of this form of DNA remain poorly understood. Among other conditions, torsional stress has been shown to stabilize Z-DNA. This project aims to study Z-DNA structures and their potential roles in the regulation of DNA replication and transcription, where torsional stress is involved. Toward this goal, a modified nucleoside, 3-cyanovinyl-carbazole nucleoside K (^{CVN}K), will be incorporated into oligonucleotides that will allow for the crosslinking of DNA duplexes either in its B- or Z-form. Thus, 3-cyanovinyl-carbazole **2** was obtained from 3-iodocarbazole **1** under Heck conditions. Subsequent reaction of 3-cyanovinyl-carbazole **2** with β-D-ribofuranose-1,2,3,5-tetraacetate **3** followed by deprotection and deoxygenation, led to the formation of ^{CVN}K. This modified nucleoside will be incorporated into oligonucleotides via the phosphoramidite chemistry-based solid phase synthesis.



Scheme 1 Synthesis of ^{CVN}K starting from 3-iodocarbazole **1**

Acknowledgement This work was supported by the Natural Sciences and Engineering Research Council of Canada.

Heteroleptic Copper-Based Complexes for Photocatalytic [2+2] Cycloadditions

Guillaume Roland, Aness Bouchouicha & Shawn K. Collins

Université de Montréal

Abstract :

Small saturated carbocycles and bicycles are now recognized as valuable three-dimensional frameworks often employed as bioisosteres of aromatic rings to improve biological activities, physicochemical properties and metabolic profiles. The inherent strain of such cyclic molecules often requires energy demanding reaction conditions and/or intermediates. Consequently, [2+2] photocycloadditions are privileged transformations that can be enabled via visible-light-mediated photocatalytic energy transfer. Herein, the development of heteroleptic copper complexes of the type Cu(NN)(PP)X is discussed and applied to the synthesis of boro-cyclobutanes and 2-oxabicyclo[2.1.1]hexanes (2-oxa-BCHs). Important structure/activity relationships, including trends in photostability, are elucidated.

C(sp^3)-H Functionalization via Short-Lived Organolithium Species

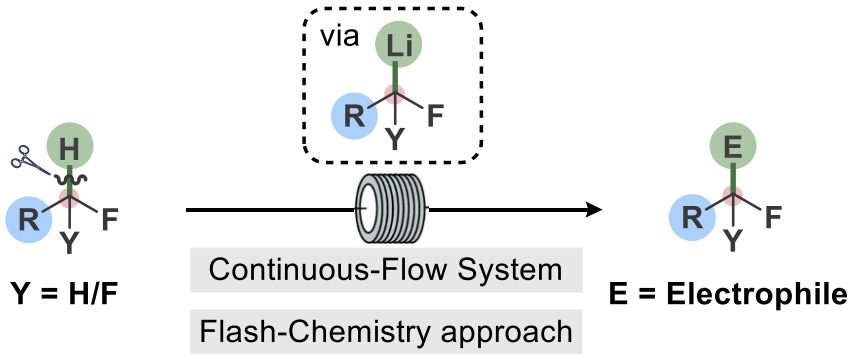
Piyas Saha, Stephen G. Newman*

Department of Chemistry and Biomolecular Sciences, University of Ottawa

....

psaha040@uottawa.ca

Deprotonation of C-H bonds using organolithium superbases is a useful tool for direct C(sp^3)-H functionalization.[1] It becomes challenging if the C-H bond is alpha to halogen atoms due to various associated decomposition pathways.[2–4] In typical batch conditions, deprotonation, and subsequent utilization of the developed organolithium is exceptionally difficult since most of them have a very short lifetime. However, forming such reactive organolithium species and using them before they decompose might be possible with precise control over reaction conditions. Flash chemistry in continuous flow systems can be a great alternative to traditional batch chemistry in this domain. With proper design of reactors, we can achieve residence time in the order of seconds to milliseconds. This current project utilizes a specific flash chemistry approach with very short residence times to tackle various problems related to such short lived organolithium species and achieving direct functionalization of C(sp^3)-H bonds.



