OMCOS XXI

Vancouver 2023

ABSTRACT BOOK

21st International Symposium on Organometallic Chemistry Directed Toward Organic Synthesis

July 24 - 28, 2023

Vancouver, BC

CANADA

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IN 1

Development and Application of Electrochemical and Photochemical Capabilities in the Pharmaceutical Industry

Dan Lehnherr*[a]
[a]Process Research & Development, Merck & Co., Inc., Rahway, New Jersey, 07065, United States.
Email: dan.lehnherr@merck.com

Electrochemistry and photoredox catalysis have rapidly gained importance in organic synthesis enabling new and different bond disconnections, with the potential to streamline synthesis and/or enable access to new regions of chemical space.[1] My presentation will highlight applications of photochemistry and electrochemistry to solve challenges in the pharmaceutical industry. These will include recent[2–5] and ongoing work related to reaction discovery, mechanistic studies, and new capabilities to efficiently explore these chemistries from milligram scale to kilogram-scale.

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Choose Your Own Adventures in Metal-Hydride Catalysis

Vy M Dong*[a]
[a]University of California at Irvine, Irvine, CA, USA
Email: dongv@uci.edu

Metal hydrides promote a wide-range of organic transformations that include both C-C bond making and C-C bond breaking processes. This lecture will highlight the development of transition-metal catalysts for use in enantioselective hydrofunctionalizations (e.g., hydroacylation, hydroamination, and hydrothiolation). In addition, a unique transfer hydroformylation will be described that allows conversion of aldehydes/alcohols to olefins. The presentation emphasizes mechanistic studies that showcase the role of counter-ions for controlling selectivities. Lastly, we disclose applications of these catalysts for transforming feedstocks into more complex building blocks and natural products.

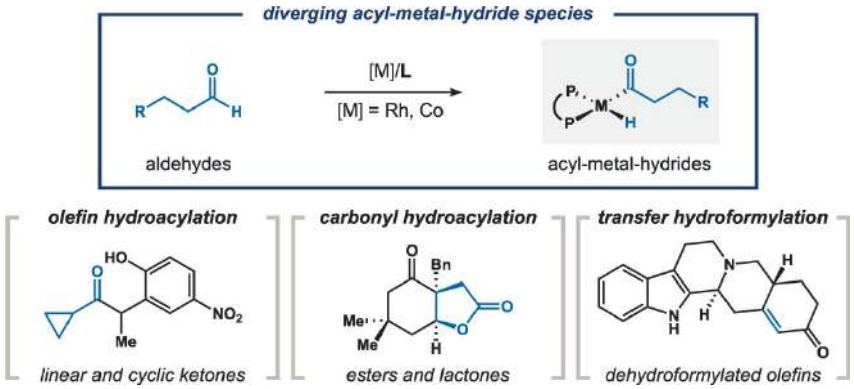

Figure 1. Aldehyde C-H Bond Transformations

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DOI: 10.1021/acs.accounts.0c00771

Organometallic Chemistry as the Driver for Earth Abundant Metal Catalysis Directed Toward Organic Synthesis

Paul J. Chirik

Department of Chemistry, Princeton University,
Princeton, NJ 08544 USA
Email: pchirik@princeton.edu

Catalysis with Earth-abundant metals has emerged as an enabling tool in organic synthesis with impactful reactions ranging from asymmetric alkene hydrogenation to alkene hydrosilylation to various types of C–C bond-forming reactions. Many examples are now known where an Earth-abundant metal catalyst is more active or selective than a more traditional precious, heavy metal alternatives. Our research has been focused on applying catalysis with iron, cobalt, molybdenum and nickel to enable chemistry outside the scope of existing precious metal catalysts. My lecture will focus on how exploring fundamental organometallic chemistry questions enables new catalytic chemistry. Examples include what governs the kinetic and thermodynamic selectivity of the oxidative addition of arenes and heteroarenes relevant to catalytic C–H borylation? Another is how to enable the chemo-, regio- and stereoselectivity of arene insertion into metal-hydride bonds in the context of asymmetric arene hydrogenation? What governs transmetallation with iron, cobalt and nickel in $C(sp^2)$–$C(sp^3)$ cross coupling? Answering these questions and their applications in pharmaceutically-relevant chemistry will be presented.

Cooperative Catalysis by Transition Metal Germylene Complexes

Jesús Campos*[a]

[a]Instituto de Investigaciones Químicas (IIQ), Consejo Superior de Investigaciones Científicas (CSIC) and Universidad de Sevilla
Avenida Américo Vespucio 49, 41092 Sevilla, Spain.
Email: jesus.campos@iiq.csic.es

The field of bimetallic cooperation in homogeneous systems has become a hot research topic with a plethora of possibilities for bond activation and catalysis. In fact, there are many important transformations that require the concerted action of pairs of active metal sites, paralleling what is often found in metalloenzymes. Besides, proximal metal sites offer tunable features beyond those found in mononuclear species, as M-M bond order and polarity or single-site versus multi-site activation.[1] Within this context, our group has recently explored the combination of transition metals and low-valent main group metals and metalloids to explore their cooperative behavior.[2] In particular, the use of divalent heavier group 14 elements (tetrylenes) is particularly appealing given their strong σ-donor properties along with an empty p-orbital that can accept electron density. This ambiphilicity permits accessing transition metal tetrylene complexes that place a reactive site adjacent to the metal, and therefore offer opportunities for cooperation.[3] In the last years we have focused on the use of Power's germylene dimers $[Ar^*GeCl]_2$,[4] where $Ar^* = C_6H_3$-2,6-Ar_2, as germylene fragments that bind transition metals with low-coordination numbers but enough kinetic stability due to the steric protection provided by terphenyl ligands. Our results pertaining the structure, bonding, cooperative reactivity and catalytic applications of several transition metal (i.e. Au, Rh, Pt, Ni) germylene complexes (Figure 1) will be discussed, including the activation and challenging catalytic conversion of ammonia.

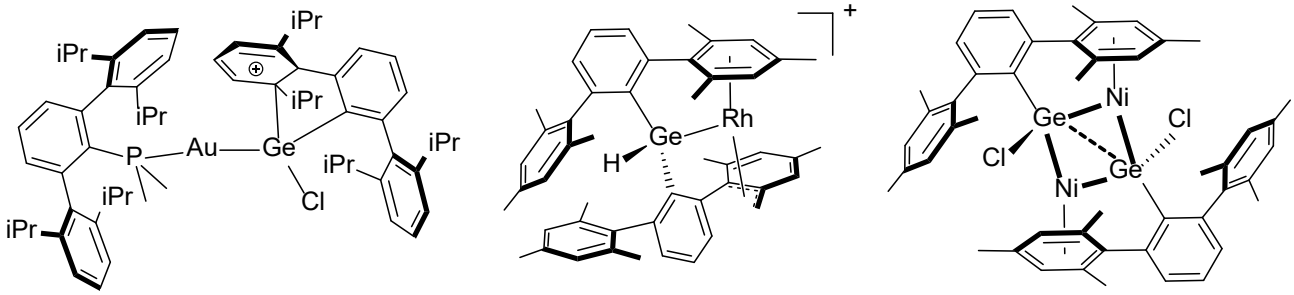

Figure 1. Representative examples of transition metal germylene complexes whose structure, cooperative reactivity and catalytic applications will be discussed.

References

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Non-noble Metal-based Transformations of (hetero)arenes

Veronica Papa,[a] Johannes Fessler,[a] Haijun Jiao,[a] Haifeng Qi,[a,b] Tao Zhang,[b] Kathrin Junge,*[a] Matthias Beller[a]
[a]Leibniz-Institute for Catalysis (LIKAT), Albert-Einstein-Str. 29a, 18059 Rostock, Germany.
[b]CAS Key Laboratory of Science and Technology on Applied Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, 116023, China.
Email: kathrin.junge@catalysis.de

The cost-effective and waste-free synthesis of materials, life science goods and all kinds of organic products require efficient chemical transformations. In this regard, development of more active and selective catalysts constitutes a key factor for achieving improved processes and providing the basis for a sustainable chemical industry. Despite continuous advancements in all areas of catalysis, still organic syntheses as well as the industrial production of most chemicals can be improved significantly in terms of sustainability and efficiency.

In the talk, it will be shown how new and improved homogeneous non-noble metal-based catalysts can be developed. Specifically, the phenomenon of cooperative catalysis will be addressed in the context of non-noble metal pincer-based catalysts for the reduction of heterocyclic compounds (Figure 1).[1] In detail, it will be demonstrated that recently developed molecular-defined manganese catalysts enable catalytic hydrogenation processes with high yields and unprecedented selectivity. Especially, the influence of different substitution patterns at the ligand backbone for the phosphorous as well as at the nitrogen site on the catalytic performance of these pincer complexes is presented.[2] Based on the experimental outcome, spectroscopic investigations and density functional theory computations mechanistic insight into the catalytic hydrogenation reaction will be given.

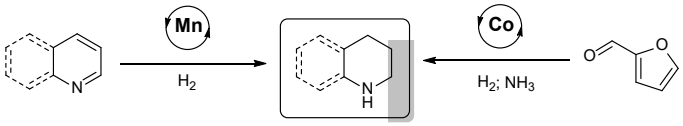

Figure 1. Non-noble metal catalyzed transformation of heteroarenes to piperidines.

In addition, the principle of cooperative catalysis will be shown in the context of modern phosphorous-free catalysts for reduction reactions.[1] By rational design novel ligands and complexes have been synthesized, which allow for unprecedented efficiency in such transformations. Finally, examples which demonstrate the potential of such catalytic processes with bio-relevant metal complexes are compared to more traditional catalytic reactions. In this respect, also the development of novel unpublished nano-structured metal catalysts is included.[3]

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Solvent-free Birch Reductions and Benzene C–H Activation/C–C Coupling mediated by a Room-Temperature Stable Electride (RoSE)

Nathan Davison,[a] James A. Quirk,[a] James A. Dawson[a] and Erli Lu*[a]
[a] Chemistry-School of Natural and Environment Sciences, Newcastle University.
Newcastle upon Tyne, UK. NE1 7RU.
Email: erli.lu@newcastle.ac.uk

Birch reduction [1] and benzene C–H activation/C–C coupling [2] are essential tools for converting arene feedstock into value-added organic compounds and to build complex molecules. However, state-of-the-art methods require hazardous reagents (e.g., Group-1 metal-liquid ammonia, solvated electrons, strong oxidants), harsh conditions (e.g., high temperatures, long reaction time), expensive and/or specialized reagents/catalysts (e.g., precious metals), and last but not least, petrochemical-derived organic solvents. From a sustainability standing point, the ideal scenario is that an easily accessible non-precious-metal reagent can mediate solvent-free Birch reduction and benzene C–H activation/C–C coupling at room temperature in short reaction time, but such an enabling reagent was unknown, until our report in 2023 [3]. We discovered an accessible and scalable Room-temperature Stable Electride (RoSE) reagent, namely $K^+(LiHMDS)e^-$ (**1**) (HMDS: $N(SiMe_3)_2$), which mediated the first solvent-free Birch reductions and facile benzene C–H activation and C–C coupling. Herein we would like to present the breakthrough and its very recent updates.

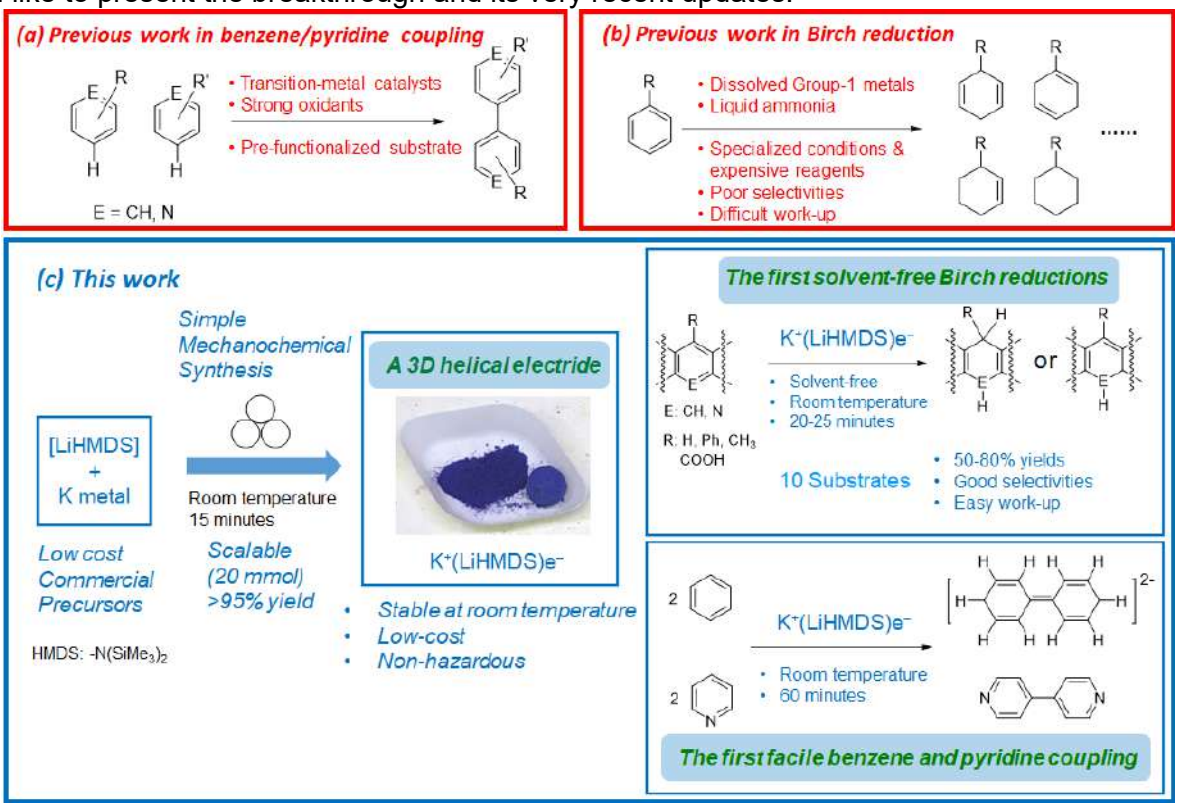

Figure 1. (a) Previous work in benzene and pyridine coupling. (b) Previous work in Birch reduction. (c) This work: mechanochemical synthesis of a room-temperature-stable, 3D electride $K^+(LiHMDS)e^-$ (**1**) and its mediated solvent-free Birch reductions and facile benzene and pyridine coupling.

References

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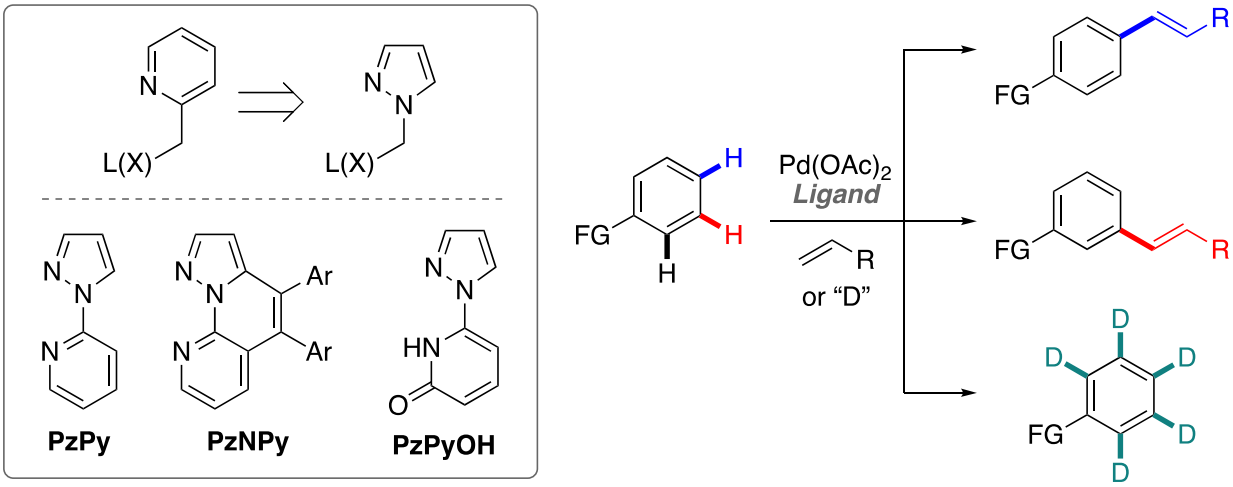
Development of New Nitrogen Ligands for Pd-Catalyzed C–H Functionalization

Jung Min Joo
Department of Chemistry, Kyung Hee University, Seoul 02447, South Korea
Email: jmjoo@khu.ac.kr

Ligand design is critical to the development of efficient transition-metal-catalyzed C–H functionalization reactions. New classes of bidentate ligands containing pyrazole were developed to enable Pd-catalyzed C–H functionalization of (hetero)arenes. A modular approach was employed to prepare a series of pyrazolopyridines (**PzPy**), pyrazolonaphthyridines (**PzNPy**), and pyrazolopyridones (**PzPyOH**). The incorporation of pyrazole into the ligand framework provides flexibility in the binding to Pd compared to strongly binding, rigid pyridine. The catalytic applications of **PzNPy** ligands were successfully demonstrated in the Pd-catalyzed aerobic C−H alkenylations of aniline, alkoxybenzene, pyrrole, thiophene, and metallocene derivatives. Furthermore, **PyPyOH** containing a 2-pyridone moiety as an internal base facilitated C−H cleavage, enabling *meta*-selective alkenylation and perdeuteration even at challenging sp^2 C−H bonds. Mechanistic studies and DFT calculations were performed to illustrate crucial factors in the ligand design for Pd-catalyzed C−H functionalization.



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Mechanochemical Synthesis of Organometallic Compounds

Hajime Ito*[a,b]
[a] Institute for Chemical Reaction Design and Discovery (WPI-ICReDD),
Hokkaido University, Sapporo, Hokkaido 060-8628, Japan
[b] Division of Applied Chemistry, Graduate School of Engineering,
Hokkaido University, Sapporo, Hokkaido 060-8628, Japan
Email: hajito@eng.hokudai.ac.jp

In the direct synthesis of main-group organometallic compounds from organohalides, the active metal is used as it is, or a metal whose surface has been activated in some way is reacted in an organohalide solution. We have recently deve
loped a method for the direct reaction of metals with organohalides using a ball mill. We have reported the synthesis and reaction of Grignard reagents, organocalcium reagents, and organomanganese reagents, which can be carried out almost solvent-free and under air. Reduction of aromatics by lithium metal under ball-milling conditions, ultra-fast mechanochemical Birch reduction was also reported recently.

In 2019, we reported a novel procedure that revolutionizes the synthesis of Grignard reagents. Our method involves ball-milling with the presence of a small amount of THF, resulting in the formation of paste-like Grignard reagents within 60 minutes. We also discovered that this technique can be used to synthesize aryl calcium compounds, known as heavy Grignard reagents, which exhibited unprecedented reactivity in substitution reactions of alkyl halides. Our ball-milling method also simplifies the synthesis of organomanganese compounds, which typically requires complicated protocols.

Mechanochemical conditions also provide a simplified approach to Birch reduction, which necessitates cryogenic and inert conditions with liquid ammonia, resulting in long processing times. However, with mechanochemical Birch reduction, the reaction is typically completed in one minute. This accelerated reaction is facilitated by the mechanical activation of the lithium surface in the presence of the aromatic substrate, which promotes the transfer of electrons from lithium metal to the substrate.

Our research has shown that mechanochemical methods are highly effective in the preparation of organometallic compounds. I believe this has great potential to open the development of new synthetic reactions involving organometallic compounds.

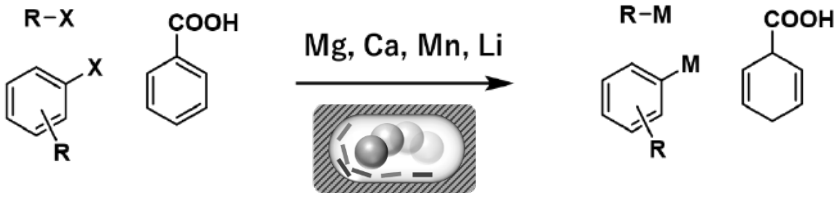

Figure 1. Mechanochemical reaction of main-group metals.

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New Catalytic Explorations on Alkali (Earth) Metal Complexes

Hui-Zhen Du, Bing-Tao Guan*

Department of Chemistry, Fudan University

Email: Bing-Tao Guan; bguan@fudan.edu.cn

Alkali (earth) metals are rich in reserves, cheap in price and good in biocompatibility, and have great potential for catalytic application.[1] However, the catalytic application of these metal complexes is facing with many problems such as poor stability of complexes, monotonous catalytic mode and limitation of substrate scope. Focusing on the scientific problems about the principle and potential of s-block metal catalysis, we adopted ate complex strategy to stabilize the active organometallic intermediates and discovered a new approach of kinetic deprotonative functionalization (KDF): the reaction under relative weak conditions via the combination of the irreversible conversion of the carbanion and constant reestablishment of the equilibrium. With the combination of ate complex strategy and the concept kinetic deprotonative functionalization, we could establish a new deprotonative equilibrium of less acidic C-H bonds and hydrogen with less basic ate complexes, and developed a series of new reactions including catalytic C-H bonds addition to olefins, catalytic hydrogenation and catalytic hydrogen isotope exchange reactions. Thus, we expanded both the reaction types and substrate scope of the alkali (earth) metal catalysts and revealed their distinct and sometimes better activity and selectivity than transition metal catalysts.[2]

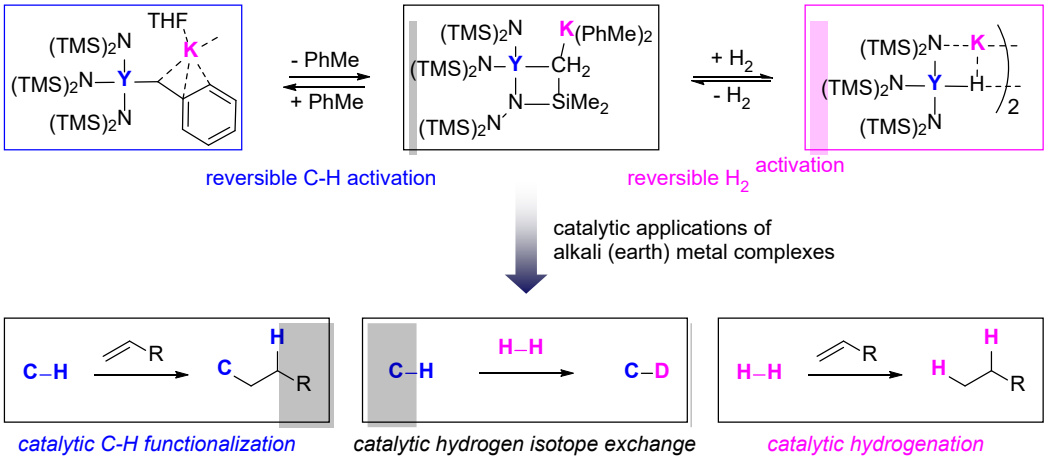

Figure 1. New catalytic reactions with alkali (earth) metal complexes.

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Recent Adventures in Catalysis and Beyond

Bill Morandi
ETH Zurich

Email: morandib@ethz.ch

In this presentation, recent developments in synthetic methodology from our group will be discussed. This will include e.g. new developments in the area of shuttle catalysis, including applications to feedstock and waste valorization. This will be completed by a discussion on further methods recently developed in our group, as well as accompanying mechanistic studies.

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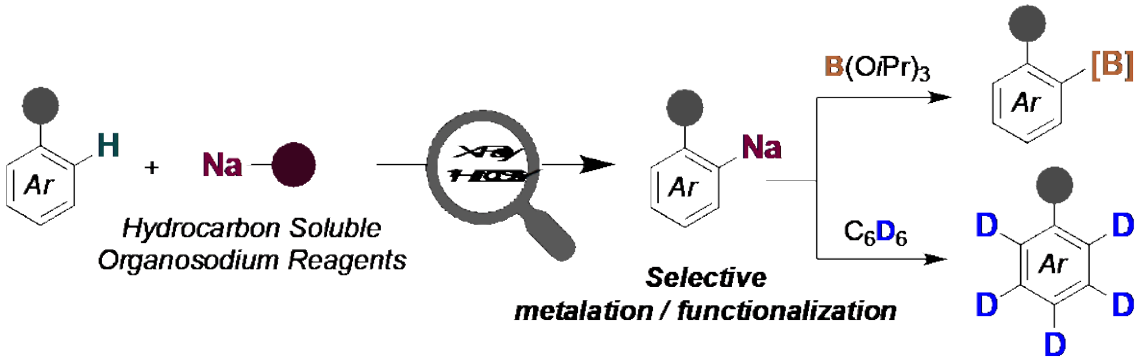
Tailoring Sodium Organometallic Reagents for Arene Functionalisation

Eva Hevia*
Department of Chemistry, Biochemistry and Pharmacy, University of Bern. Freiestrasse 3, 3012 Bern (Switzerland)
Email: eva.hevia@unibe.ch

Organosodium compounds have attracted the attention of the scientific community in recent years as an alternative to widely used organolithium reagents.[1] Lithium alkyls and amides reside at the front of organometallic synthesis as key players in countless transformations, owing to their availability, substantial stability and solubility in hydrocarbon solvents.[2] However, these desirable traits are often pitfalls of heavier alkali-metal organometallics, meaning that their applications have remained underexplored. While recent reports have hinted at the untapped potential of these reagents,[3] the constitution of the organometallic intermediates that operate in these reactions has been overlooked, missing an opportunity to tackle their high reactivity and improve their poor solubility.
Filling this gap in the knowledge, the preparation of organosodium compounds soluble in hydrocarbon solvents and the isolation and characterization of reactive sodium organometallic intermediates in the solid state and in solution by X-Ray crystallography and ^{1}H DOSY (Diffusion Ordered SpectroscopY) have allowed the development of new protocols for the functionalisation of organic molecules. Our efforts have been focused on selective deprotonative metalation reactions of synthetically attractive arenes, providing access to the selective functionalization of these scaffolds, including the borylation[5] and the perdeuteration of aromatic scaffolds,[6] and the aroylation of toluene derivatives via selective benzylic metalation.[7] The reactivity and/or selectivity obtained with organosodium compounds was different to the one with its lithium analogues, opening new vistas in the use of polar organometallic reagents for the functionalization of organic molecules.



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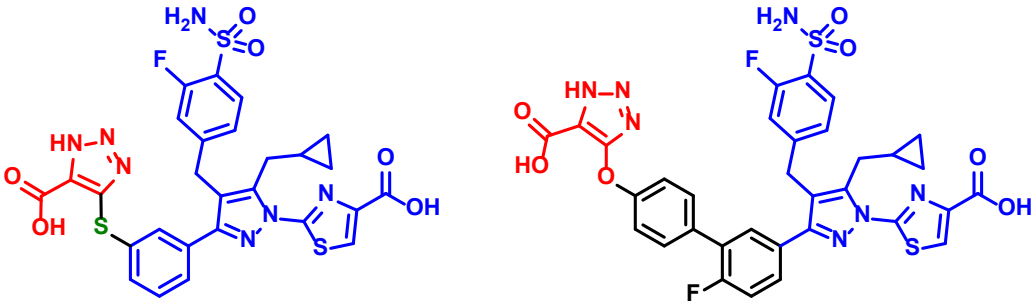
Rational design of dual glycolate oxidase/lactate dehydrogenase A inhibitors for Primary Hyperoxaluria

Jinyue Ding,*[a] Rajesh Gumpena,[b] Marc-Olivier Boily,[a] Alexandre Caron,[a] Oliver Chong,[a] Jennifer H. Cox,[a] Valerie Dumais,[a] Samuel Gaudreault,[a] Aaron H. Graff,[b] Andrew King, [a] John Knight,[c] Renata Oballa,[a] Jayakumar Surendradoss,[a] Tim Tang,[a] Joyce Wu,[a] W. Todd Lowther, Victoria Rose[a] and David A. Powell[a]

[a]Chinook Therapeutics. [b]Wake Forest School of Medicine. [c]University of Alabama at Birmingham

Email: vrose@chinooktx.com; jding@chinooktx.com

Primary hyperoxaluria (PH) is a group of devastating genetic diseases of increased hepatic oxalate production that can result in end-stage kidney disease in young patients. Both glycolate oxidase (GO) and lactate dehydrogenase A (LDHA) influence the endogenous synthesis of oxalate and are clinically validated targets for treatment of PH. Utilizing a structure-based drug design (SBDD) approach, we developed a series of novel, potent, dual GO/LDHA inhibitors to investigate whether dual inhibition of GO and LDHA may provide advantage over single agents in treating PH. Dual inhibitor **7** demonstrated inhibition of GO and LDHA in an enzymatic *in vitro* assay and oxalate reduction in an Agxt-knockdown mouse hepatocyte assay. Reduced potency observed for **7** in this hepatocyte assay and poor liver exposures *in vivo* were proposed to result from reduced cellular permeability. As such, a second generation of inhibitors, including compound **15**, was designed with more lipophilic linker moieties. Use of Pd-catalyzed Suzuki−Miyaura coupling reaction with a pinacol boronate intermediate was a key step in the synthesis of this series of compounds. X-ray crystal structures of compound **15** bound to individual GO and LDHA proteins validated our SBDD strategy. Unfortunately, second generation inhibitors also failed to demonstrate significant pharmacodynamic effect *in vivo* likely due to low liver exposures. This work highlights the challenges in optimizing *in vivo* liver exposures for diacid containing compounds and limited benefit seen with dual GO/LDHA inhibitors over single agents alone in an *in vitro* setting.



7 **15**

Figure 1. dual GO/LDHA inhibitors **7** and **15**.

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Investigation of *N*-Heterocyclic Carbene Aryl Ligands for the Undirected Borylation of Secondary Alkyl C–H Bonds

Jenna Manske,[a] Hamile Khan,[a] John Hartwig*[a]
[a]University of California, Berkeley
Email: jlmanske@berkeley.edu; jhartwig@berkeley.edu

The ubiquity and stability of alkyl C–H bonds have rendered their selective functionalization an area of great interest. The borylation of C–H bonds is an appealing transformation because the resulting compounds can be diversified through well-known reactions, enabling the installation of diverse functional groups at the position of the original C-H bond.[1] While the borylation of aryl C–H bonds is well-developed[2], borylation of alkyl C–H bonds remains a challenge. Recently, phenanthroline ligand scaffolds have been explored for the borylation of primary, secondary,[3-4] and tertiary[5] alkyl C–H bonds. We envisioned that studies of alternative, but related, ligand scaffolds could lead to insight into how to develop more stable, active, or selective catalysts, ultimately increasing the applicability of Ir-catalyzed borylation of alkyl C–H bonds. To this end, it was reported in 2019 that the computed barrier for the proposed turnover limiting step of reductive elimination to form the C–B bond from an iridium complex with an *N*-heterocyclic carbene pyridine (NHC-py) ligand was lower than from iridium ligated by phenanthroline derivatives.[6] We hypothesized that the electron-donating *N*-heterocyclic carbene moiety could stabilize the metal through strong coordination.[7] Thus, we sought to test this prediction of a superior ligand by the computational work.

We report the borylation of the secondary C–H bonds of tetrahydrofuran (THF) by iridium catalysts containing NHC-py ligands. Reactions performed with isolated carbene in combination with iridium and catalytic sodium *tert*-butoxide led to the highest yields of borylated THF. NMR studies and high yields obtained from NHC-Ar ligands support the formation of a catalytically competent cyclometallated NHC-iridium complex. The yield and selectivity from reactions conducted with an independently synthesized cyclometallated iridium complex was similar to the yield and selectivity from reactions conducted with a mixture of iridium precatalyst and ligand. In contrast to previous reports of the borylation of THF occurring exclusively at the β-position with phenanthroline ligands[3–4], and computationally predicted reactivity for these NHC-py ligands,[6] reactions catalyzed by NHC-Ar ligands, in combination with iridium, form two isomeric boryl THF products in up to a 6.5 : 1 (α : β) ratio.

Studies to determine the role of the sodium *tert*-butoxide base support association of the base to the iridium complex. Ongoing work aims to study reactions of the cyclometallated NHC-Ar iridium complexes in the presence of alkoxide base with density functional theory to evaluate binding modes of the alkoxide under catalytic conditions.

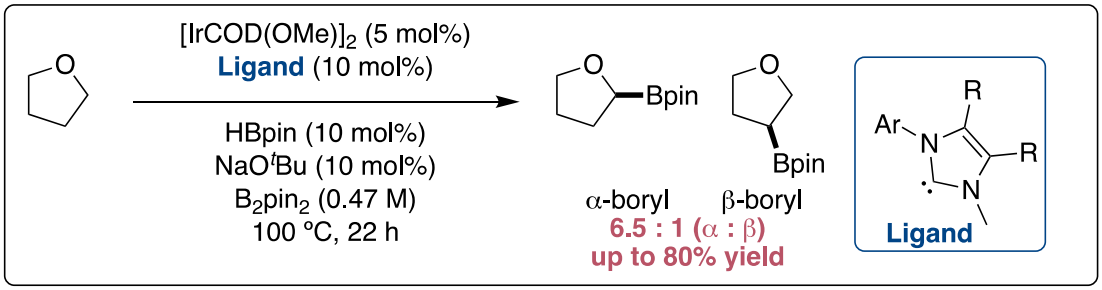

Figure 1. Conditions for the borylation of tetrahydrofuran with an iridium complex containing an NHC-Ar ligand

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Carbones with its Elusive Bonding Description and Broad Implication Complementary to NHC-Carbenes

Wen-Ching Chen,[a] Ting-Hsuan Wang,[a] Cheng-Han Yu,[a] Tiow-Gan Ong,[a,b*]
[a]Institute of Chemistry, Academia Sinica, Taipei, Taiwan, ROC. [b] bDepartment of Chemistry, National Taiwan University, Taipei, Taiwan, ROC.
Email: tgong@gate.sinica.edu.tw

Carbones (L→C←L) have emerged recently as a new class of organic molecules featuring carbon(0) directly stabilized by two electron-rich groups (L) through Lewis donor-acceptor interaction.[1] Other mesomeric features can also be understood in terms of allenic or zwitterionic form (see **Figure 1**). Owing to the peculiar bonding situation and the zero-valent nature of the central atoms, carbones have attracted much attention in the chemical community as NHC alternatives because their strong σ-donating ability broadly impacts transition-metal coordination, small molecule activation, main-group chemistry, redox non-innocent coordination, and catalysis.[2] This presentation will describe the synthetic preparation and chemical properties of the carbone as well as its application toward supporting metallic complexes for catalysis in tandem photoredox, cross-coupling reaction via tandem C-H and C-O bond activation and a new spin in diversifying FLP reactivity with co-modulator benzyl alcohol.

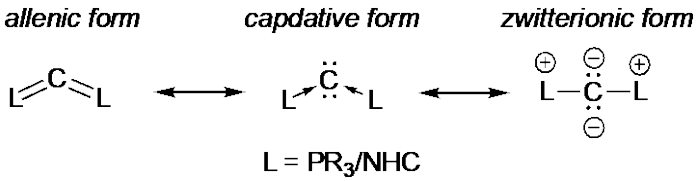

Figure 1. Mesomeric form: bonding situation of carbones.

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Recent Advancement in Gold Redox Chemistry: New Transformations and Asymmetric Catalysis

Xiaodong Shi
Department of Chemistry, University of South Florida, Tampa, FL 33620, USA
Email: xmshi@usf.edu

The recent discovery of gold(I)/gold(III) redox chemistry greatly transcends cationic gold chemistry from simple π-acid catalysis, which serves a powerful tool for C-C or C-X bond construction. However, with the high oxidation potential between Au(I) and Au(III), ca. ~1.4 eV, gold redox catalysis required the application of strong oxidants with at least stoichiometric amount. Therefore, to achieve gold redox catalysis under mild conditions, with low cost and mild oxidants, is highly desired to make the overall process practical with improved functional group tolerability. Herein, we disclosed novel approaches to facilitate oxidation of Au(I) to Au(III) through 1) Aryldiazonium salts as the mild coupling partner/ oxidant, gold catalyzed cross-coupling reactions are accomplished without any external oxidants under photocatalyst-free condition. 2) Employing sulfonium or diselenium cation as mild oxidants for the alkyne functionalization. 3) Electrochemical approach in promoting gold-catalyzed oxidative coupling.[1] These approaches open an opportunity for gold redox catalysis.

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Umpolung Reductive Functionalization of Amides via a Tandem Hydrosilylation/Photocatalytic Strategy

Tatiana Rogova,[a] Pablo Gabriel, Stamatia Zavitsanou, Jamie A. Leitch, Fernanda Duarte, Darren J. Dixon*[a]

[a] Department of Chemistry, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, United Kingdom

Email: tatiana.rogova@rwth-aachen.de; darren.dixon@chem.ox.ac.uk

α–Functionalized amines and their derivatives are integral fragments of a vast array of pharmaceutical agents, agrochemicals and natural products.[1] Therefore, the development of a novel and efficient strategy to access these functionalities would be highly relevant for both academic and industrial applications. Within the scope of recently developed methodologies, the reductive functionalization of tertiary amides provides a synthetically useful access point towards a wide range of α–branched amine structures. In particular, the use of Vaska's complex ($IrCl(CO)(PPh_3)_2$), in conjunction with a siloxane-based reductant, has come to the forefront as an effective system for chemoselective activation of these notoriously robust and ubiquitous building blocks.[2] Traditionally, using these mild hydrosilylation conditions, tertiary amides can be converted *in situ* into reactive iminium ion intermediates that can be further intercepted with a variety of nucleophilic entities.[2] It was envisioned that through further transformation of the iminium ion into a nucleophilic α-amino radical species using a photocatalytic approach, it would be possible to venture into a previously inaccessible area of chemical space.[3]

To address this outstanding synthetic challenge, a streamlined one-pot procedure for mild generation of α-amino radicals from tertiary amide building blocks has been developed.[3] The free radical species were successfully coupled to the electrophilic dehydroalanine acceptor to produce an array of novel, α-functionalised amine derivatives. Furthermore, this strategy was applied towards reductive secondary amide functionalisation, as well as intramolecular examples that yielded substituted *N*-heterocycles. In addition to the experimental investigations, Density Functional Theory (DFT) analysis was utilised to gain further insight into the reactivity and physical properties of the reaction. Finally, to demonstrate the versatility and modularity of the developed dual catalytic, reductive functionalization approach, this concept was adapted to access enantioenriched products from feedstock starting materials, with the preliminary findings of this investigation disclosed herein.

