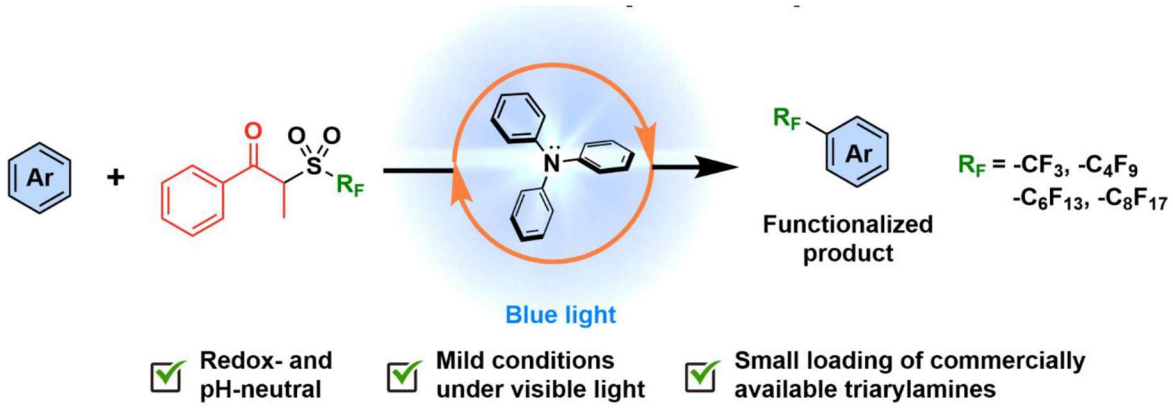
Triarylamines as catalytic donors in electron donor-acceptor complexes

Durbis J. Castillo-Pazos,[‡ab] Juan D. Lasso,[‡ab] Ehsan Hamzehpoor,[‡a] Jorge Ramos-Sánchez,[a] Jan Michael Salgado,[ab] Gonzalo Cosa,[ab] Dmytro F. Perepichka,[a] and Chao-Jun Li*[ab]

a -Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Canada
b -FRQNT Centre for Green Chemistry and Catalysis, McGill University, Montreal, Canada

Recently, photochemistry of Electron Donor-Acceptor (EDA) complexes employing catalytic amounts of electron donors have become of interest as a new methodology in the catalysis field, allowing for decoupling of the electron transfer (ET) from the bond-forming event. However, examples of practical EDA systems in the catalytic regime remain scarce, and their mechanism is not yet well-understood. In this work, we report the discovery of an EDA complex between triarylamines and α-perfluorosulfonylpropiophenone reagents catalyzing C-H perfluoroalkylation of arenes and heteroarenes under visible light irradiation in pH- and redox- neutral conditions. Additionally, we will discuss the elucidation of the mechanism for this reaction through a detailed photophysical characterization of the EDA complex, the resulting triarylamine radical cation, and its turnover event.

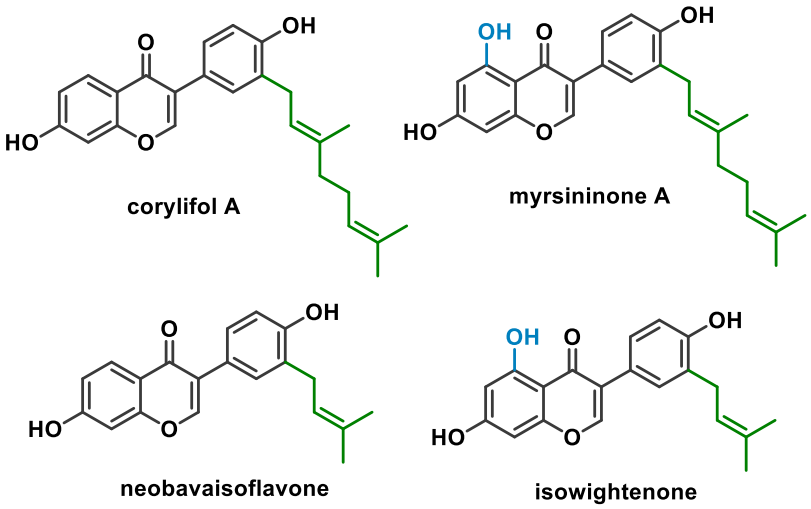


Total Synthesis of Corylifol A and Related Isoflavone Natural Products

Kaitlyn Breault, Lauren Irwin, Jakob Magolan*

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

Prenylated phenols constitute a prominent class of fungi and plant-derived natural product that demonstrate a multitude of biological effects. In general, relative to their corresponding non-prenylated parent compound, phenols with a -prenyl, -geranyl, or -farnesyl substituents tend to show enhanced bioactivities, potentially due improved cell permeation associated with greater lipophilicity. Four structurally related prenylated phenolic natural products: corylifol A, neobavaisoflavone, myrisininone A, and isowightenone are isolated from distinct fungal or plant species and associated with diverse biological profiles. Here we use these structurally related natural products as synthetic targets to showcase a new synthetic methodology for regioselective *ortho*-allylation of phenols mediated by acidic alumina. Our general approach to these compounds involves alumina-mediated prenylation phenolic boronic acids followed by Suzuki cross-coupling.



Chemoenzymatic Synthesis of Macrocycles via Dynamic Kinetic Resolution.

Javier Guerrero-Morales, Marie Scaglia, Edouard Fauran, Guillaume Lepage and Shawn K. Collins*

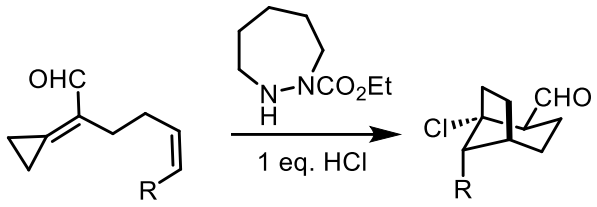
Département de Chimie, Centre for Green Chemistry and Catalysis, Université de Montréal, 1375 Avenue Thérèse-Lavoie-Roux, Montréal, QC H2V 0B3 CANADA

Abstract: Macrolactones are an important class of macrocycles with applications in pharmaceuticals, aromachemicals, agrochemicals and material science. As such, there is a need for methods that form macrolactones employing green chemistry principles that prioritize catalysis and high levels of selectivity. In the context of asymmetric synthesis, it is surprising that dynamic kinetic resolution has never been exploited as a technique for macrocyclization. The development of a macrocyclic dynamic kinetic resolution of racemic seco-acids to afford enantioenriched macrolactones using a combination of transition metal and enzymatic catalysis will be presented. An optimized protocol afforded twelve macrocycles ranging from 14-18 membered rings in excellent enantioselectivities (98-99% *ee*) for the *R* enantiomer confirmed by chemical and computational analysis. Yields of the macrocycles were typically doubled when moving from a kinetic resolution to a dynamic kinetic resolution. A variety of macrolactones were synthesized including aliphatic macrocycles, meta- and paracyclophanes as well as a macrodiolide via a dimerization protocol that was converted to the natural product macrolide (−)-Pyrenophorin.

Novel Rearrangement of Alpha-Cyclopropylidene Aldehydes Enabled by Homoaromaticity

A. Izzotti, J. Gleason
Department of Chemistry, McGill University, 801 Sherbrooke W., Montreal, QC, Canada
E-mail: anthony.izzotti@mail.mcgill.ca

In efforts to develop an enantioselective, iminium catalyzed Cope rearrangement using β-cyclopropenyl enals , a novel rearrangement was discovered. Based on DFT studies (M06-2X/6-311+G(d), level of theory), the reaction *does not* proceed through a cyclohexyl cationic intermediate, but rather a homoaromatic cation enabled by the cyclopropyl moiety. This stabilization facilitates an unprecedented fragmentation of an unactivated cyclopropyl group. This results in a bridgehead cation which cannot be stabilized by the enamine due to ring strain and is thus quenched by the conjugate base of the acid used in the reaction. HCl and TFA are compatible with the reaction transformation leading to [3.2.1] bicycles. The pendant aldehyde and newly installed halide group can be diversified in numerous ways, leading to highly complex polycyclic products. The reaction tolerates both water and air, and numerous functional groups. This rearrangement is *uniquely* enabled by our group's hydrazide carboxylate catalysts, secondary amines were shown to be ineffective. This methodology allows for straightforward synthesis of polycyclic hydrocarbons in very few steps, in decent yield and high diastereoselectivity using organocatalysis.