1. Freure, G. P. R.; Skrotzki, E. A.; Lavertu, J. D. E.; Newman, S. G. *ACS Catal.* **2021**, *11*, 12258–12263.
2. Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *J. Fluor. Chem.* **1999**, *99*, 127–131.
3. Santos, L.; Panossian, A.; Donnard, M.; Vors, J. P.; Pazenok, S.; Bernier, D.; Leroux, F. R. *Org. Lett.* **2020**, *22*, 8741-8745
4. Lee, H.-J.; Joo, J.-U.; Yim, S.-J.; Kim, D.-P.; Kim, H. *Nat. Commun.* **2023**, *14*, 1231.

Synthesis and evaluation of the anticancer properties of new boro-capsaicinoids.

Antoine Carpentier*†, Luis Misal*, Alexandre Patenaude†, Stéphane Gobeil†, René C.-Gaudreault†, Steve A. Westcott‡, Frédéric-Georges Fontaine*

*Département de Chimie, Université Laval, 1045, av. de la Médecine, Québec, QC G1V 0A6

†Centre de Recherche du CHU de Québec, 2705 Bd Laurier, Québec, QC G1V 4G2

‡Department of Chemistry and Biochemistry, Mount Allison University, 62 York St, Sackville, NB E4L 1G8

Cancer is one of the deadliest diseases in Canada. Studies show that 25% of Canadians are at risk of developing cancer during their lifetime, and that a third of them will die from it. It is of interest to develop new anti-cancer agents that are effective and selective for cancer cells. In this context, the research groups of Prof. Fontaine, C.-Gaudreault and Gobeil have combined their expertise to develop borated capsaicin derivatives with anticancer potential. The aim of this project is to synthesize and evaluate the biological properties of these novel boro-capsaicinoids. Preliminary work on this project has led to the synthesis of 15 capsaicinoids, six of which possess a boron group. The anticancer potential of these compounds was determined based on three biofunctional assays: measurement of antiproliferative activity, cell cycle progression and *In Ovo* antitumor activity. Four capsaicinoids stood out for their antiproliferative activity, inhibiting cell growth at concentrations below 90 µM. Measurement of the cell cycle progression showed that, like capsaicin, capsaicinoids arrest progression in the G0/G1 phase. *In Ovo* results show a low efficacy of the compounds studied. However, this experiment highlighted the possibility of poor distribution of the synthesized compounds in the model due to their high lipophilicity. The first-generation compounds therefore show some anticancer activity. However, it would be possible to optimize their biological and physicochemical properties. A second generation of compounds is currently in preparation.

Rhodium-Catalyzed Ring-Opening Reactions of Heterobicyclic Alkenes with Electron-Rich Heteroarenes

Eric Neufeld, Austin Pounder, Leanne D. Chen, William Tam

Institution:
University of Guelph

Abstract:
We present an experimental and computational investigation into the rhodium-catalyzed ring-opening reactions of heterobicyclic alkenes with heteroarene nucleophiles. The reaction provides a facile route to trans-substituted dihydronaphthalen-1-ol and 1-amino-dihydronaphthalene products in up to a 95% yield as a single diastereomer. This reaction is 100% atom-economic and offers C-C bond formation without prior functionalization of the coupling partners. This Rh-catalyzed reaction demonstrated tolerance for a broad scope of nucleophiles as well as various heterobicyclic alkenes. The mechanism and origins of selectivity were probed with DFT at the MN15/Def2-TZVPP level of theory. Additionally, the reactivity and energetic barriers across diverse heterobicyclic alkenes and heteroarenes were calculated to unveil their relative reactivity.