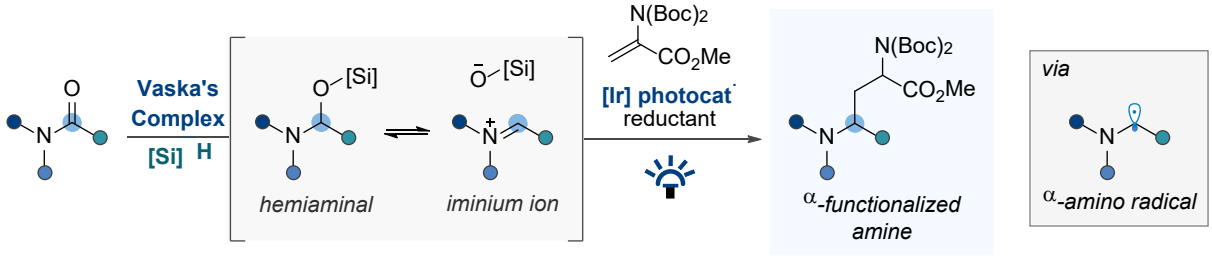

Figure 1. General strategy for umpolung reductive functionalization of tertiary/secondary amides.

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Planar Chiral Rhodium Complexes for Enantioselective Catalysis

Simon B. Blakey*[a]
[a]Department of Chemistry, Emory University, Atlanta, GA, USA.
Email: sblakey@emory.edu

The development of new reactions and catalysts for the oxidative cross-coupling of C-H bonds with C-H, N-H and O-H bonds will be discussed. Strategically, these reactions allow for the synthesis of complex molecules from their constituent components, minimizing the need for functional group activation and manipulation. A novel planar chiral catalyst platform for enantioselective reactions will be presented. Illustrative examples of emergent applications will be provided.

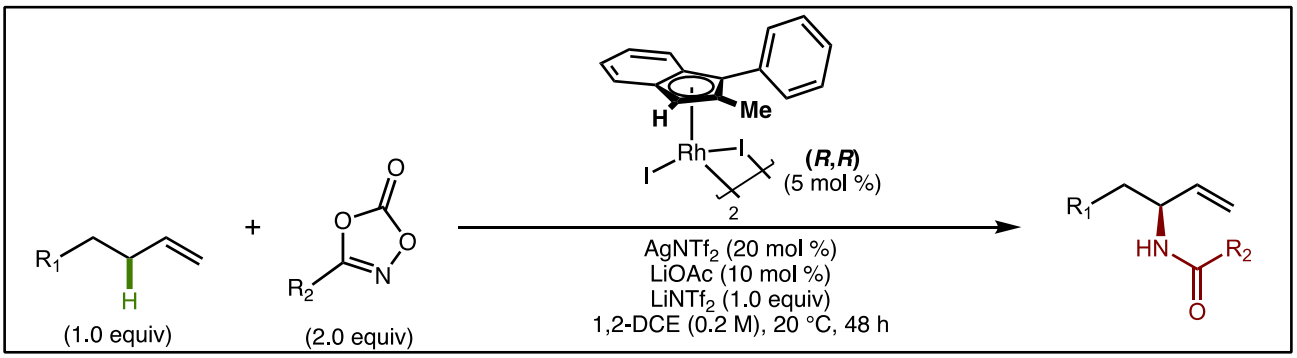

Figure 1. Illustrative enantioselective C-H amidation.

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One- and Two-electron Bismuth Redox Catalysis

Josep Cornella

Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, 45470, Germany

cornella@kofo.mpg.de

The ability of the bismuth (Bi) to maneuver between different oxidation states in a catalytic redox cycle will be presented. We will show how Bi challenges the current dogmas of main group redox catalysis by emulating canonical organometallic steps of transition metals. A series of Bi complexes capable of revolving between oxidation states Bi(I)/Bi(III) and Bi(III)/Bi(V) have been unlocked and applied in various contexts of catalysis for organic synthesis. For example, capitalizing on the Bi(III)/Bi(V) redox pair, we have developed a catalytic protocol for the C–F, C–O and C–N bond formation. We will show how bismuth is capable of a unique 5-membered reductive elimination step, which differs from the traditional 3-membered of transition metals.

Additionally, we will show how a low-valent redox manifold based on Bi(I)/Bi(III) enabled the reduction of hydrazines and nitro compounds, the catalytic decomposition of the rather inert nitrous oxide (N_2O) and the catalytic hydrodefluorination of C(sp^2)–F bonds. In addition, we will show how one-electron pathways are also accessible, thus providing a platform for SET processes capitalizing on the triad Bi(I)/Bi(II)/Bi(III) for organic synthesis. Finally, we will also show how redox-neutral organometallic steps (insertion, transmetallation and ligand exchange) can be merged in a catalytic platform to unlock novel organic transformations. For all methodologies, a combination of rational ligand design with an in depth analysis of all the elementary steps proved crucial to unlock the catalytic properties of such an intriguing element of the periodic table.

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Data Science as an Enabling Tool For Asymmetric Catalysis

Jolene P. Reid

The optimization of catalytic, enantioselective reactions is challenging as it involves the empirical evaluation of several different reaction components (e.g., reactant, catalyst, solvent, etc.) to determine the best set of conditions. We have aimed to develop several data science-based tools that streamline this process by constraining the number of experiments to be performed in the lab while increasing the proportion which yields the desired high levels of enantiomeric excess. More specifically, in this talk, I will describe how we apply a diverse set of machine learning algorithms to aid in the identification of optimal reaction conditions[1-3] and general catalyst systems.[4] A significant portion of this talk will focus on our experimental efforts in evaluating these tools for developing enantioselective reactions. Several studies will involve the reaction of organometallic compounds, including the dearomatization of naphthols and indoles as examples.

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Multicomponent Coupling Strategies via Iron Azametallacyclobutene Complexes

Jamie M. Neely*[a]
[a]Department of Chemistry, Saint Louis University, St. Louis, Missouri, USA
Email: jamie.neely@slu.edu

First row transition metals present opportunities for the discovery of novel catalytic transformations enabled by their distinct reactivity. We recently demonstrated the regioselective [2+2] cycloaddition reaction of a (β-diketiminate)iron imide with an unsymmetrical internal alkyne to afford an iron azametallacyclobutene complex (Figure 1).[1,2] This complex incorporates terminal alkynes (Figure 1a), nitriles (Figure 1b), and isonitriles (Figure 1c) with complete control over the formation of the β-alkynyl enamine, imidazole, and imidoyl ketenimine products, respectively. The stoichiometric reactivity observed establishes a foundation for the development of new catalytic multicomponent coupling methods mediated by iron azametallacyclobutene complexes that generate valuable nitrogen-containing compounds.

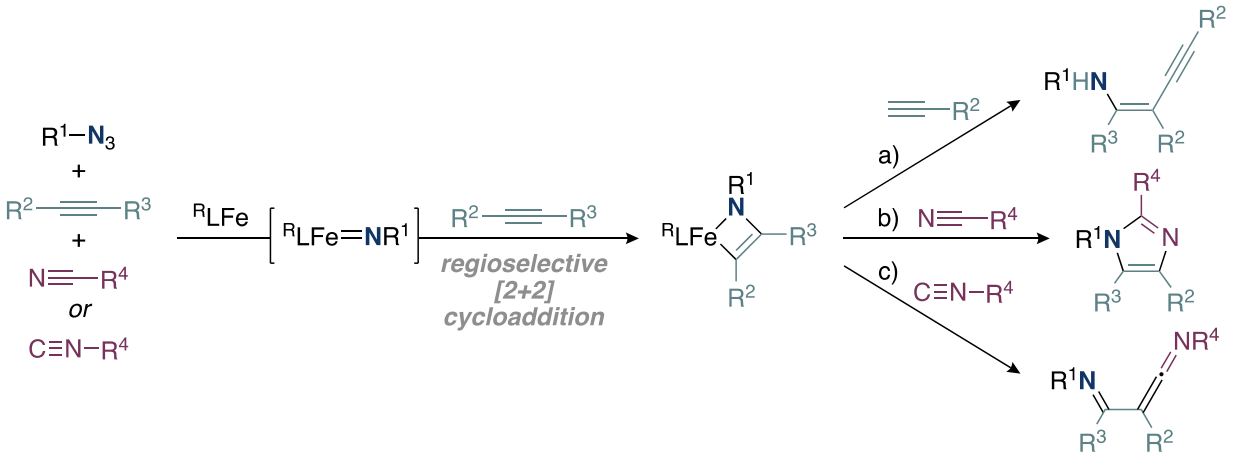

Figure 1. Iron-mediated multicomponent coupling.

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C-C Bond Nitrogenation

Ning Jiao
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China
Email: jiaoning@pku.edu.cn

Nitrogen-containing compounds are widely present in both natural products and synthetic compounds, for example, they show up within functional materials, top-selling drugs, as well as bioactive molecules. Thus, organic chemists have paid considerable attention in developing novel methodologies for their preparation. To synthesize these compounds in an efficient way, researchers have focused on the direct functionalization of hydrocarbons via C–H and/or C–C bond cleavage. Although significant progress has made in the direct functionalization of simple hydrocarbons, direct incorporation of N-atoms into the simple substrates via C–H and/or C–C bond cleavage remains challenging due to the inert chemical bonds and the unstable character of some N-sources under oxidative conditions. By using readily available reagents as nitrogen source, we recently developed some highly efficient C-H/C-C bond oxygenation,[1] nitrogenation,[2] and halogenation reactions[3] for the synthesis O-, N-, and/or halogen atom containing compounds. In this presentation, our recent progress on the direct C-C bond nitrogenation will be introduced (Figure 1).

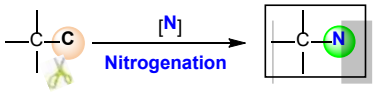

Figure 1. C-C bond nitrogenation.

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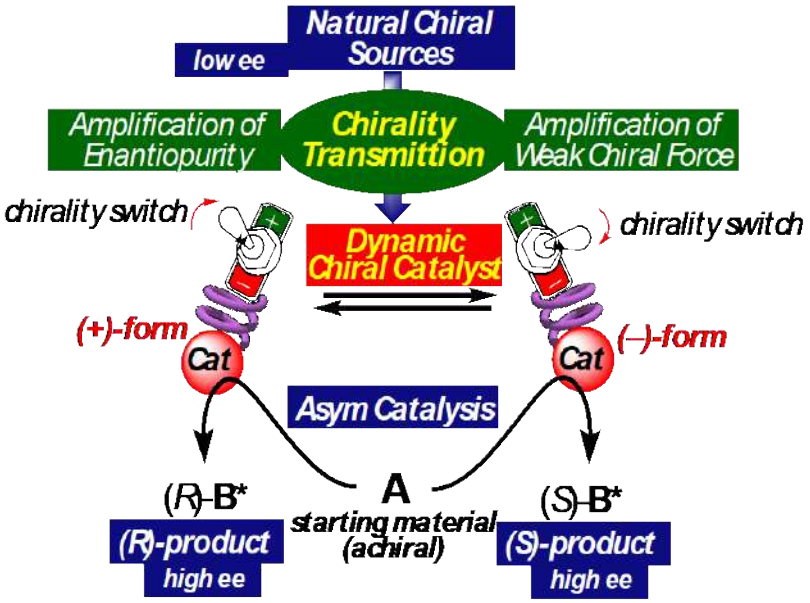
Interplay between Solvents and Modular Chirality-Switchable Macromolecular Catalysts in Asymmetric Catalysis

Michinori Suginome
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University
Email: suginome@sbchem.kyoto-u.ac.jp

The exiting development of homogeneous asymmetric catalysis in the past half century has relied on the discovery of small-molecular catalyst structures with static (fixed) molecular chirality. Establishment of several privileged structural motifs such as binaphthyl and ferrocene derivatives is particularly noteworthy. In stark contrast, utilization of chiral macromolecular structures as the chiral catalyst scaffold has gained little attention, even though the unique characteristics of polymer structures such as high recoverability, huge steric effect, and dynamic conformational change may open up new possibilities of chiral catalysts.

In this communication, new helical macromolecular chiral catalysts are described, of which helical chirality solely determines the enantioselectivities and is sharply switchable by solvent effects. A wide variation of reaction solvents from pure water to alkanes can be employed by virtue of the modifiable side chain structures, which secure the catalysts' solubility. Note that the helical chirality of the catalysts bearing chiral side chains is switchable by changing achiral reaction solvents. In an extreme case, use of cyclooctane and *n*-octane gave opposite enantiomers both with high enantioselectivities. On the other hand, those bearing only achiral side chains can be used as chiral catalysts, even though they exist as an exactly 1:1 mixture of right- and left-handed helical conformations in achiral solvents. Single-handed helix sense could be selectively induced by nonbonding interaction with chiral solvents such as *d*- or *l*-limonene. Also discussed is the effect of nonbonding chiral guests for induction of single-handed helical sense in achiral solvents.



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Exploiting Ancillary Ligation To Enable Nickel-Catalyzed C−O Cross-Couplings of Aryl Electrophiles with Aliphatic Alcohols and Phenols

Mark Stradiotto*[a]
[a]Dalhousie University, Department of Chemistry, Halifax, NS Canada B3H 4R2
Email: mark.stradiotto@dal.ca; mark.stradiotto@dal.ca

The relatively abundant and inexpensive nature of nickel, paired with its propensity to engage in oxidative addition, offers advantages in the quest to develop new and useful alternatives to copper and palladium in cross-coupling catalysis. While both photochemical and electrochemical methods have been employed to promote catalytic turnover, such protocols exhibit substrate scope limitations, including poor catalytic performance with (hetero)aryl chlorides and phenol derivatives that represent the most inexpensive/widely available electrophile classes. In an alternative (unplugged?) approach, my research group has explored the development of sterically demanding and modestly electron-donating bisphosphines (including the DalPhos series), which we envisioned might promote C-N/C-O reductive elimination within a putative Ni(0/II) catalytic cycle while circumventing catalyst deactivation arising from bis-chelation and/or comproportionation. Notably, the catalytic performance of Ni catalysts supported by these DalPhos ligands has in many instances been found to be competitive with, or superior to, the best metal catalysts known (Pd, Cu, Ni, or other). The development and application of this new DalPhos ligand family, including recent methodology and mechanistic studies thereof, will be presented (Figure 1).[1,2]

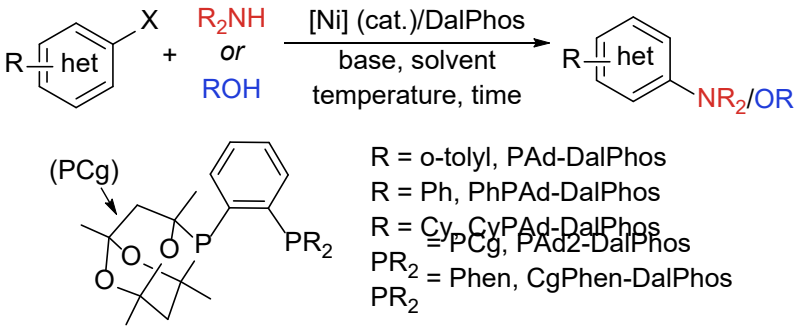

Figure 1. Ni/DalPhos enabled cross-couplings.

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[2] The author declares the following competing financial interests: Dalhousie University has filed patents on the DalPhos ancillary ligands and derived nickel pre-catalysts used in this work, from which royalty payments may be derived.

Copper-Catalyzed Aminofunctionalization of Alkenes and Dienes

Qiu Wang

Department of Chemistry, Duke University, Durham, USA
E-Mail: qiu.wang@duke.edu

Abstract

Aminofunctionalization of alkenes represents a direct and powerful strategy to transform simple and readily available olefins into richly functionalized nitrogen-containing compounds of great value. Toward this end, we have developed copper-catalyzed alkene aminofunctionalization reactions by exploring electrophilic amination and the coupling reactions of versatile nucleophiles. These methods afford a rapid and direct access to a diverse range of 1,2-amino alcohols,[1] 1,2-amino halides,[2] and medicinally valuable (hetero)arylethylamines.[3] Mechanistic studies on these reactions have revealed a novel electrophilic amination-initiated activation pathway that has great potentials for a general, powerful platform for designing regio- and stereoselective new functionalization transformations of alkenes and dienes.

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A Process Chemistry Perspective on Transitioning from Palladium to Nickel Catalysis for C-B and C-C Bond Formations

Matthew J. Goldfogel[a]*
[a]Chemical Process Development, Bristol Myers Squibb, New Brunswick NJ, USA
Email: matthew.goldfogel@bms.com; https://orcid.org/0000-0002-6911-3068

A key goal for the pharmaceutical process chemist is to improve synthetic efficiency and sustainability while supplying active pharmaceutical ingredients (APIs) to patients. This puts a premium on replacing expensive and difficult to source rare-earth catalysts with more widely available base-metals. The Miyaura borylation and Suzuki cross-coupling reactions are frequently used palladium-catalyzed transformations to construct C-B and C-C bonds respectively, often in sequence. This makes it an impactful target for implementing base-metal nickel catalysis as an alternative to established palladium methods. Many literature approaches to nickel-catalyzed C-B and C-C bond formations are challenging to adapt to process chemistry due to the use of unstable Ni(0) pre-catalysts, heterogeneous reaction conditions, and reduced compatibility with complex heteroaryl substrates. However, nickel benefits from improved scope of the electrophile, abundant catalysts, and facile metal purge – advantages that compound when processes are scaled to metric tons. This talk details our ongoing efforts to transition Miyaura borylation and Suzuki coupling reactions from palladium to nickel catalysis. We have developed process-relevant screening platforms for C-B and C-C coupling reactions and applied them to the synthesis of key intermediates in our portfolio on multi-kg scale. Parallel efforts to understand the mechanism of catalyst activation, as well as on-cycle vs off-cycle metal speciation, led to the discovery of a more robust aqueous nickel-Suzuki method. The improved aqueous nickel-catalyzed Suzuki reaction conditions allowed us to directly telescope nickel-catalyzed Miyaura borylation reaction streams into Suzuki couplings to improve process efficiency. Through this focused effort on nickel catalysis, we have significantly improved our mechanistic understanding, allowing for more consistent application of nickel catalysis to our portfolio moving forward.

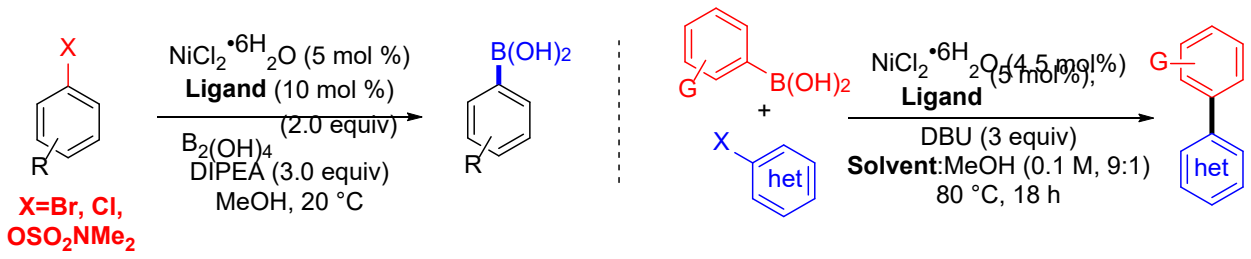

Figure 1. Process focused methods for nickel-catalyzed C-B and C-C bond formations

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Leveraging Ligand Fluxionality in Organonickel Catalysis

Keary M. Engle*[a]
[a] Department of Chemistry, The Scripps Research Institute, 10550 N Torrey Pines Road, La Jolla, CA 92037, USA
Email: keary@scripps.edu

Nickel(0) complexes bearing quinones and related ligands are bench-stable, isostructural analogs of the canonical nickel(0) complex, $Ni(COD)_2$ (COD = 1,5-cyclooctadiene).[1–3] In many contexts, such as in cross-coupling reactions, these Ni(0)–quinone complexes are able to perform equivalently to $Ni(COD)_2$, with their enhanced stability allowing reactions to be conveniently set up without an inert-atmosphere glovebox. Beyond their operational convenience, Ni(0)–quinone complexes have recently begun attracting attention for their unique reactivity profiles in catalysis, which stems from the ability of the quinone ligand to adopt multiple coordination modes, each with a distinct steric and electronic profile (Figure 1). This seminar will discuss the genesis of this family of pre-catalysts, the current understanding of their mechanisms of action, and applications in enabling otherwise challenging alkene functionalization reactions.

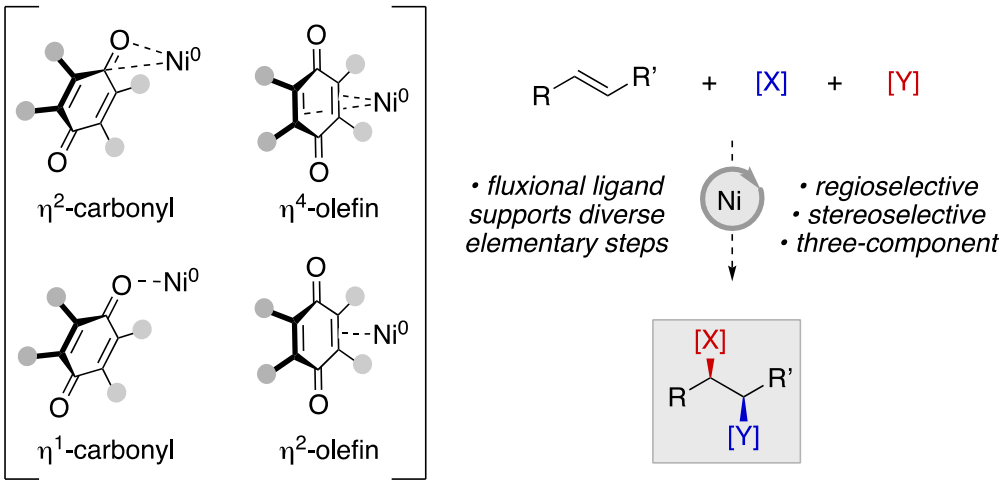

Figure 1. Overview of Ni(0)–quinone coordination modes and applications in alkene functionalization.

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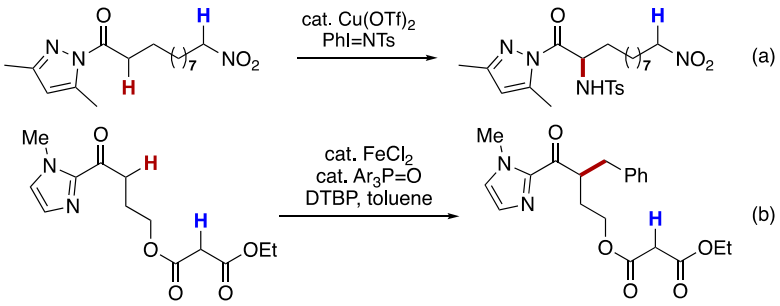
Catalytic Chemoselective Enolate Formation of Carboxylic Acids

T. Ohshima,* R. Yazaki,* T. Tanaka, Y. Koga, and Y. Honda
Graduate School of Pharmaceutical Sciences, Kyushu University
Email: ohshima@phar.kyushu-u.ac.jp

The ubiquitous carboxylic acid is an ideal carbonyl donor for synthesizing functional carboxylic acid derivatives. In recent years, they have also attracted attention as radical precursors for redox catalysis. Carboxylic acids are innately Brønsted acidic, which inhibits the deprotonation of α-protons to form enediolate. Therefore, even recent enolization methods still require stoichiometric amounts of base.[1] Due to the difficulty of catalytic enolization of carboxylic acids, we first developed reactions using carboxylic acid equivalents instead of carboxylic acids. For example, *N*-acylpyrazole can be activated by Lewis acidic metals to form enolates even under weakly basic conditions, allowing catalytic enolization without adding an external base.[2] Under this reaction condition, it is possible to chemoselectively generate *N*-Acylpyrazole enolates even in the presence of α-protons of more acidic nitro groups (eq. a). Similarly, the enolization of 2-Acylimidazole, which has a ketone structure but can be easily converted to carboxylic acid, is also readily proceeded by iron catalysts.[3] In catalytic enolate cross-coupling reactions and dehydrogenative alkylation reactions of 2-Acylimidazole, the Lewis acidity of the redox-active iron catalyst selectively activated 2- acylimidazole, even in the presence of more acidic α-protons (eq. b).



We then turned our attention to the more challenging catalytic enolization of carboxylic acids. Previous enolization methods have only been applied to redox-neutral couplings with 2e⁻ electrophiles, and catalytic α-functionalization of carboxylic acids by 1e⁻ radical processes has not been achieved date. We therefore developed direct α-oxidation of carboxylic acids via radical process through redox active Lewis acid activation strategy.[4] The present catalysis required no external Brønsted base and exhibited wide functional group tolerance. In this reaction, alkali metal in molecular sieves substantially increased the catalytic activity. This catalytic system was found to be a bimetallic cooperative catalytic system of iron and alkali metals that efficiently enolize carboxylic acids. This mechanism enables the chemoselective functionalization of carboxylic acids in the presence of carbonyl compounds such as ketones, esters, and amides (eq. c). Recent studies on catalytic α-deuteration of carboxylic acids[5] will also be presented.

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New Directions in Nickel Catalysis

Abigail Doyle*[a]
[a]Department of Chemistry and Biochemistry, University of California Los Angeles
Email: agdoyle@chem.ucla.edu

One of the most important considerations when developing a transition metal-catalyzed synthetic method is the selection of an ancillary ligand. With thousands of unique ligand structures designed to complement equally diverse metal/substrate chemical space, identification of an effective ligand can be challenging, as the ability to rationalize and predict how ligands will impact catalyst structure and reactivity often requires extensive study. Thorough mechanistic investigations have elucidated many of these ligand structure–reactivity relationships (SRRs) with Pd, leading to substantial advances in ligand and precatalyst design for cross-coupling reactions. However, a similar mechanistic understanding of ligand effects is lacking for Ni, limiting its widespread adoption in synthesis as a practical alternative and complement to precious metal catalysts. This lecture will discuss my group's efforts to design new ligands for Ni, develop a mechanistic understanding of Ni's unique structure-reactivity relationships, and apply these advances to the development of improved and new catalytic methods for chemical synthesis.

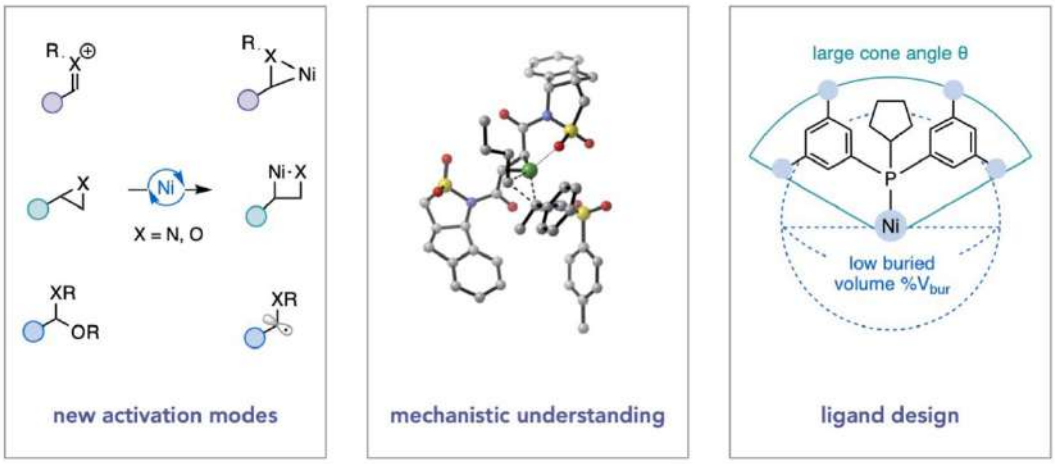

Figure 1. Doyle group program in Ni-catalyzed cross-coupling

Accelerating Advances in Catalysis – Concepts, Insights, Strategies

Franziska Schoenebeck*[a]
[a]RWTH Aachen University, Institute of Organic Chemistry, Landoltweg 1, 52074 Aachen
Email: franziska.schoenebeck@rwth-aachen.de

Modern catalytic strategies frequently rely on substantial optimization and high throughput screening for the identification of optimal conditions. To reach the next frontier in the construction of molecules *via* automation and programmable synthetic approaches, novel and fully orthogonal catalysis regimes are imperative to enable synthetic manipulations in an orthogonal manner to established bond forming approaches and associated catalysis regimes. This talk will give insights and developments towards this goal from our laboratory. The focus will be on multinuclear palladium[1] and nickel catalysis[2] of oxidation state (I), the exploration of organogermanes[3] as coupling partner as well as strategies to accelerate the identification of new catalysts.[4]

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A Cooperative Photoredox/Cobalt/Brønsted Acid Catalysis

Hirohisa Ohmiya
Institute for Chemical Research, Kyoto University
Email: ohmiya@scl.kyoto-u.ac.jp

In this presentation, we describe Markovnikov hydrofunctionalization of alkenes through a cooperative catalysis consisting of photoredox, cobalt and Brønsted acid catalysts under visible light irradiation. For example, we disclosed a triple photoredox/cobalt/Brønsted acid catalysis enabling Markovnikov selective hydroalkoxylation of alkenes with alcohols.[1] Therein, a cobalt(II) complex receives an electron and a proton from a photoredox and a Brønsted acid catalyst, respectively, to form a cobalt(III) hydride species, which undergoes metal hydride hydrogen atom transfer (MHAT) to an alkene producing an alkyl radical with complete Markovnikov selectivity.

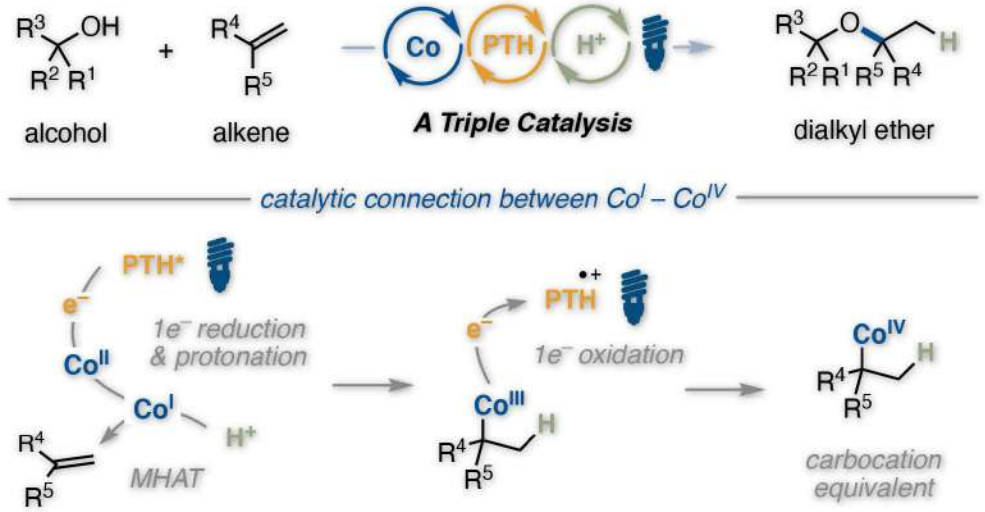

Figure 1. A Triple Photoredox/Cobalt/Brønsted Acid Catalysis Enabling Markovnikov Hydroalkoxylation of Unactivated Alkenes

Reference

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New Tools in Organopalladium Catalysis: Pd(0) Precatalysts and Quantitative Reactivity Models

David C. Leitch*[a]
[a]Department of Chemistry, University of Victoria
Email: dcleitch@uvic.ca

Organopalladium catalysis remains among the most powerful and versatile methods in the synthesis of complex organic molecules. To best utilize these methods at the lowest catalyst loadings possible, our research group is developing new tools to enable efficient reaction screening and scale-up, and to enhance synthetic planning to maximize reactivity and selectivity.

We recently disclosed an alpha-diimine coordinated Pd(0) complex – ^{DMP}DAB-Pd-MAH – that is an easily prepared and general precatalyst specifically designed for high-throughput experimentation.[1] In addition to applications in cross-coupling chemistry, we have applied this compound to access new chiral Pd(0) catalysts for asymmetric allylic alkylation (Figure 1, *left*).[2]

The application of statistical modeling to chemical reactivity is leading to advances in computer-aided synthesis design and deeper mechanistic understanding.[3] Our approach to building quantitative models for catalytic reactivity hinges on studying elementary steps in catalytic cycles to maximize generality across multiple reaction classes. Our first report in this area centers on predicting oxidative addition reactivity for (hetero)aryl ((*pseudo*)halides to Pd(0). The resulting model makes accurate quantitative predictions about rate and selectivity for myriad catalytic reactions.[4]

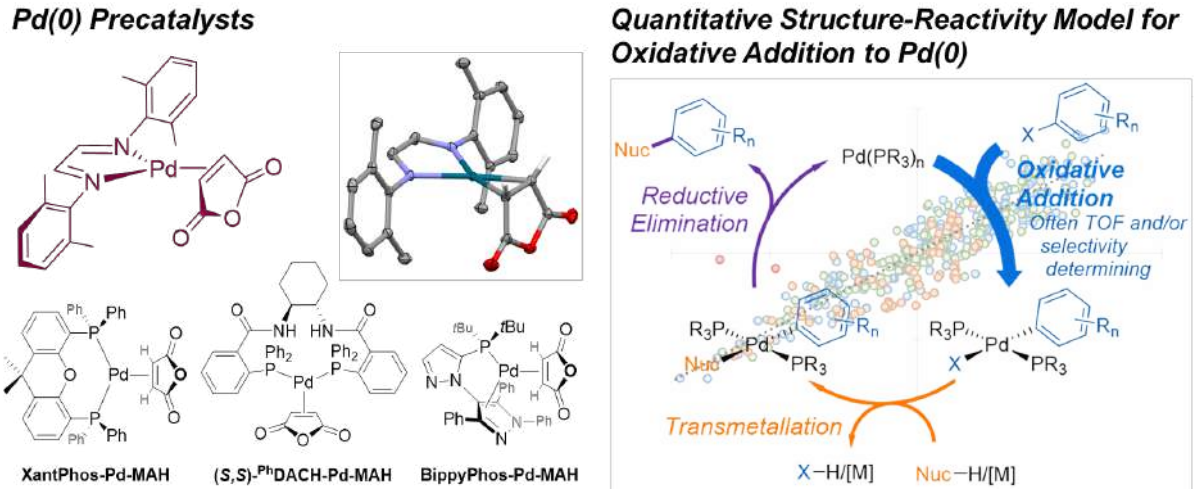

Figure 1. Recent developments in organopalladium chemistry, including new Pd(0)-based precatalysts for cross-coupling and allylic alkylation (*left*), and predictive models for oxidative addition rates to Pd(0) (*right*).

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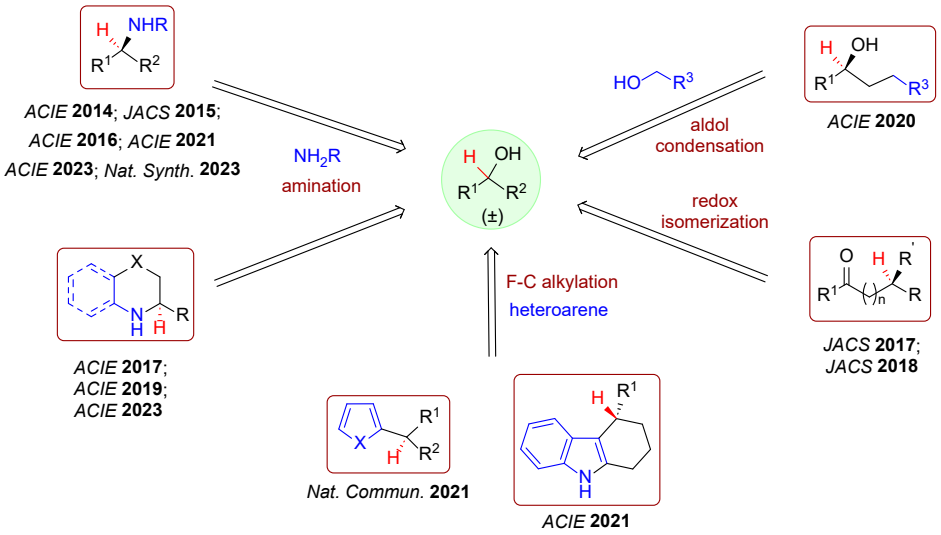
Catalytic Enantioselective Redox-Neutral Processes for Efficient Chemical Synthesis

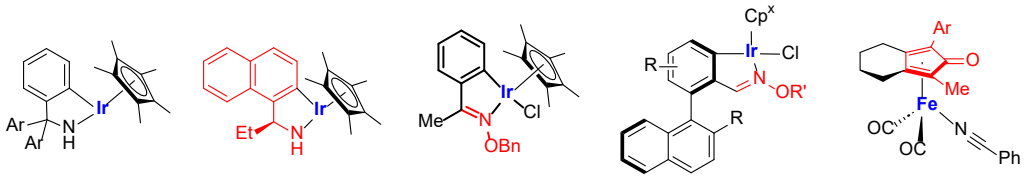
Yu Zhao
3 Science Drive 3, Department of Chemistry, National University of Singapore
Email: zhaoyu@nus.edu.sg

The development of economical and selective catalytic methods is of significant importance for the promotion of sustainable chemical synthesis. My group at National University of Singapore has focused on the identification of catalytic enantioselective redox-neutral transformations that directly convert feedstock materials to valuable chiral entities with wide application in organic synthesis. In particular, we have achieved a series of direct stereoconvergent "substitution" of readily available racemic alcohols via borrowing hydrogen catalysis for economical access to chiral amines, *N*-heterocycles, alcohols and ketones. Recent progress made along these lines will be discussed in details in this presentation.

Direct enantioconvergent functionalization of alcohols via borrowing hydrogen catalysis



New catalysts introduced in our lab for redox-neutral transformations of alcohols:



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New Developments in Ni-Catalyzed Transnitrilation

Sophie Rousseaux*[a]
[a]Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada
Email: sophie.rousseaux@utoronto.ca

The synthesis of nitrile-containing building blocks has garnered considerable attention from the community for over a century due to their prevalence in pharmaceuticals and their versatility as synthetic intermediates. In this field, the use of toxic cyanide salts (and their equivalents) or HCN as a source of nitrile to forge C–CN bonds remains a problem. My group has developed new synthetic methods for the synthesis of nitrile-containing building blocks that use non-toxic, bench-stable, nitrile-transfer reagents.[1,2] This presentation will highlight our contributions to this field, with a particular focus on the development of Ni-catalyzed methods for the synthesis of nitriles.[2]

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Spirobipyridine Ligand for Remote Steric Control in Iridium-Catalyzed C–H Borylation of Arenes

Sobi Asako,* Yushu Jin, Boobalan Ramadoss, Laurean Ilies*
RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan
Email: sobi.asako@riken.jp; laurean.ilies@riken.jp

Transition-metal-catalyzed regioselective C–H functionalization of arenes has been achieved by taking advantage of various attractive interactions such as hydrogen-bonding, ion-pair, and Lewis acid-base interactions, or by electronically biasing the substrate. However, the regioselective functionalization of simple arenes such as alkylbenzenes, lacking in such interactions has remained arduous. The steric control strategy has been successful in blocking the proximal *ortho* position, but differentiation of remote positions such as *meta* and *para* is challenging.[1,2] We report here a conceptually new ligand, **SpiroBpy-Bpin**, that sterically protects the remotest *para* site besides the *ortho* site to achieve *meta*-selective C–H activation in the iridium-catalyzed borylation.[3] Thus, the rigid Bpin group on three-dimensionally expanded **SpiroBpy** functions as a "steric roof" to create a molecular pocket that accommodates the substrate approaching the catalytic center only in the *meta* orientation. The strategy proved general, and a variety of monosubstituted arenes including alkylbenzenes, anilines, phenols, and drug molecules could be selectively borylated at the *meta* position. We also found that the iridium/**SpiroBpy** catalyst accelerates the C–H borylation reaction and the reactions of reluctant electron-rich arenes proceeded more efficiently than with commonly used ligands such as dtbpy and tmphen.