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.

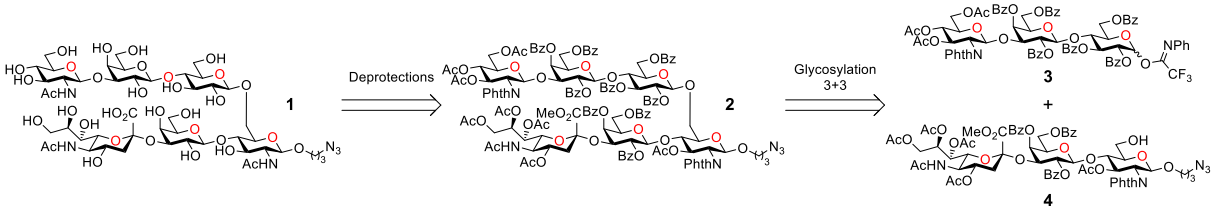


Figure 1. Retrosynthetic analysis of target **1**

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Designing Simulated Cytoplasmic Fluids

Mariam El-Morched, Razvan Simionescu and Tony Yan*
Department of Chemistry, Brock University, St. Catharines, ON; tyan@brocku.ca

The majority of studies performed on the structures and functions of biomolecules are conducted in dilute buffers. Studies carried out under these conditions may lead to results that are different from those found in *in vivo* environments. This is partly attributed to not accounting for a phenomenon known as macromolecular crowding, as the cytoplasm of a cell is a restrictive and crowded environment where 30 to 40 % of the overall volume is occupied by macromolecules. (Mittal, S. *et al.* 2015)

This study aims to design a simulated cytoplasmic fluid which closely mimics the cytoplasmic fluid of *E. coli* DE3 cells. Cytoplasmic fluid was extracted from cells and studied on the basis of their viscosity, specific gravity, diffusion coefficient as well as their T1 and T2 relaxations times of water. A series of artificial molecularly crowded conditions were subsequently examined against these parameters. It was concluded that a mixture of 7.5 % (w/v) sucrose and 19 % (w/v) PEG 10,000 most closely mimicked the extracted cytoplasm with a protein concentration of 100 mg/mL.

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Fluorescent nucleobase analogue *trans*-Stilbene thymine is sensitive to DNA lesions O^6-methylguanine and O^6-methylguanine methyltransferase activity

William Copp,[1] Ashkan Karimi[1] and Nathan W. Luedtke[1]

[1] Department of Chemistry, McGill University, H3A-0B8 Montreal, Canada

Abstract

DNA is susceptible to damage from numerous endogenous and exogenous chemical agents. O^6-methylguanine (MeG) lesions are common, mutagenic and potentially carcinogenic. O^6-methylguanine DNA methyltransferase (MGMT) is a DNA repair protein that restores the integrity of DNA via the direct repair pathway. In contrast, MGMT is implicated in chemotherapeutic resistance and thus monitoring its activity is of utmost importance. Traditional techniques such as qPCR and Western blots suffer from limitations such as being indirect, low sensitivity and lack of real-time measurements thus fluorescent probes have garnered interest. Recently, the Luedtke lab developed a fluorescent nucleobase thymine analogue with a *trans*-Stilbene functional group (^{ts}T) whose molecular rotor properties are exhibited by high brightness when well-matched with adenine, but not when mismatched. In this study we evaluated DNA duplexes containing ^{ts}T probes in strands opposing MeG and observed distance-dependent fluorescence quenching. Furthermore, restoration of ^{ts}T's fluorescence was exhibited after a repair event by MGMT had occurred.

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The showcase of a spectacular reaction cascade : towards the Total Synthesis of (+)-Havellockate

Chad Normandin, Pr. Louis Barriault
cnorm102@uottawa.ca
University of Ottawa

The diterpene marine natural products of the cembranoid and norcembranoid families have been extensively reported through isolation but scarcely synthesized due to their highly complex structures, with only a handful members reported so far.[1] Of this family, Havellockate (**1**) , initially isolated in 1998, possesses an unique and densely decorated [5,5,6,5] core featuring a spirolactone moiety attached to an all-syn fused tricyclic scaffold.[2] To access the tetracyclic core of **1**, we have developed a spectacular reaction cascade initiated from alkyne **2**, which we designed to conveniently possess an electron-poor diene "trap". We exposed the alkyne **2** (synthesized in 8-10 steps) and iodoacrylic acid **3** to standard *Sonogashira* cross-coupling reaction conditions to access the expected coupled adduct. However, under these reaction conditions, the carboxylic acid adduct isn't isolated, but further reacts *in situ,* through a Pd-catalyzed *5-Exo-Dig* cyclisation, to afford an exomethylenelactone moiety. The substrate now becomes primed to undergo an inverse-demand *Diels-Alder* cycloaddition with the aforemented diene to afford the tetracyclic intermediate **4** in a highly diastereospecific manner and high yield.

We are now working the advanced compound **4** through a last handful of transformations in order to complete our enantioselective synthesis of (+)-Havellockate**.** This would also be, to our knowledge, the first reported application of an intramolecular lactonization / cycloaddition sequence to access spirolactone-containing cyclohexenes. We plan to further exploit this reaction cascade towards the synthesis of numerous other norcembranoid natural products.

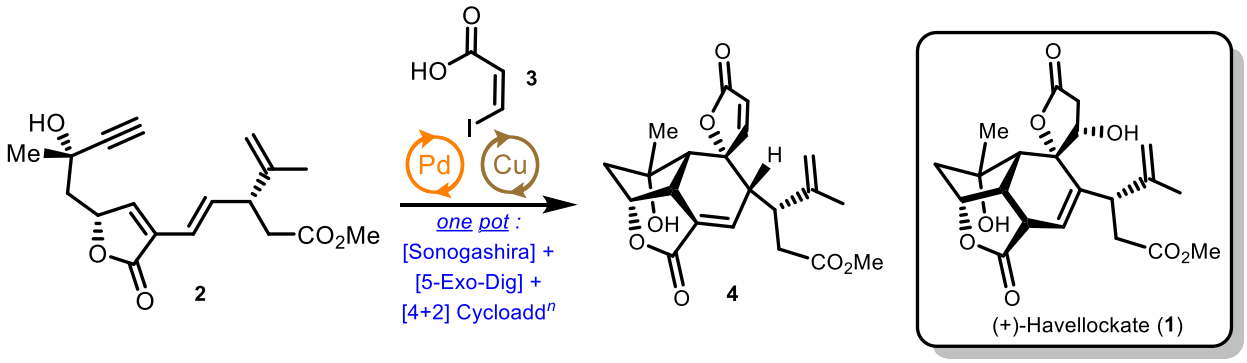

***Figure 1** : Reaction cascade yielding the tetracyclic core of Havellockate*

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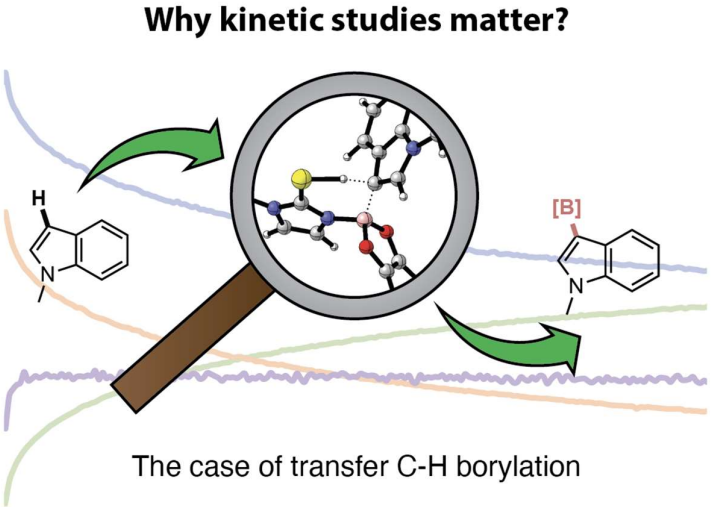
Title: Transfer C-H borylation under investigation: why kinetic studies matter