Asymmetric reduction of prochiral α-CF_3 and α-SF_5 ketones

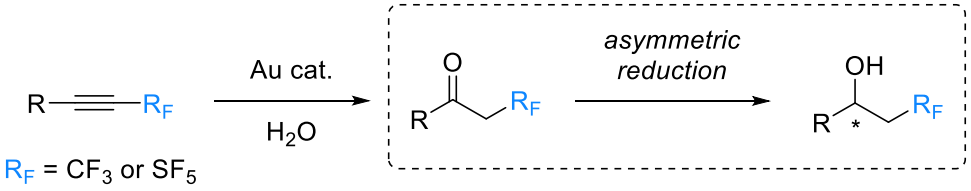
Kelly Burchell-Reyes, Chloé Depoumps, Jean-François Paquin*

CCVC, PROTEO, Département de chimie, Université Laval, 1045 Avenue de la Médicine, Québec, Canada

**e-mail: jean-francois.paquin@chm.ulaval.ca*

A variety of CF_3- and SF_5-containing compounds have found applications in fields ranging from drug development [1, 2, 3] to material sciences [4]. Given the relevance of chirality in bioactive molecules [5], it is topical to study the synthesis towards novel CF_3- and SF_5-motifs.

Our group has previously described a regioselective gold-catalyzed hydration to efficiently obtain α-CF_3 and α-SF_5 ketones from their corresponding alkynes [6]. We are thus developing enantioselective transformations of these prochiral α-CF_3 and α-SF_5 ketones (Scheme 1). We initially focused on asymmetric reductions to obtain β-CF_3 and β-SF_5 alcohols using tailored reaction conditions. This presentation will provide an overview of our initial results.



Scheme 1. Asymmetric reduction of α-CF_3 and α-SF_5 ketones.

References

[1] Sowaileh, M. F.; Hazlitt, R. A.; Colby, D. A. *ChemMedChem*, **2017**, *12*, 1481.

[2] Sani, M.; Zanda, M. *Synthesis* **2022**, *54*, 4184.

[3] Kordzexhadian, R.; Li, B.-Y.; Zogu, A.; Demaerel, J.; De Borggraeve, W. M.; Ismalaj, E. *Chem. Eur. J.* **2022**, *28*, e202201491.

[4] Chan, J. M. W. *J. Mater. Chem. C* **2019**, *7*, 12822.

[5] Calcaterra, A.; D'Acquarica, I. *J. Pharm. Biomed. Anal.* **2018**, *147*, 323.

[6] Cloutier, M.; Roudias, M.; Paquin, J.-F. *Org. Lett*. **2019**, *21*, 3866.

Title:

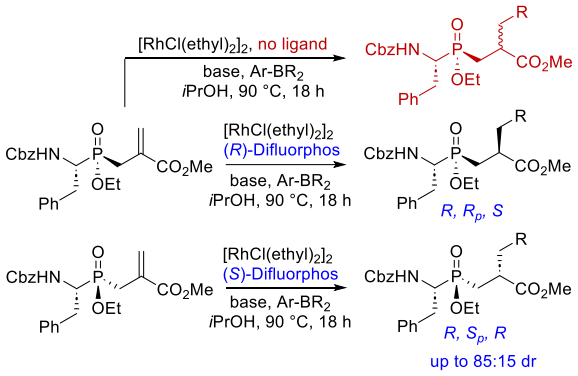
Diastereoselective Synthesis of Phosphinyl Peptides via Rh-catalyzed 1,4-Addition in Co-participation of a P-Chiral Moiety and Difluorphos

Authors:

Taeok Kim,[†] Fuqing Jin,[†] Hatem Titi,[†] and Youla S. Tsantrizos[†‡*]

[†]Department of Chemistry, McGill University, Montreal, Quebec, Canada, H3A 0G8
[‡]Department of Biochemistry, McGill University, Montreal, Quebec, Canada, H3G 0B1