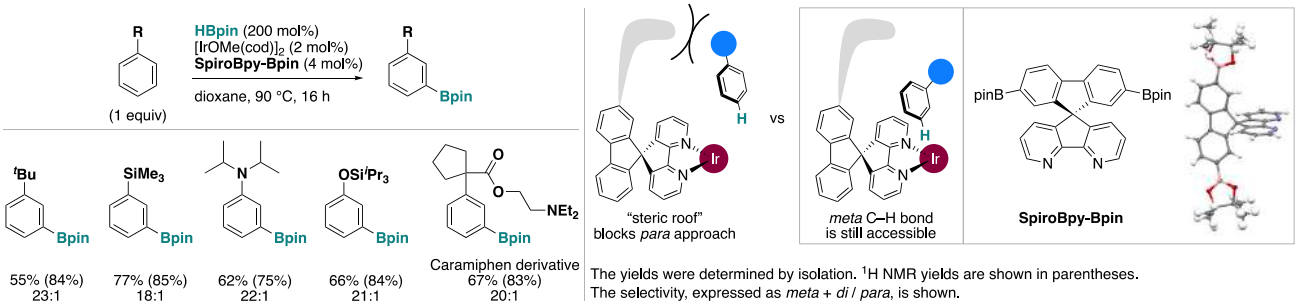

Figure 1.

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Enantioselective Desymmetrization of a Versatile Cyclobutene Scaffold via Dual-Catalyzed Photoredox Cross-Coupling

Dawson Konowalchuk,[a] Dennis G. Hall*[a]
[a]Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2, Canada
Email: dennis.hall@ualberta.ca

Four-membered carbocycles are important structural motifs found in several drugs and natural products.[1] Many studies have reported the enantioselective synthesis of a wide range of cyclobutanes, however, methods to access chiral cyclobutenes are scarce and generally limited in terms of diversification, furnishing only mono–, di–, and, rarely, tri- and tetrasubstituted cyclobutenes.[2] Cyclobutenes are highly advantageous as intermediates because the residual olefin allows for greater synthetic freedom, leading to a plethora of various saturated and unsaturated analogs. Consequently, there is a pressing need to design new strategies for accessing chiral cyclobutenes; syntheses that can provide universal access to various functionalities and substitution patterns. Drawing on the attractive yet underexplored approach of enantioselective desymmetrization, prochiral 1,2-dihalocyclobutene imides were subjected to a novel dual Ir/Ni-catalyzed photoredox C(sp^2)–C(sp^3) cross-coupling with alkyltrifluoroborate salts to install a convertible carbon fragment (R^2) in good yields and >90% enantiomeric excess (Figure 1). Optimization of the key desymmetrization step focused on the chiral ligand, choice of cross-coupling partner, and other factors to limit side products and enhance enantioselectivity. To demonstrate the utility of this new method, the resulting chiral 1,2,3,4-tetrasubstituted cyclobutenes were transformed in a divergent manner into several other potentially valuable four-membered carbocycles while maintaining optical purity. For example, a second cross-coupling of the residual C(sp^2)–X bond followed by regioselective imide opening leads to chiral 1,2,3-4-tetrasubstituted cyclobutene products functionalized with four different carbon-based substituents; a selective outcome that would be difficult to achieve with alternative strategies such as direct [2+2] photocycloadditions.

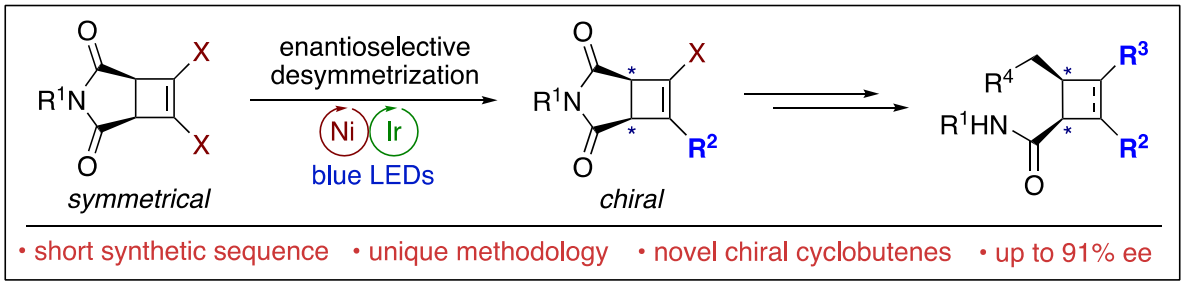

Figure 1. Enantioselective desymmetrization of 1,2-dihalocyclobutene imides.

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Using Genetic Code Expansion to Access Artificial Metalloenzymes

Amanda G. Jarvis*[a]

[a] School of Chemistry, Joseph Black Building, University of Edinburgh, Edinburgh, UK.
Email: amanda.jarvis@ed.ac.uk

Genetic code expansion has drastically increased the number of amino acids we can incorporate into protein scaffolds, including expanding the range of metal-binding amino acids.[1] Unnatural amino acids containing rigid bidentate ligands as side chains, such as bipyridylalanine **1**,[2] offer different structural binding motifs to the canonical amino acids. This allows the possibility of building up very different metal active sites to those found in natural metalloproteins, enabling new-to-nature chemistry to be introduced to the biological toolbox.[3] Here I will present my group's work on expanding the genetic code to include unnatural amino acids **2** and **3**, and how we have used these amino acids alongside bipyridylalanine to design artificial metalloenzymes (Figure 1). I will cover both structural studies and their applications in transition metal catalysis.

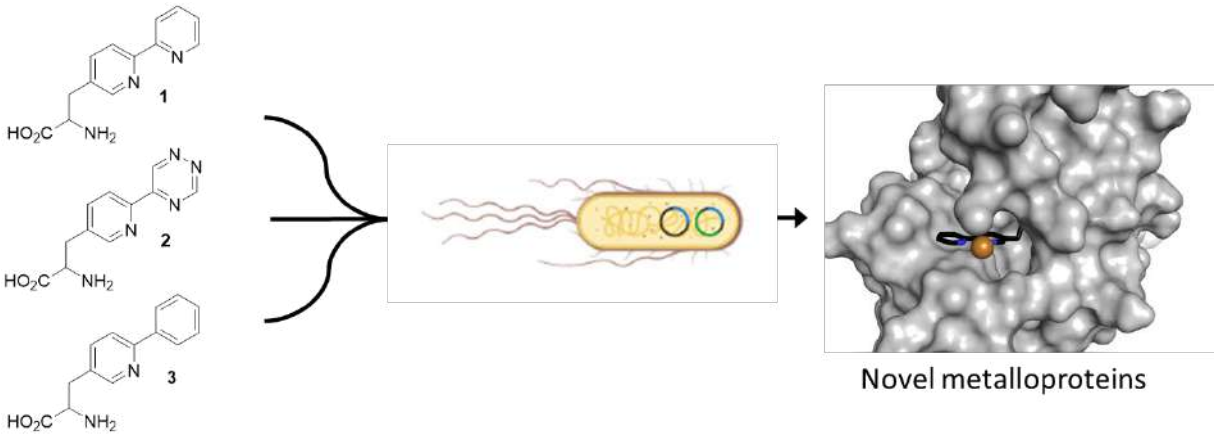

Figure 1. Production of novel metalloproteins containing unnatural amino acids **1** to **3**, via genetic code expansion using amber stop codon suppression in *E.coli.*

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From the Design of Original Reagents to their Applications: A Highway to Fluorinated Scaffolds

Tatiana Besset*[a]
[a]Normandie Univ, INSA Rouen UNIROUEN, CNRS, COBRA (UMR 6014), Rouen, 76000, FRANCE
Email: tatiana.besset@insa-rouen.fr

Organofluorine chemistry is a fascinating research field in rapid expansion. Beyond the strong interest that represents fluorinated molecules in materials science, pharmaceuticals and agrochemicals as well as modern drug design,[1] innovation is still required to push further the boundaries of knowledge in this appealing research field and to achieve new synthetic challenges.[2] Besides, the development of more sustainable transformations and among them, reactions based on transition metal catalyzed direct C-H bond functionalization have reshaped the field of organic chemistry over the last decade.3 In that context, aiming at designing new tools to access original fluorinated molecules, our group developed approaches combining organofluorine chemistry and transition metal catalyzed C C-H bond functionalization.4 Such advances were possible thanks to the design of original reagents. [5]

Figure 1. Overview of our research interests.

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Establishment of a High-Throughput Experimentation Culture for Process Chemistry at Sanofi

Alan H. Cherney[a]
[a]High-Throughput Innovation Technologies, Drug Substance Late Development, Sanofi
Email: alan.cherney@sanofi.com

To counteract the increasing complexity, diversity, and volume of Sanofi's small molecule pipeline, we established the High-Throughput Innovation Technologies (HIT) team within Process Chemistry to develop platforms that utilize high-throughput experimentation (HTE)[1] to drive high-quality route identification and route development. Key priorities for our team are to 1) rapidly and thoroughly evaluate route scouting ideas for new programs; 2) use our parallel kinetics[2] and solubility platforms to provide critical process data and support scale-up and modeling; and 3) lower the barrier to the adoption of lab automation and parallel experimentation among process development scientist and engineer end-users. To advance our ambitions, we have developed workflows for metal-catalyzed transformations, high-pressure reactions, and photocatalyzed reactions. To improve the sustainability of our manufacturing routes, we also incorporate base-metal screening and biocatalytic investigations. Our efforts to strengthen the culture of HTE across the department, including end-user trainings and a customized laboratory notebook and data management system, are currently underway.

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Strategic Activation of Organoboron Compounds for the Creation of Chemical Space with Complexity

Hong Geun Lee*[a]

[a]Department of Chemistry, Seoul National University
1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea
Email: hgleee@snu.ac.kr

Novel reactivities of organoboron reagents for the formation of covalent bonds at a carbon atom with sp^3- or sp^2-hybridization are explored. New synthetic modalities that are based on electrochemical oxidation and transition metal catalyzed processes enabled the formation of C–heteroatom and C–C bonds with unprecedented efficiencies. Ultimately, general synthetic platforms towards the formation of hindered linkage or the introduction of stereochemical information at a C(sp^3)-based reaction center has been established.

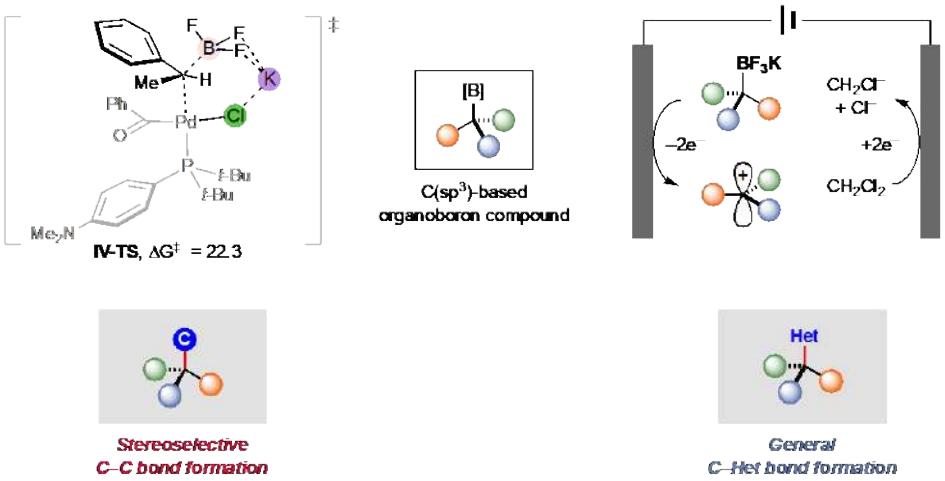

Figure 1. Activation of C–B Bonds

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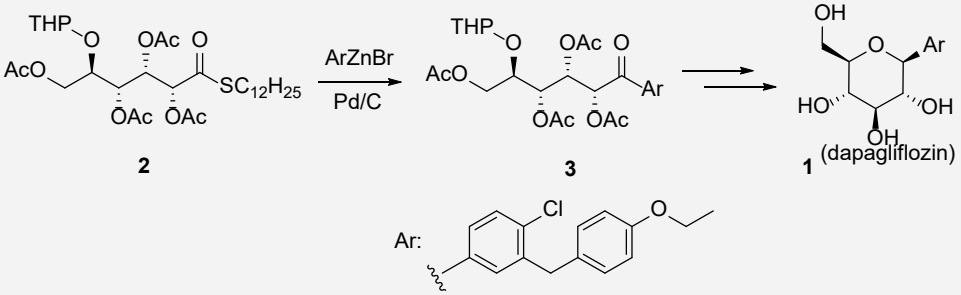
Synthesis of SGLT2 Inhibitors by Means of Fukuyama Coupling Reaction

Dr Masahiko Seki, Dr Sandeep Tapkir, Dr Maheshwara Reddy, Dr Shaheen Mulani, Prof Kazushi Mashima

Masahiko Seki*, [1, 2], Tapkir Sandeep Ramesharao,[2] Maheshwara Reddy Nadiveedhi, [2] **S**haheen Kasim Mulani[2] and Kazushi Mashima*, [2]

R&D Planning Department, Tokuyama Corporation,[1] Graduate School of Pharmaceutical Science, Osaka University[2]

Sodium dependent glucose transporter 2 (SGLT2) inhibitors **1** have received keen attention as a diabetes drug due to high efficacy and safety.[1] Recent discoveries on additional potency of those drugs for nephritis and heart failure have enhanced the importance as a therapeutic agent significantly.[2] SGLT2 inhibitors have b-C-glycoside motif as a common structure where sugar unit is combined with aromatic substituent by b-orientation.[3] Previous synthetic methods have a serious issue of need of cryogenic conditions (-78 °C) to install the characteristic structure itself. To address the drawback, we have developed new synthesis which can be undertaken at ambient temperature for the key step.[4] The method consists of a new ketone synthesis from **2** to **3** through Fukuyama coupling reaction. The mild conditions enable use of labile acetyl protecting group.



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Automatic peak assignment and feedback-controlled synthesis of complex one-pot multistep Suzuki-Miyaura couplings.

Mason Guy, **Jason E. Hein***
University of British Columbia
Email: mguy068@chem.ubc.ca; jhein@chem.ubc.ca

The synthesis of laser dye molecules via iterative one-pot Suzuki-Miyaura coupling (SMC) involves multiple reaction components and is further complicated by multiple potential side reactions, making their optimization incredibly difficult and time consuming (**Figure 1**). We have developed an adaptive, automated synthesis tool that utilizes online high-performance liquid chromatography to monitor the progress of a reaction in real time. This live monitoring allows enables the system to execute actions based on the reactivity of different substrates. The platform also utilizes the temporal reaction profiles combined with component information such as ultraviolet spectroscopy and polarity to determine the identity of side/decompositions products, intermediates, and other reaction components, bypassing the need for isolation and quantification of unknown species. By combining the real time decision making and component identification, we analyzed and optimized the synthesis of three laser dyes via iterative one-pot SMC from nine chemically distinct starting materials.

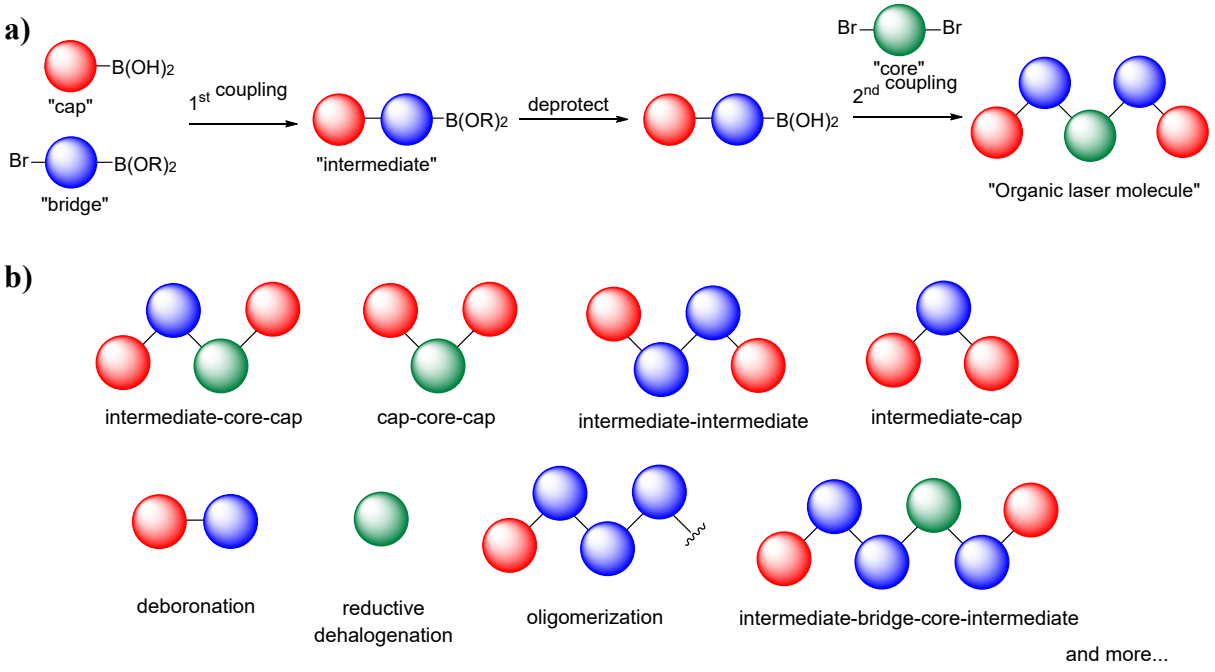
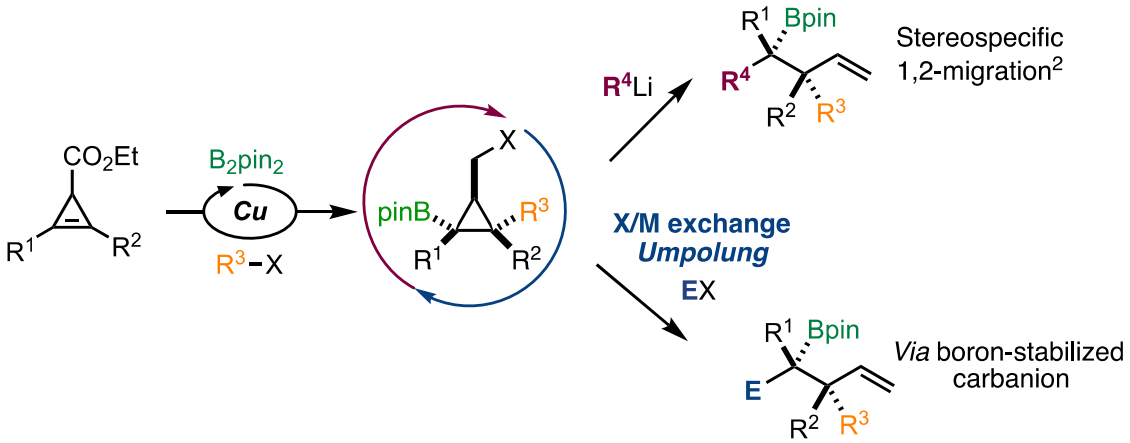


Figure 1. Assembly of organic laser molecules. a) building block, one-pot iterative coupling approach b) non-exhaustive list of potential undesired side products.

Ring Opening of Borylated Cyclopropanes: Beyond 1,2-Metalate Rearrangement

Tereza Pavlickova,[a] **Ilan Marek***[a]
[a] Schulich Faculty of Chemistry, Technion – Israel Institute of Technology, Technion City, Haifa, 3200009, Israel
Email: tereza.p@campus.technion.ac.il; chilanm@technion.ac.il

Controlled construction of congested stereogenic centers within acyclic systems represents an acute challenge in stereoselective organic synthesis. The main obstacle is the conformational flexibility of these organic frameworks compared to cyclic systems. An elegant solution to this problem involves introduction of stereocenters to cyclopropanes as highly strained carbocycles and subsequent selective ring opening.[1]
Previously, we reported synthesis and 1,2-metalate rearrangement-mediated ring opening of polysubstituted borylated cyclopropanes by various alkyl-, aryl- and alkynyllithium reagents.[2] Here, we present a selective metal-halogen exchange-mediated ring fragmentation of cyclopropyl pinacolboranes exploiting the anion-stabilizing effect of the boronic ester moiety. This *umpolung* strategy represents an original approach to boron-stabilized carbanions. Subsequent reaction of these species with electrophiles provides various acyclic frameworks with high levels of diastereoselectivity.



Scheme 1.

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Synthetic Possibilities of Multifunctional Nucleophiles in Homogeneous Catalytic Carbonylation Reactions

László Kollár[a], Attila Takács[a], Csilla Molnár[a], Andrew Kovács[a], László T. Mika[a], Péter Pongrácz*[a]

[a]Department of Inorganic Chemistry, University of Pécs, Hungary
[b]Budapest University of Technology and Economics, Hungary
Email: pongracz@gamma.ttk.pte.hu

Homogeneous catalytic carbonylation reactions performed in the presence of various nucleophiles are excellent synthetic tools for the production of valuable fine chemicals, such like amides, esters, thioesters. Several studies have been reported for the utilization of simple amines and alcohols as model reactants, only a few works focused on the investigation of carbonylation reactions in the presence of homo- and even heterobifunctional nucleophiles. However, the application of the latter open alternative and easier synthetic routes for the construction of complex molecular structures. Our investigation was focused on the selective transformation of iodoarenes with various aminoethanols to get the corresponding amides or amide-ester derivatives. It was showed, that the substrate-nucleophile ratio and the base have crucial role on product distribution. Furthermore, interesting correlation was found between the substituents of the aryl iodides and the rate of amino/alkoxy-carbonylation reactions. Additionally, trifunctional nucleophiles were also tested with various iodobenzene amounts. Surprising results showed increased affinity on 'tricarbonylated' products, which phenomena were explained by mechanistic considerations.
Additionally, some selected aminoethanols were reacted with *ortho*-dihalogenated aromatic substrates under carbonylation conditions. Iodo- and bromo-aromatic structures showed diverse reactivity and selectivity with the selected heterobifunctional nucleophiles. As it was expected, iodobenzenes and amines were much more reactive compared to bromo analogues and O-nucleophiles, but latter structural items are also suitable coupling partners and showed interesting behaviour under the applied conditions.

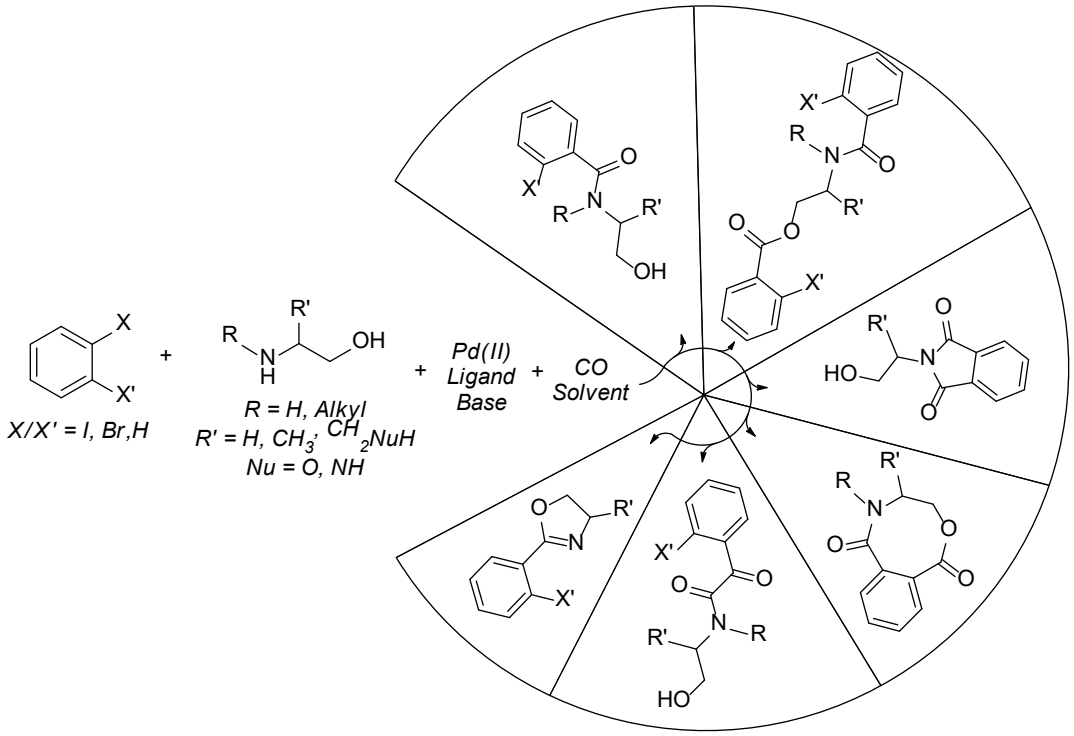

Figure 1. Carbonylation reaction of aryl halides in the presence of bifunctional N,O-nucleophiles

P(III)-Directed C–H Activation

Zhuangzhi Shi*[a]

[a]State Key Laboratory of Coordination Chemistry, Chemistry and Biomedicine Innovation Center (ChemBIC), School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093 (China)
Email: shiz@nju.edu.cn

Prized for their ability to generate chemical complexity rapidly, catalytic carbon–hydrogen (C–H) activation and functionalization reactions have enabled a paradigm shift in the standard logic of synthetic chemistry. Directing group strategies have been used extensively in C–H activation reactions to control regioselectivity with transition metal catalysts. Compared to oxygen and nitrogen atoms, phosphorus coordinates strongly with metals and is therefore challenging to use as a director in catalytic C−H activation (Figure 1). During the past five years, substantial progress has been made by our group in ligand modification through P(III)-directed C−H activation.[1-2] We have also demonstrated the viability of using phosphorus directing groups for the site-selective C−H functionalization of indoles at the benzene core.[3-6] In addition, enantioselective C–H activation directed by a phosphorus center to rapidly construct libraries of axially chiral phosphines has also been uncovered through dynamic kinetic resolution. This reaction mode significantly expands the pool of enantiomerically enriched functional phosphines, some of which have shown excellent efficiency for asymmetric catalysis.

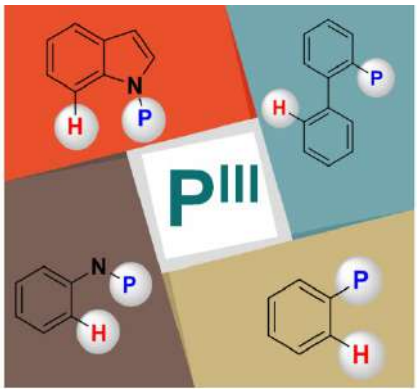

Figure 1. Examples of P(III)-directed C–H activation

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Organometallic Catalysis under Visible Light

Louis Fensterbank
Institut Parisien de Chimie Moléculaire, Sorbonne Université
4, place Jussieu,75005 Paris, France
Email: louis.fensterbank@sorbonne-universite.fr

Over the last decade, we have been involved in the implementation of organometallic catalysis to the development of more sustainable synthetic radical chemistry. We have notably introduced hypercoordinated bis-catecholato silicates as versatile sources of alkyl radicals upon visible light photocatalysis.[1] Using Ir(III) as catalytic photooxidant, or an organic dye, a series of alkyl radicals, including primary ones can be generated and engaged in intermolecular reactions. Interestingly, the photocatalyzed process can be merged with nickel-catalyzed C_{sp2}-C_{sp3} cross-coupling reactions (see Figure 1)
In the same vein and following our interest in gold catalysis, our recent efforts in photoredox/gold dual catalysis will also be presented.[2] In the context of these studies, we have evidenced the first examples of photosensitized oxidation additive to a gold(I) complex leading to C_{sp2}-C_{sp} cross-couplings.[3] Recently, photocatalyst-free conditions have been applied to the synthesis of indoles.[4]

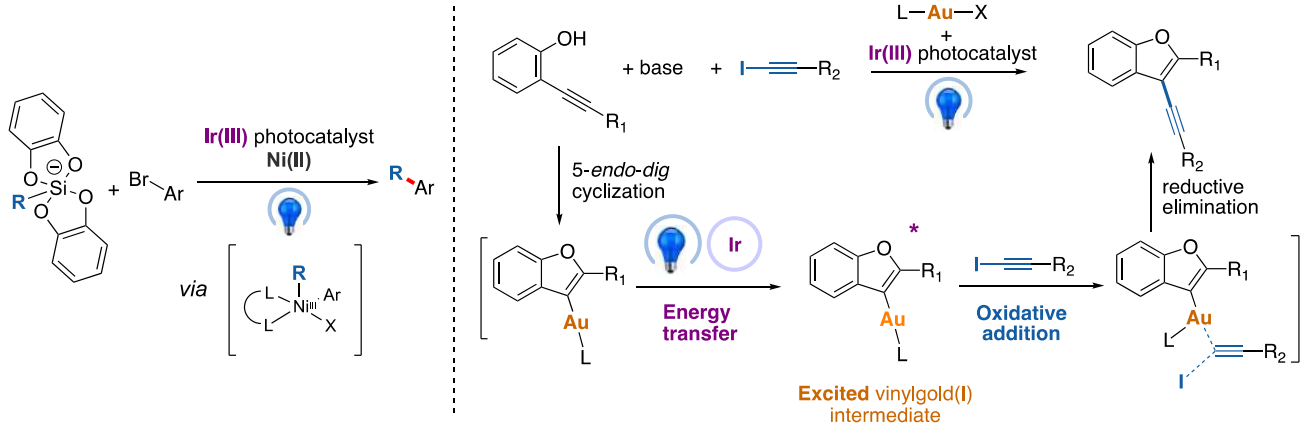

Figure 1. Dual photoredox/Ni and photosensitization/Au catalysis

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Asymmetric Rh Diene Catalysis under Liquid and Solid Confinement – When Polarity, Domain Size and Flexibility Matter

Sabine Laschat,*[a] **Manuel Kirchhof**,[a] **Max Deimling**,[a] **Anna Zens**[a]
[a] Institut für Organische Chemie, Universität Stuttgart, D-70569 Stuttgart, Germany
Email: sabine.laschat@oc.uni-stuttgart.de

Asymmetric catalysis with chiral Rh diene complexes has received increasing interest over the last two decades.[1] Taking inspiration by enzymes, researchers have recognized the important role of confinement on catalytic reactions with respect to reaction rate, yield, mechanism, product ratio, chemo- and regioselectivity, diastereomeric and enantiomeric ratio.[2-4] However, confinement effects have only been rarely exploited in Rh diene catalysis. Therefore, we studied the Rh-catalyzed 1,2-addition of phenylboroxine to *N*-tosylimines as a benchmark reaction both under liquid confinement in microemulsions[5,6] as well as solid confinement in mesoporous silica SBA-15[7] and silica-inverse opals SiO_2-IO.[8] The role of polarity (and charge), domain or pore size, steric bulkiness and flexibility of linkers between catalyst and support in such confined catalyses will be discussed and methods to determine the accessibility and spatial distribution of Rh diene complexes in pores will be presented.[9]

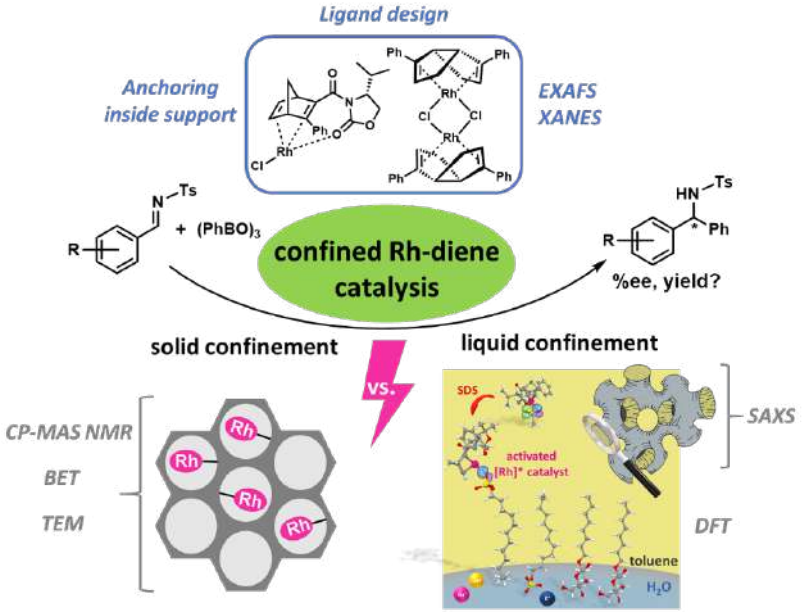

Figure 1. Asymmetric catalysis with chiral Rh diene complexes under solid and liquid confinement

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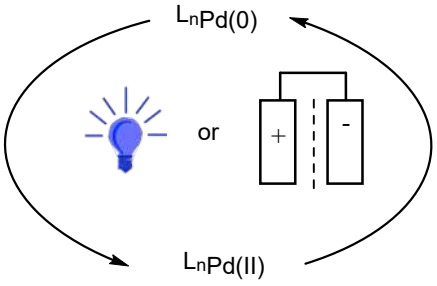
Alternative Energy Drivers in Palladium Catalyzed Coupling Reactions

Bruce A. Arndtsen[a]
[a]Department of Chemistry, McGill University, 801 Sherbrooke St. W., Montreal QC H3A 0B8 Canada
bruce.arndtsen@mcgill.ca

The ability of transition metal catalysts to mediate new bond forming reactions has had a dramatic impact on modern molecular synthesis. Nevertheless, a central feature in these reactions is need to balance of reverse operations on the catalyst so it is regenerated at the end of each cycle of product formation, which can limit catalytic activity and the scope of many transformations. This talk will describe our efforts to address these challenges by introducing alternative, often renewable, energy sources into catalysis, and from this create new bond forming reactions. These include using visible light excitation directly on active palladium catalysts to drive the oxidative addition/reductive elimination cycle in coupling reactions independent of the classical limits in thermal catalysis, or the use of electrochemistry to change the nature of the metal throughout the cycle.[1] Combining these with the favored energetics of carbon monoxide conversion to carboxylic acid derivatives can be used to drive the build-up of reactive products from stable reagents. The use of this chemistry to create ambient temperature and general catalysts for carbonylation reactions, multicomponent transformations, acyl halide or even super-electrophile formation, or new avenues to C-H bond functionalization, will be discussed, as will the mechanistic origins of these influences, and their ability to enable the use of earth abundant catalysts in traditionally precious metal catalyzed reactions.



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Enone as a Process Aid for the Highly Efficient Synthesis of the Age-old Karstedt's Catalyst

Souvagya Biswas,*[a] Zhanjie Li,*[b,] Andrew R. Millward, [b] Paulami Majumdar,[a] Sukrit Mukhopadhyay[a]

[a] Core R&D, Dow, 1776 Building, Midland, Michigan 48667, United States.

[b] Dow Performance Silicones, Dow, 5300 Eleven Mile Road, Auburn, Michigan 48611, United States

Email: sbiswas5@dow.com

While a plethora of catalysts have been developed over the years to promote hydrosilylation reactions, homogenous platinum-based catalysts such as Speier's catalyst and Karstedt's catalyst are still the workhorse for hydrosilylation processes.[1] Karstedt's catalyst is usually manufactured at scale by using either chloroplatinic acid or platinum halide as the platinum source.[2] The synthesis of Karstedt's catalyst from anhydrous, low valent $PtCl_2$ requires the presence of a polar solvent (methylethylketone, MEK) and divinyl tetramethylsiloxane (dvtms) as the reagent. Despite being practiced over several decades, the reaction suffers from several limitations such as low conversion (poor yield of the catalyst), long reaction time (8-10 hours), and thermal decomposition of the catalyst over longer period, to name a few. Through an approach that relies mostly on mechanistic insights and systematic investigation of all reaction parameters, we identified that pre-soaking or milling $PtCl_2$ in MEK at room temperature led to the formation of crystalline $Pt_6Cl_{12}\cdot(MEK)_{1.5}$ material which drastically improved the reaction conversion (4 hours, 99% conv.). As our understanding of the mechanism of this reaction improved, we discovered that small amounts of $PtCl_2$(enone) complexes were formed in-situ from the pre-heated mixture of $PtCl_2$ and MEK in absence of dvtms. These enone compounds were likely formed via aldol condensation of MEK, followed by a dehydration reaction. We have since found that these β, γ -enones are superb process additives and can be independently added (as low as 1wt%) to improve the reaction rate (<4 hrs) and conversion (>98% conv., Figure 1). Computational studies further suggest that enones behave as phase-transfer additives. Once MEK disrupts the $PtCl_2$ lattice, enones facilitate the dissolution process via complexing with the individual molecular $PtCl_2$ moieties, thus stabilizing them in the homogenous phase. In addition, the calculated energy landscape suggests that once the solid $PtCl_2$ is brought into the homogeneous liquid phase, the formation of the Karstedt's catalyst itself is energetically downhill, overcoming only moderate activation barriers for a Pt(II) to Pt(0) reduction process. The details of these studies will be presented during the talk.

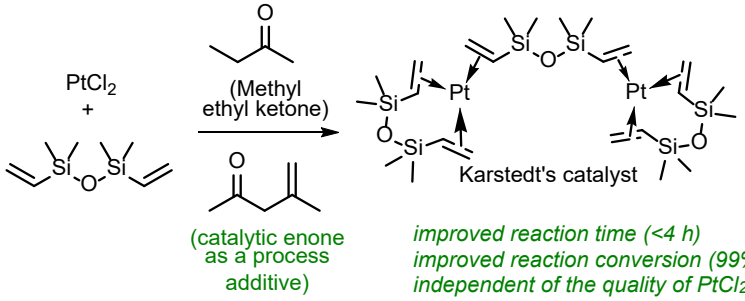

Figure 1. Enone as a process aid for synthesis of the Karstedt's catalyst.