Authorship : Vincent Desrosiers[a]*, Andres-Garcia Domingez[b], Guy Lloyd-Jones[b], Frédéric-Georges Fontaine[a]
** Presenter*

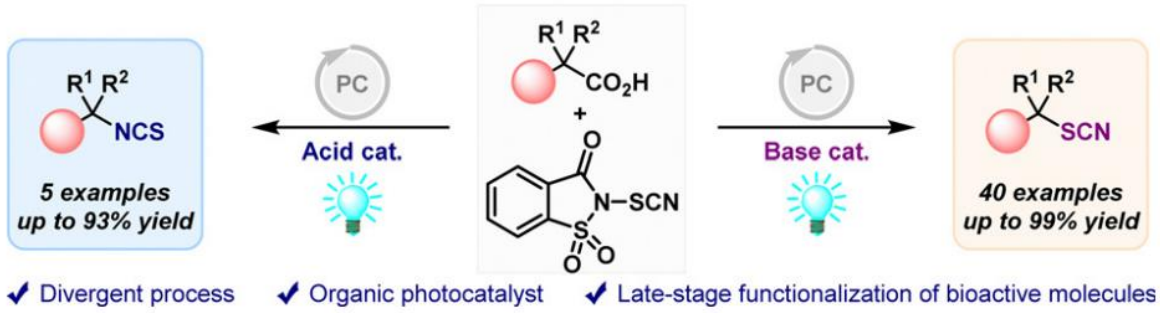
Affiliations : [a] *Département de Chimie, Université Laval, 1045 Avenue de la Médecine, Quebec City, Quebec, G1V 0A6, Canada.*
[b] *School of Chemistry, University of Edinburgh, David Brewster Rd, Edinburgh EH9 3FJ, United Kingdom*

Abstract: Kinetic studies are an essential tool for mechanistic understanding. However, they are often overlooked as too tedious and time-consuming. However, when it comes to catalysis, kinetic investigation is the best way to uncover the problems specific to a given system, such as catalyst deactivation, or product inhibition. This presentation is a case study that highlights very well the importance of kinetics. The present case is that of transfer C-H borylation, a Lewis pair catalyzed transformation that can transfer a boron group from one molecule to another using no transition metal. Importantly, this transfer process uses stable and commercially available arylboronates as boron sources. Replacing conventional borylation agents like hydroboranes (B-H) or haloboranes (B-X) with arylboronates (B-C) means that the approach is suitable to borylate sensitive substrates such as alkynes and alkenes. However, lacklustre catalytic performance plagued this system and there was no clear explanation for this poor performance. In this presentation, we tell the story of how we diagnosed transfer C-H borylation using reaction monitoring and kinetic experiments. These studies have led to substantial improvements in catalytic performance and provided a better understanding of the C-H borylation processes and should hopefully demonstrate the relevance of kinetics studies for catalysis.



The case of transfer C-H borylation

Divergent process for the catalytic decarboxylative thiocyanation and isothiocyanation of alkyl carboxylic acids promoted by visible light



Organothiocyanate compounds are key intermediates that provide access to a wide variety of sulfur-containing molecules, and for this reason the search for new methods to access organothiocyanate compounds has received a great deal of attention. Although a number of C-H bond functionalization methods have recently emerged, their applications remain limited due to the number of substrates available. In this context, the use of carboxylic acids as starting substrates is an interesting approach due to the wide availability of these substrates. Herein, we report an unprecedented transition metal-free photoinduced process for the divergent and selective synthesis of thiocyanate or isothiocyanate molecules from a variety of primary, secondary, and tertiary alkylcarboxylic acids. Key features of the methods are a simple and metal-free catalytic system, the use of an organic photocatalyst, no pre-activation steps for the carboxylic acids, complete selectivity toward the formation of the SCN or NCS-containing molecules, and a versatile process that can be efficiently applied to carboxylic acids as well as phenoxy and thiophenoxyacetic acids. Several bioactive drug derivatives were efficiently obtained using this molecular editing strategy. Mechanistic studies were performed and a plausible mechanism based on a photoinduced radical chain process was proposed for this transformation. This methodology represents a sustainable and efficient strategy that makes the best use of highly available raw materials, is carried out under mild reaction conditions, and does not use transition metals. It allows the synthesis of more complex molecules while responding to contemporary societal concerns.

Synthesis of a novel class of nucleoside analogues bearing a C2' stereogenic all-carbon quaternary center with therapeutic potential

Carla Eymard[1,2], Amarender Machoju[1], Abir Almazloum[3], Hiba Komati[3], Mona Nemer[3], Starr Dostie[1], Michel Prévost[1], Yvan Guindon[1,2,3]

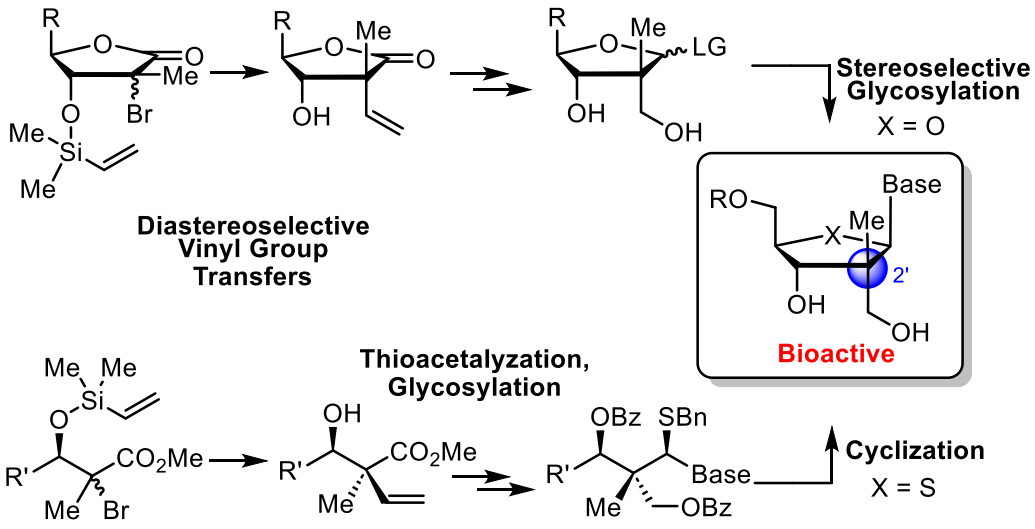
[1] *Bio-Organic Chemistry Laboratory, Institut de Recherches Cliniques de Montréal (IRCM)*

[2] *Department of Chemistry, Université de Montréal*

[3] *Department of Biochemistry, Microbiology, and Immunology, University of Ottawa*

Novel bioactive molecules consisting of a nucleoside analogue bearing an all-carbon quaternary center at C2' have recently been designed and synthesized by our group. Formation of these novel molecules required the development of acyclic diastereoselective photoredox catalyzed group transfer to construct their all-carbon stereogenic centers[1]. Additionally, new *N*-glycosylations reactions were developed, in particular for the formation of thiofuranoside analogues, a series of molecules which represents a major synthetic challenge.

These novel nucleoside analogues have interesting activities against a platform of biological targets including viruses, cancer, and cardiovascular disease. We have recently demonstrated that compounds of this family inhibit SARS-CoV-2 RNA-dependent RNA polymerase[2] while others have shown potential to rescue cardiomyocytes damaged by commonly used chemotherapeutic drugs.