Peptidomimetic compounds containing a phosphinic acid moiety, as a transition state mimic of enzymatic proteolysis, have found useful applications in drug discovery, particularly in the design of inhibitors targeting zinc metalloproteases. The most significant challenge is setting the chirality of the substituent at Cβ to the phosphinic acid moiety. Here, the asymmetric Rh-catalyzed 1,4-addition of various aryl and heteroaryl moieties to α,β-unsaturated esters *via* the co-participation of a P-chiral phosphinyl moiety and (*R*)- or (*S*)-Difluorphos will be described. This methodology expands the synthetic toolbox available for the preparation of structurally diverse and diastereomerically highly enriched phosphinyl peptides having common protecting groups at both the N- and C-terminus.



Borylation sans métal de thiophènes pour des applications électroniques organiques

Audrey Gaudy[a], Vincent Desrosiers[a] et Frédéric-Georges Fontaine[a,*]

[a] *Département de Chimie, Université Laval, 1045 Avenue de la Médecine, Québec, Québec, G1V 0A6, Canada.*

audrey.gaudy.1@ulaval.ca, frederic.fontaine@chm.ulaval.ca*

Les composés organoborés sont des substrats essentiels pour la synthèse de produits électroniques organiques tels que les cellules solaires et les photodétecteurs organiques. Cependant, leur synthèse se fait habituellement à l'aide de métaux de transition comme le palladium ou l'iridium. Malheureusement, ceux-ci comportent plusieurs inconvénients tels que leur toxicité et leur coût élevé. La catalyse sans métal est donc une avenue intéressante pour contrer ces problèmes. De plus, les thiophènes borylés sont des composés fréquemment utilisés pour la synthèse de composés électroniques organiques par couplage de Suzuki. C'est pourquoi, dans cette présentation, une optimisation de la borylation des thiophènes à l'aide d'une paire de Lewis et d'un catalyseur sans métal sera détaillée.

Developing Chemical Probes for Polyurethane Biodegradation

Sheng Li*, Zhenyu Hu, Graeme Howe, David L. Zechel
Department of Chemistry, Queen's University

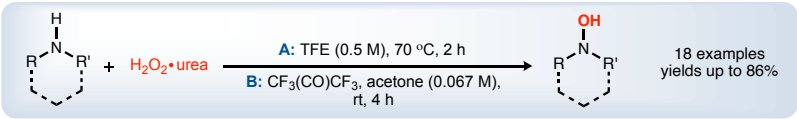
PU is a polymer class derived from the condensation of a polyol (comprised of a polyester or polyether) with an isocyanate. Depending on the composition of the polyol and the isocyanate, PUs can exhibit a wide array of structures and properties that can be used for a variety of applications. Biodegradation is one strategy using enzymes to break down wasted plastics for a sustainable future. However, finding ways to characterize the activities of potential enzyme candidates remains challenging. And we intend to develop chemical probes for the functional screening of PUases.

Our first-generation probe is designed based on 4-methylumbelliferone and has been successfully synthesized. Since the urethane bond contains a chemical structure similar to that of PET, we first tested the probe with a reported enzyme, FAST-PETase, showing the ability of the synthesized probe to detect enzyme activities. Then, kinetic studies of FAST-PETase and an in-house expressed enzyme have been carried out to compare their activity. Next, we did the same screening and kinetic study for one of our in-house expressed enzymes. The result shows the promising application of this probe for screening enzymes that can break down urethane bonds and future work will be testing more enzyme candidates with the probe as well as developing the next-generation probe, which is based on Förster resonance energy transfer (FRET)-quenched substrates.