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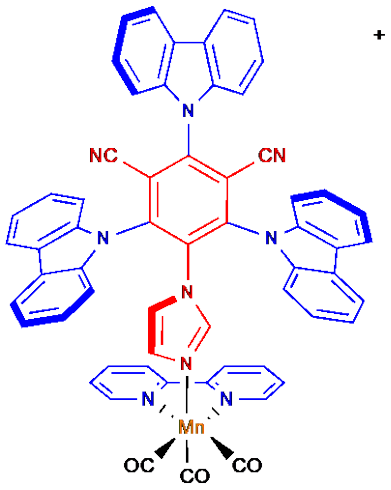
New NHC- and Imidazole-Functionalized Carbazole Dyes for Visible-Light Organic- and Solar Fuels Photoreactions Over Homogeneous- and Heterogeneous Photocatalysts.

Steven H. Bergens*[a], Octavio Martinez Perez[a], Elizabeth Murphy[a], Jinkun Liu[a], Dominic Lavergne[a], Mona Amiri[a], Loorthuraja Rasu[a],

[a] Department of Chemistry, University of Alberta.
Email: sbergens@ualberta.ca.

We have developed straight-forward methods to prepare new amine-, imidazole-, and free N-heterocyclic carbene (NHC)- derivatives of the recently reported push-pull dye 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN). Intersystem crossing from the excited singlet- to triplet-states of 4-CzIPN is facile, and the triplet state undergoes useful photoreactions. We utilize our new dyes in homogeneous and heterogeneous photocatalysis. For heterogeneous systems, we bond the dyes to ITO, TiO_2, and carbon supports via either diazonium grafting, coordination of the free NHC group to TiO_2, or most recently, by direct electropolymerization. For homogeneous systems, we have prepared Mn- and Re- complexes with the imidazole- or NHC- dyes and utilized them for the visible-light photoreductions of CO_2. The detailed electrochemistry and photochemistry of the Mn- and Re- complexes will be presented.



Homogeneous and Heterogeneous Catalysts for Alkene Isomerization and Hydrosilylation

Amanda K. Cook*[a]
[a]University of Oregon
Email: akcook@uoregon.edu

The mechanism of hydrosilylation has been extensively studied when using platinum catalysts,[1] and much less is known when using palladium and nickel. Relevant to palladium-catalyzed hydrosilylation and C-Si cross coupling reactions, we have elucidated the mechanism of a proposed elementary step of the catalytic cycle, oxidative addition of Si–H and Si–X bonds to Pd(0),[2,3] and we have shown that trends in oxidative addition are transferrable to catalysis. Additionally, we have developed methods for nickel-catalyzed alkene isomerization and hydrosilylation, which forms branched organosilanes in excellent selectivity over the linear organosilanes.[4] Mechanistic work supports a two-electron pathway for the nickel-catalyzed reactions.

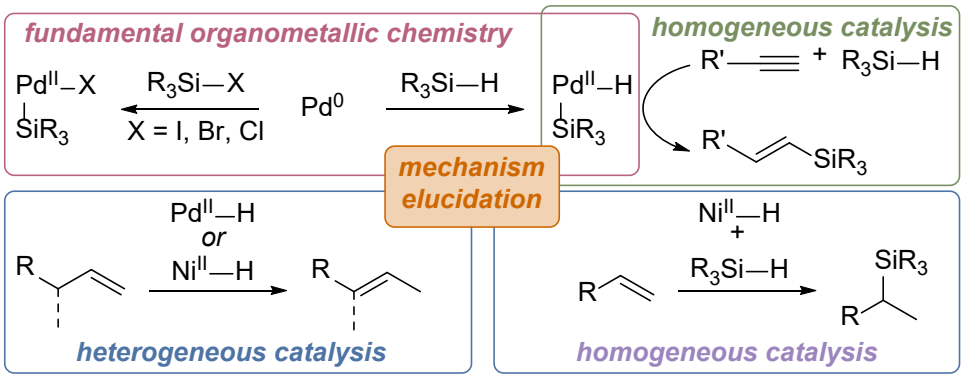


Figure 1. Oxidative addition of Pd to Si-H and Si-X bonds, Pd-catalyzed alkyne hydrosilylation and alkene isomerization, and Ni-catalyzed alkene isomerization and hydrosilylation.

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Designing New Synthetic Concepts for Imparting Molecular Complexity with C-1 Sources

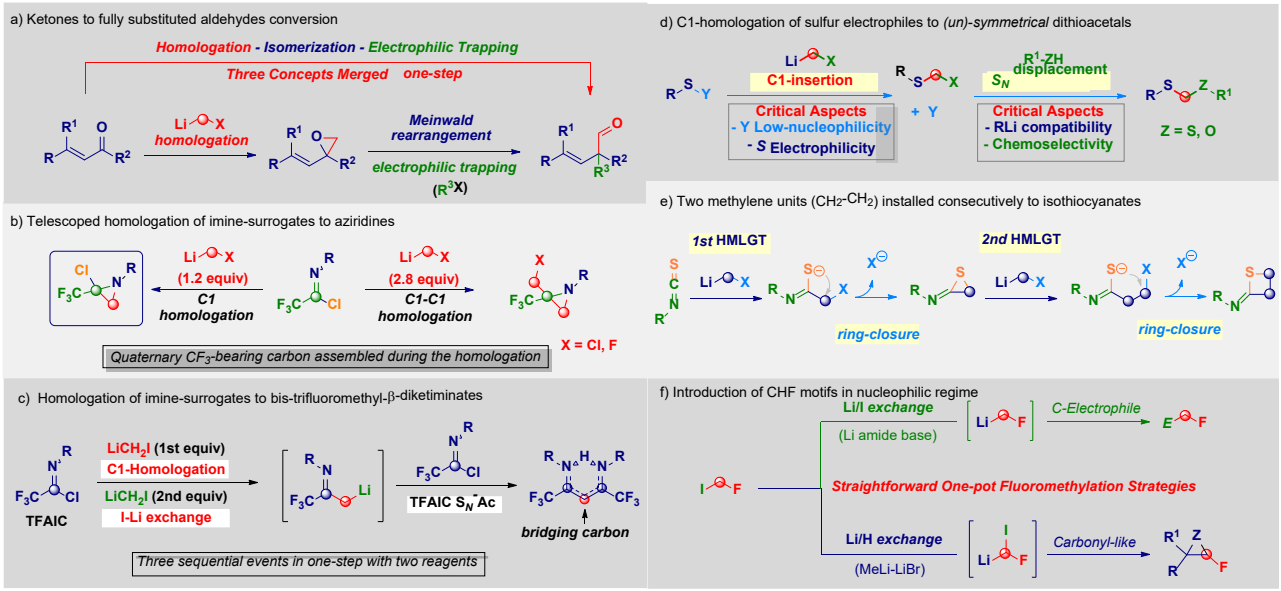
Vittorio Pace,[*a,b]

[a] University of Vienna, Department of Pharmaceutical Sciences, Josef-Holaubek-Platz 2, 1090 Vienna, Austria

[b] University of Turin, Department of Chemistry, Via Giuria 7, 10125 Turin, Italy

Email: Vittorio.pace@univie.ac.at

The direct transfer of a reactive nucleophilic CH_2X element into an existing linkage enables the formal introduction of this moiety with the precisely defined degree of functionalization.[1] Upon the fine tuning of the reaction conditions governing the transformation, the initial homologation event can serve as the manifold for triggering unusual rearrangement sequences leading to complex architectures through a unique synthetic operation.[2] The direct – full chemoselective - conversion of a ketone into the homologated all-carbon quaternary aldehyde (*via a*),[3] the telescoped homologation of imine-surrogates to quaternary aziridines (*via b*)[4] and bis-trifluoromethyl-β-diketiminates (*via c*)[5] will illustrate these unprecedented concepts. Notably, also sulfur-centered electrophiles are amenable substrates for homologations, thus providing (un)-symmettrycal dithioacetals (*via d*).[6] Cognizant of the inherent difficulties of using β-substituted metalated reagents, we developed a formal double C2-homologation strategy enabling the sequential insertion of two -CH_2- units for assembling four-membered cycles through a single synthetic operation (*via* e).[7] Furthermore, the one-step mono-fluoromethylation of carbon electrophiles with extremely labile fluoromethyllithium reagents will provide a novel entry to valuable fluorinated building-blocks without the needing of using protecting elements for fluoro-containing carbanions (*via f*).[8]



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N-Heterocyclic Carbenes as Ligands for Molecules and Materials

Cathleen M. Crudden*[a,b]
[a]Department of Chemistry and Carbon to Metals Coating Institute–C2MCI, 90 Bader Lane, Queen's University, Kingston, ON, K7L 3N6, Canada
[b]Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Nagoya 464-8602, Japan
Email: cruddenc@chem.queensu.ca

The use of N-heterocyclic carbenes (NHCs) to modify homogeneous metal catalysts is widespread since the high metal–NHC bond strength renders high oxidative and chemical stability to the resulting metal complexes. Recent work has shown that these ligands are also powerful choices for the modification of metal surfaces.[1] We will describe the modification of planar metallic surfaces with NHCs, where the nature of the surface overlayer is strongly dependent on the structure of the NHC.[2] Similarly, NHCs are shown to be useful new ligands for the stabilization of metal clusters, with the structure of the cluster being strongly influenced by the nature of the NHC.[3] The unique properties of these NHC-stabilized clusters, including their photophysical properties, stability and catalytic activity will be addressed.

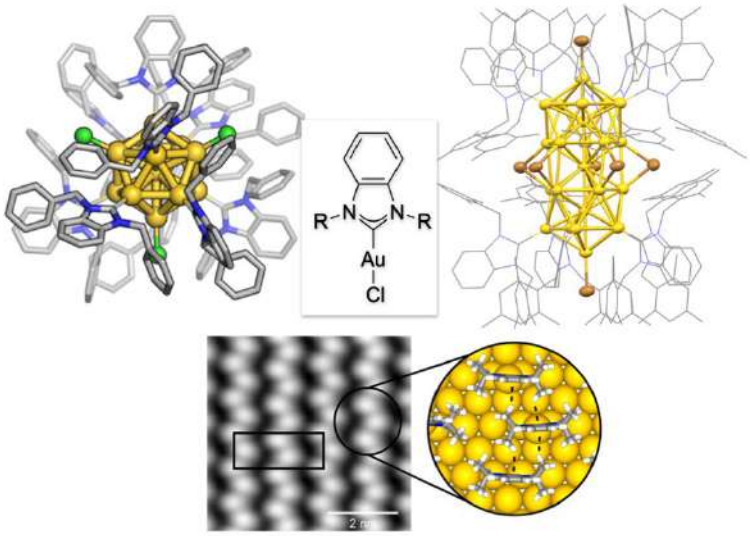

Figure 1. N-heterocyclic carbenes as ligands for molecules, clusters and surfaces.

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Enantioselective C-H Arylation Based on Umpoled Indoles

Nguyen H. Nguyen,[a] Seunghoon Shin,*[a]
[a]Department of Chemistry, Hanyang University
Email: sshin@hanyang.ac.kr

Due to the importance of heterobiaryl synthesis in bioactive compounds, chiral ligands, and materials chemistry, their synthesis through C-H/C-H coupling has seen remarkable advances. Notable approaches include hypervalent iodine chemistry, electrochemical synthesis, photoredox catalysis, and organocatalysis.[1,2] Despite these advances, control over chemo- and regioselectivity as well as atropselectivity remains very challenging.

We recently reported a C-H/C-H biaryl coupling between phenols and N-carboxyindole (**1**), where cross-coupling occurred in an exclusive chemo- (absence of biphenols), and regioselectivity (ortho-to phenols).[3] Herein, we developed an enantioselective C-H/C-H heterobiaryl coupling, by employing Cu(I)/chiral bisphosphine. Through an extensive screening of ligands, we found a system with $Cu(CH_3CN)_4(PF_6)$/**L1** can deliver the desired atropisomer in excellent yield (upto 96%) with good enantioselectivity (up to 95:5 er).[4] The current Cu(I)/**L1** system turned out to be exceptionally general in terms of phenolic coupling partners. The utility of the products could be demonstrated in the synthesis of a new type of axially chiral monophosphine ligands.

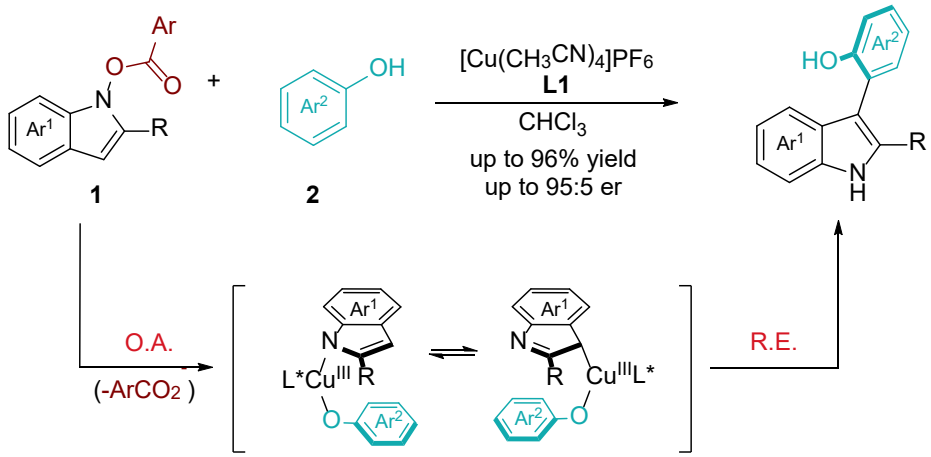

Figure 1. Atropselective arylation of N-carboxyindoles

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Transition Metal Catalyzed C-C Bond Activation of Strained Systems: A Useful Strategy in Organic Synthesis

Ponneri C. Ravikumar*[a]

[a]National Institute of Science Education and Research (NISER), Bhubaneswar, INDIA

Email: pcr@niser.ac.in

Abstract: During the last century direct functionalization of inert bond such as C-C bond has been largely ignored due to its high bond strength and extreme inertness. Since the beginning 21st century there has been renewed interest in functionalizing inert bonds through transition metal catalyst for the synthesis of many useful organic molecules. As compared to C-H bond functionalization, C-C bond functionalization is far more difficult due to the high thermodynamic barrier in breaking the C-C bond. One useful strategy to overcome high thermodynamic barrier is to use strained ring systems as substrates.[1] In our group we have employed this strategy[2-5] for the synthesis of heterocycles and useful organic scaffolds. A brief overview of the works completed so far and our ongoing works will be presented (Figure 1).
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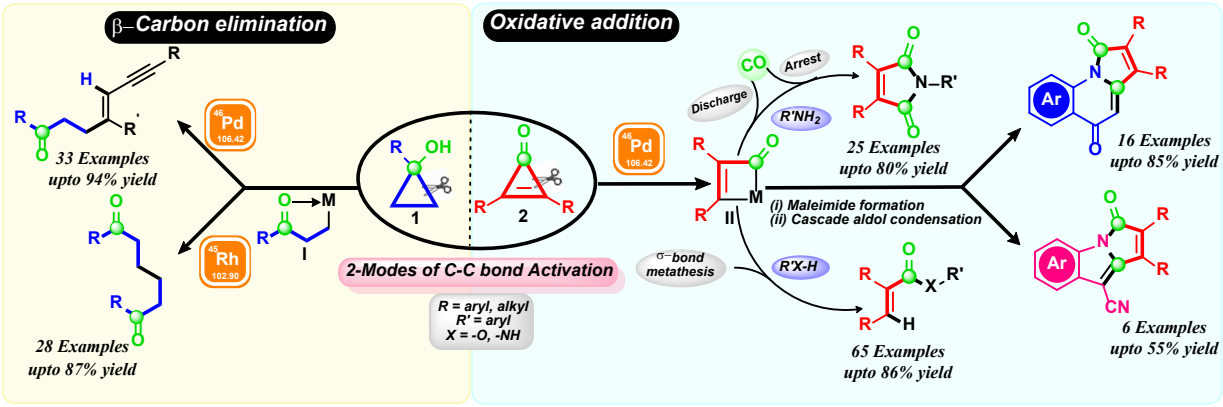

Figure 1. C-C bond activation and functionalization of cyclopropenone and cyclopropanol.

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Translational Science: The Chemistry-Biology-Medicine Continuum

Paul A. Wender
Department of Chemistry, Department of Chemical and Systems Biology
Stanford University, Stanford, CA 94305 USA
Email: wenderp@stanford.edu

Our research integrates chemistry, computer-based design, synthesis, biology, medicinal chemistry and material science into studies directed at unsolved synthetic, biological and clinical problems. Over the years, these studies have led to the introduction of numerous metal-catalyzed 2-, 3-, and 4-component cycloadditions including 5+2, 4+2, 3+2, 4+4, 6+2; 2+2+1, 2+2+2, 4+2+1, 4+2+2, 5+2+1; and 2+2+2+2, 5+2+1+1 cycloadditions; serialized versions (e.g., 5+2/4+2; 5+2/Nazarov; 4+2/4+2) and metal-catalyzed reactions in water (*Synlett* **2003**) and even in cells (*Bioconj.Chem*. **2016**). Some of these studies have figured in our function-oriented synthesis (FOS) philosophy which seeks step- and time-economical functional outcomes (cures, vaccines, catalysts, diagnostics, imaging agents, etc) through synthesis-informed structure design (e.g., *Current Drug Discovery Tech* **2004**, *Accts* **2008**, *NP Reports* **2014**, *JOC* **2020** 15116). Our FOS studies have more recently focused on HIV/AIDS eradication (*Virology* **2023** on line, *Nature Chem* **2022**, 1421; *Nature Commun.* **2022**, 13:121; *Cell Reports Medicine* **2020**, 100162; *Blood Advances* **2020**, 4244; *PNAS* **2020**, 10688; *Science* **2017**), Alzheimer's disease and neurological disorders (*Cell Chem Biol* **2021**, 537; *ACS Chemical Neuroscience* **2020**, 1545), antigen-enhanced CAR T and NK cell therapies (*Nature Chem.* **2022**, 1421; *Nature Commun* **2020,** 1879), resistant and metastatic cancer (*Cancer Research* **2019**, 1624; *Gynecologic Oncology* **2012**, 118), therapeutic and prophylactic vaccination and immuno-oncology including a cure for cancer in mice (*Proc. Natl. Acad. Sci.* USA **2018**, E9153) and a Covid vaccine (*ACS Central Science* **2021**,1191), resistant infectious diseases (*JACS* **2018**, 16140; ACS *Chemical Biology* **2019**, 2065; *Antimicrob Agents Chemother* **2021**, 65:e02416), multiple sclerosis and neurological disorders (*Cell Chemical Biology* **2021**, 537) and new delivery systems for polyanions (e.g., RNA, DNA, CRISPR-Cas, etc: *PNAS* **2017** E448, **2018** E5859; *JACS* **2019** 8416; *Bioconj Chem* **2023**; *Nature Biotech*, **2022**; *Biomacromol.* **2022**). This lecture will provide an overview of the above topics.

PS 1

A Fluorescent Probe for Sensing Dopamine: Syntheses Involving Suzuki Cross-Coupling Reactions

Bin-Han Yang, Kuangsen Sung*
Department of Chemistry, National Cheng Kung University, Tainan, Taiwan.
Email: kssung@mail.ncku.edu.tw

Dopamine is an important neurotransmitter in human brain. Any sensor that is used to monitor dopamine is in high demand.[1] In this report, I will show synthesis of a potential fluorescent probe for sensing dopamine. The synthesis of the fluorescent probe **3** involves four steps. (Figure 1) The first step is to convert 1-bromopyrene to pyrenylboronic acid through lithium-halogen exchange reaction. The second step is to undergo Suzuki Cross-Coupling reaction of pyrenylboronic acid with 2,6-dibromopyridine in the presence of $Pd(OAc)_2$ catalyst to form compound **1**. The third step is to undergo Suzuki Cross-Coupling reaction of compound **1** with 2-(2-Bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of $Pd(OAc)_2$ catalyst to form compound **2**. The last step is to convert the bromo group of compound **2** to a boronic acid group through lithium-halogen exchange reaction, forming the final product **3**.

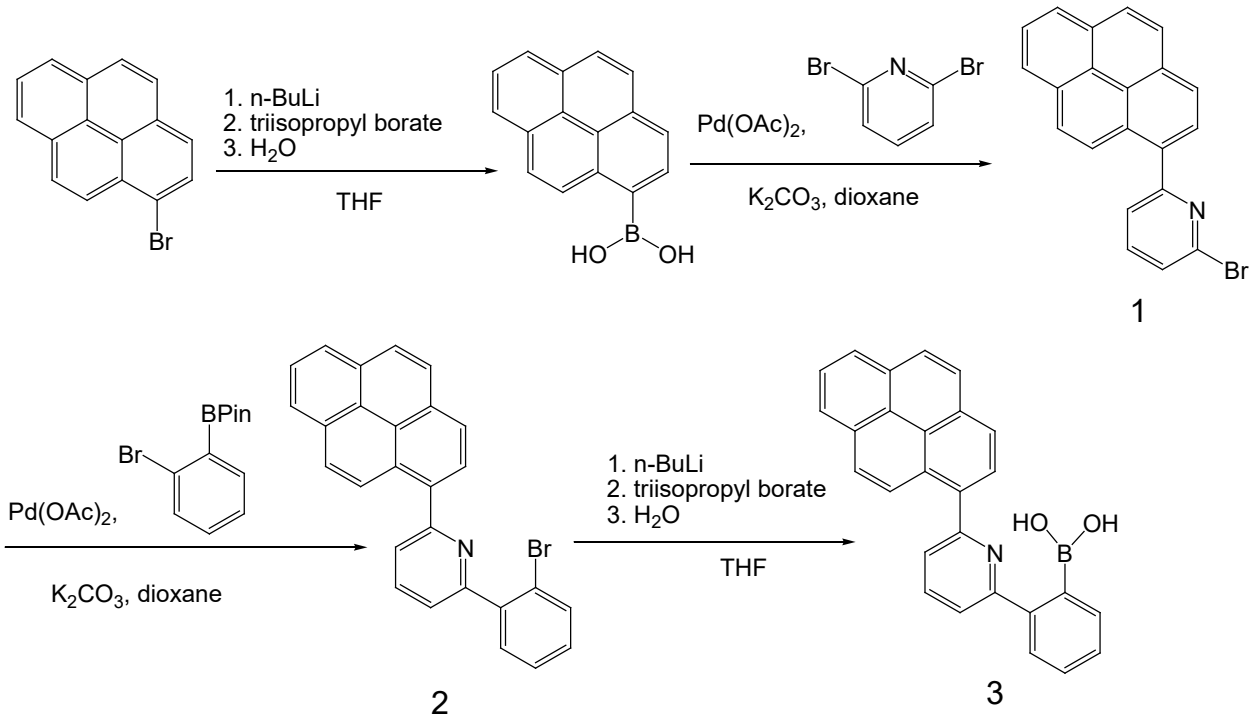

Figure 1. Synthesis of a fluorescent probe for sensing dopamine.

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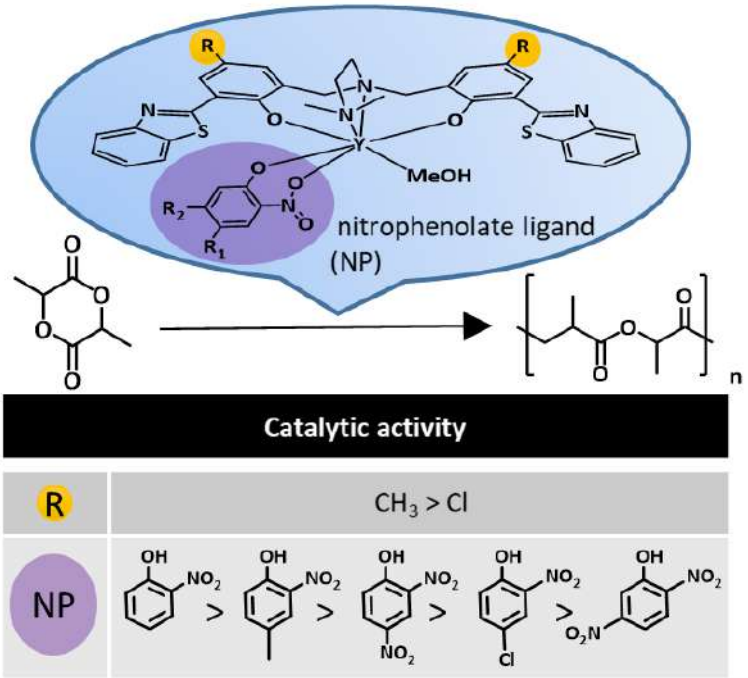
Investigation of the correlation between ligand electronic effects and the catalytic activity of yttrium complexes in the ring-opening polymerization

Ming-Yeng Tsai, Yu-Chia Su, Ting-Yu Chiu, Bao-Tsan Ko and Po-Heng Lin* [a]
[a]Department of Chemistry, National Chung Hsing University, 250, Kuo Kuang Rd., Taichung, 402 Taiwan, R.O.C.
Email: poheng@dragon.nchu.edu.tw

Amine-bis(benzothiazole phenol) ligands, ^{C1NN}**BiBTHP-H$_2$** and ^{CLNN}**BiBTHP-H$_2$** ligands, were designed for yttrium complexes with analog structures. A series of nitrophenolate (NP)-type of ligands possessing R substituents with variable electronic properties (R= NO_2, Cl, H, CH_3) on ortho and/or para position attached to the phenolate rings have been selected as secondary ligands for complexes syntheses. The syntheses, structures, and catalytic properties for lactones polymerization of ten novel yttrium complexes, [Y(^{C1NN}**BiBTHP**)(NP)(MeOH)] (**1-5**) and [Y(^{CLNN}**BiBTHP**)(NP)(MeOH)] (**6-10**) where the secondary ligand NP = 2,4-dinitrophenol (**1** and **6**), 2,5-dinitrophenol (**2** and **7**), 2-nitrophenol (**3** and **8**), 4-chloro-2-nitrophenol (**4** and **9**) and 4-methyl-2-nitrophenol (**5** and **10**). All the core structures and coordination geometries for complexes **1-10** were isostructural. All complexes were demonstrated to be active catalysts for lactide (LA) polymerization, and the catalytic performance for these complexes was compared. Comparing a series of nitrophenolate co-ligands in two different ligand systems, we presented the first example to study the correlation between electronic effect of the ligands and catalytic properties for mononuclear rare-earth complexes.



Synthesis and Reactivity of New Ni-TEMPO, Ni-Imine and Di-Nuclear Ni-Triazole Complexes

[a] **Rajib Kumar Sarker,** **Davit Zargarian** *[a]
[a] University of Montreal.

Email: rajib.kumar.sarker@umontreal.ca; zargarian.davit@umontreal.ca

An increasing number of reports appearing over the last two decades have introduced efficient nickel(II)-catalyzed methodologies for the direct functionalization of relatively inert C−H bonds. In vast majority of these functionalization strategies, the nickellacyclic intermediates generated at the C−H metallation step are allowed to react in-situ with various reagents to furnish the targeted functionalized product. On the other hand, isolation of such intermediates represents an opportunity to systematically explore their reactivities.
In this context, our group has developed facile synthetic routes to nickellacyclic intermediates via orthometalation of the aryl phosphinites ArOP(i-Pr)$_2$.[1] Isolation of such compounds has allowed us to study their reactivities with various substrates as simple models for C−H functionalization processes alluded to above.[2] This presentation will highlight the reactivities of a series of dimeric intermediates obtained from C–H nickellation of aryl phosphinites with hydroxylamines, TEMPO, and a triazole.

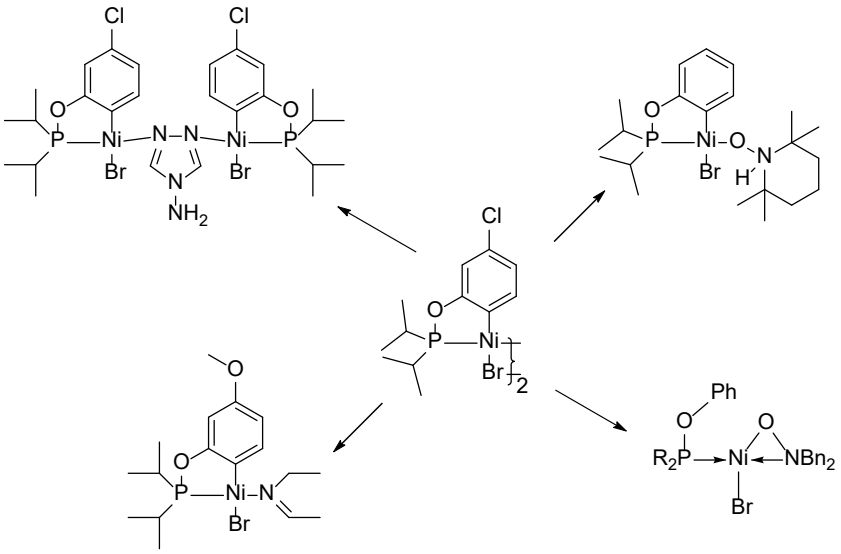


Figure 1. Formation of Ni-TEMPO, Ni-imine and Ni-triazole complexes.

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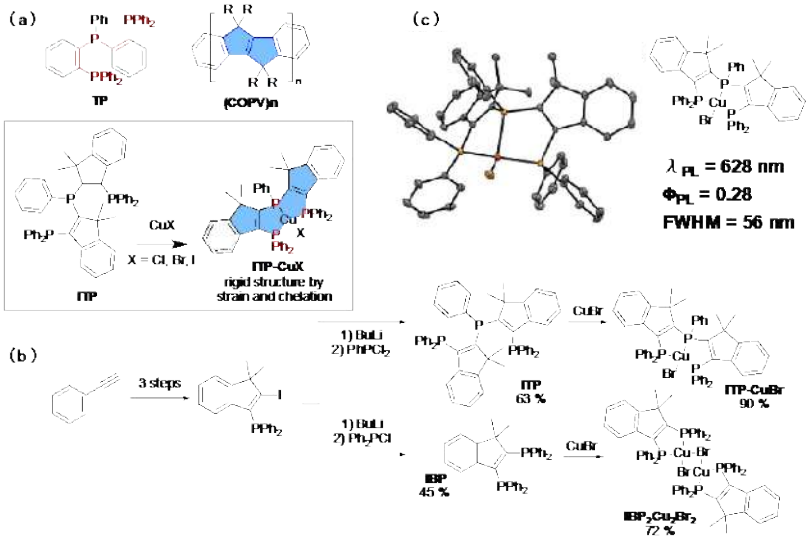
Structurally Rigid Copper(I) Trisphosphine Complexes with Indene Backbones for Sharp Red Emission

Shota Fukuma,[1] **Rui Shang***,[1] **Eiichi Nakamura***[1]
[1]Graduate School of Science, the University of Tokyo

Email: fukuma@chem.s.u-tokyo.ac.jp

Luminescent Cu(I) complexes have been intensively studied due to the superior photophysical properties arising from the fast and efficient conversion of both singlet and triplet energies into photons.[1] However, the developments of red-emitting Cu(I) complexes still face low photoemission quantum yield (PLQY) and low color purity due to the structural flexibility of the Cu(I) complex. The reports on red-emitting Cu(I) complexes with high PLQY above and narrow full-width at half maximum (FWHM) (< 100 nm) are still limited.[2] We consider that the structural rigidity by introducing ring strain offers a solution for improved emission. Inspired by our previous works on rigid 1,4-dihydropentalene congeners featuring high structural rigidity endowed from fused five-membered rings[3] and the emissive properties of Cu(I) trisphosphine (**TP**) complexes,[4] we herein report the design of chelating bis- and trisphosphines incorporating two *1H*-indene backbones as ligands. The bidentate and tridentate indene-based ligands were synthesized in four steps from commercially available materials utilizing the stepwise, regioselective lithiation-electrophile trapping of diiodoindene. These ligands formed stable complexes with Cu(I) halides and the complexes showed orange to red emission. Especially, the Cu(I) complexes of trisphosphine of *1H*-indene backbones (**ITP**) possessing four fused five-membered rings chelating Cu(I) generate a rigid skeleton. The structural strain in *1H*-indene-based Cu(I) complexes was demonstrated by the reduced P–C=C bond angles after coordination and the molecular rigidity has been supported by TD-DFT calculations, in which **ITP-CuX** showed almost minimum structural reorganization after excitation. The **ITP-CuX** showed narrow photoluminescence spectra peaking at 628 nm with FWHM of 56 nm and a PLQY of 28 %, presenting a very small FWHM among known red emitting Cu(I) complexes reported, and a high PLQY among the red-emitting Cu(I) complexes. This work demonstrated strain-based structural rigidification in ligand design for enhancing luminescence properties in metal complexes.



Figures. (a) molecular design of ligands and complexes (b) synthesis of indene-based chelating lingads and complexes (c) crystal structure of ITP-CuBr

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Chirality-Switchable Phosphoramidite Ligands Attached on the Dynamic Helical Polymer

Yusuke Matsumoto,[a] **Takaya Fujie**,[a] **Takeshi Yamamoto**,*[a] **Michinori Suginome***[a]
[a]Graduate School of Engineering, Kyoto University, Katsura, Kyoto, 615-8510, Japan
Email: yamamoto@sbchem.kyoto-u.ac.jp; suginome@sbchem.kyoto-u.ac.jp

Phosphoramidite is one of the most promising ligand structures in transition-metal-catalyzed asymmetric reactions. Taking advantage of its high modularity, a variety of chiral phosphoramidite ligands have been synthesized to achieve the development of precise asymmetric catalysts. We have developed chirality-switchable helical polymer ligands by attaching achiral coordination units onto helical poly(quinoxaline-2,3-diyl)s (PQXs), whose helicity can be controlled by solvents.[1] In this study, a helically chiral polymer ligands bearing phosphoramidite units (**PQXpham**) were prepared by post-polymerization functionalization of PQXs bearing achiral diol units. **PQXpham** served as a chirality-switchable ligand in copper-catalyzed asymmetric conjugate addition reactions, giving either of the enantiomeric products with good enantioselectivities owing to the solvent-dependent screw-sense induction to the main chain of PQX. Control experiments using low-molecular-weight model ligands suggested that the enantioselection was solely dependent on the induced axial chirality regardless of the configuration of P-stereogenic center of the phosphoramidite moieties.

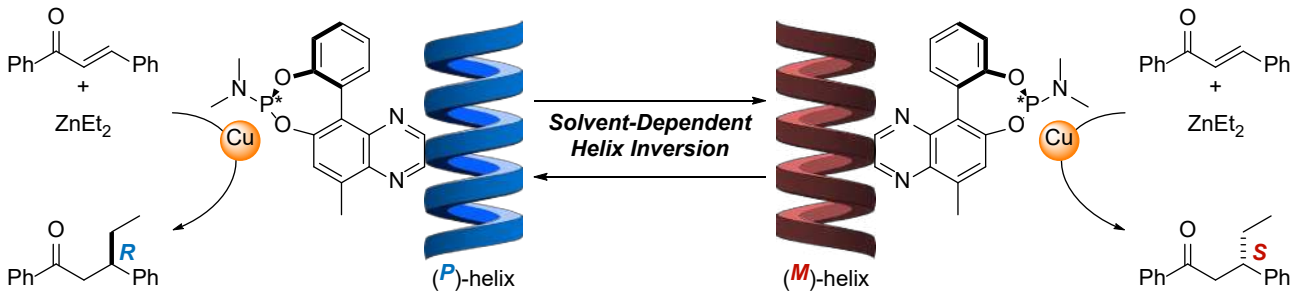

Figure 1. Cu-catalyzed asymmetric conjugate addition reactions using a chirality-switchable ligand

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Synthesis And Characterization Of Planar Chiral Ferrocenyl Imidazolilydene Transition Metal Complexes

OHSAWA Kazuki, SHIMIZU Shungo, FUKUZAWA Shin-ichi*
Department of Applied Chemistry, Graduate School of Science and Engineering, Chuo University, 1-13-27 Kasuga. Bunkyo-ku, Tokyo, 112-8551, Japan.

Email: a19.adw8@g.chuo-u.ac.jp; orgsynth@kc.chuo-u.ac.jp

N-Heterocyclic carbene (NHC) ligands are known for their strong electron-donating ability, especially in transition metal complexes. In addition, the substituent on NHC ligands can be easily changed, allowing the development of a wide variety of NHC ligands.[1a] Recently, asymmetric catalysis using NHC ligands has attracted considerable attention. Many asymmetric NHC ligands with central chirality have been developed; however, examples of NHC ligands with only planar chirality are limited.[1b,c] Since ferrocene can easily introduce planar chirality, we have focused our attention on synthesizing planar chiral NHC ligands using ferrocene.
The planar chiral ferrocenyl triazolylidene ligands we have developed showed good stereoselectivity and strong electron-donating ability.[2] However, the ligands required multiple synthetic steps for synthesis. In addition, the syntheses of optically active ferrocenyl azides and ferrocenyl alkynes were necessary to form triazolylidenes for the click reaction. To solve this problem, we planned to synthesize new imidazolylidene ligands from optically active ferrocenyl amines via diimines.[3] In this study, we synthesized a planar chiral ferrocenyl imidazolylidene ligand from a single optically active ferrocenyl amine. Furthermore, we successfully synthesized rhodium and iridium complexes with the new NHC ligand. The catalytic activity of the rhodium complexes was evaluated by the hydrogenation of olefins. We also synthesized iridium-carbonyl complexes to calculate the Tolman electric parameter which is a measure of the electron-donating ability of the ligands. These results revealed the unique properties of planar chiral ferrocenyl imidazolylines.

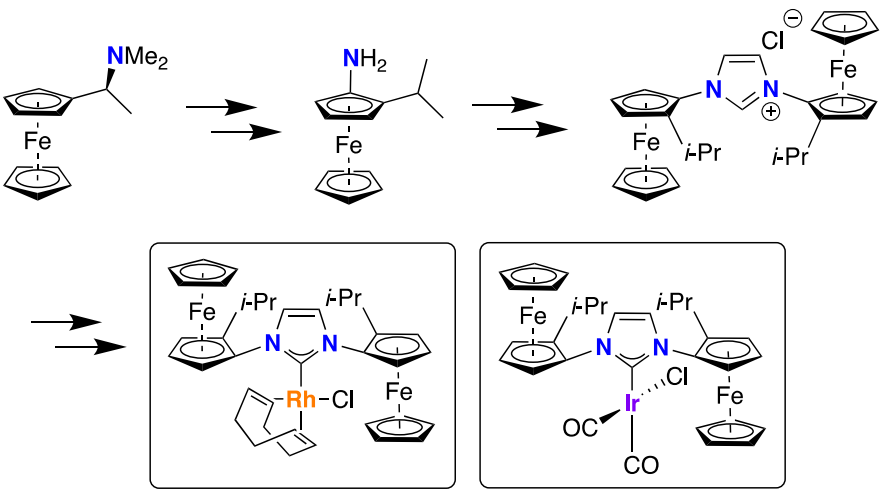

Figure 1 The present work.