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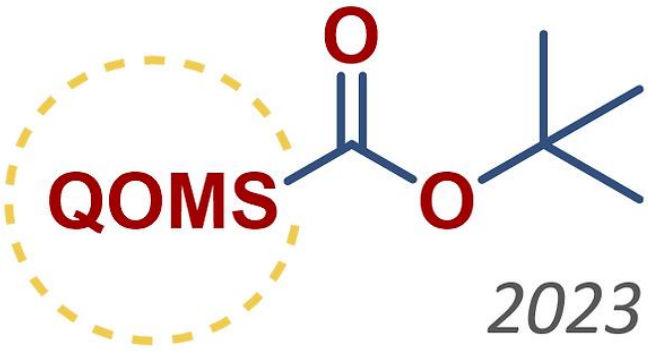


November 10 to 12, 2023

Name: Hoang-Minh To

University (or other affiliation): Université Laval

Research Group (i.e. name of PI): Professor Thierry Ollevier

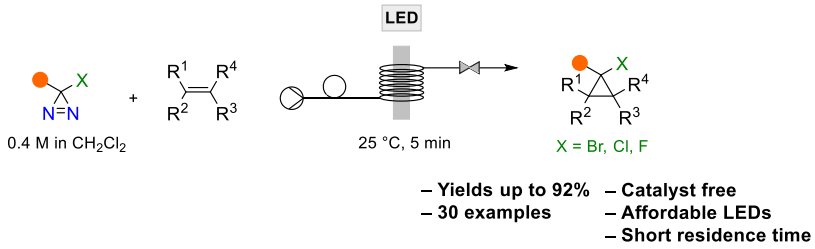
I am: MSc Graduate Student (specify number of years in program: 2)

Ref #
(to be added)

Cyclopropanation of Alkenes with Halodiazirines as Halocarbenes Precursors in Continuous Flow

Hoang-Minh To and Thierry Ollevier*
Département de chimie, Université Laval, 1045 avenue de la Médecine, Québec (Québec), G1V 0A6. E-mail: thierry.ollevier@chm.ulaval.ca

Continuous flow chemistry has been regarded as a tool that enables a safer and more economical approach than traditional batch chemistry which is being widely adopted by industry, and it is a valuable method in photochemical carbene chemistry.[1] Diazirines are well known carbene precursors and versatile reagents in organic synthesis.[2] Halodiazirines have been used as promising precursors of halocarbenes.[3] There have been some reports on cyclopropation of halodiazirines,[4] but either the limited scope of substrates or hard conditions are involved. We disclose a new method that allows the access to a wide scope of halocyclopropanes in metal free and mild conditions using flow chemistry. This method should find broad application in the preparation of halocyclopropanes.



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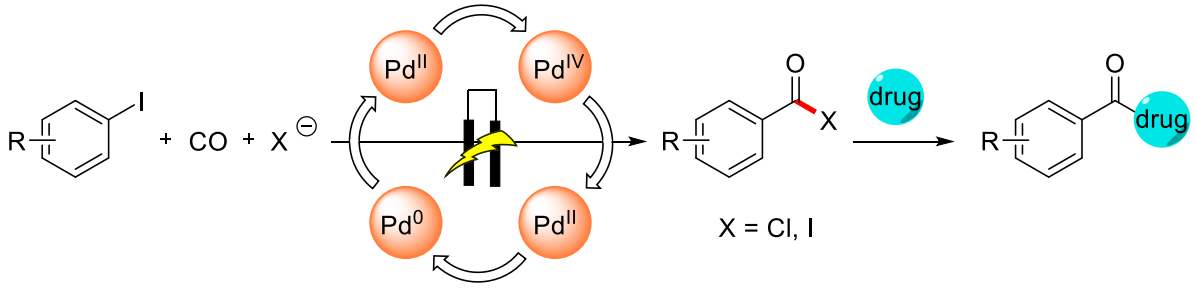
Electrifying Palladium Catalyzed Carbonylations: Reversible Multi-Electron Transfer as a Catalyst Driving Force

K. M. Tam[1], P.-L. Lagueux-Tremblay[1], M. Jiang[1], B. A. Arndtsen[1]*
[1]*McGill University, Montreal, Canada*

kwan.tam@mail.mcgill.ca

Transition metal catalyzed carbonylation reactions have had an enormous impact on modern synthetic chemistry, offering an efficient method to incorporate feedstock CO into molecular scaffolds. However, these methodologies are usually limited to the use of relatively simple or reactive substrates at high temperatures and pressures.[1,2] In addition, the rational design of catalyst is key to balancing distinct operations in the catalytic cycle, namely oxidative addition and reductive elimination. As mechanistic reverse of each other, catalyst features favoring one step inevitably hamper the other. In principle, changes to the oxidation state of a metal center throughout a catalytic cycle could allow each step to proceed in a favorable manner. We describe herein our studies towards such a system, exploiting the use of electrochemistry to energize redox neutral palladium catalysis. Applications of this methodology enable the first catalytic synthesis of high energy aroyl halide electrophiles at simply ambient temperature and pressure, uncovering unique reactivities of acid iodides for the late-stage derivatization of pharmaceutically relevant molecules.



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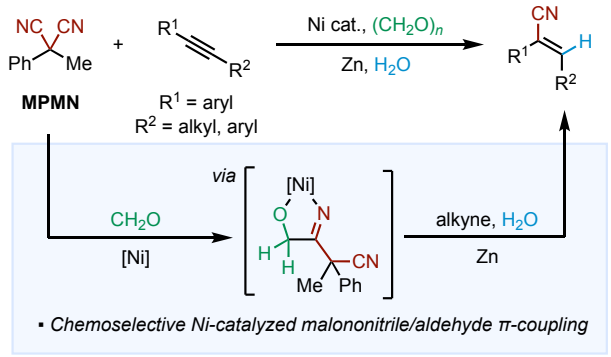
Nickel-Catalyzed Reductive Hydrocyanation of Alkynes Enabled by Malononitrile and a Formaldehyde Additive

Benjamin S. Y. Chiu‡, Anthony F. Palermo‡, Purvish Patel, and Sophie A. L. Rousseaux*

Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6

Ni-catalyzed reductive couplings of π-type electrophiles are efficient methods to synthesize complex molecular structures.[1,2] The alkyne group is commonly used as a π-electrophile for couplings with nitriles or aldehydes, generating functionalized products such as substituted pyridines or allylic alcohols.[3,4] These couplings typically proceed via mechanisms involving an oxidative cyclization between alkyne and either nitrile *or* aldehyde catalyzed by a low-valent Ni species.[5,6] However, selective Ni-catalyzed couplings between nitriles and aldehydes have not been reported. Herein, we present our recent discovery of a Ni-catalyzed reductive coupling between 2-methyl-2-phenyl-malononitrile (MPMN) and formaldehyde, which enabled the development of a Ni-catalyzed reductive alkyne hydrocyanation methodology to access alkenyl nitrile products.[7] This work demonstrates a novel mode of reactivity for malononitriles, which is distinct from prior reports by our group using MPMN as an electrophilic CN source for Ni-catalyzed aryl halide cyanation.[8] The discovery of the effect of formaldehyde and mechanistic studies to probe its role in enabling hydrocyanation will be discussed, as well as further applications of Ni-catalyzed nitrile/aldehyde reductive couplings.



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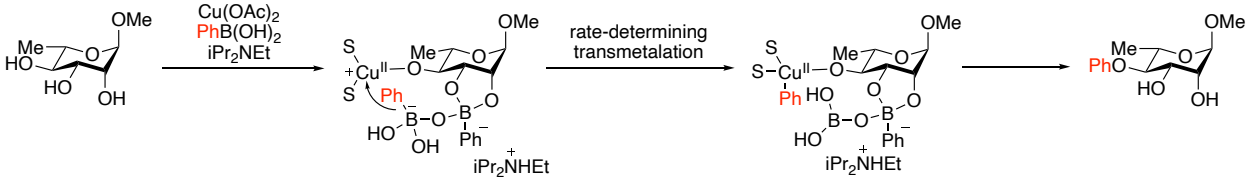
Mechanistic Investigation of Site-Selective *O*-Arylation of Carbohydrates and Application of Results to Other Cross-Couplings

Sofia Jdanova, Robin Groeters, Mark S. Taylor*

University of Toronto

Carbohydrates are one of the most abundant classes of natural products that are involved in a wide array of biological functions. Site-selective functionalizations of carbohydrates provide access to a variety of unique compounds that can be useful in drug development, chiral ligand design, and glycobiology studies. A common challenge in the synthesis of carbohydrate derivatives is the selectivity of functionalizing hydroxy groups with minimal protecting group manipulations. In 2017, our group has published on a methodology to site-selectively O-arylate carbohydrates using copper catalysis, via a boronic ester intermediate.[1] This is a unique transformation since site-selective O-arylation is difficult to achieve, but it would be interesting to understand the mechanism of this reaction in order to use this information to improve methodologies of other similar reactions. In my presentation, I will be discussing kinetic and spectroscopic studies done in order to gain insight into the mechanism of the Cu-catalyzed arylation of carbohydrates.[2] Our studies show that the likely mechanism of the reaction involves an intermolecular coupling between the boronic ester derivative of the carbohydrate and the Cu-aryl intermediate, with the rate-determining step being the transmetalation reaction to form the Cu-aryl intermediate. Substituent effects have also been studied, where we found that electron-rich substituents on the arylboronic acid couple more favourably than electron-poor boronic acids. We have found that forming the boronic ester intermediate with the carbohydrate helps facilitate the rate-determining transmetalation, and in the last part of my talk, I will be discussing how this effect can help improve other cross-coupling methodologies with rate-determining transmetalation.