Oxidative Syntheses of *N,N*-Dialkylhydroxylamines

Daniel Barriault, Meredith Allen, Huy Minh Ly, Monica Gill, André M. Beauchemin*, Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, ON, K1N 6N5, dbarr011@uottawa.ca

Hydroxylamines have broad uses throughout the scientific landscape, being used as amination reagents with metal catalyzed reactions,[1] a *N*-centered radical precursors,[2] and as reagents with alkenes or alkynes via Cope-type hydroamination.[3] However, the widespread use of hydroxylamines is hindered by their inefficient syntheses. Secondary hydroxylamines can be synthesized via various oxidative routes, however, overoxidation and poor chemoselectivity are common issues. Two practical oxidative methods for the synthesis of *N,N*-dialkylhydroxylamines using secondary amines and a urea hydrogen peroxide adduct (UHP) as the oxidant will be presented. Product isolation and purification will also be discussed, and an operationally simple isolation method utilization oxalate salt formation will also be reported (for acyclic substrates)



References:

1. Sabir, S.; Kumar, G.; Jat, J. T. *Org. Biomol. Chem.* **2018**, *16*, 3314.
2. Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. *Chem. Eur. J.* **2018**, *24*, 12154.
3. Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893-17906

Unprotected alcohols as electrophiles in cross-coupling reactions: From high-throughput to Hammett analysis

Adam Cook, Piers St. Onge, Stephen G. Newman*

Centre for Catalysis Research and Innovation, Department of Chemistry and Biomolecular Sciences, University of Ottawa, 10 Marie Curie, Ottawa, Ontario K1N 6N5.

Email: acook093@uottawa.ca

Conventional cross-coupling chemistry utilizes organohalides as electrophilic coupling partners. While reliable, the low natural occurrence of organohalides alongside issues regarding their metabolic and environmental stability has prompted chemists to ask: what is the alternative? Alcohols have emerged as an attractive option due to their natural abundance, synthetic ubiquity, economic availability and generation of water as the only by-product via deoxygenative processes.[1] While strides have been made in the establishment of methods that utilize alcohols in these transformations,[2] strategies that feature *non-activated* alcohols in cross-coupling chemistry remain scarce.

Through hypothesis-driven high-throughput experimentation, our group has disclosed a method that utilizes dual nickel and bismuth catalysis to engage unprotected, non-activated alcohols in arylation reactions.[3] Recent progress has shown that this method can be generalized, enabling access to valuable C(sp^3)-C(sp^2), C(sp^3)-C(sp) and C(sp^3)-N bonds through Suzuki, Sonagashira and *N*-alkylation pathways, respectively. Mechanistic experiments suggest these reactions proceed by a unified Lewis acid-catalyzed C(sp^3)-O bond breaking step to generate a carbocation that is sequestered by a nickel catalyst. A range of kinetic techniques (including visual time normalization, Eyring, Hammett and isotope analyses) have been utilized to generate a mechanistic landscape for this transformation.

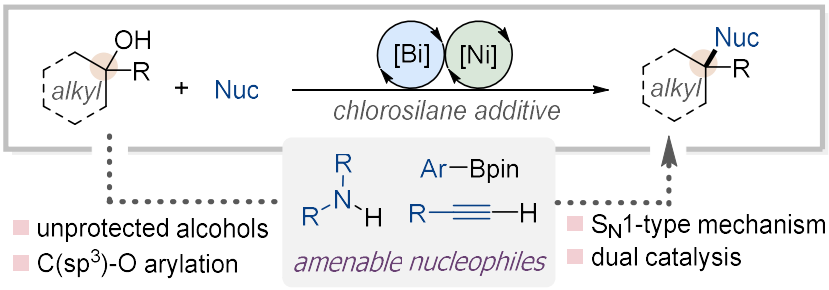


Figure 1. Employing alkyl-hybridized, unprotected alcohols as electrophiles in cross-coupling reactions

References

[1] Yu, D.-G.; Li, B.-J.; Shi, Z.-J. Exploration of New C-O Electrophiles in Cross-Coupling Reactions. *Acc. Chem. Res.* **2010**, *43,* 1486-1495.