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Ligand Design in the Direct Asymmetric Reductive Amination

P. D. Engel,[a,b] M. Menche,[a,b] P. Klein,[a] J. Gallardo-Donaire,[a] M. Hermsen,[a] F. Rominger,[c] O. Trapp,[a,e] R. Konrath,[a] T. Ghosh,[a] J. Wysocki,[a] M. Ernst,[b] A. S. K. Hashmi,[a,c] A. Schäfer,[b] P. Comba,[d] T. Schaub.* [a,b]

[a] Catalysis Research Laboratory (CaRLa), Im Neuenheimer Feld 584, 69120 Heidelberg, Germany.
[b] BASF SE, Carl-Bosch-Str. 38, 67056 Ludwigshafen, Germany.
[c] Organisch-Chemisches Institut, Heidelberg University, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany.
[d] Anorganisch-Chemisches Institut and Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany.
[e] Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, 81377 München, Germany.

Email: philipp.engel@carla-hd.de; thomas.schaub@basf.com

The asymmetric ruthenium-catalyzed reductive amination employing ammonia and hydrogen to primary amines is a promising access to important chiral building blocks. After we demonstrated the capability of our catalyst to perform the chemo- and enantioselective reaction while using simple ammonia gas as a reagent, one of the most attractive and industrially relevant nitrogen sources, the mechanism of this reaction was investigated by means of density functional theory. We found a viable pathway, which explains the observed trends and magnitude of enantioselectivity through the halide series in good agreement with the experimental data. The in-depth investigation of substrate conformers during the reaction turned out to be crucial in obtaining an accurate prediction for the enantioselectivity.[1] Subsequently, a predictive model based on the ligand bite angle was developed to allow for a big data approach in screening different ligands. A selected set of ligands was tested and validated with DFT calculations and experiments, which revealed a variety of difficulties and drawbacks of such approaches. The examples strongly support our believes that computations and experiments work best and most effectively hand-in-hand with constant exchange and guided our next steps in enantioselectivity prediction to be more effective.[2]

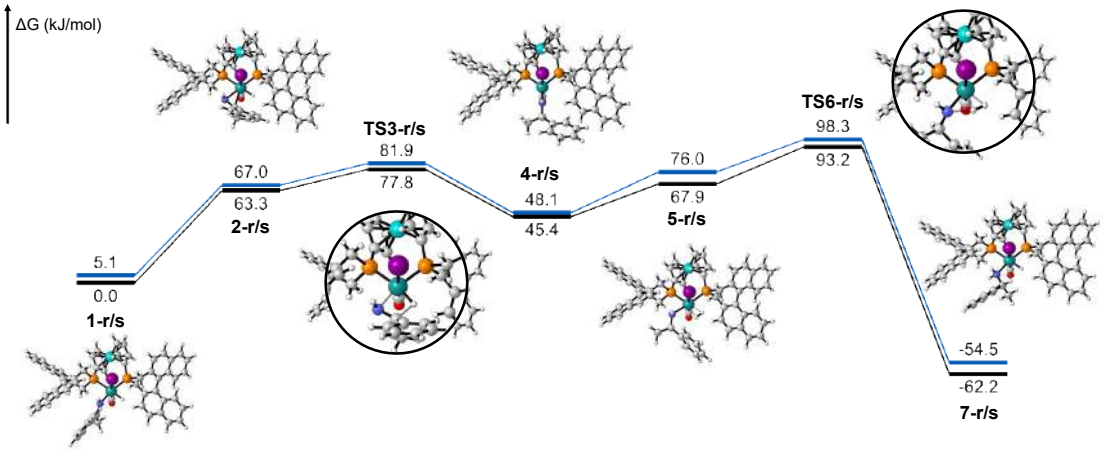

Figure 1. Lowest energy paths in the catalytic cycle leading to the R (black) and S (blue) enantiomer of 1-phenylethylamine.

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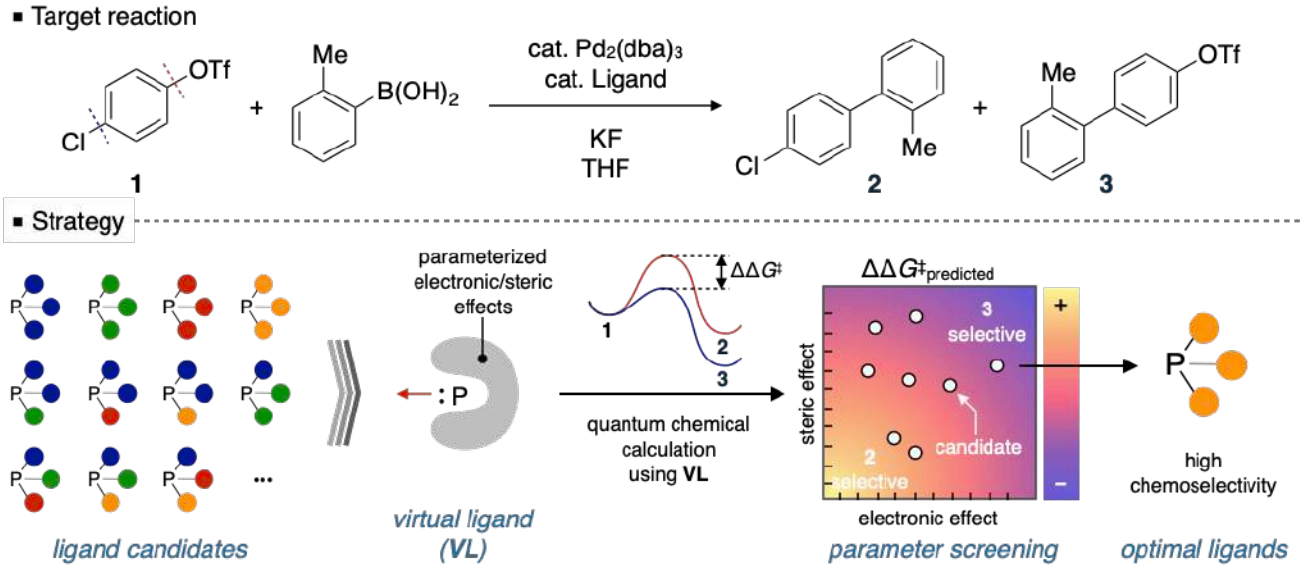
Virtual Ligand-Assisted Screening toward *ab initio* Catalyst Design: Case Study of Suzuki–Miyaura Cross Coupling

Wataru Matsuoka[*ab], **Yu Harabuchi**[abc], **Yuuya Nagata**[bc], **Satoshi Maeda**[*abc]
[a]Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Hokkaido 060-0810, Japan. [b]ERATO Maeda Artificial Intelligence for Chemical Reaction Design and Discovery Project, Hokkaido University, Sapporo, Hokkaido 060-0810, Japan. [c]Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido 001-0021, Japan.

Ligand screening is a crucial step in the development of transition metal catalysis, as it involves identifying the optimal ligand for a particular reaction from a large pool of candidate molecules. Conventionally, this process is performed through an experimental trial-and-error, which can be time-consuming and resource-intensive. One of the ideal strategies for streamlining this process is an *ab initio* approach based on transition state theory (TST). This approach relies on quantum chemical calculations, rather than experiments, and aims to design optimal catalysts that results in the best energy profile for the desired reaction. However, the implementation of TST-based ligand screening remains challenging mainly due to the large number of potential ligands that need to be individually evaluated through quantum chemical calculations. To streamline this process, we have previously proposed a computational method called virtual ligand-assisted (VLA) screening.[1] In this method, quantum chemical calculations are performed using virtual ligands which reproduce and parameterize the electronic and steric effects of real ligands. By optimizing the electronic and steric parameters of the virtual ligands to maximize the efficiency and/or selectivity of the desired reaction, the optimal features of ligands for the reaction can be rapidly identified. In this presentation, we report a case study of the VLA screening.[2] The electronic and steric features of phosphine ligands that maximize chemoselectivity in the Suzuki–Miyaura cross-coupling (SMC) reaction of *p*-chlorophenyl triflate (**1**) were determined through quantum chemical calculations using virtual ligands, and several phosphine ligands were suggested to exhibit high chemoselectivity. Based on this suggestion, we successfully found that tri(1-adamantyl)phosphine and tri(neopentyl)phosphine show high to excellent selectivity for the C–Cl bond activation. This case study suggests that the VLA screening strategy could be a useful tool for ligand screening.



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Activation of terminal alkynes by an iridium(III) bis(thiophosphinite) pincer complex: application in alkyne dimerization towards enynes

Alexander Linke,*[a] Hans-Joachim Drexler,[a] Torsten Beweries[a]
[a] Leibniz Institute for Catalysis, Albert-Einstein-Str. 29a, 18059 Rostock, Germany
Email: alexander.linke@catalysis.de

In the last two decades, bis(phosphinite) Ir pincer complexes of the type [(^{R}POCOP^{R})Ir(H)(X)] {^{R}POCOP^{R} = κ^3-1,3-(OPR$_2$)$_2$-C$_6$H$_3$; R = organic substituent; X = H, Cl} have been applied as versatile catalysts in many organic transformations.[1a] A prominent example in this context is the transfer dehydrogenation of alkanes, which was carried out by the group of Brookhart using complexes of the type [(^{R}POCOP^{R})Ir(H)(Cl)].[1b]
We were recently able to synthesize the corresponding Ir(III) bis(thiophosphinite) complexes **2-R** from suitable Ir precursors in refluxing toluene and an atmosphere of H_2.[2] We found that in the case of **1-*i*Pr** H_2 is crucial for successful C–H activation, whereas **2-*t*Bu** could be synthesized in absence of H_2 under reflux as well, but only in low yields.

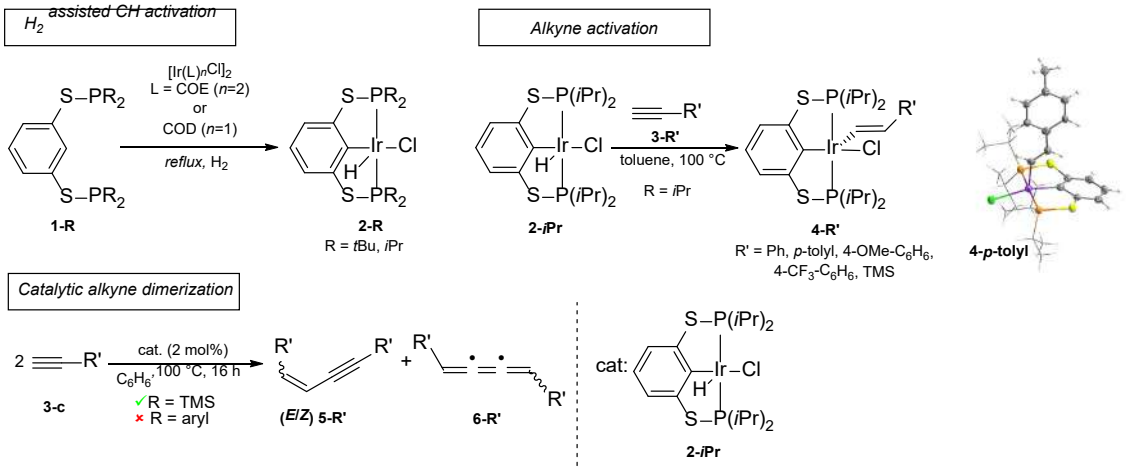

Figure 1. Synthesis of new Ir(III) bis(thiophosphinite) complexes and application in alkyne activation and dimerization.

Moreover, we were able to activate differently substituted, terminal alkynes **3-R'** with **2-*i*Pr**, yielding the first Ir(III) bis(thiophosphinite) vinyl pincer complexes **4-R'**. Because of the scarcity of Ir(III)-catalyzed alkyne dimerizations[3], we investigated the catalytic hydroalkynylation of **3-R'**. Surprisingly, quantitative conversion is only found for **3-TMS**, giving selectively (*Z*)-enyne **5-TMS** and traces of 1,2,3-triene **6**. This reaction even proceeds at room temperature, which is in stark contrast to terminal aryl alkynes, where either no or only very little conversion (**3-Ph**: 20–30% conversion) was found.

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Strategic Activation of Organoboron Compounds for the Creation of Chemical Space with Complexity

Hong Geun Lee*[a]

[a]Department of Chemistry, Seoul National University
1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea
Email: hgleee@snu.ac.kr

Novel reactivities of organoboron reagents for the formation of covalent bonds at a carbon atom with sp^3- or sp^2-hybridization are explored. New synthetic modalities that are based on electrochemical oxidation and transition metal catalyzed processes enabled the formation of C–heteroatom and C–C bonds with unprecedented efficiencies. Ultimately, general synthetic platforms towards the formation of hindered linkage or the introduction of stereochemical information at a C(sp^3)-based reaction center has been established.

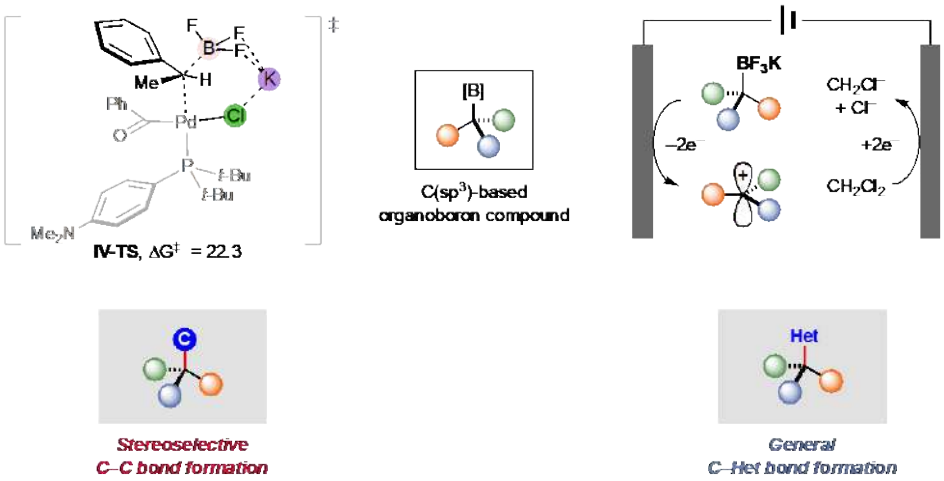

Figure 1. Activation of C–B Bonds

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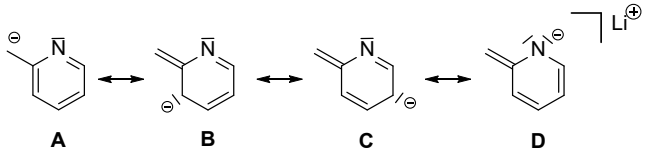
Reactivity and Bonding in s-Block Organometallic from Charge Density and DOSY NMR

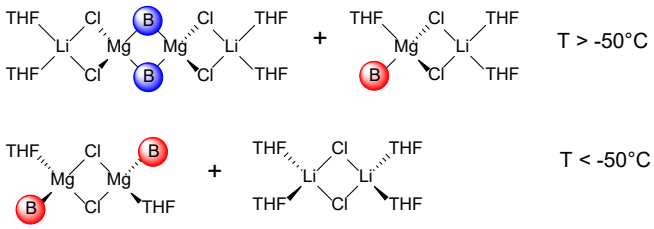
Dietmar Stalke*
Universität Göttingen, Institut für Anorganische Chemie, Göttingen, Germany.

Email: dstalke@chemie.uni-goettingen.de

Especially in the area of reactive organometallics it is essential to get information about the involved species, in the solid-state but, even more important, in solution, since structural changes in solution like solvation and aggregation determine the reactivity and selectivity in organic syntheses and the product range. s-Block organometallics are readily applied in numerous preparative protocols, ranging from deprotonation of weakly acidic reagents to C–C bond formation in organic group transfers as well as in industrial large-scale late-stage transformations. The structure-reactivity-relationship is still the Holy Grail to be found in this class of compounds because the metallated species determine the composition, yield and stereo chemistry of the product. Charge density investigations can provide insight into the bonding and reactivity of these labile molecules. For example, picolyllithium $[(C_6H_6NLi{\cdot}NC_6H_7)]_2$[1] is an excellent candidate for a detailed structure-reactivity-relationship investigation of carbanion (**A**) vs. amide (**D**).[2]



On the other hand, structural information from the solid state would not necessarily correctly describe the reactive species in the course of the reaction sequence. Here DOSY NMR bridges the gap.[3] The talk will exemplify this with the Turbo Hauser base $^{i}Pr_2NMgCl{\cdot}LiCl$ in THF and the influence of LiCl on the Schlenk-Equilibrium.[4]



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(n-Bu)$_4$NBr-Promoted N_2 Splitting to Molybdenum Nitride

Dan-Dan Zhai[1, ‡], Shuo-Qing Zhang[2, ‡], Si-Jun Xie[1], Rong-Kai Wu[2], **Feng Liu[1]**, Zhen-Feng Xi[3], Xin Hong[2,4,5*], and Zhang-Jie Shi[1*]

[1]Department of Chemistry, Fudan University, Shanghai, 200438, China.
[2]Center of Chemistry for Frontier Technologies, Department of Chemistry, State Key Laboratory of Clean Energy Utilization, Zhejiang University, Hangzhou, 310027, China.
[3]Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing, 100871, China.
[4]Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, School of Science, Westlake University, Hangzhou, 310024, China.
[5]Beijing National Laboratory for Molecular Sciences, Zhongguancun North First Street NO. 2, Beijing 100190, PR China.

Email: hxchem@zju.edu.cn; zjshi@fudan.edu.cn

Splitting of N_2 via six-electron reduction and further functionalization to value-added products is one of the most important and challenging chemical transformations in N_2 fixation. However, most N_2 splitting approaches rely on strong chemical or electrochemical reduction to generate highly reactive metal species to bind and activate N_2, which is often incompatible with functionalizing agents. Catalytic and sustainable N_2 splitting to produce metal nitrides under mild conditions may create efficient and straightforward methods for N-containing organic compounds. Herein, we present that a readily available and nonredox (n-Bu)$_4$NBr can promote N_2-splitting with a Mo(III) platform. Both experimental and theoretical mechanistic studies suggest that simple X^- (X = Br, Cl, etc.) anions could induce the disproportionation of $Mo^{III}[N(TMS)Ar]_3$ at the early stage of the catalysis to generate a catalytically active $\{Mo^{II}[N(TMS)Ar]_3\}^-$ species. The quintet Mo^{II} species prove to be more favorable for N_2 fixation kinetically and thermodynamically, compared with the quartet Mo^{III} counterpart. Especially, computational studies reveal a distinct heterovalent $\{Mo^{II}-N_2-Mo^{III}\}$ dimeric intermediate for the N≡N triple bond cleavage.

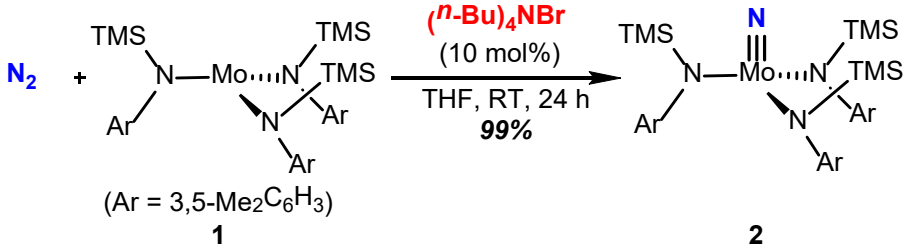

Figure 1.

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Identifying Halide Effects in Diastereoselective Addition Reactions of Grignard Reactions: An Enabling Tool for C4'-Modified Nucleoside Synthesis

Garrett Muir,[a] Guillermo Caballero-García, [a] Robert Britton*[a]
[a]Simon Fraser University, 8888 University Dr W, Burnaby, BC V5A 1S6.
Email: garrettm@sfu.ca; rbritton@sfu.ca

Nucleosides are key building blocks in both DNA and RNA and play important roles in processes such as cell signaling and metabolism. Synthetic nucleoside analogues (NAs) can disrupt various biological processes and have been widely exploited in medicinal chemistry. NAs represent a large class of small molecule anti-viral drugs and play key roles in oncology and anti-fungal treatments. Furthermore, over the last two decades, there has been increased use of NAs in oligonucleotides where they have demonstrated profound effects on stability and potency.[1]

One common site for modification in NAs is at the C4'-position on the ribose ring.[2] Structural changes here can impact conformation, metabolic stability, and enhance membrane permeability. However, the synthesis of C4'-modified NAs is challenging and the production of these compounds often requires lengthy synthetic sequences and expensive chiral starting materials. Furthermore, the syntheses of C4'-modified NAs are generally not amenable to rapid diversification, which is a critical step in assessing structure-activity relationships.

Our group has previously reported the synthesis of NAs using a key fluorohydrin intermediate, which can be accessed in two steps from inexpensive and achiral starting materials.[3] Here, we describe the controlled addition of Grignard reagents and the unique impact of the halide atom on the Grignard reagent in controlling the diastereoselectivity of these processes. In particular, we show that the addition of alkyl magnesium chloride reagents affords mixtures of 1,2-addition products while alkyl magnesium iodide reagents give predominantly the desired 1,3-syn diols. Furthermore, using DFT calculations and experimental results, we show how the halide impacts the Lewis acidity of an intermediate magnesium chelate. A subsequent cyclization event now provides access to correctly configured C4'-modified NAs. Exploiting this halide effect, we can now rapidly create diverse libraries of NAs to support drug discovery efforts.

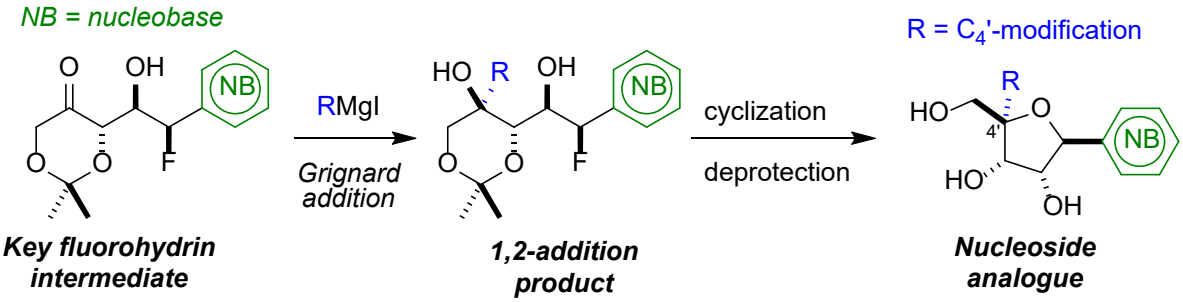

Figure 1. Overview of controlled Grignard addition strategy for the synthesis of C4'-modified nucleosides.

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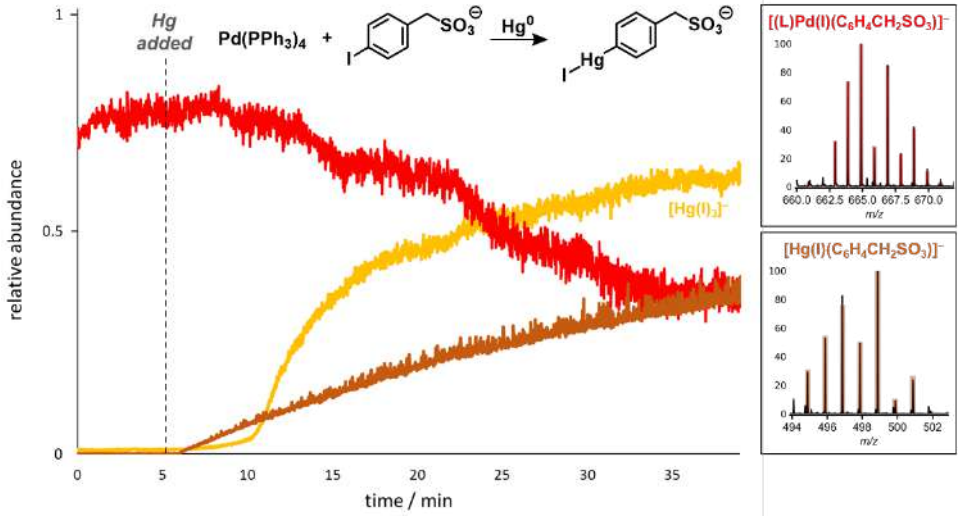
Real-Time Mass Spectrometric Investigation of the Effect of Elemental Mercury On Pd(0) and Pd(II)Arx Intermediates

Ian C. Chagunda, Tiago Fischer, Makenna Schierling, J. Scott McIndoe*
Department of Chemistry, University of Victoria,
PO Box 1700 STN CSC, Victoria, BC V8W 2Y2, Canada.
Email: chagunda@uvic.ca; mcindoe@uvic.ca

Palladium-catalyzed cross coupling is a widely used tool in synthetic chemistry, that relies on catalytically active species generally classified as homogeneous or heterogeneous.[1] Despite its widespread use, there has been much debate over the true nature of the catalytically relevant species and how reaction conditions influence pathways for both catalyst activation and decomposition.[2,3] The mercury drop test is often used to distinguish between true homogeneous and heterogeneous catalysis. It is based on the assumption that elemental mercury will amalgamate with heterogeneous catalysts, eliminating their catalytic activity, while homogeneous catalytic species remain unaffected.[4] To better understand these reactions, pressurized sample infusion (PSI) combined with an electrospray ionization mass spectrometer (ESI-MS) was used to offer real-time reaction analysis, providing mechanistic data for catalytically significant reaction intermediates.[5] When the mercury drop test was applied to a model cross-coupling reaction, the limits of the test became evident as Hg(0) reacted with a number of homogeneous Pd(0) and Pd(II) species through a variety of off-cycle reaction pathways. The use of PSI-ESI-MS gave valuable insights into the nature of palladium-catalyzed cross coupling reactions, and the limitations of the mercury drop test, highlighting the importance of further research to better understand these reactions and their mechanisms.



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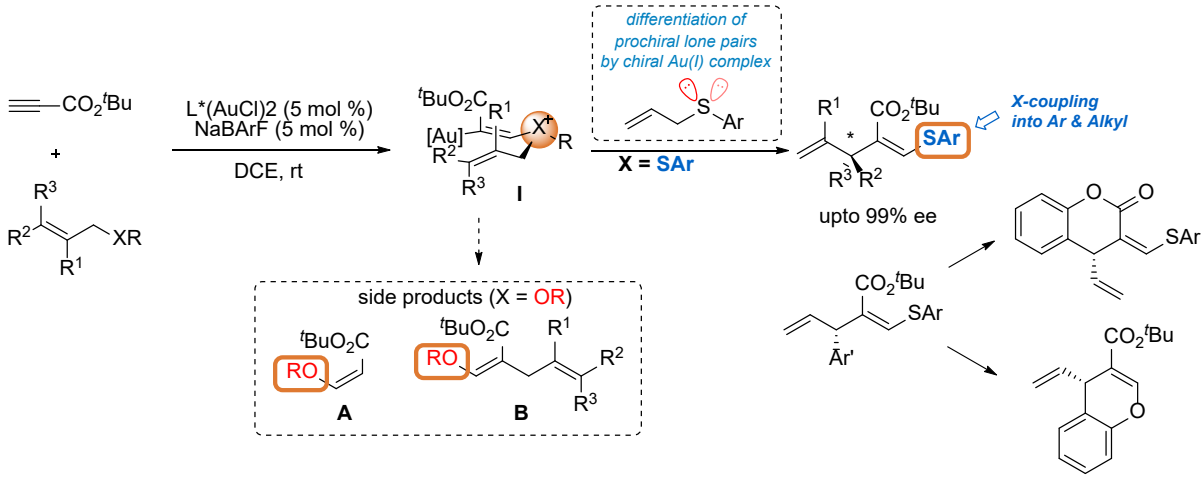
Enantioselective Gold-Catalyzed Claisen Rearrangement Based on Sulfonium Intermediates

Jiwon Jang,[a] **Youngjin Bae**,[a] **Seunghoon Shin***[a]
[a]Department of Chemistry, Hanyang University, Seoul, 04763, Korea

Email: jiwon1630@hanyang.ac.kr; sshin@hanyang.ac.kr

Formation of onium salts is useful strategy to accelerate sigmatropic rearrangements.[1] In this context, we envisioned an in-situ generation of the allyl vinyl sulfonium **I** (X = SAr) via gold-catalyzed addition of allyl sulfides to propiolates (Figure 1).[2] In contrast to the corresponding oxonium-based Claisen rearrangements (X = OR)[3] where the scope of allyl group is very limited due to the facile C-O cleavage (formation of **A** and **B**), the sulfonium-based Claisen rearrangement tolerated a range of allyl substitutions. For example, skipped dienes containing quaternary centers could be obtained in good yield and high %ee. Allyl thioethers having cinnamyl group have presented significant challenge due to the facile allyl dissociation. We recently addressed this problem, by employing Au(I)/CyPF-Cy JosiPhos system. The products could be applied in the synthesis of optically active privileged oxacycles, such as 3-chromanones and 4*H*-chromenes.[4]



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Rapid, Column-Free Peptide Coupling Using A Novel Sulfur(IV) Reagent

Joey Lai,[a] Kathleen T. Downey,[a] Carlota Bahri,[a] Mai P. Truong,[a] Glenn M. Sammis*[a]
[a]Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V7T 1Z1, Canada.

Email: joeylai@chem.ubc.ca; gsammis@chem.ubc.ca

Peptide couplings have been a subject of investigation for over a century, and modern research seeks to discover new methodologies that minimize purification steps, minimize reagent expense, and decrease reaction times. The utility of thionyl fluoride (SOF_2) in column-free amino acid couplings with minimal epimerization in one to two hours has been previously demonstrated.[1] Here we report an improved protocol for nucleophilic acyl substitutions using the solution-stable SOF_2 analog, *N*-methylimidazolium sulfinyl fluoride hexafluorophosphate (MISF), that can effect similar epimerization- and column-free amino acid couplings in comparable yields in 15 minutes at room temperature. The reaction proceeds through acyl pyridinium/imidazolium intermediates. In comparison, the use of sulfuryl fluoride (SO_2F_2) to construct peptide linkages leads to significant amounts of racemization.[2] The mild conditions utilized here are tolerant of both natural and unnatural amino acids, in addition to a wide variety of protecting groups. Biologically relevant peptides were accessed and derivatized using this method through sequential liquid phase peptide synthesis (LPPS). We also demonstrate that esters, thioesters, and acyl fluorides can be quickly accessed with this optimized method.

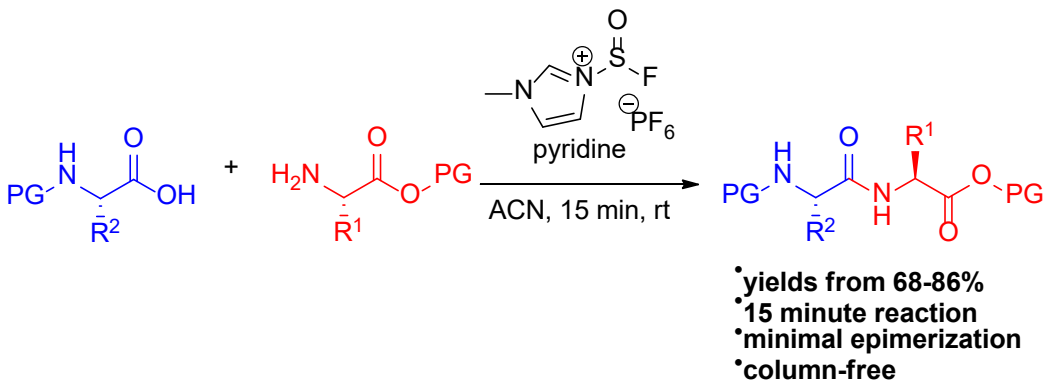

Figure 1. Rapid, column-free peptide coupling mediated by *N*-methylimidazolium sulfinyl fluoride hexafluorophosphate (MISF).

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Conversion of Biomass-Derived Glycerol and CO_2 to Glycerol Carbonate Using CaO as Dehydrating Agent

Katsuhiko Takeuchi,[a] Kazuhiro Matsumoto,[a] Norihisa Fukaya,[a] Kazuhiko Sato,[a] Jun-Chul Choi*[a]

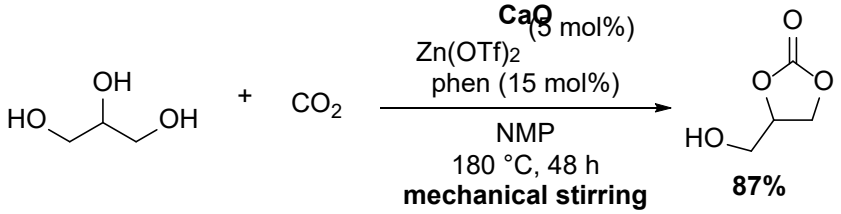
[a]*National Institute of Advanced Industrial Science and Technology (AIST).*

Email: junchul.choi@aist.go.jp

In order to stop global climate change, various efforts are also being made in the field of chemical manufacturing to reduce CO_2 emissions. For example, the production of useful chemicals from CO_2 or biomass resources have attracted attention as technologies that contribute to reduce CO_2 emissions. Therefore, we considered that the chemical synthesis that contributes to CO_2 reduction can be achieved more effectively by combining these two technologies.

In this study, we report that the synthesis of glycerol carbonate, a high value-added chemical, using glycerol, byproducts of biodiesel production, and CO_2 with regenerable dehydrating agent CaO and $Zn(OTf)_2$/1,10-phenanthroline catalyst (Figure 1).[1] In this reaction, stirring with a magnetic stirrer bar was not suitable because the calcium component solidifies after dehydration, and mechanical stirring was preferable. Since CaO is a regenerable dehydrating agent, the only byproduct is practically H_2O. In addition, the carbon atoms of biomass-derived glycerol are derived from CO_2 fixed by plant photosynthesis, and thus all carbon atoms of glycerol carbonates synthesized by our method can be regarded as derived from CO_2. Furthermore, this method can also be applied to the synthesis of other cyclic carbonates.

We thank the Carbon Recycling Fund Institute (CRF) for partially supporting this research (2020 CRF Grant Program).



- Use a reusable dehydrating agent CaO instead of sacrificial one
- Mechanical stirring enables use of CaO that solidifies in dehydration
- Use a surplus biomass resource of glycerol and inexhaustible CO_2
- All elements in glycerol carbonate essentially derived from CO_2

Figure 1. Research overview.

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Exploring Palladium-Catalyzed Aerobic Oxidative Amination of 1,3-Dienes and Elucidation of Catalytic Intermediates

Kazuki Tabaru,[a] Tetsuaki Fujihara,[b] Kazuyuki Torii,[a] Takeyuki Suzuki,[c] Yasushi Obora[a]*
[a]Faculty of Chemistry, Materials and Bioengineering, Kansai University, Japan
[b]Graduate School of Engineering, Kyoto University, Japan
[c]SANKEN, Osaka University, Japan
Email: k322136@kansai-u.ac.jp; obora@kansai-u.ac.jp

Cross-coupling reactions, such as the Suzuki-Miyaura reaction and Mizoroki-Heck reaction, are promising strategies in organic chemistry for connecting two fragments. However, they require prefunctionalization of substrates to prepare organohalide and optional nucleophiles. Oxidative coupling reactions are a more atom- and step-economical alternative that can bypass these steps.[1] Oxidative amination is one type of oxidative coupling and powerful tool for building carbon-nitrogen bonds.[2] This reaction also involves dehydrogenative bond formation catalyzed by palladium complexes and uses molecular oxygen as a re-oxidant of the catalyst, making it a green catalysis system. While unsaturated hydrocarbons such as electron efficient and inefficient alkenes can be used as substrates for oxidative amination, there are limitations to their scope. For example, the use of 1,3-dienes, which are essential building blocks in organic synthesis to form natural products, drug candidates, and polymers, can produce problematic by-products that make the reaction intractable. In this study, we have developed a Pd-catalyzed aerobic oxidative amination of 1,3-dienes to form nitrogen-containing conjugated 1,3-dienes. This reaction enables the functionalization of simple 1,3-dienes with aniline derivatives to form carbon-nitrogen bonds at the methyl position of the diene. The key catalytic intermediate is *in situ* generated palladium nanoparticles (Pd NPs). The Pd NPs were characterized using transmission electron microscopy and various X-ray techniques including X-ray absorption fine structure (XAFS), small angle X-ray scattering (SAXS) and X-ray diffraction (XRD). Mechanistic studies were conducted to investigate the behavior of the Pd NPs during the oxidative amination using XAFS and SAXS analysis. These studies showed that the Pd NPs underwent morphological changes due to the additions of substrates, providing important insights into the reaction mechanism. Furthermore, computational studies using density functional theory were employed to gain a deep understanding of the reaction mechanism for the Pd complex-catalyzed oxidative amination.

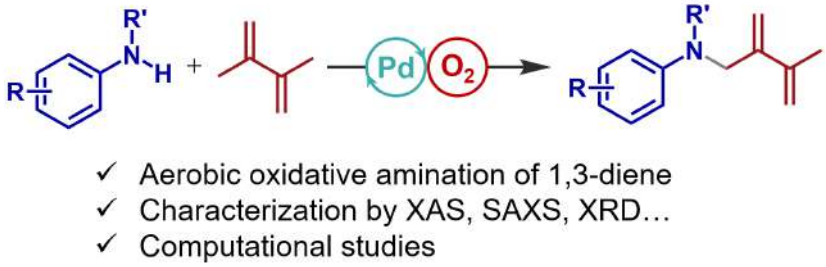

Figure 1. Pd-catalyzed oxidative amination of 1,3-diene

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Nature-Inspired [Ni] Pyridone Complexes for Cooperative Catalysis and Mechanistic Insight

Medina Afandiyeva,[a] Abhishek Kadam,[a] Xijue (Jade) Wu,[a] C. Rose Kennedy*[a]
[a]University of Rochester, Department of Chemistry, 252 Elmwood Ave, Rochester, New York 14627.

Email: mafandiy@UR.Rochester; c.r.kennedy@rochester.edu

Pyridones are powerful ligands that play an important role in biological processes, such as dihydrogen (H_2) activation by [Fe] hydrogenase via a metal-ligand cooperative (MLC) mechanism.[1] Analogous cooperativity has also been demonstrated in biological systems for reactions such as alcohol (de)hydrogenation.[1] Nevertheless, limited access to single-component complexes hampers mechanistic insight and application in more complex systems. This presentation will describe the synthesis, novel structural properties and hydroboration reactivity of highly electron-rich Ni(0) complexes supported by unsymmetric NHC-pyridone ligands.[2] Both stoichiometric and control experiments suggest an important role of the pyridone oxygen in the formation of the hydroboration product. Preliminary work on the application of these Ni(0) complexes in functionalization of unactivated and naturally abundant electrophiles will be described, highlighting some unusual mechanistic outcomes.