How can we use these results to improve efficiency in other systems?

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QOMSBOC 2023

TOWARDS MOLECULAR MATERIALS DERIVED FROM BENZENETETRAMINE

Sosoe, Johann O. E.; Malveau, C.; Maris, T.; Iftimie, R.; Wuest, J. D.
Université de Montréal

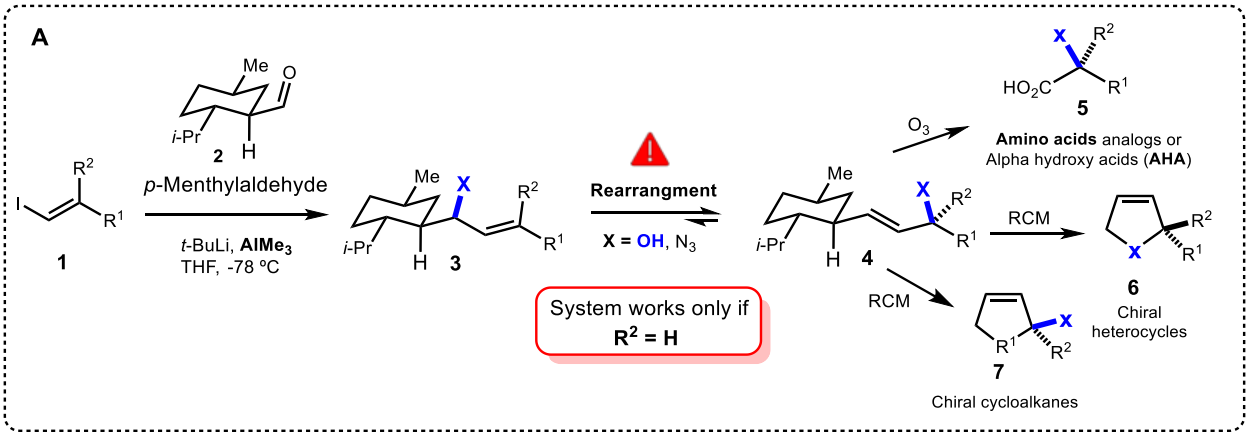
People have never been able to travel and communicate as swiftly and extensively as they do now. Modern transportation and telecommunication democratize these capabilities, but they also cause depletion of natural resources, giving rise to global environmental and socio-economic concerns. Some of these challenges can be addressed by designing new sustainable electronic materials. To make these materials by design, strategies for controlled bottom-up construction are desirable. Molecular moieties such as benzenetetramine (BTA) and its derivatives represent an attractive class of starting materials for predictable construction. Indeed, such motifs can take part in defined supramolecular interactions, as well as in reversible redox processes. Despite the structural simplicity of BTA derivatives, their reactivity and organization in the solid state are little studied. We show how a deeper understanding of these aspects was achieved by using a combination of improved methods of synthesis, computation, spectroscopic studies, and structural analyses. Such new knowledge is expected to accelerate exploitation of the compounds in areas of materials science where desirable properties can only be attained by properly controlling the organization of molecular components.

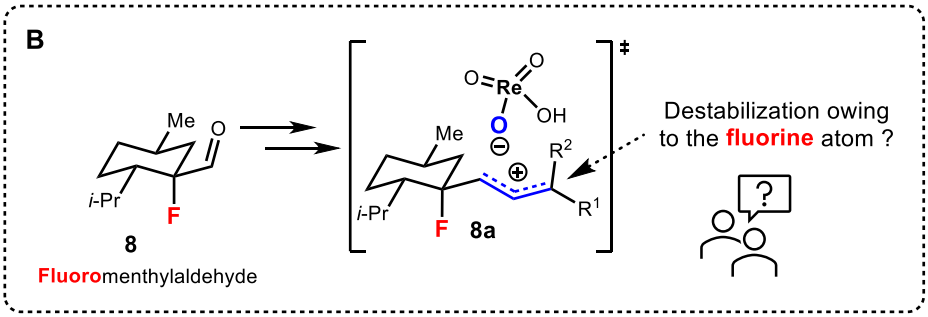
Keywords
supramolecular chemistry; organic materials; redox compounds; crystal engineering

Novel Fluorinated Chiral Auxiliary for the Synthesis of Stereogenic Tertiary Alcohols

Roxanne Lessard, Edouard Caron-Duval, and Claude Spino. Faculty of Sciences, Department of Chemistry, Université de Sherbrooke. Roxanne.Lessard2@usherbrooke.ca
www.linkedin.com/in/roxanne-lessard

p-Menthylaldehyde, a chiral auxiliary developed by Prof. Spino's group grants access to strategic **chiral** synthons **5**-**7** via stereoselective rhenium(VII) catalyzed transposition of **allylic alcohols** and other rearrangements [1,2] (Scheme **A**). This auxiliary, although very versatile, exhibits certain problems in its use in the laboratory and in the scope of its applications. To provide **stereoselective control**, the method requires the use of pyrophoric and environmentally hazardous trimethylaluminum ($AlMe_3$) [1] (Scheme **A**). Also, the unwanted formation of an allylic carbocation during the 1,3-transposition prevents access to stereogenically pure tertiary alcohols (Scheme **A**).[1,2] This project would correct this situation by adding a **fluorine atom** permanently to the chiral auxiliary **8** (Scheme **B**). The research hypothesis is that this *fluoro*menthylaldehyde would provide increased stereocontrol without the need for $AlMe_3$, while allowing the preparation of stereogenic tertiary alcohols (Scheme **B**). The synthesis of the new fluorinated chiral auxiliary was achieved in good yield, and we are currently testing out our research hypothesis.





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Synthesis of Tertiary Alkyl Fluorides by Hydrofluorination of Alkenes and Deoxyfluorination of Alcohols

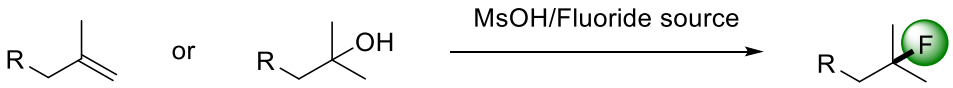
Xavier Bertrand,[1,2] Laurent Chabaud,[2] Jean-François Paquin[1*]

[1] *CGCC, PROTEO, Département de chimie, Université Laval, Québec, Canada, G1V 0A6*
[2] *Institut des Sciences Moléculaires, UMR 5255, CNRS, Université de Bordeaux, 33405 Talence, France*

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

Alkenes being one of the most abundant functional groups, they can be used as interesting building blocks for the synthesis of fluorinated molecules [1]. This talk will present a method for the hydrofluorination of alkenes using cheap, commercially available, and easy-to-handle reagents. The use of a methanesulfonic acid/triethylamine trihydrofluoride combination allows for the synthesis of alkyl fluorides in up to 78% [2]. By changing the fluoride source for another halogen source, hydrochlorination, hydrobromination and hydroiodination could also be performed [3].

The synthesis of fluorinated compound from alcohol is a well-known reaction, commonly done with deoxyfluorination reagents, such as DAST, Deoxofluor, and XtalFluor-E [4]. However, the deoxyfluorination of tertiary alcohols remains a challenge due to the ease of elimination. Inspired by our hydrofluorination method, we developed conditions that allow for the deoxyfluorination of tertiary alcohols without the need for prederivatization. Tertiary alkyl fluorides are obtained in excellent yields, with no elimination observed [5].