[2] (a) Dong, Z.; MacMillan, D. W. C. Metallaphotoredox-Enabled Deoxygenative Arylation of Alcohols. *Nature* **2021**, *598*, 451-456. (b) Suga, T.; Ukaji, Y. Nickel-Catalyzed Cross-Electrophile Coupling between Benzyl Alcohols and Aryl Halides Assisted by Titanium Co-reductant. *Org. Lett.* **2018**, *20*, 7846-7850. (c) Li, Z.; Sun, W.; Wang, X.; Li, L.; Zhang, Y.; Li, C. Electrochemically Enabled, Nickel-Catalyzed Dehydroxylative Cross-Coupling of Alcohols with Aryl Halides. *J. Am. Chem. Soc*. **2021**, *143*, 3535-3543.

[3] Cook, A.; St. Onge, P.; Newman, S. G. Deoxygenative Suzuki-Miyaura Arylation of Tertiary Alcohols. *Nature Synthesis*, **2023**. doi: 10.1038/s44160-023-00275-w

Methylation of Aryl and Heteroaryl Electrophiles via Nickel-Catalyzed Cross-Coupling with Formaldehyde Hydrazone

Daliah Farajat,† Léa Philippe,† Anastasiia Afanasenko,† Durbis J. Castillo-Pazos,† Juan D. Lasso,† Yiram Kim,† Joaquín Barroso-Flores,‡¥ Chao-Jun Li*†

†Department of Chemistry, and FQRNT Centre for Green Chemistry and Catalysis, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A0B8, Canada

‡ Institute of Chemistry, National Autonomous University of Mexico, Ciudad Universitaria, CDMX, México 04510, Mexico

¥ Centro Conjunto de Investigación en Química Sustentable, UAEM-UNAM, Instituto de Química, Universidad Nacional Autónoma de México, Carretera Toluca-Atlacomulco Km 14.5, C. P. 50200 Toluca, Estado de México, Mexico

ABSTRACT: Methyl groups play a vital role in pharmaceutical substrates, where their installation onto aryl and heteroaryl moieties can often lead to enhanced drug-target interactions. This phenomenon has been termed the “magic methyl effect”, and it has become an important tool for the improvement of therapeutic potency during lead optimization stages in drug development. In recent years, the use of hydrazones as latent carbanions for nucleophilic addition reactions or as coupling partners has shown robust reactivity and has been utilized under mild reaction conditions while extruding inert by-products such as nitrogen gas and water. Herein, a new methodology for the hydrazone-mediated methylation of various phenols as tosylates as well as aryl halides is reported. Substrate methylation was achieved via a Ni-catalyzed cross-coupling by introducing a new bench-stable methylating reagent in the form of formaldehyde hydrazone. The reaction produces moderate to good yields on a structurally diverse set of aryl and heteroaryl electrophiles. Experimental and computational investigations were carried out to support the proposed mechanism for this reaction.