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Automatic peak assignment and feedback-controlled synthesis of complex one-pot multistep Suzuki-Miyaura couplings.

Mason Guy, **Jason E. Hein***
University of British Columbia
Email: mguy068@chem.ubc.ca; jhein@chem.ubc.ca

The synthesis of laser dye molecules via iterative one-pot Suzuki-Miyaura coupling (SMC) involves multiple reaction components and is further complicated by multiple potential side reactions, making their optimization incredibly difficult and time consuming (**Figure 1**). We have developed an adaptive, automated synthesis tool that utilizes online high-performance liquid chromatography to monitor the progress of a reaction in real time. This live monitoring allows enables the system to execute actions based on the reactivity of different substrates. The platform also utilizes the temporal reaction profiles combined with component information such as ultraviolet spectroscopy and polarity to determine the identity of side/decompositions products, intermediates, and other reaction components, bypassing the need for isolation and quantification of unknown species. By combining the real time decision making and component identification, we analyzed and optimized the synthesis of three laser dyes via iterative one-pot SMC from nine chemically distinct starting materials.

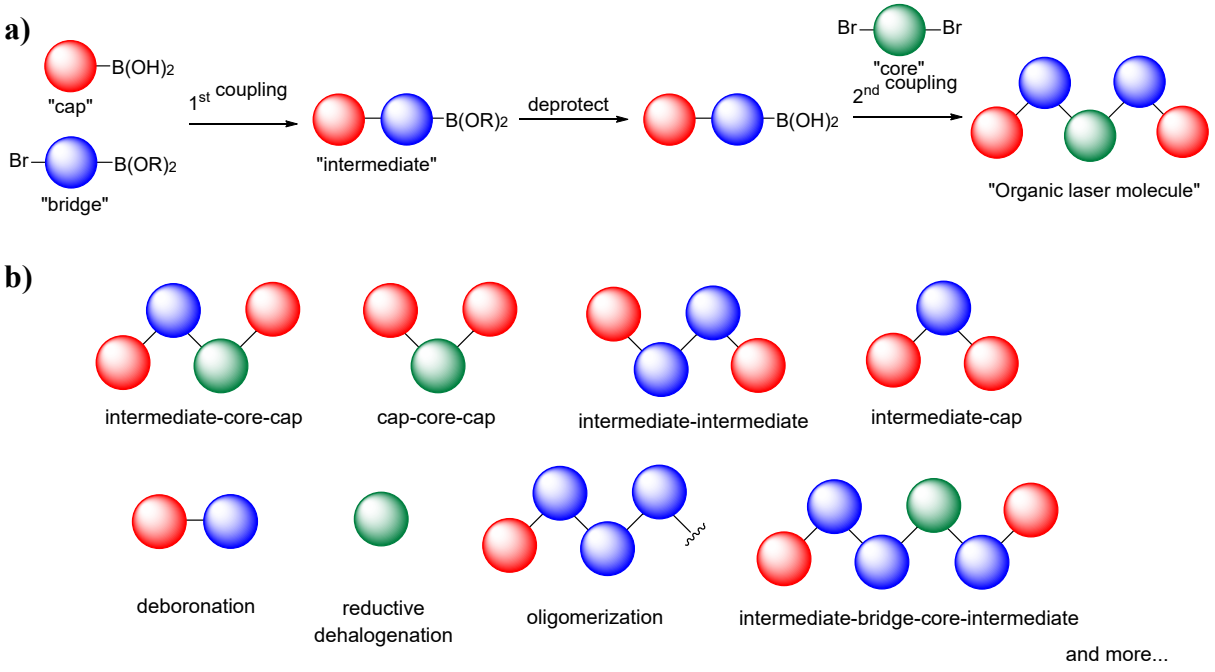

Figure 1. Assembly of organic laser molecules. a) building block, one-pot iterative coupling approach b) non-exhaustive list of potential undesired side products.

Rhodium(III)-Catalyzed Anti-Markovnikov Hydroamidation of Unactivated Alkenes Using Dioxazolones as Amidating Reagents

Noah Wagner-Carlberg, Tomislav Rovis*
Columbia University

Email: ndw2119@columbia.edu; tr2504@columbia.edu

The amide is one of the most prevalent functional groups in all of pharmaceuticals, and for this reason, reactions that introduce the amide moiety are of particular value. Intermolecular hydroamidation of alkenes remains an underexplored method for the synthesis of amide-containing compounds. The majority of hydroamidation procedures exhibit Markovnikov regioselectivity, while current methods for anti-Markovnikov hydroamidation are somewhat limited to activated alkene substrates or radical processes. My poster will disclose details of a general method for the intermolecular anti-Markovnikov hydroamidation of unactivated alkenes under mild conditions, which utilizes Rh(III) catalysis in conjunction with dioxazolone amidating reagents and isopropanol as an environmentally friendly hydride source. The reaction tolerates a wide range of functional groups and efficiently converts electron-deficient alkenes, styrenes, and 1,1-disubstituted alkenes, in addition to unactivated alkenes, to their corresponding linear amides. Mechanistic studies reveal an unselective and reversible rhodium hydride migratory insertion step, leading to exquisite selectivity for the anti-Markovnikov product.

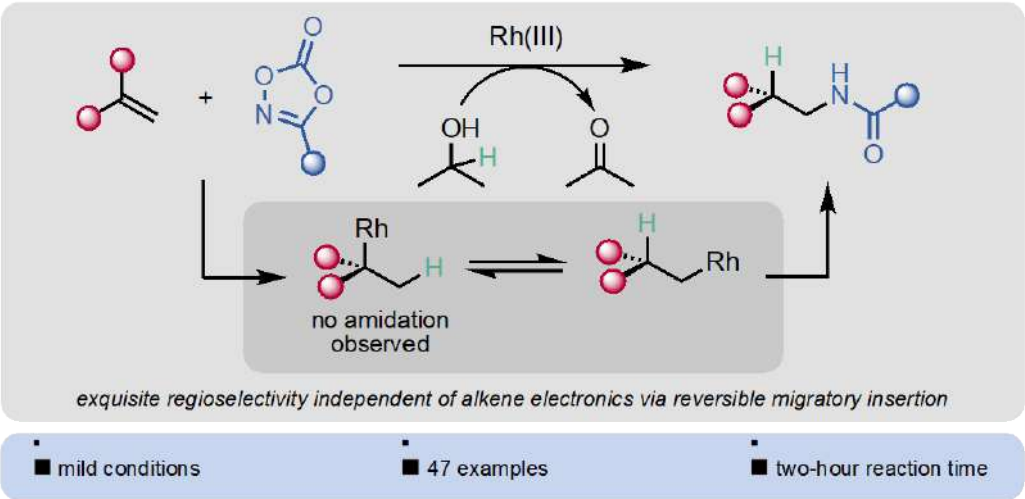

Figure 1. Reversible rhodium hydride migratory insertion enables highly selective anti-Markovnikov hydroamidation of unactivated alkenes

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A Generalized Computer-Vision-Based System for Real-Time Automated Monitoring and Control

Rama El-khawaldeh[1], Mason Guy[1], and Jason E. Hein*[1]

[1]*Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada*

E-mail: ramaelk@chem.ubc.ca

Chemists spend significant time performing menial tasks that rely on visual cues such as observing colour changes, monitoring liquid levels, detecting crystal formation, etc.[1] Digital cameras can be combined with computer vision (CV) algorithms to automatically capture, process, and analyse such visual inputs.[2] However, traditional CV systems are rigid in functionality when they are inherently designed to target specific tasks while exclusively relying on colour, grayscale, or edge identification for image analysis.[3] Previously, the Hein Lab has focused on building fully integrated automated monitoring and control systems using flexible hardware and CV for liquid-level monitoring.[4] Herein, we present a generalizable CV and machine learning model that was trained on images from a diverse array of chemical and non-chemical processes. Our newly developed system can be used for automated real-time monitoring and control of experiments and can be readily trained to adjust to the ever-changing needs of the experiments. Compared with conventional CV systems that rely on selective parameterization for data analysis,[5] our model simultaneously monitors multi-parameters (*e.g.,* liquid level, homogeneity, turbidity, solid, residue, and colour), offering a method for rapid data acquisition and deeper analysis from multiple visual clues. We demonstrated a single platform (consisting of CV, machine learning, and automated robotics) to monitor and control vision-based experimental techniques, including titration, solvent swap distillation, liquid-liquid extraction, solid-liquid mixing, crystallization, and solvent evaporation. Both qualitative (video capturing) and quantitative data (parameters measurement) were obtained which provided a method for data cross-validation. Our CV model's ease of use, generalizability, and non-invasiveness make it an appealing complementary option to *in situ* and real-time analytical monitoring tools. Additionally, our platform is integrated with Mettler-Toledo's iControl software, which acts as a centralized system for real-time data collection, visualization, and storage. With consistent data representation and infrastructure, we were able to efficiently transfer the technology and reproduce results between different labs. This ability to easily monitor and respond to the dynamic situational changes of the experiments is pivotal to enabling future flexible automation workflows.

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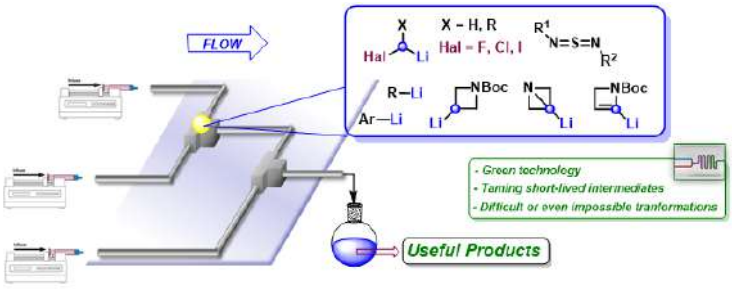
Flow chemistry as an enabling technology for developing organometallic-mediated sustainable synthetic tactics

Renzo Luisi*[a]
University of Bari "A. Moro" FLAME-Lab – Flow Chemistry and Microreactor Technology Laboratory, Department of Pharmacy – Drug Sciences, Via E. Orabona 4, 70125 – Italy
E-mail: renzo.luisi@uniba.it

In the field of enabling technologies, the potential of flow chemistry for developing sustainable synthetic processes as well as for accessing new chemical space exploiting the reactivity of highly unstable intermediates is nowadays widely recognized.[1] In this lecture the use of organolithiums, halocarbenoids, strained heterocycles and overlooked sulfur functional groups will be discussed jointly to the key role of flow technology and flash chemistry concept in the development of synthetic strategies.[2-5] The outperformance of flow technology with respect to batch processing will be central in this discussion.



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Development of Lewis Acidic Weakly Coordinating Anions and their Application to Catalytic Regioselective C-H Functionalization

Ryo Mandai, Takanori Iwasaki*, Kyoko Nozaki*
Graduate School of Engineering, The University of Tokyo
Bunkyo-ku, Tokyo 113-8656, Japan
Email: mandai-ryo281@g.ecc.u-tokyo.ac.jp; iwasakitakanori@g.ecc.u-tokyo.ac.jp; knozaki@g.ecc.u-tokyo.ac.jp

In recent years, new catalyst designs owing multiple active sites, such as multi-metallic and metal-ligand cooperative catalysts, have been intensively investigated to realize challenging transformations. In this purpose, design of supporting ligands and their combination with metal atoms are mainly focused. In contrast, counter anions, coexisting with cationic transition metal complexes, have been much less studied as a candidate for incorporating a catalytic function in transition metal catalysis except for serving as a Brønsted base including chiral phosphate or sulfonate.[1, 2] Weakly coordinating anions (WCA) are often employed as counter anions of cationic metal complexes to open their coordination sites, but they do not contribute to activating substrates.

We envisioned that a novel WCA endowed with Lewis acidic property would serve as a new class of multi-active site catalyst when combined with a cationic transition metal catalyst. A Lewis acidic WCA recognizes polar functional groups in substrates, such as halogens, carbonyls, and nitriles, by acid-base interaction to control orientation of the substrates. At the same time, the electrostatic interaction between the ion pair approximates the captured substrate to transition metal center.

We synthesized tetraarylborate **BB** bearing tri-substituted boryl groups as Lewis acidic sites. Borate **BB** was employed as the counter anion to the Ir-catalyzed hydrogen isotope exchange of 1,4-difunctionalized arenes. For instance, when H/D exchange reaction of *p*-nitroacetophenone was examined using **BB** as a counter anion under D_2, significantly high regioselective of k_{ortho}/k_{meta} = 15.7 was observed. Almost no regioselectivity was observed with a commonly employed WCA, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate **BAr^F**, under the same conditions (k_{ortho}/k_{meta} = 1.21)[3], which demonstrated the concept of Lewis acidic WCA to realize a regioselective C-H activation.

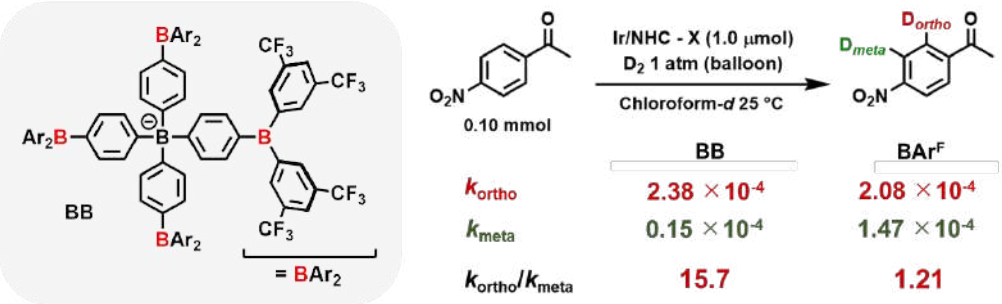

Figure 1. Structure of borate **BB** and H-D exchange reaction catalyzed by Ir complex bearing **BB** or **BAr^F**.

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Double Hydroelementation of N-Heteroarenes

Ruibin Wang,[a] Sehoon Park*[a]
[a]Departement of Chemistry, Guangdong-Technion Israel Institute of Techniology, China
Email: sehoon.park@gtiit.edu.cn

Catalytic dearomative reduction of N-heteroarenes is of important transformations in organic synthesis as well as medicinal chemistry. A number of organo(metallic) catalysts have been documented for selective hydrosilylation and hydroboration of pyridines to provide a broad range of dihydro-products.[1] However, double hydroelementation of pyridines possibly leading to a new family of tetrahydro-products bearing a sp^3 C–E bond (E = Si, B-based moieties), had been unknown until we disclosed.

In this talk, we describe the full aspects of the *first* double hydrosilylation and hydroboration of quinolines and pyridines catalyzed by $B(C_6F_5)_3$.[2] And, we present the Rh-catalyzed regio- and enantioselective double hydroboration of quinolines as an advanced catalytic system.[3] Finally, we discuss about the Rh-catalyzed double hydroboration of pyridine, where a combination of mechanistic experiments and DFT calculations reveal the origin of the chemo- and regioselectivities.[4] This Rh system represents the *first* example of a metal-catalyzed double hydroboration of N-heteroarenes.

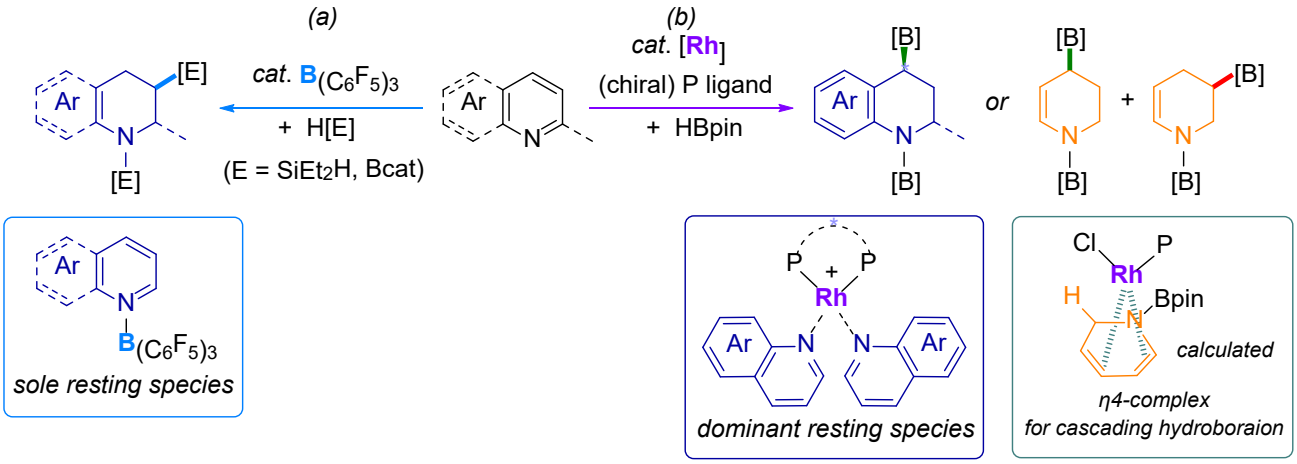

Figure 1. Double hydroelementation of N-heteroarenes.

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Ni-catalyzed Cross-coupling Reaction of Silyl Difluoroenolates

Taiki Negoro,[a] Koki Kajiwara,[a] Ryohei Doi,*[a] Sensuke Ogoshi*[a]
[a]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita 565-0871, Osaka, Japan.

Email: t_negoro@chem.eng.osaka-u.ac.jp, rdoi@chem.eng.osaka-u.ac.jp, ogoshi@chem.eng.osaka-u.ac.jp

Organofluorine compounds have been attractive synthetic target molecules because fluorine substitution is commonly used in contemporary medicinal chemistry to improve metabolic stability and lipophilicity and to adjust acidity1). Especially compounds that have a fluorine-containing quaternary stereogenic center are important target molecules. Some synthetic methods have been reported, including catalytic enantioselective reactions,[2-4)] though the scope is limited to cyclic compounds. We envisioned that the silyl fluoroenolate would be a valuable precursor of an acyclic fluorine-containing quaternary stereogenic center. However, the regioselective synthesis of a silyl fluoroenolate remains elusive.
Herein, we disclose a Ni-catalyzed cross-coupling reaction of silyl difluoroenolate with organozinc reagents in the presence of lithium salt. The regioselective coupling reaction gave a Z isomer in perfect selectivity (Figure 1). The use of bulky IPr* ligand suppressed further reaction of monofluoroenolate to diphenylenolate. The geometry of the alke moiety was unambiguously determined by 1H-19F HOESY of an E/Z mixture, which was obtained by treatment of the coupling product with tetrabutylammonium difluorotriphenylsilicate (TBAT). We next tested the asymmetric Tsuji-Trost reaction of our silyl monofluoroenolate to construct an acyclic fluorine-containing quaternary stereogenic center. As a result, we obtained desired products with moderate enantioselectivity by using tert-Bu PHOX ligand (Figure 2).

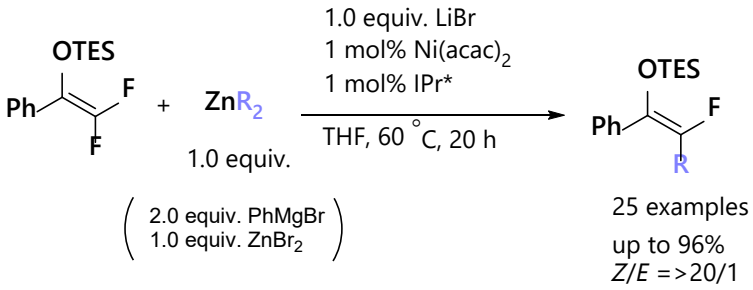

Figure1. Ni-catalyzed cross-coupling reaction of difluoroenolate and organozinc reagent

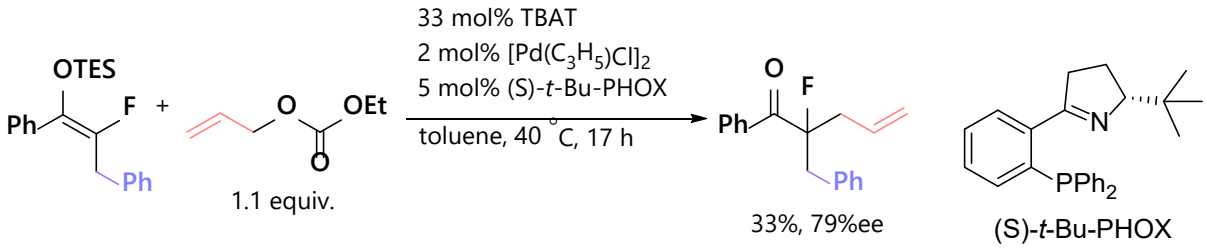

Figure 2. Tsuji-Trost allylation of silyl monofluoroenolate

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Nickel or Palladium-Catalyzed Decarbonylative Transformations of Acyl Fluorides and Chlorides

Yasushi Nishihara,*[a] Zhenhua Wang,[b] Xiu Wang,[b] Yasuyuki Ura[c]
[a]Research Institute for Interdisciplinary Science, Okayama University, Okayama, Japan. [b]Graduate School of Natural Science and Technology, Okayama University, Okayama, Japan. [c]Department of Chemistry, Biology and Environmental Science, Faculty of Science, Nara Women's University, Nara, Japan.

Email: ynishiha@okayama-u.ac.jp

Given the growing concerns about environmental and sustainable events of our society, carboxylic acids, which are naturally abundant and readily available, are in high demand as alternatives to commonly used carbon feedstocks. Recently, we have intensively studied the decarbonylative molecular transformations of acyl fluorides, one of the carboxylic acid derivatives, as the substrates.[1,2] Since Schoenebeck disclosed the palladium-catalyzed decarbonylative trifluoromethylation of acyl fluorides in 2018,[3] we have reported the Ni-catalyzed decarbonylative ethylation[4] and borylation[5] of acyl fluorides. Under optimal conditions, it was found that acyl fluorides with functional groups such as cyano, halides (F and Cl), ketone, and ester were well tolerated.
As shown in Figure 1, we have established an efficient and practical method for nickel-catalyzed decarbonylative cyanation of acyl chlorides with TMSCN to convert a variety of acyl chlorides to nitriles in good to excellent yields. Mechanistic studies suggest that the phosphine ligands (PPh_3) facilitate the decarbonylation and reductive elimination steps. When the stronger electron-donating ligand PEt_3 was employed, the oxidative adduct was less prone to release CO in the absence of TMSCN, which allowed us to isolate the acyl–Ni complex as an intermediate. On the other hand, in the presence of TMSCN, transmetalation occurred smoothly prior to decarbonylation.

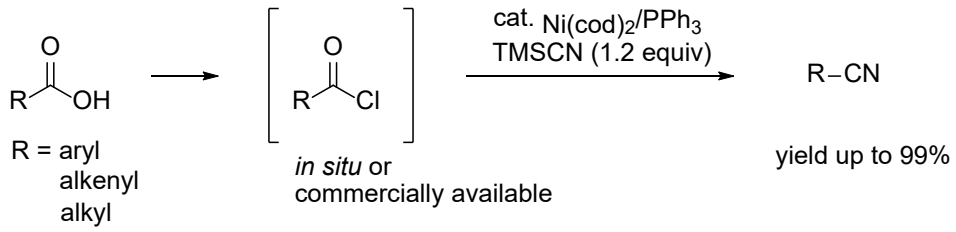

Figure 1. Ni-catalyzed decarbonylative cyanation of acyl chlorides.

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Applying Online HPLC-MS to Elucidate Decomposition Processes During Pd-Catalyzed Reactions

Isabelle Cai[a], Lauren E. Sirois[b], Thomas C. Malig[b], Kenji L. Kurita[b], Joshua S. Derasp[a], Andrew J. Kukor[a], Jason E. Hein[*a]

[a] Department of Chemistry, The University of British Columbia, Vancouver, British Columbia, V6T 1Z1, Canada.

[b] Department of Small Molecule Process Chemistry, Genentech, Inc., South San Francisco, California, 94080, United States.

Email: icai1@chem.ubc.ca; jhein@chem.ubc.ca

Mechanistic analysis is important for the development and optimization of catalytic reactions. Real-time reaction monitoring coupled with process analytical technology provides a broad perspective of the reaction system and its kinetics, which in turn may allow for mechanistic elucidation. During the development of a Pd-catalyzed C-N coupling to access a chiral active pharmaceutical ingredient (API), the transformation was profiled using kinetic analysis and optimized for yield, but several phenomena related to substrate/product degradation and epimerization during the reaction remained understudied and less well understood.

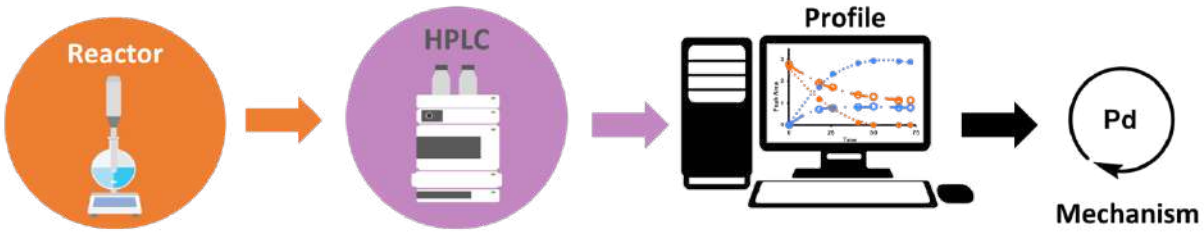

Figure 1. Schematic of online HPLC sampling system.

Online HPLC-MS was employed to acquire time course profiles to delineate epimerization behavior, identify and mitigate decomposition pathways, and study the effects and nature of the Pd species. Our investigation provides practical insight on the execution and optimization of reactions susceptible to similar epimerization and decomposition processes. We further show that it is possible to interrogate the catalyst speciation via online HPLC-MS, giving the distribution of the Pd-precatalyst and its oxidative addition complexes over time. Altogether, we demonstrate that online HPLC-MS is a unique and powerful tool for directly interrogating complex catalytic systems and for the optimization of chemical processes.

Non-covalent Immobilization of Chiral Transition Metal Complexes for Continuous-flow Enantioselective Catalysis

Yuki Saito,[a] Shu Kobayashi*[a]
[a]Department of Chemistry, School of Science, The University of Tokyo
Hongo, Bunkyo-ku, Tokyo, Japan, 113-0033.

Email: y-saito@chem.s.u-tokyo.ac.jp; shu_kobayashi@chem.s.u-tokyo.ac.jp

Continuous-flow reactions with chiral heterogeneous catalysts enable efficient, safe, and environmentally benign synthesis of optically active compounds, and catalysts can be separated and reused continuously. Despite these advantages, continuous-flow enantioselective transition metal catalysis is hardly explored due to the lack of efficient chiral heterogeneous catalysts. Therefore, the development of efficient and versatile immobilization methods of chiral transition metal catalysts is in high demand.

We have designed a heteropoly acid/amine-functionalized SiO_2 composite as support for chiral cationic transition metal complexes and developed continuous-flow enantioselective catalysis using chiral heterogeneous catalysts (Fig. 1). Heteropoly acid forms acid-base salts with amines on the surface of SiO_2, and cationic metal catalysts are immobilized on anionic heteropoly acids via electrostatic interaction. Characteristic points of this method are that no modification of chiral ligands is necessary for the immobilization, and high mass transfer ability is attained by the use of mesoporous SiO_2.

As a proof of concept of this method, we have developed enantioselective hydrogenation of enamides using chiral heterogeneous Rh(I) catalysts in 2020.[1] The catalysts exhibited high activity and enantioselectivity and the target optically active amides could be obtained in quantitative yields with >99% ee's for >90 h without leaching of Rh. This type of chiral heterogeneous Rh(I) catalysts could be applicable for different types of Rh(I) catalyses such as enantioselective reductive cyclization of 1,6-en-ynes and enantioselective hydroacylations under continuous-flow conditions. In this work, we have also demonstrated sequential-flow synthesis of useful molecules by connecting with other heterogeneous catalyses. Moreover, this method could be applicable for chiral Sc Lewis acid catalysis and continuous-flow enantioselective Friedel-Crafts type reaction was developed.[2] Throughout these studies, we have discovered that the structure of SiO_2, surface amine, and heteropoly acid are essential and the catalyst activity and selectivity can be tuned by changing their structure, which is essential for high efficiency and versatility of this immobilization method.

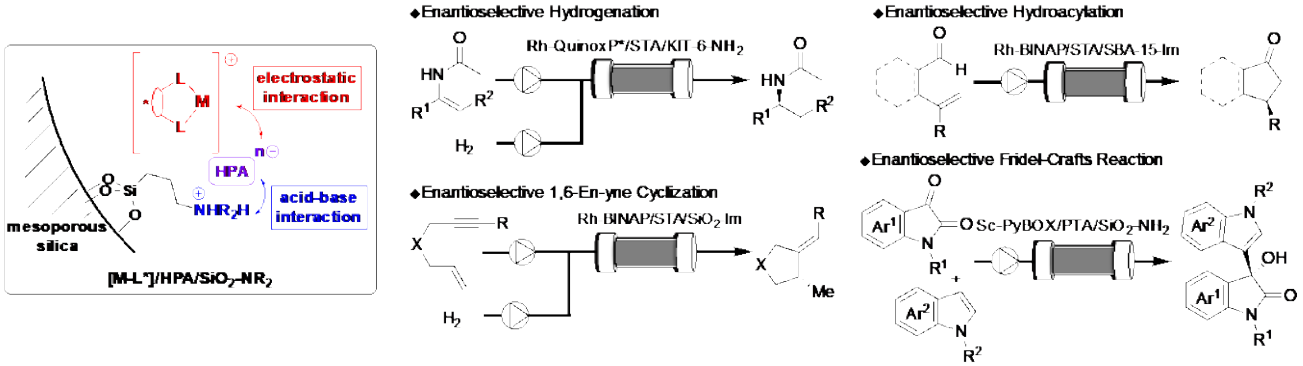

Figure 1. Design and Application of Chiral Heterogeneous Catalysts

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Black Titanium Dioxide Photocatalyst for Continuous-Flow Degradation of Pharmaceuticals

Nelson Rutajoga, Mahzad Yagmaei, Daliane R.C. da Silva, Sara Currie, Yiran Li, Morgan Vallieres, Neeraj Joshi, Bowen Wang and Juan C. Scaiano*
Department of Chemistry and Biomolecular Science, University of Ottawa

Email: nruta040@uottawa.ca

In recent decades, increasing amounts of pharmaceuticals have been found in bodies of water with endocrine-disrupting chemicals (EDCs), such as 17β-estradiol, raising distinct concern. [1] Titanium dioxide (TiO_2) has been greatly studied as a semiconductor for photodegrading pharmaceutical pollutants. However, with a bandgap of 3.2 eV, standard white TiO_2 only uses 4 % of the solar spectrum for photocatalytic processes. This study aimed to design a black TiO_2-based catalyst, to photodegrade of organic water contaminants under visible light. Black TiO_2 has a reported bandgap of 1.54 eV and thus allows for upwards of 40% of the solar spectrum to be utilized. [2]

The synthesis of the target photocatalyst was achieved by loading titanium isopropoxide onto a glass fiber support and adding deionized water to induce the deposition of TiO_2. The resulting material is then dried and reduced with ethanol under inert conditions to form black TiO_2. Crocin, a natural yellow-red pigment, was chosen as a surrogate molecule for preliminary studies. The elimination of crocin and 17β-estradiol from aqueous solutions was examined using a bench top flow system comprised of a mechanical pump, glass tubing, a flow-through cuvette, and white LED panels to provide visible light irradiation. This continuous flow setup allowed for cyclical circulation of aqueous solutions containing the organic pollutants.

The black TiO_2 material was effective in degrading both organic water contaminants. Crocin experiments, performed in Milli-Q water, were monitored using UV-vis spectroscopy and demonstrated that the degradation of the surrogate molecule occurred at a greater rate, by a factor of 1.83, when using black TiO_2 as opposed to standard white TiO_2 under the same experimental conditions. The degradation of 17β-estradiol was conducted in an acetonitrile/Milli-Q water and aliquots were collected for analysis using high-performance liquid chromatography (HPLC). HPLC results indicated that up to 90 % of the 17β-estradiol content in a 1 mM solution was eliminated using black TiO_2 under white light irradiation for 4 hours. Estrone, a common product of 17β-estradiol oxidation, was identified amongst other products as is shown in **Figure 1**. Current efforts aim to optimize reaction conditions to achieve mineralization of targets EDCs.

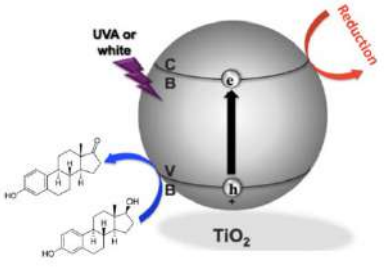

Figure 1. Black TiO_2 catalyst photodegrading 17β-estradiol via an oxidation reaction.

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Nickel-Catalyzed Selective Cleavage of C(sp^3)–O Bond of 1-Aryloxy-3-Amino-2-Propanols: A Study Towards Epoxy Resin Degradation

Yumeng Liao,[1] Kohei Takahashi,[1] and Kyoko Nozaki[1,*]
[1]Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8656, Japan.

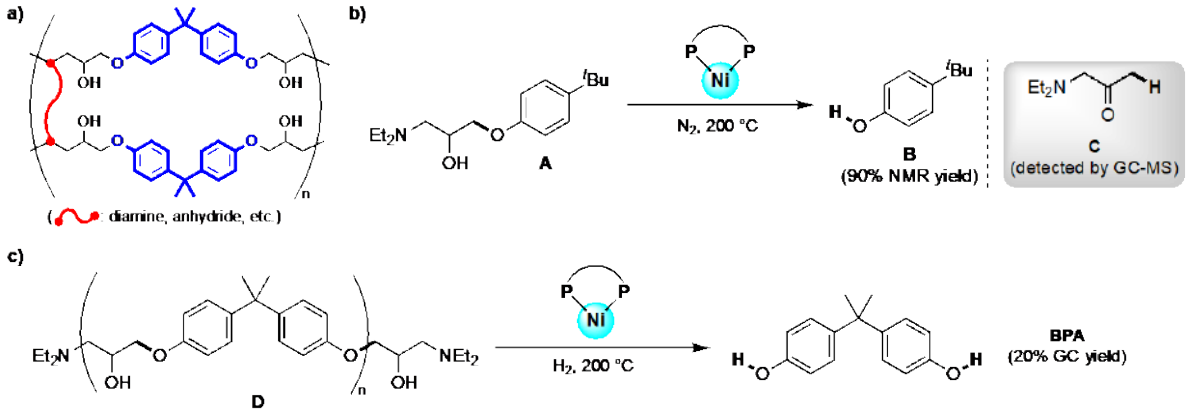
Email: yliao@g.ecc.u-tokyo.ac.jp; nozaki@chembio.t.u-tokyo.ac.jp

Ethereal C–O bond serves as a crucial linkage in various plastic materials, including epoxy resin.[1] In the case of cured bisphenol A (BPA)-based epoxy resin (Scheme 1a), the selective cleavage of ethereal C(sp^3)–O bond would allow a direct recovery of BPA. This would provide an appealing recycling approach for gaining valuable chemical feedstocks from discarded plastic wastes. However, previous examples of homogeneous catalytic cleavage of ethereal C–O bonds have typically targeted C(sp^2)–O bonds, despite the co-existence of C(sp^3)–O bonds.[2] While a rare example of selective demethylation of aryl methyl ethers by an Ir catalyst under H_2 atmosphere was reported by Nozaki,[3] indicating the potential for degrading BPA-based epoxy resin for recovering BPA, but the high cost and synthetical complexity of the Ir complex restrict its industrial implementation.

Herein, we synthesized 1-aryloxy-3-amino-2-propanol (**A**) (aryloxy = 4-*tert*-butylphenoxy, amino = diethylamino) as a model compound of amine-cured epoxy resin, and treated **A** with bisphosphine ligand-supported Ni complex at 200 °C to successfully resulted corresponding phenol **B** in 90% NMR yield (Scheme 1b), where the C–O cleavage selectively occurred at sp^3 carbon. To be noted, aminoacetone **C** was also detected by GC-MS, which strongly suggested a transfer hydrogenolysis pathway in this reaction where the hydroxy group acts as the hydrogen donor.

Furthermore, when employed this method to Et_2NH-ring-opened epoxy resin prepolymer **D** (Scheme 1c), the C(sp^3)–O cleavage also proceeded to afford 20% GC yield of BPA. This promising result shows the potential application in the selective degradation of actual epoxy resin for the recovery of BPA.

Scheme 1. Outline of This Work



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Palladium-catalyzed β-heteroarylation of Cyclic Enones

Aishabibi Kassymbek,[a] Philipp C. Roosen,[b] Stephen G. Newman*[a]
[a] Centre for Catalysis Research and Innovation, Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario K1N 6N5. [b]Pfizer Chemical Research and Development, Pfizer Inc., Groton, Connecticut 06340, United States.

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

Cyclic α,β-unsaturated carbonyls are versatile intermediates in the synthesis of active pharmaceutical compounds. One of the ways of functionalizing cyclic enones is through β-arylation using Mizoroki-Heck reaction.[1] However, Heck reaction of cyclic enones with aryl halides is a challenging transformation and remains underexplored in the literature.[2]
We report palladium-catalyzed Mizoroki-Heck reaction of cyclic enones with aryl bromides, including heteroaryl bromides. Some challenges of the reaction include deactivation of the catalyst by heteroaryl bromides, homocoupling of aryl bromides, and reduction of β-arylated enone. Our method containing catalytic palladium with BippyPhos ligand promotes cross-coupling reactions of wide range of aryl bromides with cyclic enones in good to excellent yields under mild conditions.

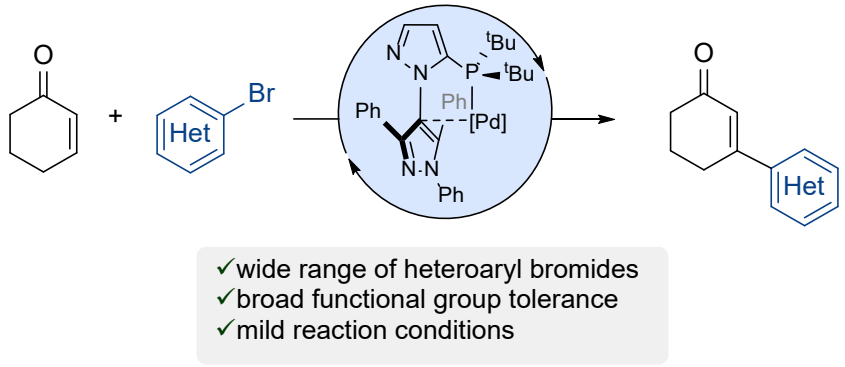

Figure 1. Pd-catalyzed β-arylation of cyclohexenone

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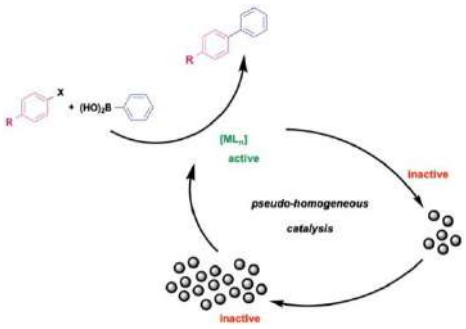
Recyclable Homogeneous and Pseudo-Homogeneous Transition Metal Catalysts: Applications in Cross Coupling, Hydrosilylation and Reduction Reactions

Andrew K. King,[a] Aneelman Brar,[a] Adineh Rezaei-Bazkiaei[b],and Michael Findlater*[a]
[a]Department of Chemistry & Chemical Biology, University of California, Merced, 5200 N. Lake Road, Merced, CA, USA. [b] Department of Chemistry & Biochemistry, Texas Tech University, Lubbock, TX, USA.