Scheme 1. Synthesis of fluorinated compounds from alkenes and alcohols

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Manufacturing Rings: Development of Crown Ethers Using Solid Phase Synthesis

Sarah Nasri,[a] Chitra Bidlon,[a] John F. Trant*[a]

[a] Department of Chemistry and Biochemistry, University of Windsor, Windsor, ON

Since the discovery of crown ethers, these macromolecules have become instrumental for developing supramolecular systems of increasing chemistry, however, the synthesis of crown ethers themselves has remained virtually unchanged -- high dilution and slow addition with the presence of a templating cation. Only a limited selection of common crown ethers can be purchased at a reasonable cost, which leads to limitations in the exploration of their application, especially with larger macrocycles. Synthesis involves large volumes of solvents and requires purification from inevitable polymeric by-products. In addition, the difficulty of the desired macrocyclization increases for larger ring sizes and/or those with asymmetric backbones; the competing oligomerization becomes dominant greatly reducing the yields of the desired material.

We evade this complication by employing a resin solid phase support, which to our knowledge, has not been reported previously. By immobilization, issues of concentration and addition cease to matter as oligomerization is prevented by spatially inhibiting the interaction of the individual molecules.

The team is currently in the middle of optimizing conditions for producing asymmetric Benzo-18C6 crown ethers without the need of chromatography and applying similar conditions to synthesize larger rings cavities.

New Reactions of Masked Isocyanates with Organometallic Reagents

*Alshimaa M.A. Mohamed, Frédéric Vuillermet, Monica Gill, André M. Beauchemin**
amoha342@uottawa.ca
The Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, ON, K1N 6N5

Despite the apparent maturity of the isocyanate industry and ~100,000 publications using isocyanates, heteroatom-substituted, masked (blocked) isocyanates have received little literature attention. Our view is that these reagents hold considerable synthetic potential for the incorporation of the N-NCO and O-NCO motifs in bioactive molecules, taking the advantage of blocking group strategy, which allow a high degree of control over the reactivity.[1] In this context, anticipating Grignard reactivity for carbon-carbon bond formation with the electrophilic carbonyl of *O*- and *N*-substituted masked isocyanates has been explored (Figure 1a). The formation of 5-membered chelate after Grignard addition, is the key difference which distinguishes the reactivity of heteroatom-substituted isocyanates from their C-substituted counterpart. In addition, the reactivity of sp^2 *N*-substituted isocyanates with α-hydrogen toward Grignard was explored, resulting in the formation of 1,2-dihydro-*3H*-pyrazol-3-ones (Figure 1b). Selected optimization efforts, reaction scope and mechanistic insights will be presented.

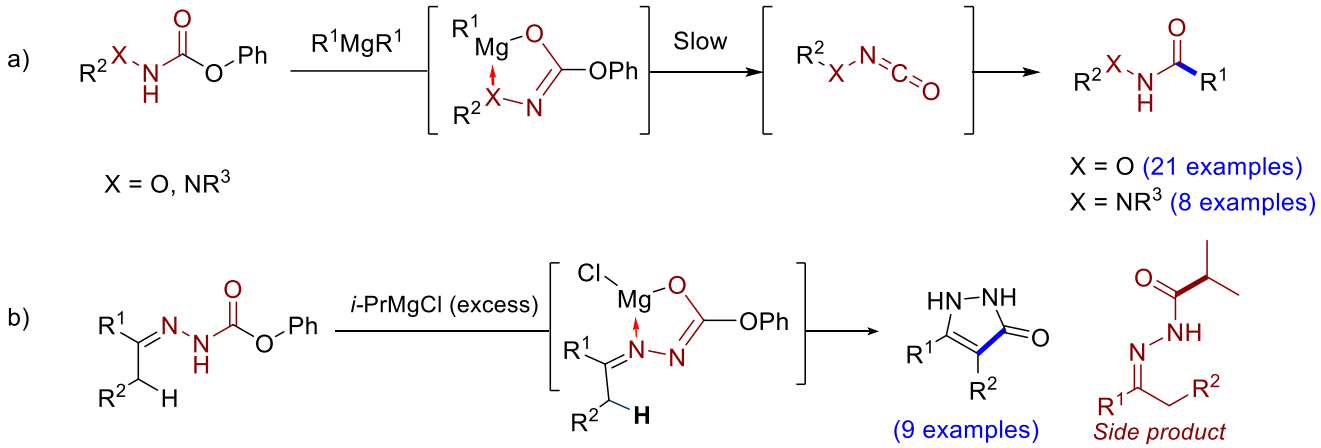

Figure 1. a) Heteroatom-substituted, masked isocyanates and C-C bond formation with Grignard reagents, b) synthesis of pyrazolones by cyclization of *N*-substituted masked isocyanate precursors.

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The Ring of Power: Improving the Pharmacokinetic Properties of TG2 radiotracers through the incorporation of a 64Cu-NODAGA Complex.

Complete authorship & Institutions

Sammir Shad[a], Jens Pietzsch[b,d], Markus Pietsch[c], Reik Löser[b,d], Jeffrey Keillor[a], Robert Wodtke[b,*]

[a] Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, ON K1N 6N5, Canada

[b] Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research, Bautzner Landstraße 400, 01328 Dresden, Germany

[c] Institutes I & II of Pharmacology, Center of Pharmacology, Faculty of Medicine and University Hospital of Cologne, University of Cologne, 50931 Cologne, Germany

[d] Technische Universität Dresden, School of Science, Faculty of Chemistry and Food Chemistry, Mommsenstraße 4, 01069 Dresden, Germany

Abstract:

Tissue transglutaminase (TG2) is a multifunctional enzyme expressed in almost all cell types. Its primary role is crosslinking proteins through the formation of N-ε(ɣ-glutaminyl)lysine bonds using a Cys-His-Asp catalytic triad. The non-regulated crosslinking activity is implicated in celiac disease, liver fibrosis as well as cancer, underscoring the importance of designing imaging probes which target this enzyme. Previously, a 18F-labeled irreversible inhibitor provided quantitative data on the expression profile of transglutaminase 2 in mouse organs and selected tumors for the first time. However, its hydrophobicity resulted in poor pharmacokinetics. In this study, we designed a 64Cu-labeled N-εacryloyllysine piperazide that demonstrated a similar inhibitory potential (kinact/KI = 3563 ± 617 M-1 s -1) and improved pharmacokinetics. This was demonstrated in murine liver microsomes and human plasma, as well as in healthy mice. These advancements in pharmacokinetic stability bring us closer to the use of 64Cu-NODAGA radiotracers for targeting active TG2.

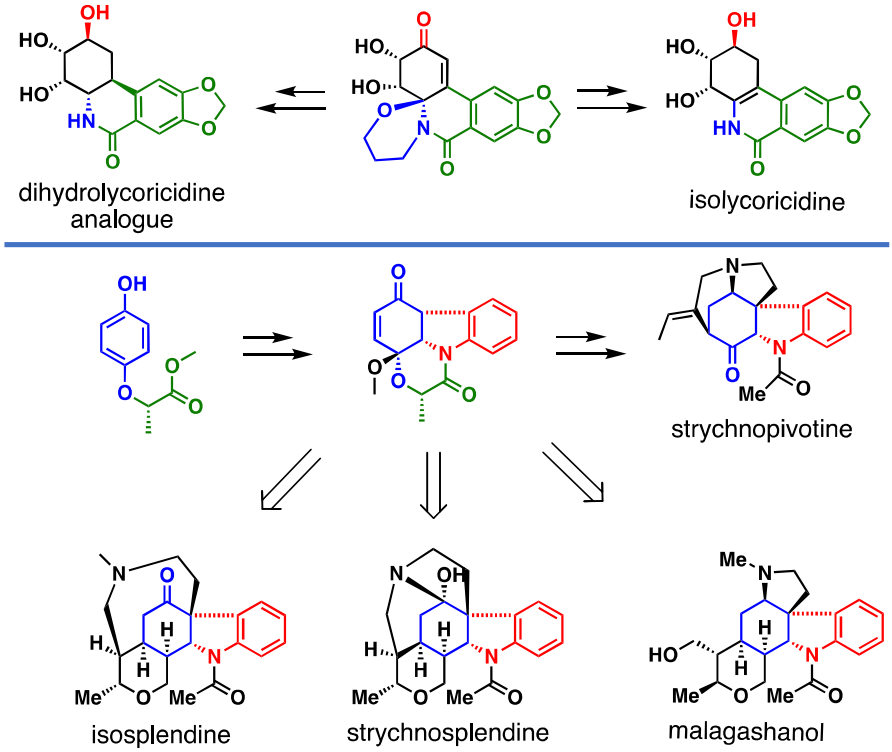
Abstract – Maxime Denis – Oral presentation