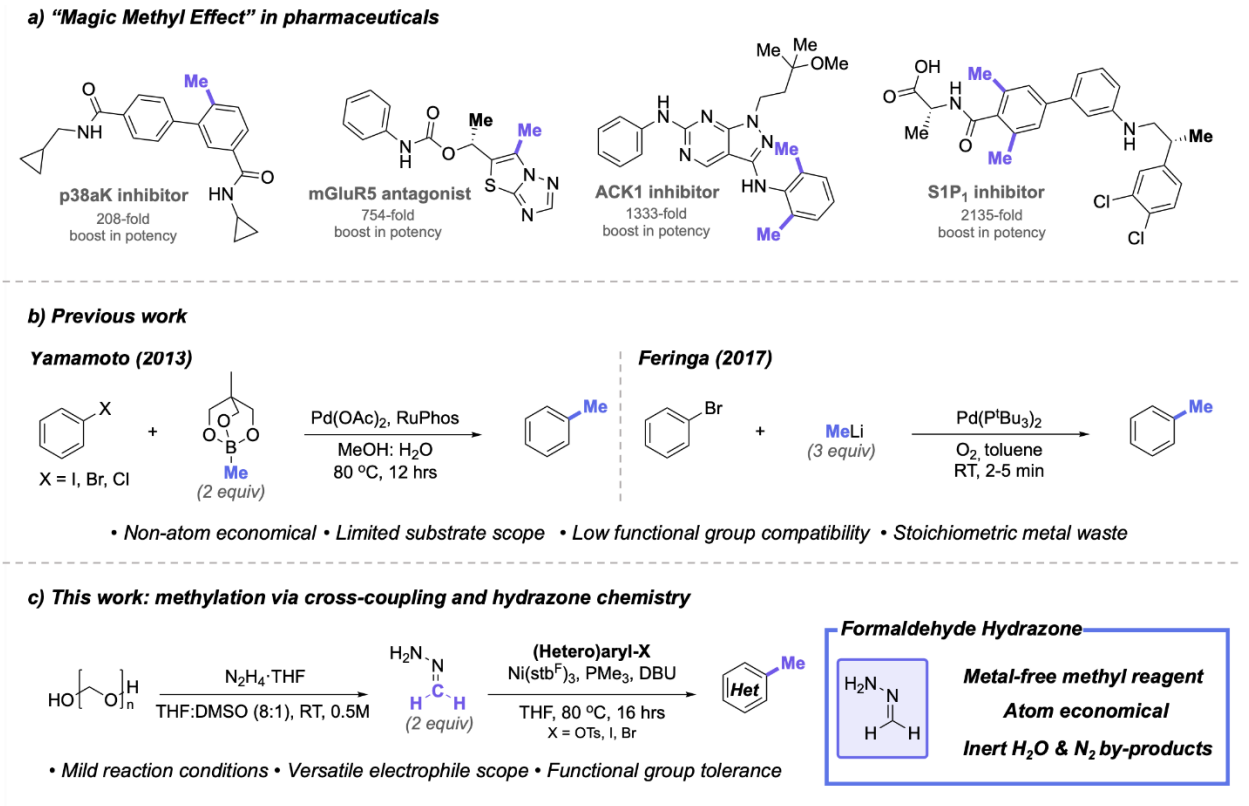


Figure 1. a) Examples of potency boost upon substrate methylation, referred to as “Magic Methyl Effect”, b) Previous work (selected examples) cross-coupling reactions utilizing aryl halides and methyl anion reagents, c) This work: methylation via cross-coupling and hydrazone chemistry involving new synthesis and use of formaldehyde hydrazone as carbanion equivalent.

A New Method for the Synthesis of Betsylated Amino Acids Using Aqueous Buffered Sodium Hypochlorite Solution

Cedric Bertin, Benjamin Chung, and John Mancuso

Peptide Synthesis Platform, NuChem Sciences Inc. (Sygnature Discovery), 201-2350 rue Cohen, Saint-Laurent, QC H4R 2P6

We report a new method for the synthesis of *N*-benzo[*d*]-thiazol-2-sulfonyl (Bts, betsyl)-protected amino acids, yielding building blocks amenable to solid-phase peptide synthesis (SPPS) in one step from their corresponding free amino acids.

The procedure uses sodium benzo[*d*]-thiazol-2-sulfinate (sodium betsylate) and aqueous oxidative conditions in order to generate unstable benzo[d]-thiazol-2-sulfonyl chloride (Bts-Cl) *in situ*. Preliminary analyses and optimization revealed the importance of pH control for sufficient conversion, achieved by using either carbonate or phosphate buffers.

Preparation of a dipeptide using betsylated phenylalanine indicated that epimerization does not occur during the betsylation process. The betsylated amino acid can be cleanly isolated from crude reaction mixtures by acid/base extraction in most cases. This method has enabled the synthesis of a library of betsylated amino acids containing various protected and unprotected side chains.