Email: aking33@ucmerced.edu; michael.findlater@ucmerced.edu

Homogeneous catalysis has many advantages over heterogenous catalysis including high product selectivities and that the processes are often easy to characterize and study, hence making them easier to modify to improve reactivity. However, one of the key disadvantages associated with homogenous catalysis is that the separation of the products and the catalyst is often not feasible. Traditional methods in homogeneous catalysis rely heavily on platinum group metal catalysts to facilitate reactivity.[1] Strategies to recycle these expensive and in-abundant metals are highly desirable.
The use of a metalla-GAP strategy (GAP = Group-Assisted-Purification) in homogeneous catalysis, which allows simple recovery and re-use of a homogeneous metal catalyst will be presented in addition to a recyclable pseudo-homogenous palladium nanoparticle based system.[2-4] Palladium-based catalysts exhibit excellent reactivity in Suzuki coupling reactions while delivering a broad substrate scope (25 examples, up to 95% isolated yield) and high functional group tolerance. Zinc-based catalysts exhibit excellent reactivity in hydrosilylation reactions (29 examples, up to 92% isolated yield). The origins of the reactivity present in the palladium- and zinc-catalyzed transformations, and recyclability studies will be discussed.

Figure 1. Recyclable pseudo-homogenous catalysts for Suzuki couplings.



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Accessing highly strained nickellacycles with hemilabile P,N Ligands for realizing challenging C−H bond functionalization reactions

Ben E. Nadeau,[a] Eric G. Bowes,[a] Laurel L. Schafer*[a], Jennifer A. Love*[b]
[a] Chemistry, The University of British Columbia, Vancouver, BC, Canada.
[b] Chemistry, University of Calgary, Calgary, AB, Canada
Email: bnadeau@chem.ubc.ca; schafer@chem.ubc.ca*, jennifer.love@ucalgary.ca*

Designing hemilabile ligated transition metal complexes that can undergo rapid ligand association/dissociation and exchange in solution allows for modulation of coordination number and electrophilic properties at reactive metal centers for organometallic catalysis. Hybrid phosphorus, nitrogen (PN) donor ligands have proven to be superior to bidentate diamine (NN) and diphosphine (PP) ligands in numerous catalytic applications.[1] Decreasing the bite-angle of these ligands increases strain, promotes ligand dissociation of a labile N donor and facilitates reactivity of the resultant complex. Additionally, both steric and electronic effects of the phosphorus donor have also been shown to promote new coordination modes and can facilitate various C-E (E = O, N, X) bond forming reactions.[2-4]

In this work, we have synthesized a new class of highly strained κ_2-P,N Ni(II) complexes with a variety of pyridylphosphine and aminophosphine bidentate ligands. These complexes have been characterized by ^{1}H and ^{31}P NMR spectroscopy as well as single-crystal X-ray diffraction. The electronic features of the N donor have a dramatic influence on the coordination geometry of the resulting Ni(II) complexes. Initial reactivity investigations with these complexes shows promising results for C(sp^3)−H bond functionalization reactions and provides insights into the design criteria for optimizing Ni catalysts in productive small molecule activation.

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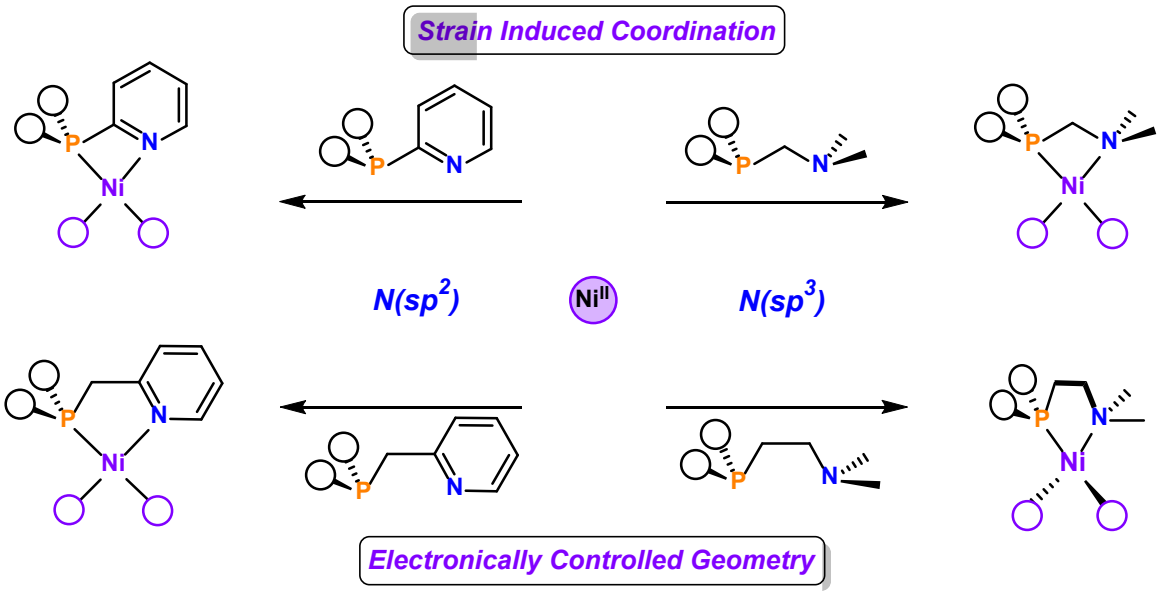

Figure 1. Coordination geometry of hemilabile P,N Ligands with Ni(II).

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Tantalum-Catalyzed Hydroaminoalkylation To Access Nitrogenous Heterocyclic Frameworks

Cameron H.M. Zheng[a], Ole F. Dreßler[a], Carla A. Hoefer[a], Ben E. Nadeau[a], Rebecca C. DiPucchio[a], Laurel L. Schafer[a]*

[a]The University of British Columbia, Vancouver, Canada.

Email: czheng@chem.ubc.ca; schafer@chem.ubc.ca

Hydroaminoalkylation is an atom-economic method to form new C_{sp}^3—C_{sp}^3 bonds by reacting alkenes with a C—H bond α to an amine.[1] If inexpensive and low toxicity early transition metal catalysts are employed in hydroaminoalkylation, no protecting or directing groups are required, thus increasing synthetic efficiency, and minimizing waste generation. A recently developed in-situ tantalum-catalyst system can be assembled using $Ta(CH_2SiMe_3)_3Cl_2$ and a ureate ligand with catalyst loadings as low as 5 mol%.[2] This tantalum ureate system displays a wide tolerance for aryl amines, dialkyl amines, and in particular saturated *N*-heterocycles are reactive with a variety of alkenes, in contrast to other early transition metal hydroaminoalkylation catalysts that have shown limited utility with saturated *N*-heterocycles.[3] This catalyst system features reduced reaction temperatures and times, increased TONs and TOFs and enhanced substrate functional group tolerance and provides promising opportunities for post-hydroaminoalkylation transformations. A series of diastereoselectively alkylated saturated N-heterocyclic hydroaminoalkylation products created from ortho-chlorostyrenes and alkenyl alcohols can be prepared (Figure 1). All saturated *N*-heterocycles used are commercially available and the resultant products are primed for ring-closure. This presentation will discuss high-yielding one-pot multi-catalytic strategies toward diverse *N*-heterocyclic scaffolds accessed via sequential one-pot hydroaminoalkylation and Buchwald-Hartwig amination. As well, a one-pot strategy featuring a hydroaminoalkylation/S_N2 cyclization strategy is also discussed, furnishing natural- product-like bicyclic saturated *N*-heterocyclic products.

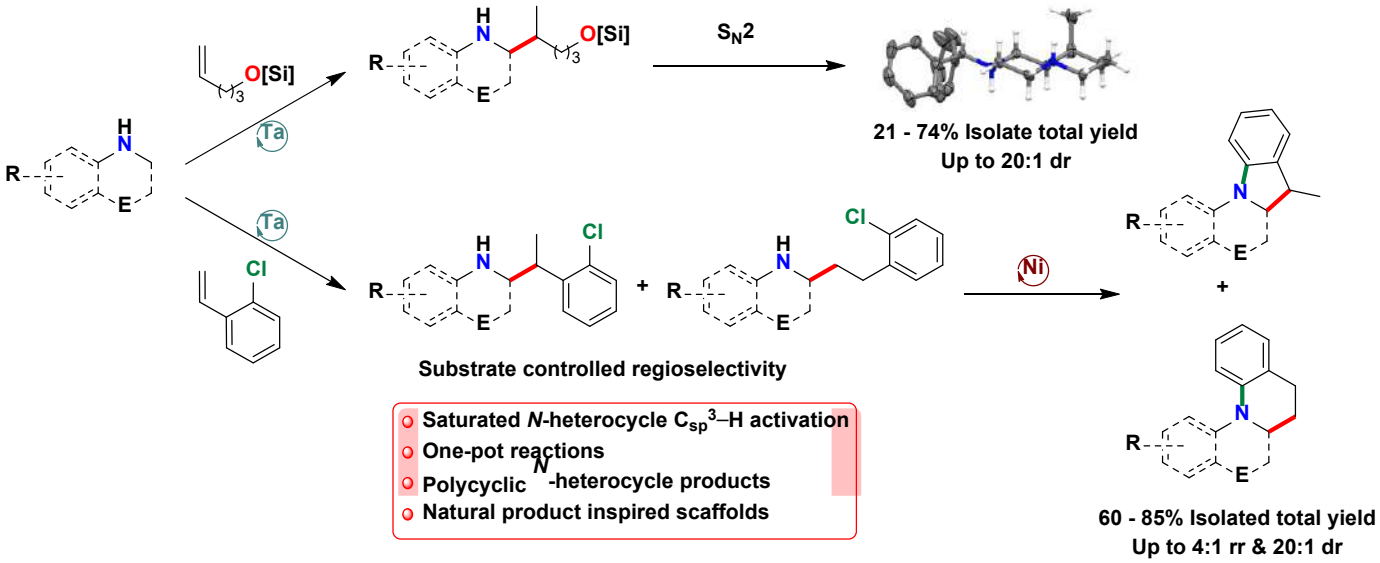

Figure 1. One-pot strategies for bicyclic and tricyclic *N*-heterocycles

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Palladium-Catalyzed Diastereoselective Arylation of the Bis-Lactim Ether with Aryl Chlorides

Daniel Sowa Prendes, **Florian Papp**, **Nagesh Sankaran**, **Nardana Sivendran**, **Lukas J. Gooßen***

Email: daniel.sowaprendes@rub.de; lukas.goossen@rub.de

Chiral α-aryl amino acids are important structural motifs present in various pharmaceuticals like the penicillin derivative amoxicillin. Usually, these important compounds are synthesized by asymmetric variants of the Strecker synthesis[1] or the Petasis-Borono Mannich reaction[2], which are however limited to the use of toxic cyanide sources or prefunctionalized expensive boronic acids. For this reason, in the last decades the direct arylation of glycine derivatives was explored, while only few examples for the asymmetric synthesis of arylglycines are reported.[3–6] In previous works, the group of Barrett explored a diastereoselective aryne-mediated arylation of the Schöllkopf bis-lactim ether using aryl halides and n/sec-BuLi at low temperatures.[7] In this work, a Pd-catalysed diastereoselective arylation of the bis-lactim ether with cheap and broadly abundant aryl chlorides under mild reaction conditions was achieved (Figure 1). This method has opened up an expedient access to a wide variety of chiral arylglycines including derivatives of commercially available drugs, sequential arylation-alkylation sequences and mild deprotection strategies.

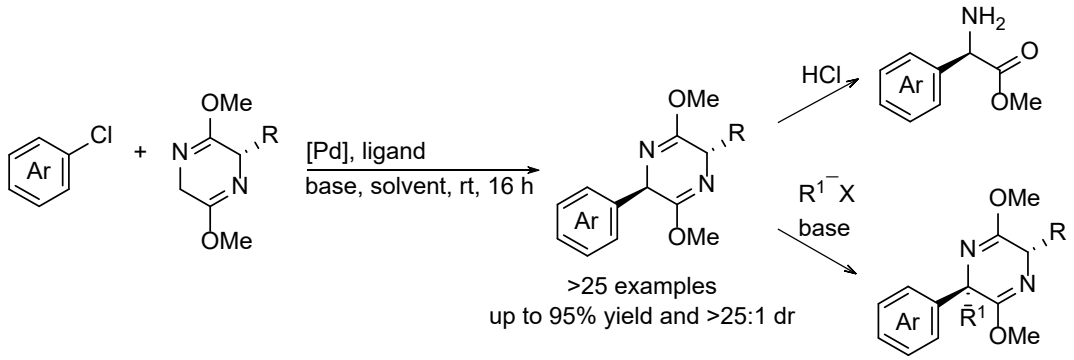

Figure 1. Pd-catalyzed asymmetric arylation of the bis-lactim ether with aryl chlorides.

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Highly Reactive Hydrocarbon Soluble Alkylsodium Reagents for Benzylic Aroylation of Toluenes using Weinreb Amides

David E. Anderson,[a] Prof. Dr. Eva Hevia*[a]
[a] Departement für Chemie, Biochemie und Pharmazie, Universität Bern. Freiestrasse 3, 3012 Bern.
Email: david.anderson@unibe.ch; eva.hevia@unibe.ch

Alkyl sodium reagents have been proposed as an alternative to organolithiums, one of the workhorses of synthetic chemistry.[1] Several factors, however, have hindered their wider synthetic application in organic synthesis. They are plagued by poor solubility in hydrocarbon solvents and low stability in donating ethereal solvents. These impediments have made them inconvenient for widespread use by synthetic chemists, leading to a lower accessibility when compared with their lighter lithium congers. Despite these limitations, recent reports in the field of organosodium chemistry have focused on the development of new reactivity and have demonstrated the potential of these powerful reagents in synthesis, surpassing the reactivity obtained with other organometallic reagents.[2][3] However, the nature of the sodiated intermediates in both the solid state and in solution remains poorly understood, missing an opportunity to improve upon these systems.
In this communication, we report on the exploitation of the Lewis basicity of PMDETA (N,N,N',N'',N''-pentamethyldiethylenetriamine) to access and characterise a hydrocarbon soluble alkyl sodium reagent. This astoundingly soluble reagent was subsequently used towards the development of a facile and selective route for benzylic metalation of the corresponding nonactivated toluene derivatives. We demonstrate the reactivity of the formed benzyl sodiums through application in benzylic aroylation with a Weinreb amide to access synthetically useful 2-aryl acetophenones, and in their reactivity towards C=X double bonds (X = C, N or O). Reaction intermediates were characterised using a combination of X-ray crystallography and ^{1}H DOSY (Diffusion Ordered SpectroscopY) NMR, providing the first reported synthetic and structural insights on the constitution of the intermediates in these reactions, advancing our understanding of how these systems operate in solution.[4]

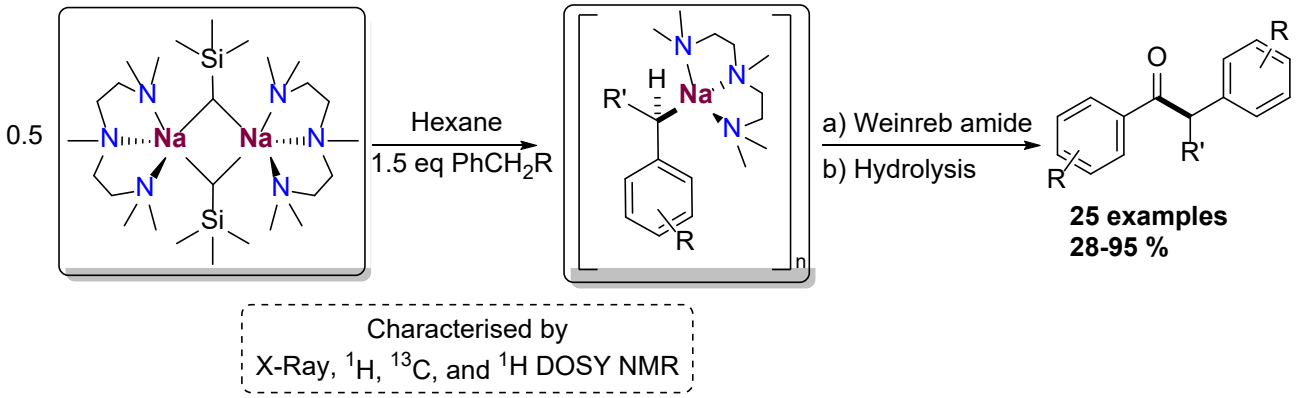

Figure 1. Alkyl sodium mediated benzylic aroylation.

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Selenium Complexes for C-H Amination of Alkenes and Alkynes

John R. Tabor, Derek C. Obenschain, Wei Pin Teh, Alex F. Dohoda, T. Parker Maloney, Forrest E. Michael*[a]

[a]University of Washington

Email: fmichael@uw.edu

Selective C-H amination of complex molecules is a powerful strategy for introduction of new nitrogen functionality, but control over selectivity remains a principal challenge. We have developed a new class of selenium catalysts bearing NHC and phosphine ligands, and employed their use in several highly selective and general C-H amination reactions of complex molecules. The low cost and easy availability of these selenium-based catalysts makes them ideal for use in late-stage functionalization and other synthetic applications. The high selectivity and functional group tolerance of these catalysts derives from the unique mechanisms of the selenium-catalyzed transformations.

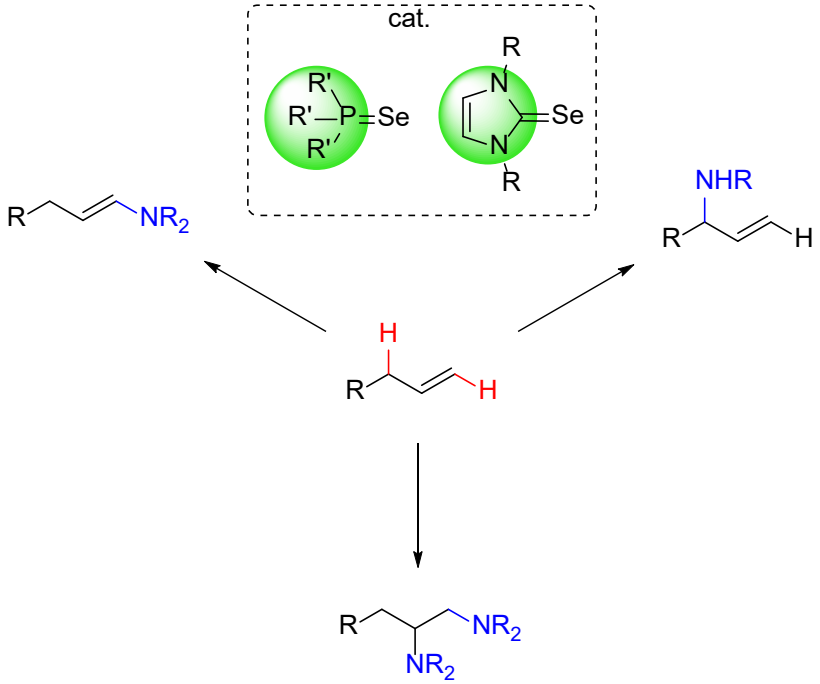

Figure 1. Selenium-catalyzed amination reactions

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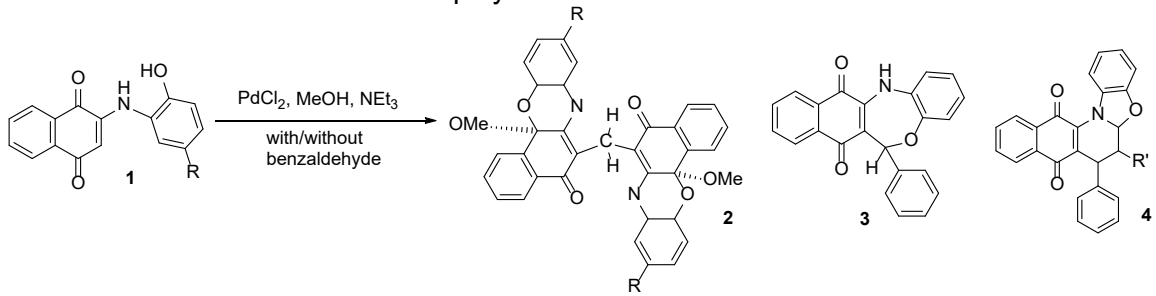
Methanol and Benzaldehyde as the Sources of Methylene Moieties in the Palladium Catalyzed Reactions of Amino-substitued 1,4-Naphthalenequinones

Jun-Hong Gao, Ming-Han Chiang, Yu-Ling Hsieh, and Fung-E Hong*
Department of Chemistry, National Chung Hsing University,
250 Kuo-Kuang Road, Taichung 40227, Taiwan

E-mail: fehong@dragon.nchu.edu.tw

In this study, amino-substitued 1,4-naphthoquinones (**1**) was employed as the starting material in the presence of methanol, amine and divalent palladium salt for the purpose of carrying out one-pot catalytic reaction (Scheme 1). Interestingly, a structurally fascinating product (**2**) was obtained. It was characterized by spectroscopic methods as well as X-ray single crystal diffraction methods (Fig. 1). The structure of **2** reveals that two newly formed fragments containing morpholine rings are linked by a methylene moiety. It is believed that palladium-catalyzed intra-molecular C-H/O-H bond coupling processes indeed took place. Unexpectedly, the source of this newly generated methylene moiety in these compound is from the solvent, methanol, used here. It was further confirmed by the disappearance of the corresponding signals in ^{1}H NMR spectrum by employing deuterated methanol (CD_3OD) as the reactant. It is proposed that a palladium carbene moiety was firstly generated and subsequently participated in successive reaction steps. Similar reaction of **1** was carried out, except replacing methanol by benzaldehyde, and led to the formations of **3** and **4** with oxazepine and oxazole rings, respectively. Several corresponding **2**, **3** and **4** derivatives were also obtained while various substituted **1**-dervtaives were employed as the reactants.



Scheme 1. The palladium-catalyzed reactions of **1** under diverse conditions leading to the formations of **2**, **3** and **4**, respectively.

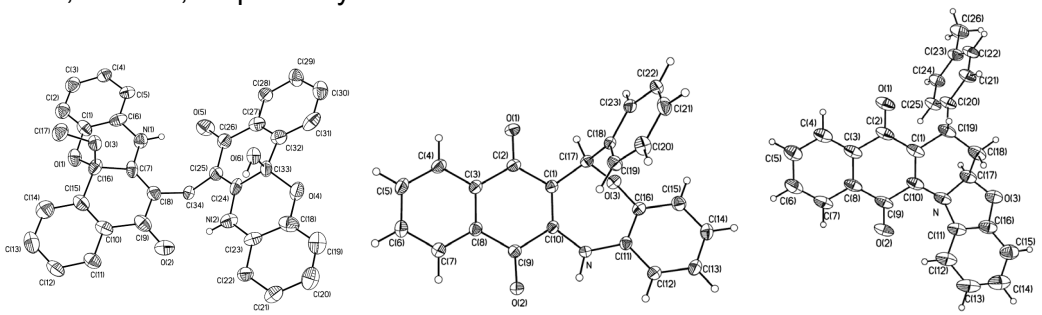


Figure 1. The ORTEP drawings of 2, 3, and 4

Ni-Catalyzed Selective C2-Arylation of Dichloropyridine Derivatives

Geraldo Duran-Camacho,[a] Douglas C. Bland,[b] Fangzheng Li,[b] Melanie S. Sanford*[a]
[a]Department of Chemistry, University of Michigan. [b]Product & Process Technology R&D, Corteva Agriscience.

Email: durancam@umich.edu; mssanfor@umich.edu

Dihalo(hetero)arenes have attracted considerable attention due to their great versatility as substrates for transition metal-catalyzed cross-coupling. Selective monofunctionalization of dihalo(hetero)arenes can afford monohalobiaryls, which are prevalent in bioactive molecules, in addition to serving as intermediates for the synthesis of multisubstituted (hetero)arenes. A relevant example are dichloropyridines, which can serve as linchpin to numerous pharmaceuticals and agrochemicals.[1] Methods employing Pd-catalyzed Suzuki-Miyaura cross-coupling conditions have been developed for the selective monoarylation of dichloropyridines.[1,2] In contrast, we demonstrate that many Ni-based catalysts promote selective formation of diarylation products with these substrates, even under conditions where arylboronic acid is the limiting reagent (Scheme 1A). To address this challenge, we have developed a Ni-phosphine catalyst system for the selective monoarylation of dichloropyridines with aryl boronic acids (Scheme 1B). Compatibility, selectivity, and reactivity challenges will be addressed. In addition, we provide preliminary insights into the mechanism of diarylation.

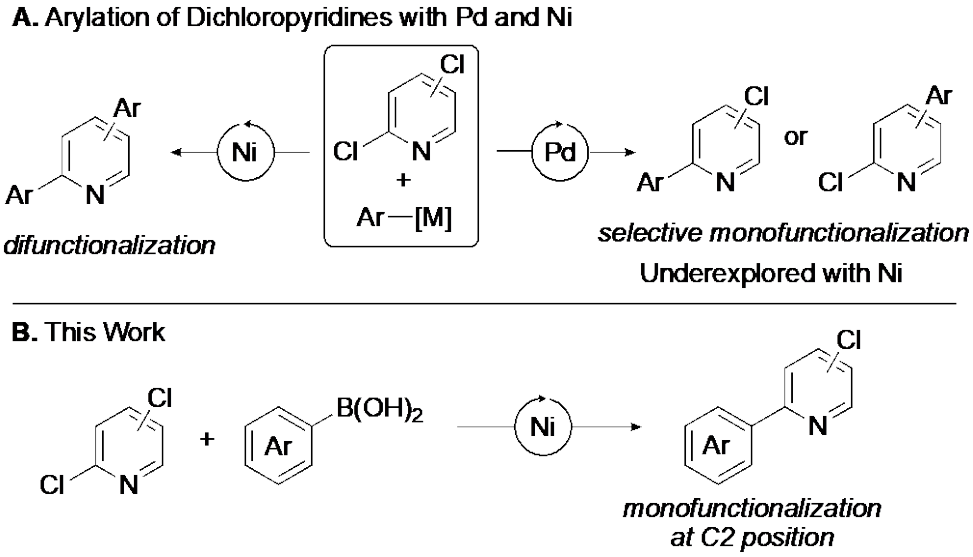


Figure 1. Selective cross-coupling for monoarylation of dichloropyridines

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Investigation of powerful 1,5-diaza-3,7-diphosphacyclooctanes ligands in the reductive 1,2 arylation of isatins

Amrah Nasim,[a] Gilian T. Thomas,[a] Stephen G. Newman*[a]
[a]University of Ottawa
Email: gilian.t.thomas@gmail.com; stephen.newman@uottawa.ca

Nucleophilic addition to the 3-position of the pharmaceutically-relevant isatin backbone produces 3-substituted-3-hydroxy-2-oxindoles which are of particular interest as a scaffold in bioactive natural products. Previous synthetic methods used to access this scaffold typically are subject to harsh conditions, have a limited scope, and use stoichiometric organometallic reagents. Herein we present a method for reductive 1,2-arylation that allows access to a range of 3-hydroxy-3-aryl-2-oxindole derivatives using a novel Ni/1,5-diaza-3,7-diphosphacyclooctane (P_2N_2) catalyst with yields up to 91%. Two of these Ni/P_2N_2 species are crystallized and catalytically active, providing evidence for a modified carbonyl-Heck-type mechanism.

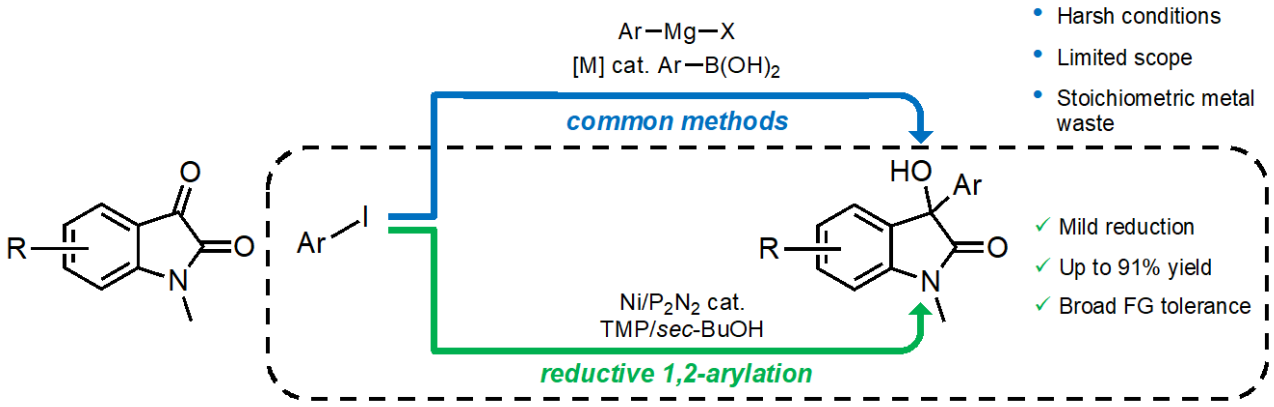

Figure 1. Summary of classical 1,2-addition and Ni/P_2N_2-catalyzed methods of coupling aryl iodides and isatins to form 3-hydroxyoxindoles.

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Mechanistic Insights into A Base-Free, Air-Stable, Palladium Cross-Coupling Reaction of Alkenyl Carboxylates and Aryl Boronic Acids

Gregory Gaube,[a] **Gilian T. Thomas,**[a] **J. Scott McIndoe,**[a] **David C. Leitch***[a]
[a]University of Victoria.

Email: greggaube@uvic.ca; dcleitch@uvic.ca

Alkenyl carboxylates are an interesting subsection of C–O bonds, as they had been thought of as nearly unreactive in palladium cross-coupling.[1] However, a report from the Leitch group highlighted their efficacy in a base-free, air-stable, palladium cross coupling reaction with aryl boronic acids.[2] Electrospray ionization mass spectrometry with a charge tagged boronic-acid allowed for key cationic intermediates to be identified. This, in tandem with hetereonuclear NMR, allowed us to propose a Pd(II) only mechanism with the critical step of a doubly ligated palladium aryl species dissociating a phosphine ligand to coordinate with the alkenyl carboxylate.

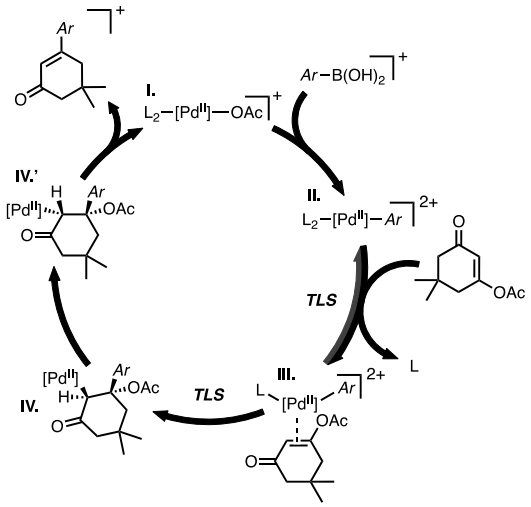

Figure 1. Proposed mechanism using a charge-tagged boronic acid

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Reductive *anti*-Dizincation of Alkynes

Haruka Yamaguchi, Fumiya Takahashi, Takashi Kurogi, Hideki Yorimitsu*
Department of Chemistry, Kyoto University

Email: yamaguchi@org.kuchem.kyoto-u.ac.jp; yori@kuchem.kyoto-u.ac.jp

Polar 1,2-dimetalloalkenes can engage in bond formations at the two adjacent carbon–metal bonds to afford various multi-substituted alkenes. Despite their promising utility, there are few general methods for the preparation of polar 1,2-dimetalloalkenes. Recently, we have reported the reductive *anti*-1,2-dimagnesiation and dialumination of alkynes by means of sodium metal.[1] However, similar 1,2-dizincation has only been achieved indirectly by transmetallation of the corresponding 1,2-dimagnesioalkenes to zinc.[2] Herein, we report an efficient method for the direct preparation of 1,2-dizincioalkenes from alkynes without the intermediacy of organo magnesium species (Figure 1). Reduction of diarylacetylenes with sodium metal in the presence of a Zn salt resulted in the formation of *trans*-1,2-dizincioalkenes. We also performed subsequent Pd-catalyzed cross-coupling of dizincioalkenes with aryl iodides to give tetraarylalkenes.

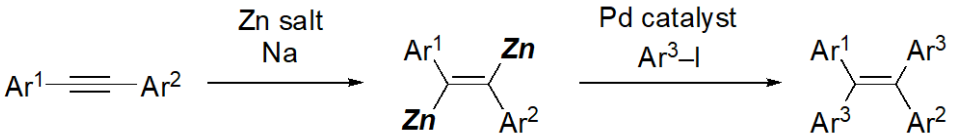

Figure 1. Reductive *anti*-dizincation of alkynes and subsequent cross-coupling reaction.

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Batch and Flow Organic Transformations by Silicon Nanowire Array-Metal Nanoparticle Hybrid Catalysts

Heeyoel Baek,[a] **Yasuhiro Uozumi**,[b] **Yoichi M. A. Yamada***[a]
[a]RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan
[b]Institute for Molecular Science, Okazaki, Aichi 444-8787, Japan
Email: ymayamada@riken.jp

Well-ordered nanostructured heterogeneous catalysts have been favored to achieve efficient organic transformations due to their inherent advantages like reusability and control of metal leaching. Although nanostructure supports for metal nanoparticles are attractive candidates, their stability and selectivity for heterogeneous catalytic systems are still developing.
Herein, we present silicon nanowire array-metal nanoparticle hybrid catalysts (SiNA-MNP) as novel platforms for a variety of organic transformations such as the Mizoroki-Heck reaction, the C-H functionalization, the hydrogenation, and the hydrogenative decarboxylation (Figure 1).[1-4] Hybrid catalysts consisted of ordered silicon nanowire arrays and metal nanoparticles where metal-silicon bonds as gradually gradated metal silicide provide abundant nano-size reaction fields, high stability, and robustness. Monometallic and bimetallic SiNA-MNP catalysts were prepared by metal-assisted chemical etching and metal depositing. SiNA-Pd achieved the high turnover number (TON) and turnover frequency (TOF) of 2,000,000 and 40,000 h^{-1}, respectively, in the Mizoroki-Heck reaction. Moreover, SiNA-Pd showed the high reusability over 150 times in the hydrogenation. A flow reductive alkylation by using a silicon wafer-based catalyst as a novel microflow reaction device was investigated where the TON reached 4.0 x 10^4 in a continuous run over 24 h (3.9 kg/day). SiNA-Rh promoted the hydrogenative decarboxylation of fatty acids with great selectivity and catalytic activity under microwave irradiation to afford bio-jet and bio-diesel fuels.

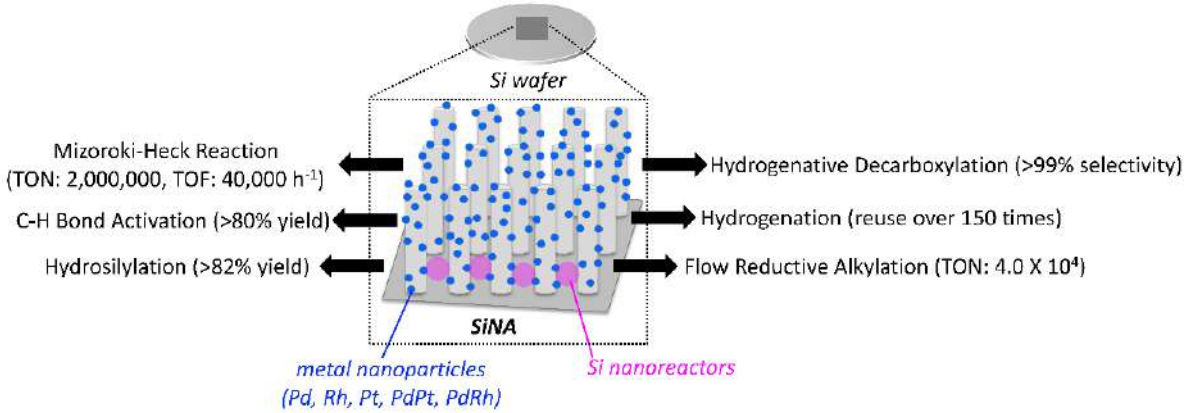

Figure 1. A schematic image of a variety of organic transformations catalyzed by SiNA-MNP.

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Copper-Catalyzed Regio- and *trans*-Selective Silylboration of Internal Alkynes

Hirokazu Moniwa,[a] Ryo Shintani*[a]
[a]Division of Chemistry, Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University.
Email: hmoniwa@poc.chem.es.osaka-u.ac.jp; shintani.ryo.es@osaka-u.ac.jp

Multi-substituted alkenes are one of the basic skeletons of organic compounds and can be found in a variety of bioactive substances and organic electronic materials. It is therefore very important to synthesize alkenes with the control of their regio- and stereoselectivity because each isomer can have different properties. In particular, alkenes having silicon and boron as substituents are known to be useful synthetic intermediates for various organic compounds since both silyl and boryl groups can be readily converted to various other functional groups. For the synthesis of these alkenes, silylboration of alkynes, which simultaneously introduces silicon and boron into the carbon–carbon triple bond of alkynes, is the most straightforward and powerful approach.[1] However, most of the existing methods employ terminal alkynes or symmetric internal alkynes as substrates, and only a few reports have been made that could achieve silylboration of unsymmetric internal alkynes regio- and stereoselectively.[2] Among them, *trans*-selective reactions have been limited to certain alkynes having electron-withdrawing groups.[3] In this context, herein we describe the development of regio- and *trans*-selective silylboration of unactivated internal alkynes in the presence of a copper catalyst and a metal alkoxide base (Figure 1).[4,5]

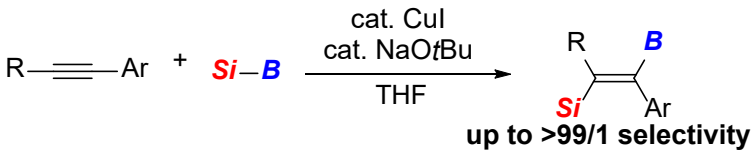

Figure 1. Copper-catalyzed regio- and *trans*-selective silylboration of internal alkynes.