Title : Syntheses of challenging bioactive alkaloids from *amarillidaceae* and *strychnos* families

Authorship : Maxime Denis, Samuel Blais, Gaëtan Maertens, Elsa Deruer, Sylvain Canesi*

Insitution : UQAM

A stereoselective synthesis of isolycoricidine, a natural product belonging to the Amaryllidaceae alkaloids family was produced. In addition, a synthetic study on the main core of lycoricidine led to the formation of analogues and a diastereomer of dihydrolycoricidine. Our strategy was based on an oxidative phenol dearomatization, a stereoselective Heck process, a selective dihydroxylation on a dienone system, several stereoselective reductions, and an oxidative retro-Michael procedure as an amine-deprotecting group strategy. Furthermore, two steps highlight the usefulness of hypervalent iodines in total synthesis of natural products. Hypervalent Iodine reagent in tandem with palladium coupling is a strong method also used in the total synthesis of (-)-strychnopivotine and of a common key intermediate of several alkaloids.



Kien TRAN
Postdoctoral Fellow, IRIC, Université de Montréal

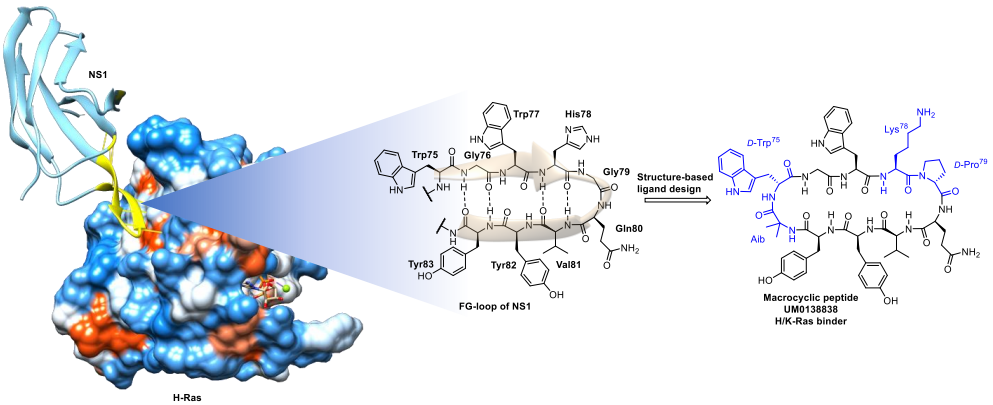
Title: Macrocyclic peptides targeting new binding site of H-Ras and K-Ras

Kien Tran[1], Hugo Lavoie[3], Amal Wahhab[1], Marc-André Poupart[1], Damien Garrido[3], Chang Hwa Jo[3], Tarun Arya[3], Ryan Killoran[3], Cédric Dicaire-Leduc[1], Faraz Shaikh[1], Alexandre Beautrait[1], Doris Schuetz[1], Eric Bonneil[4], Pierre Thibault[2,4], Matthew Smith[3], Pierre-Louis Beaulieu[1], Marc Therrien[3], Anne Marinier[1,2]

Affiliation
[1]Drug Discovery Unit, Institut de Recherche en Immunologie et en Cancérologie (IRIC), Université de Montréal
[2]Department of Chemistry, Université de Montréal
[3]Department of Pathology and Cell Biology, Faculty of Medicine, Université de Montréal
[4]Proteomics Core Facility, IRIC, Université de Montréal

Abstract

RAS (H/K/N-RAS) are among the most frequently mutated oncogenes, ranging from 30% in lung cancer up to nearly 90% in pancreatic ductal adenocarcinoma. The mutated Ras proteins (G12X and Q61X) were trapped in the active GTP-bound form and trigger downstream signalings driving cellular proliferation and cancer formation. Several KRAS G12C inhibitors are in the market, however they do not have high affinity against GTP-bound form and the resistance rises quickly. Others Ras mutants, such as G12D, G12V and Q61K, are not yet addressed by those drugs, which highlights the imminent need of new Ras inhibitors. The monobody NS1 was discovered recently and demonstrates a unique acting mechanism. By disrupting the Ras clustering on the cell membrane, NS1 inhibits the Ras-MAPK pathway and induces apoptosis on the Ras mutant cell lines. Based on the FG loop of NS1, we designed 10-mer macrocyclic peptides which mimic the β-sheet architecture of this loop and bind to H-Ras and K-Ras. Further optimization of the first hit led to analogs having single digit micromolar affinity for both H-Ras (UM0154715, K_D 1.4 µM) and K-Ras (K_D 2.7 µM), which were measured by both Trp quench assay and surface plasmon resonance (SPR). The lead analogs also show similar binding across multiples Ras mutant (HRAS G12D, G13R, Q61K; KRAS G12D, G12V) and display similar binding affinity between GDP- and GTP-bound forms of Ras. The rich information from SAR studies also allows us to determine four key pharmacophores of the molecule. Three over four of them were then connected using chemical modification guided by rational design, which forms a core motif for the development of smaller Ras allosteric inhibitors.



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A Condensed, Scalable Synthesis of *rac*-Koningic Acid, a natural GADPH inhibitor.

Authors:
Guillaume Barbe, David Chai, Bin Chen, Daniel Guay, Eric Levesque (presenter), John Mancuso.
Corresponding author : Brian DeChristopher

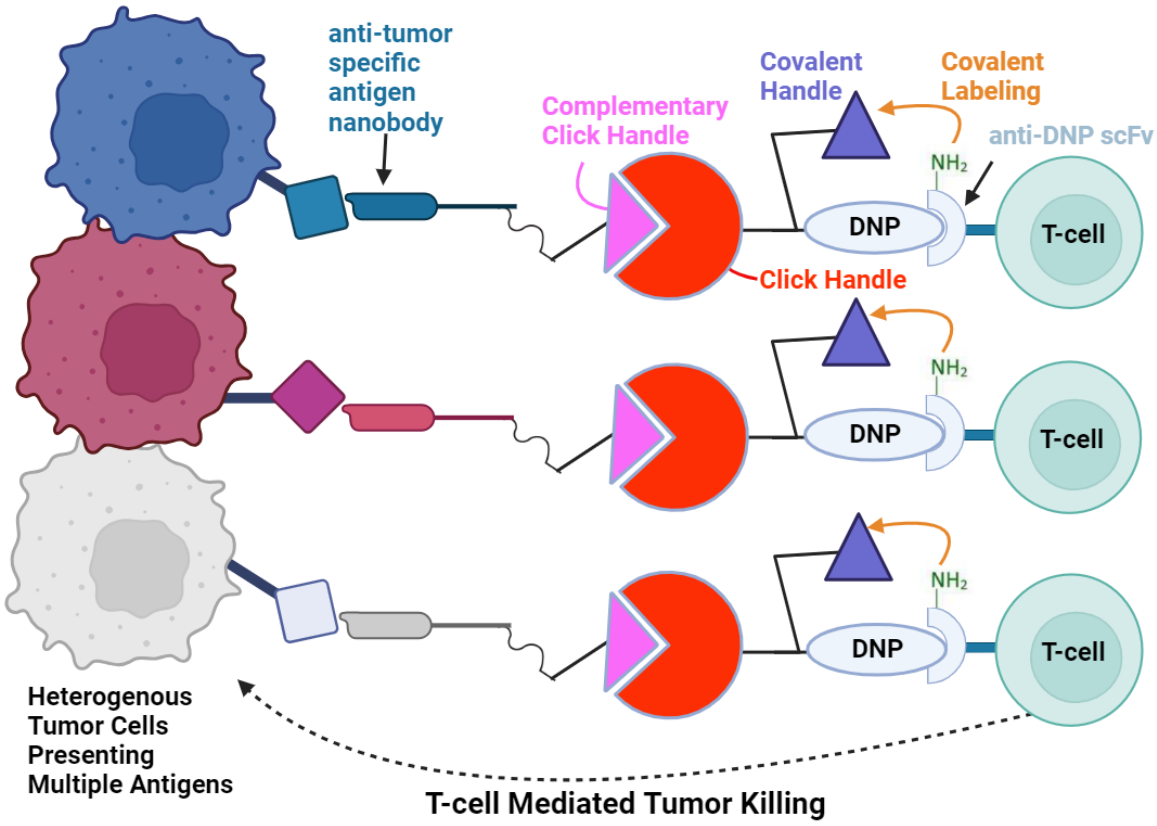
Institutions :
Rheos Medicines Inc., Cambridge, Massachusetts 02139, United States
NuChem Sciences., Saint-Laurent, QC, Canada H4R 2N6

Abstract :
The natural sesquiterpene koningic acid (KA) is a selective covalent inhibitor of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a critical node in the glycolysis pathway. While KA is available commercially, sources are limited and its cost becomes rapidly prohibitive beyond the milligram scale. Here we detail a new route that is operationally safer, scalable and offers a five-step reduction in the previously reported longest linear sequence. Key steps include an alkenyl-cuprate 1,4-addition and a counterion-free Wittig olefination.

Development of Semi-Synthetic Proteinogenic Covalent Immune Engagers for Tumor Immunotherapy

Srayeddin, A., Bramson, J., and Rullo, A.F

Covalent immune recruiters (CIRs) are small molecules equipped with a tumor targeting ligand, an immune antigen, and a bio-compatible electrophile to covalently engage immune receptors of interest. Current CIRs are limited to tumor targeting small molecule ligands which can reduce accessibility to heterogenic tumor targets containing multiple different antigens. To broaden CIR tumor targeting capabilities, we sought to modularly incorporate biologic targeting domains into the CIR scaffold using a variety of tumor antigen specific nanobodies and engineered derivatives that are readily available. As a proof of concept, this study aims to incorporate clickable tumor targeting nanobodies into CIRs specific for anti-DNP immune receptors. To accomplish this, we synthesized azide-oxaziridine, a biotin-reactive handle, for the *in-situ* attachment of click handles to biotinylated nanobodies. Simultaneously, DNP-functionalized CIRs were modified to incorporate click handles. Using click chemistry, the facile attachment of the complementary click handles between the nanobody and CIR allows for the formation of CIR-nanobodies and modular recruitment of immune receptors to any biotinylated nanobody. Biolayer interferometry was used to validate covalent recruitment of anti-DNP antibody to the respective nanobody antigens. This strategy allows for the modular installation of diverse biologic tumor targeting motifs while enabling covalent proximity induction with immune receptors, for an immunotherapeutic effect.



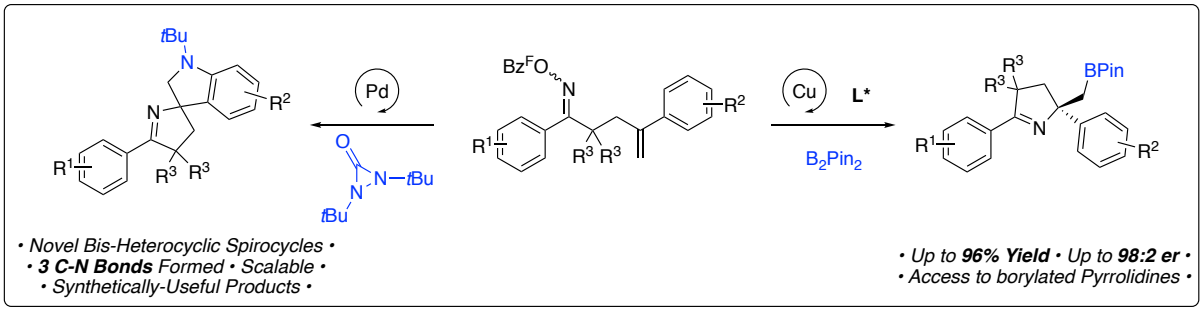
Jonathan Bajohr
Oral Presentation Abstract
October 9th, 2023

Novel Transition-Metal-Catalyzed Domino Reactions Towards Highly Functionalized Pyrrolines

J. Bajohr,[1] A. Dupeux,[1] S. Li,[1] D. Schenk,[2] B. Mirabi,[1] C. Jans,[1] Lautens, M.[1]
[1]*Department of Chemistry, University of Toronto, Toronto, Canada*
[2]*Institut für Chemie, Technische Universität Berlin,10623 Berlin, Germany*

Jonathan.Bajohr@utoronto.ca

The ongoing development of novel transition-metal-catalyzed domino reactions underscores their importance in modern organic synthesis.[1] These reactions are known to form highly functionalized hetero- and carbocyclic scaffolds, as two or more bond forming steps occur under a constant set of reaction conditions, and react sequentially at the functionality created by the preceding step.[2] We have recently developed domino reactions targeted at the synthesis of pyrrolines, heterocycles which can be commonly found in natural products, biologically active molecules, and allows access to functionalized pyrrolidines.[3,4] Using palladium catalysis, alkene-tethered oxime esters can undergo sequential domino Narasaka-Heck/C–H activation/amination reactions, forming three C–N bonds in a single reaction and generating novel spirocyclic pyrrolines.[4] Additionally, the styrene unit in these substrates can be leveraged for an asymmetric borylcupration/amination sequence, generating highly functionalized borylated pyrrolines in excellent yield and enantioselectivity.[5]



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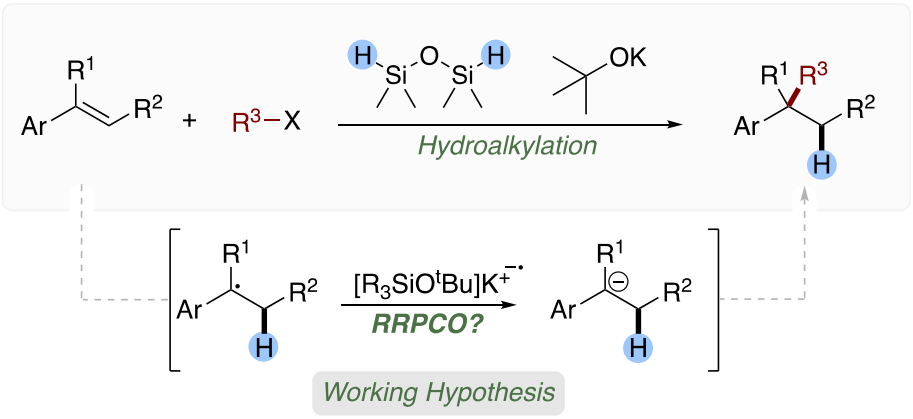
TMDSO and KO^{t}Bu Enabled Hydroalkylation of Vinyl Arenes

Piers St. Onge, Hana Nugraha, Stephen G. Newman
University of Ottawa, Ottawa, Ontario, Canada

Email: pston102@uottawa.ca

Access to methods enabling the synthesis of C(sp^3)-C(sp^3) bonds is of current interest to big pharma, owing to the high propensity saturated molecules have to reach the drug market.[1] Thus, the discovery and development of these protocols has attracted a great deal of attention. In recent years, the combination of potassium alkoxide bases and silicon hydride species has been reinvestigated, not for their hydridic properties but rather the unique myriad of transformations they promote which are thought to occur through exotic silicon-based intermediates proposed in the literature.[2,3] Recently our group disclosed the TMDSO and KO^{t}Bu mediated de-trifluoromethylation of 2-trifluoromethylpyridines where we found not only pyridines to undergo reduction, but styrene-like molecules as well.[4] A serendipitous discovery was made when styrene, KO^{t}Bu, TMDSO, and an alkyl halide were combined in one-pot affording the C(sp^3)-C(sp^3) hydroalkylated product. The scope of vinyl arenes has thus far proven to be broad allowing one to access molecules otherwise challenging to make, using cost-effective reagents. Preliminary mechanistic experiments point towards a pathway involving a benzylic radical and possibly a benzyl anion that give rise to the hydroalkylated products.



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