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Silver-Catalyzed Ring Expansion of Activated N-Heteroarenes via 1,4-Dearomative Addition of Diazomethylphosphonates

Hyundug Jen,† Sekwang Baek,† and Eun Jeong Yoo*

† There authors equally contributed to this work

Department of Applied Chemistry, Kyung Hee University, Yongin 17104, Republic of Korea.

Email: jeonhd96@khu.ac.kr; tprhkd96@khu.ac.kr; ejyoo@khu.ac.kr

Since medium-sized N-heterocyclic scaffolds are prevalent in natural products, and biologically active molecules, their synthesis has attracted attention in various fields of chemistry. Among them, seven-membered azepines and diazepines are some of the most significant pharmacophores exhibiting diverse biological activities. Azepine derivatives, which are core structures of market drugs such as Benazepril, Mianserin, and Tolvaptan, have been prepared through conventional synthetic approaches, electrocyclizations, higher-order cycloadditions, and cross-coupling reactions.

Our group has developed synthetic methods of N-aromatic zwitterions, which are site-switchable reagents for the construction of diverse N-heterocycles. Although N-aromatic zwitterions are practical and readily available starting materials, they have structural limitations that furnish cyclic products, inevitably fused with six-membered piperidine scaffolds. To overcome such shortcomings, we envisioned a cascade reaction using N-aromatic zwitterion, a formation of a strained small-ring followed by its expansion, to construct medium-sized N-heterocycles.[1] In this presentation, we discuss synthetic methods for the construction of azepine derivatives through cycloadditive ring-expansions of N-aromatic zwitterions. It has been revealed that diazo acetates[2] and diazo methylphosphonates are suitable to undergo cyclopropanations of N-aromatic zwitterions in the presence of a silver catalyst to provide the cyclopropane-fused intermediates, which are further expanded into desired azepines.[3] The developed cycloadditive expansion reaction has been characterized by broad substrate scope, mild reaction conditions, easy scale-up reactivity, and easy synthetic applicability.

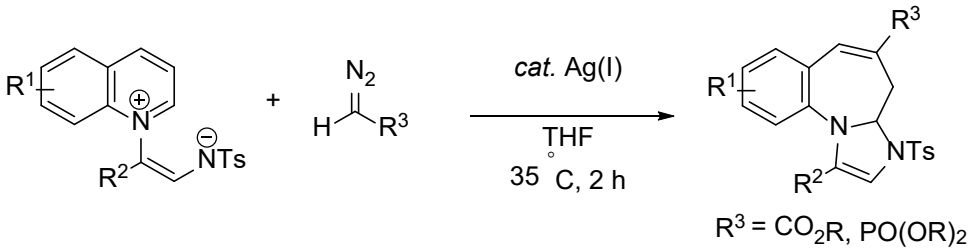

Figure 1. Silver(I)-catalyzed ring-expansion between the quinolinium zwitterion and diazo compounds.

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The Total Synthesis of (+)-Archangiumide

Jack L. Sutro, Alois Fürstner*
Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim-an-der-Ruhr, Germany.

Email: sutro@kofo.mpg.de; fuerstner@kofo.mpg.de

The first total synthesis of the macrocyclic natural product (+)-Archangiumide has been accomplished. This macrolide, isolated by Li and Wu *et al.* from an *Archangium* myxobacterium, exhibits several interesting structural features, including two *E*-configured alkenes, six oxygen-bearing stereocenters and an additional stereogenic element in an endocyclic vinylallene within a 17-membered macrocycle.[1] Whilst access to such a structure would present challenges for classical organic chemistry, the use of state-of-the-art transition metal catalysis has enabled a modular and efficient synthesis. Molybdenum-catalysed ring-closing alkyne metathesis and gold-catalysed rearrangement served as key steps; catalytic transformations using palladium, copper, and ruthenium were also brought to bear. Driven by these modern synthetic methodologies, the total synthesis of the target compound was achieved in an expedient and convergent manner. Moreover, this synthesis was used to probe the stereochemical course of a gold-catalysed π-bond transposition.

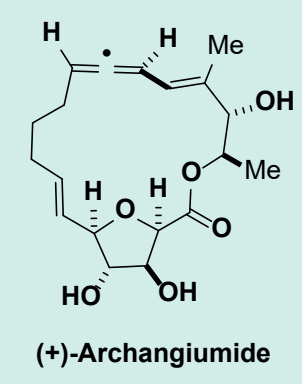

Figure 1. The structure of (+)-archangiumide, the natural product synthesised in this work.

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Tantalum-Ureate Catalyst for Hydroaminoalkylation: Exploring Reactivity

Jacqui Higgins, [a] **Cameron H.M. Zheng,** [a] **Rebecca C. DiPucchio,** [a] **Laurel L. Schafer** *[a]
[a]The University of British Columbia, Vancouver, Canada.

Email: jhiggins@chem.ubc.ca; schafer@chem.ubc.ca

The emergence of a new alkene hydrofunctionalization reaction with amines, hydroaminoalkylation (HAA), offers new opportunities to improve sustainability, efficiency, and diversity in constructing amines as they are biologically important compounds.[1] Our group has world-leading technology in catalytic HAA that features the use of inexpensive, relatively earth-abundant and non-toxic, early-transition metal catalysts. HAA is the atom economic formation of a new Csp^3-Csp^3 bond by adding a C-H bond α to an amine across a C-C double bond in a single step synthesis. We have reported multiple generations of early transition metal catalysts equipped with hemilabile 1,3-*N,O* chelating ligands that successfully perform HAA each overcoming the challenges of the predecessors in terms of reactivity and stability. Initial findings with a tantalum mono-amidate catalyst **1** demonstrated the increased stability offered by the N,O ligands results in better reactivity (lower temperatures) while requiring long reaction times.[2] Subsequently a phosphoramidate tantalum catalyst **2** was employed at room temperature to perform HAA for amines and alkenes with steric and electronic variability but was light and heat sensitive.[3] Afterwards, to improve robustness and have less steric congestion, a 2-pyridonate tantalum catalyst **3** was designed that can catalyze unactivated and sterically demanding *E* and *Z* internal alkenes.[4] Recently, our group further improved synthetic utility of these catalysts with in-situ catalyst formation by combining $Ta(CH_2SiMe_3)_3Cl_2$ and an ureate ligand to perform HAA under relatively mild conditions. Previously reported work required changing the ureate ligand to yield high reactivity with external or internal alkenes respectively.[1] Therefore, the development of a single ligand that can achieve high yields under mild conditions for both a diverse set of internal and external alkenes and amines is disclosed here for the first time. This in-situ formed catalyst can perform HAA with external, internal alkenes and various amines at mild conditions with temperature, time, and catalyst loadings as low as 110°C, 2 h and 1 mol % obtaining pharmaceutically useful amines in high yields and selectivities.

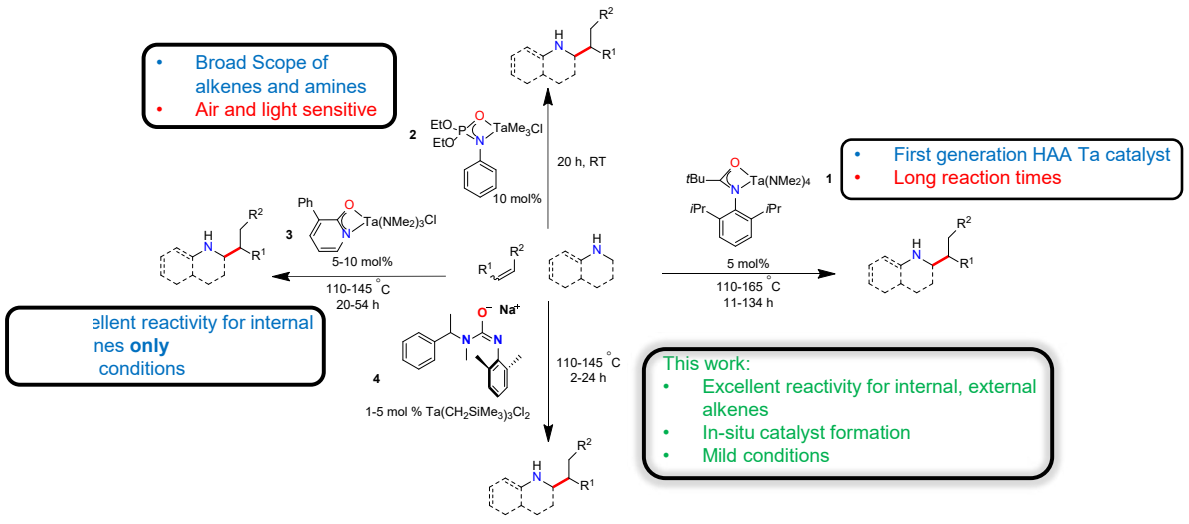

Figure 1. Summary of our group's process on tantalum catalyzed HAA reaction.

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Investigation of *N*-Heterocyclic Carbene Aryl Ligands for the Undirected Borylation of Secondary Alkyl C–H Bonds

Jenna Manske,[a] Hamile Khan,[a] John Hartwig*[a]
[a]University of California, Berkeley
Email: jlmanske@berkeley.edu; jhartwig@berkeley.edu

The ubiquity and stability of alkyl C–H bonds have rendered their selective functionalization an area of great interest. The borylation of C–H bonds is an appealing transformation because the resulting compounds can be diversified through well-known reactions, enabling the installation of diverse functional groups at the position of the original C-H bond.[1] While the borylation of aryl C–H bonds is well-developed[2], borylation of alkyl C–H bonds remains a challenge. Recently, phenanthroline ligand scaffolds have been explored for the borylation of primary, secondary,[3-4] and tertiary[5] alkyl C–H bonds. We envisioned that studies of alternative, but related, ligand scaffolds could lead to insight into how to develop more stable, active, or selective catalysts, ultimately increasing the applicability of Ir-catalyzed borylation of alkyl C–H bonds. To this end, it was reported in 2019 that the computed barrier for the proposed turnover limiting step of reductive elimination to form the C–B bond from an iridium complex with an *N*-heterocyclic carbene pyridine (NHC-py) ligand was lower than from iridium ligated by phenanthroline derivatives.[6] We hypothesized that the electron-donating *N*-heterocyclic carbene moiety could stabilize the metal through strong coordination.[7] Thus, we sought to test this prediction of a superior ligand by the computational work.

We report the borylation of the secondary C–H bonds of tetrahydrofuran (THF) by iridium catalysts containing NHC-py ligands. Reactions performed with isolated carbene in combination with iridium and catalytic sodium *tert*-butoxide led to the highest yields of borylated THF. NMR studies and high yields obtained from NHC-Ar ligands support the formation of a catalytically competent cyclometallated NHC-iridium complex. The yield and selectivity from reactions conducted with an independently synthesized cyclometallated iridium complex was similar to the yield and selectivity from reactions conducted with a mixture of iridium precatalyst and ligand. In contrast to previous reports of the borylation of THF occurring exclusively at the β-position with phenanthroline ligands[3–4], and computationally predicted reactivity for these NHC-py ligands,[6] reactions catalyzed by NHC-Ar ligands, in combination with iridium, form two isomeric boryl THF products in up to a 6.5 : 1 (α : β) ratio.

Studies to determine the role of the sodium *tert*-butoxide base support association of the base to the iridium complex. Ongoing work aims to study reactions of the cyclometallated NHC-Ar iridium complexes in the presence of alkoxide base with density functional theory to evaluate binding modes of the alkoxide under catalytic conditions.

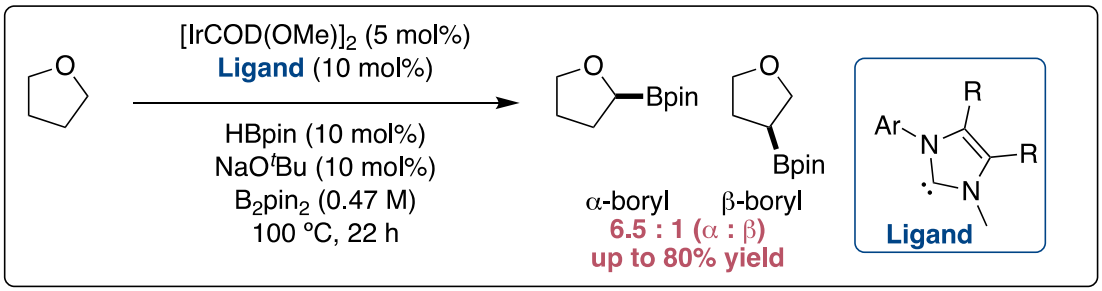

Figure 1. Conditions for the borylation of tetrahydrofuran with an iridium complex containing an NHC-Ar ligand

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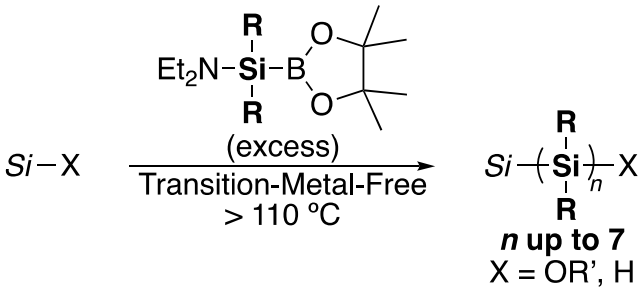
Synthesis of Oligosilanes via Transition-Metal-Free Silylene Transfer from Silylboronic Esters

Jiaying Li,[1] Yusuke Matsumoto,[1] Ikuo Sasaki,[1] Toshimichi Ohmura,[2] Michinori Suginome[1]

[1]Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan
[2]Faculty of Molecular Chemistry and Engineering, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan.

Email: ohmura@kit.ac.jp; suginome@sbchem.kyoto-u.ac.jp

Polysilanes have been synthesized by Wurtz-type reductive coupling of dihalodiorganosilanes using a stoichiometric amount of alkali metals. Disproportionation of disilanes is another way to synthesize oligosilanes, which requires high reaction temperature and limits substituents on the silicon atoms.[1] The establishment of a new concept of oligosilane synthesis that allows various substituents on the silicon atoms and can carry out under mild conditions is highly demanded.
Recently, we have reported a transition-metal-free silylene transfer from silylboronic esters to alkoxysilanes, where the Si–O bond undergoes insertion of silylene to afford alkoxydisilanes.[2] Based on this finding, we envisioned that an efficient silylene transfer system would realize the sequential insertion of silylene into Si–O and other σ bonds by means of the use of an excess amount of silylboranes. Herein, we describe the synthesis of oligosilanes via the continuous insertion of silylene into the Si–O bond of alkoxysilanes and the Si–H bond of hydrosilanes. We found that methoxysilane is a suitable alkoxysilane in sequential silylene insertion, and octasilane was given as the longest oligosilane when the reaction was carried out with 8 equiv of silylboronic ester. We also found that hydrosilanes are efficient acceptors of the continuous insertion of silylene. Details of the reaction will be discussed in this presentation.



Scheme 1. Synthesis of Oligosilanes via Sequential Insertion of Silylene into σ Bonds

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Kinetically Controlled Carboxylation of Secondary Alkyl Bromides Through Dual Photoredox and Nickel Catalysis

Jacob Davisa, **Julien R. Lyonnet**[a,b], Bjørn Carvalho, Basudev Sahoo[a], Craig S. Day[a,b], Yaya Duan[a], Marc Obst, Per-Ola Norrby, Kathrin H. Hopmann, Ruben Martin[a,c*]

[a]Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Països Catalans 16, 43007 Tarragona, Spain. [b]Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, c/Marcel·lí Domingo, 1, 43007 Tarragona, Spain. [c]ICREA, Passeig Lluís Companys, 23, 08010 Barcelona, Spain

Email: jlyonnet@iciq.es; rmartinromo@iciq.es

Synthesizing aliphatic carboxylic acids has undergone substantial synthetic innovation from early methods requiring stochiometric amounts of harsh, organometallic reagents. Modern methods of metal-catalyzed reductive carboxylation reactions of organic halides with carbon dioxide feedstocks have shown to be particularly desirable as they offer mild and site-selective methods to these precursors.[1] Notable advances have been made in nickel-catalyzed reactions with alkyl halides and carbon dioxide that functionalize the aliphatic chain at the site where nickel is most thermodynamically stable, irrespective of the initial site of the alkyl halide. "Chain-walking" type mechanism explains the results obtained in such reports.[2,3] As elegant as those methodologies are, there is to this day still a lack of possibilities when it comes to internal functionalization of unactivated aliphatic sites. Therefore, in realizing such a goal, we investigated a protocol that allows for the *ipso*-carboxylation of unactivated alkyl bromides (Figure 1). The ligand choice and homogeneous environment proved critical for its outcome.

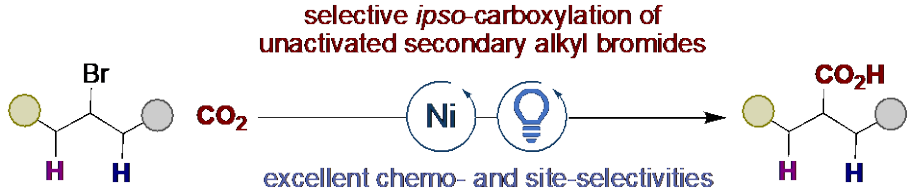

Figure 1. *Ipso*-carboxylation of secondary alkyl bromides.

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Palladium-Catalyzed Enantioselective [3 + 2] Cycloaddition of N-Aromatic Zwitterions and Vinylcyclopropanes

Juno Im, Eun Jeong Yoo*
Department of Applied Chemistry, Kyung Hee University, Yongin 17104, Republic of Korea.

Email: gkfdkqja1234@khu.ac.kr; ejyoo@khu.ac.kr

In the presence of a palladium catalyst, vinylcyclopropanes (VCPs) readily convert Pd-allyl cation intermediate followed by ring-opening of cyclopropanes and act as 1,3-dipoles, which have been utilized to construct five-membered cyclic compounds via 1,3-dipolar cycloaddition. This approach to generating practical 1,3-dipole has been also used to structure various molecular skeletons, such as seven-membered ring systems, multi-fused cyclic compounds, and spiro compounds. In our laboratory, cycloadditions of N-aromatic zwitterions have been developed, which provide diverse N-heterocyclic compounds whiles switching compatible reacting partners in a modular manner. For example, we have successfully developed a series of [m + 2] cycloadditions via the cycloaddition between N-aromatic zwitterions and 1,n-dipolar species bearing palladium-allyl cation moiety.

In this symposium, we discuss a [3 + 2] cycloaddition of N-aromatic zwitterions and VCPs in the presence of palladium catalyst and electron-rich phosphine ligands to afford fused five-membered cyclic systems. Also, an asymmetric version of the developed cycloaddition, which gives a wild range of N-heterocycles with high enantiomeric excess, is presented. The developed methodology is significant in the field of heterocyclic synthesis because it can provide biologically active molecular skeletons with a high degree of complexity in a single operation.

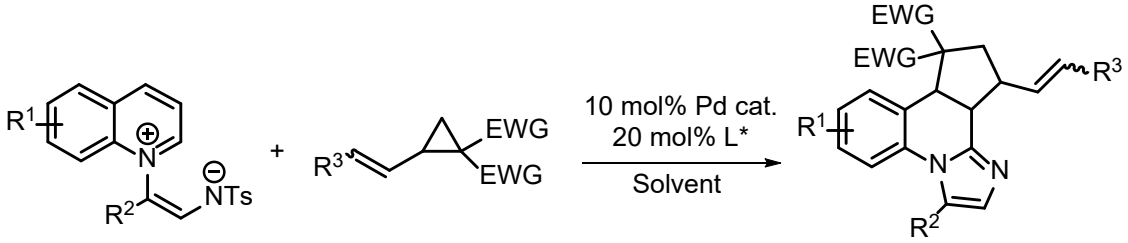

Figure 1. [3 + 2] cycloaddition of N-aromatic zwitterions and VCPs.

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Dual Catalysis of Au_{25} Nanocluster Functionalized by Peptide Dendron Thiolate toward Photooxidative Alkynylation of Amines

Kenta ISERI, Katsuhiro ISOZAKI, Masaharu NAKAMURA
Institute for Chemical Research and Graduate School of Engineering, Kyoto University,
Email: iseri.kenta.22v@st.kyoto-u.ac.jp

Ligand-protected gold nanoclusters show characteristic photophysical properties and reactivity much different from those of gold complexes, gold nanoparticles, and bulk gold; thus, they are expected to make unique functional catalysts. Thiolate-protected gold nanoclusters have been extensively studied due to their thermodynamic stability based on strong gold–sulfur bonds. Among them, $[Au_{25}(SR)_{18}]^-$ nanoclusters ($Au_{25}NC$) constructed of Au_{13} superatomic core surrounded by six $Au_2(SR)_3$ staples have been applied to various catalytic reactions.[1] Several photocatalytic oxidation reactions were reported using $Au_{25}NC$ as the photosensitizer generating singlet oxygen. We have reported the oxidative cyclization of amino alcohols photocatalyzed by peptide dendron thiolate-functionalized $Au_{25}NCs$.[2] These photocatalytic properties originate from the photosensitization of the Au_{13} superatomic core, and the surface $Au_2(SR)_3$ staples show negligible effect. In contrast, surface $Au_2(SR)_3$ staples are catalytically active sites for several catalytic reactions, such as A_3 coupling.[3] From these backgrounds, there has been no report using both two structural components of $Au_{25}NC$, Au_{13} superatomic core, and $Au_2(SR)_3$ staples cooperatively in catalytic reactions. Here, we report the first dual catalysis of $[Au_{25}(SR)_{18}]^-$ nanoclusters facilitating photooxidative alkynylation of tertiary amines, in which the photosensitization property of Au_{13} superatomic core and C–C bond-forming catalysis of gold–thiolate staples cooperate (Figure 1).

Typically, tertiary amines and terminal alkynes were reacted in the presence of a catalytic amount of $Au_{25}NC$ under an oxygen atmosphere by irradiating visible light at 680 nm, producing corresponding propargylic amine products. The scope of the substrate was investigated for amines and alkynes, and 16 different propargylic amine products were obtained. As a result, aliphatic tertiary amines and aryl- and alkyl-substituted terminal alkynes were revealed to participate in this reaction. A ligand-mixed gold nanocluster bearing both thiolate and alkynyl ligands was synthesized to gain insight into the reaction mechanism. This nanocluster was confirmed to act as a photosensitizer generating singlet oxygen and as a dual catalyst in the photooxidative alkynylation of amine, clarifying that alkynyl-substituted $Au_{25}NC$ is the active catalytic intermediate. This presentation will also discuss the effect of the peptide dendron thiolate ligand as a supramolecular reaction field and plausible reaction mechanism based on experimental and computational studies.

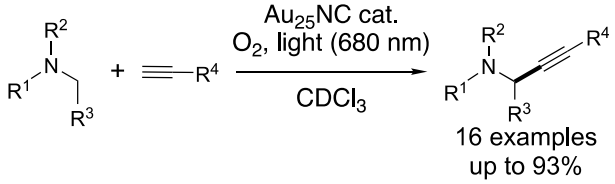

Figure 1. Photooxidative alkynylation of amine dual catalyzed by Au_{25} nanocluster.

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Air-Stable Palladium(II) Precatalysts and their Application in Cross-Coupling Reactions

Kevin H. Shaughnessy*[a]
[a]Department of Chemistry & Biochemistry, The University of Alabama, Tuscaloosa, AL, USA
Email: kshaughn@ua.edu

Palladium(0) is a powerful catalyst for nucleophilic substitution at sp^2 carbon-halogen bonds. Air-stable palladium(II) precatalysts with a single supporting ligand are convenient precursors to the LPd^0 active species required for these reactions.[1] The precatalyst must undergo a reduction process in order to be activated. Our group has explored the use of palladium(II) precatalysts activated by external reductants[2] as well as those containing reducing ligands.[3] For example, palladium(II) phosphine complexes with amine ligands provide effective active species for C-N coupling reactions (Figure 1). The identity of the amine ligand has a significant effect on the catalyst performance. The development of these and related complexes, their application, and their mechanisms of activation will be presented.

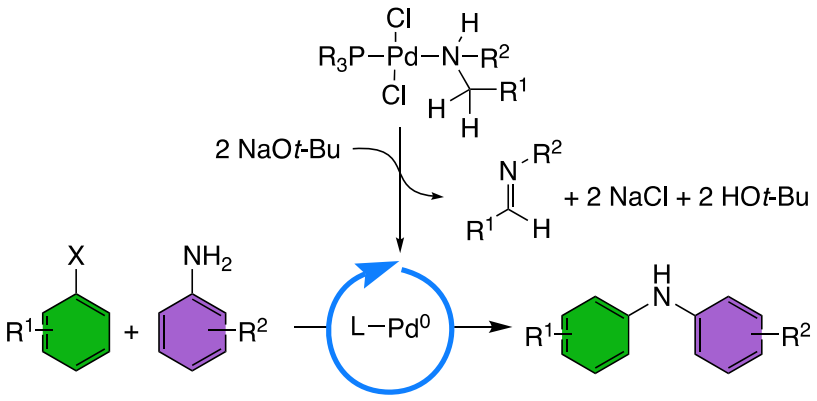

Figure 1. Palladium-amine complexes as precatalysts for C-N cross-coupling

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Direct catalytic carboxylation of arenes with CO_2 using molecular Pd(II)-catalysts

Gregor Kemper,[a,b] Markus Hölscher,*[a] Walter Leitner*[a,b]
[a]Institut für Technische Chemie und Petrolchemie, RWTH Aachen University, Aachen, Germany. [b]Max-Planck-Institut für chemische Energiekonversion, Mülheim (Ruhr), Germany
Email: hoelscher@itmc.rwth-aachen.de

The utilization of the nonfossil and nontoxic low value "waste" material carbon dioxide (CO_2) has the potential to play a key role in designing sustainable future processes and chemicals in chemical industry. Among the many interesting and challenging reactions with CO_2 the direct C-H carboxylation of arenes, enabled by only catalytic amounts of organometallic compounds, remained unsolved so far. This reaction, which is therefore often referred to as *dream reaction*, represents a highly atom efficient procedure for the generation of aromatic carboxylic acids - the latter being a frequent motive in high value chemicals. Accordingly, this catalytic reaction provides the potential to satisfy most of the principles of green chemistry; especially when achieving high turnover numbers, chemo- as well as regioselectivity and the avoidance of additional solvents and additives.
In recent years we have conducted various computational and experimental studies[1] to develop active molecular catalysts for the carboxylation of arenes with CO_2 and have recently reported on a stochiometric reaction.[2] In this work, we present a thorough experimental study on the direct catalytic carboxylation of a variety of arenes together with detailed DFT studies for one exemplified substrate (Figure 1).[3]
We show that with sulfonamidophosphane ligands surprisingly active Pd-catalysts can be synthesized and applied in direct carboxylations of CO_2. The results of catalytic carboxylations for various arenes are reported. Both experiments and DFT studies show that electron rich arenes are carboxylated easily, while electron poor substrates undergo the reaction with low conversion.

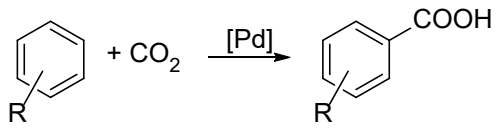

Figure 1. Catalytic carboxylation of arenes ([Pd] = molecular palladium catalyst).

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Gold-Catalyzed Conversions of Ynamides Towards Enol Esters and Spirooxindoles

Martin C. Dietl,[a] **Yaowen Liu**,[a] **A. Stephen K. Hashmi***[a]
[a]Organisch-Chemisches Institut, Heidelberg University, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Email: martin.dietl@oci.uni-heidelberg.de; hashmi@hashmi.de

Enol esters represent an intriguing substance class that has been used as versatile building blocks in a variety of reactions such as hydrogenations, polymerizations or in natural product synthesis. A synthetic access to highly functionalized enol esters was elaborated, harnessing the potential of oxidative gold chemistry. A robust reaction protocol was developed, in which ethynylbenziodox- olones (EBXs) transfer both their carboxylate as well as their alkylyl unit onto ynamides in perfect atom economy under mild conditions This cascade comprises the *in situ* generation of an alkynyl gold(III) species, a stereoselective C(sp)−C(sp^2) bond formation and a C−O coupling at the alkynyl position of the ynamides. This transformation tolerates a diverse set of functionalities, yielding a broad scope of amide enol 2-iodobenzoates (Figure 1a). The synthetic potential of the reaction was further demonstrated by several selected postsynthetic modifications, leading to a manifold range of highly functionalized compounds. Due to its excellent bioactivity profile that is increasingly utilized in pharmaceutical and synthetic chemistry, spirooxindole is an important core scaffold. In order to access this promising structural motif, an efficient method for the construction of was developed. A gold-catalyzed cycloaddition reaction of terminal alkynes or ynamides with isatin-derived ketimines led to highly functionalized spirooxindoles. Herein, readily available starting materials were converted into cyclic carbamates under mild conditions at low catalyst loadings. The great compatibility towards a broad range of functional groups led to a vast scope of compounds. The underlying mechanistic proposal for the formation of the spirooxindolecarbamates was investigated by DFT calculations. Some of the target products exhibit good to excellent antiproliferative activity on human tumor cell lines. In addition, one of the most active compounds displayed a remarkable selectivity towards tumor cells over normal ones.

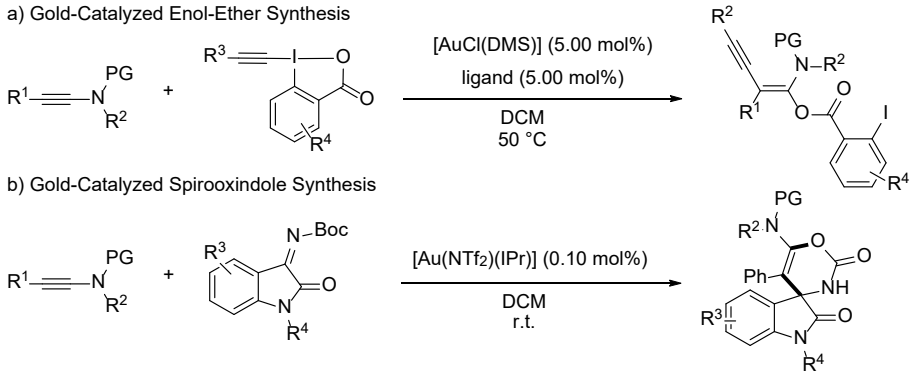

Figure 1. Gold-catalyzed transformations to enol ethers (Figure 1a) and spriooxindoles (Figures 1b).

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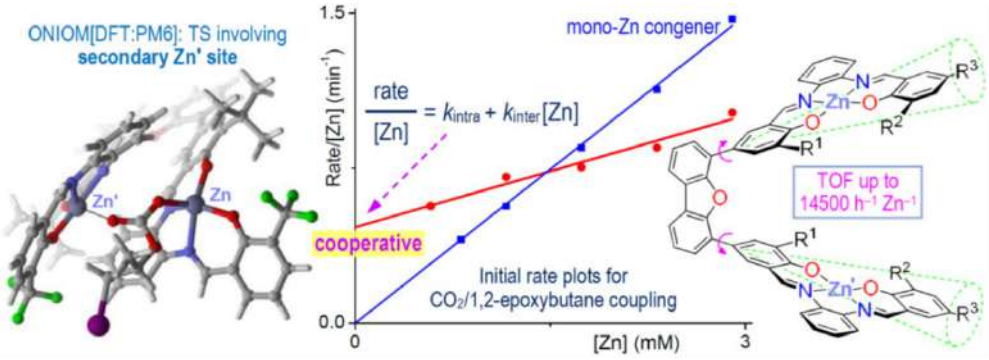
Shape-Persistent Bimetallic Design Approach: Catalysis and Cooperativity

Michael C. W. Chan,*[a] Yeqing Xia,[a] Junhui Bao,[a] and Hajime Hirao*[b]
[a]Department of Chemistry, City University of Hong Kong, Kowloon, Hong Kong, China.
[b]Warshel Institute for Computational Biology, School of Medicine, Life and Health Sciences, The Chinese University of Hong Kong, Shenzhen, China.

Email: mcwchan@cityu.edu.hk

The exploration of shape-persistent bimetallic catalytic frameworks has been undertaken in our laboratory. Initially, a series of rigidly linked cofacial bis-(Zn-salphen) complexes was developed that functions as efficient catalysts for cyclic carbonate formation from CO_2 and epoxides under mild conditions. Conformational changes for these frameworks are essentially limited to axial rotation of the Zn-salphen moieties; however, such geometric constraints crucially permits subtle tuning of the intermetallic separation and geometry to potentially augment catalytic activity (and cooperative effects).
Newly devised Zn_2 catalysts have been investigated for CO_2-epoxide coupling reactions in conjunction with $^nBu_4NI$, and selected dibenzofuran-linked derivatives are significantly more active than their mononuclear analogues under identical conditions and concentration of Zn sites. High initial turnover frequencies (up to 29000 h^{-1}; 14500 h^{-1} per Zn) and excellent efficiencies under mild conditions have been achieved. The molecular structures of key catalysts have been determined by X-ray crystallography. Kinetic studies using in-situ (React-IR) spectroscopy and DFT calculations have been performed to examine the reaction mechanism; the former reveal the existence of an intramolecular rate component, while the latter indicate a preference for the intramolecular, cooperative pathway as well as transition states that depict the Zn sites operating in tandem. Taken as a whole, these results provide strong evidence of cooperative reactivity for these bimetallic catalysts.
New developments regarding shape-persistent multinuclear frameworks that can mediate catalytic reactions with enhanced efficiency and cooperativity will be presented.



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Li vs Na: Divergent Reaction Patterns between Organo–Lithium and –Sodium Complexes, and Ligand-catalyzed Ketone/Aldehyde Methylenation

Nathan Davison[a], Claire L. McMullin[b], Lu Zhang[c], Shu–Xian Hu[c], Paul G. Waddell[a], Corinne Wills[a], Casey Dixon[a], Erli Lu[a]*

[a]Chemistry-School of Natural and Environmental Sciences, Newcastle University, Newcastle upon Tyne, UK; [b]Department of Chemistry, University of Bath, Bath, BA2 7AY, UK; [c]School of Mathematics and Physics, University of Science and Technology Beijing, Beijing 100083, P. R. China

Email: n.davison1@newcastle.ac.uk; erli.lu@newcastle.ac.uk

Alkali metal alkyl reagents are essential tools in synthetic chemistry. Alkali metal organometallics aggregate in solution and solid-state. The relationship between structure and reactivity has been of great interest for many decades and, in general, by breaking the alkali metal organometallics into smaller aggregates, the reactivity can be increased.[1] The monomeric organosodium complex [Na(CH_2SiMe_3)(Me_6Tren)] (**1**-Na) was found to exhibit a distinct reaction pattern in sharp contrast with its organolithium counterpart [Li(CH_2SiMe_3)(Me_6Tren)] (**1**-Li) (methylenation vs nucleophilic addition). Moreover, using **1**-Na as a platform, the versatile reactivity of organosodium complexes depending on their aggregate sizes (monomer vs polymer) and nature of incoming substrates was demonstrated (Figure 1a). Based on these observations, ligand-catalyzed ketones/aldehydes methylenations were designed using [$NaCH_2SiMe_3$]$_\infty$ and catalyzed by as low as 5 mol% of the Me_6Tren ligand (Figure 1b).[2,3]

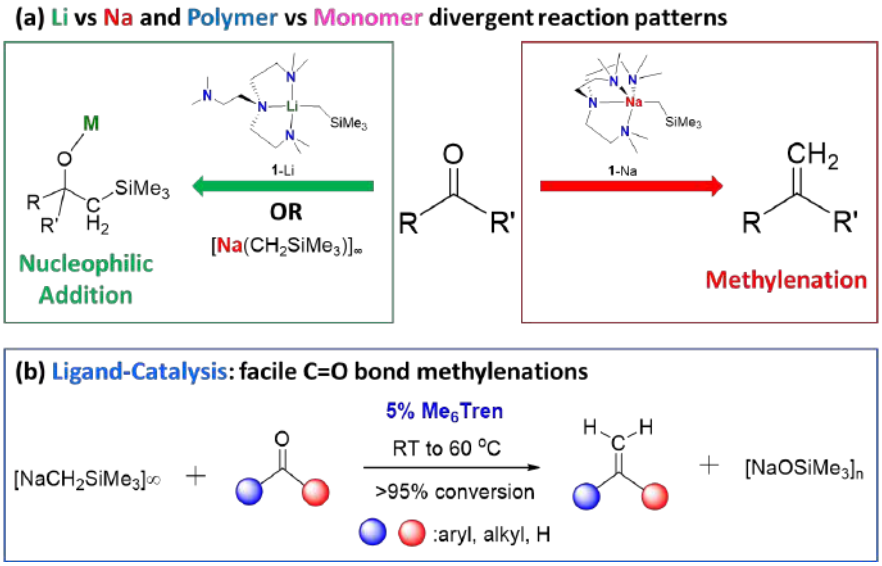

Figure 1 (a) Divergent reaction patterns between organosodium and organolithium complexes and organosodium polymer vs monomer. (b) Ligand-catalysed C=O bond methylenation.

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Synthesis of Chiral Primary Amines via Direct Asymmetric Reductive Amination Using Ammonium Salts

Qin Yin*, **Xumu Zhang***
Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences.

Email: qin.yin@siat.ac.cn

α-Chiral primary amine subunits are widespread structural units in numerous pharmaceutical molecules and are key intermediates toward the preparation of many amine-containing drugs.[1] Additionally, chiral primary amines can serve as ligands or organocatalysts which can be applied in organic synthesis. Therefore, efficient synthetic routes toward chiral primary amines have attracted tremendous attention. Asymmetric chemo-catalytic reactions that are capable of directly preparing chiral primary amines remain scarce. Transition-metal-catalyzed asymmetric reductive amination[2] (ARA) using ammonium salts as the amine sources can directly yield chiral primary amines from prochiral ketones and are thus highly attractive and of great significance. This reaction faces several major challenges, including: (1) the presence of competitive ketone reduction as the side reaction; (2) NH_3 or the produced primary amines can coordinate to the metal center which results in catalyst poisoning effect; (3) the coordination of amine ligand to the metal center may lead to ligand exchange that enhances the challenge on asymmetric control; (4) the produced primary amines may undergo further alkylation process via double reductive amination. Aiming to solve these challenges and extent the applicable scope of this important reaction, we have carried out systematic studies in the last five years.[3] Now, simple aryl alkyl ketones, α- or β-functionalized ketones, diary ketones can be directly transformed to the corresponding chiral primary amines in excellent enantioselectivities.

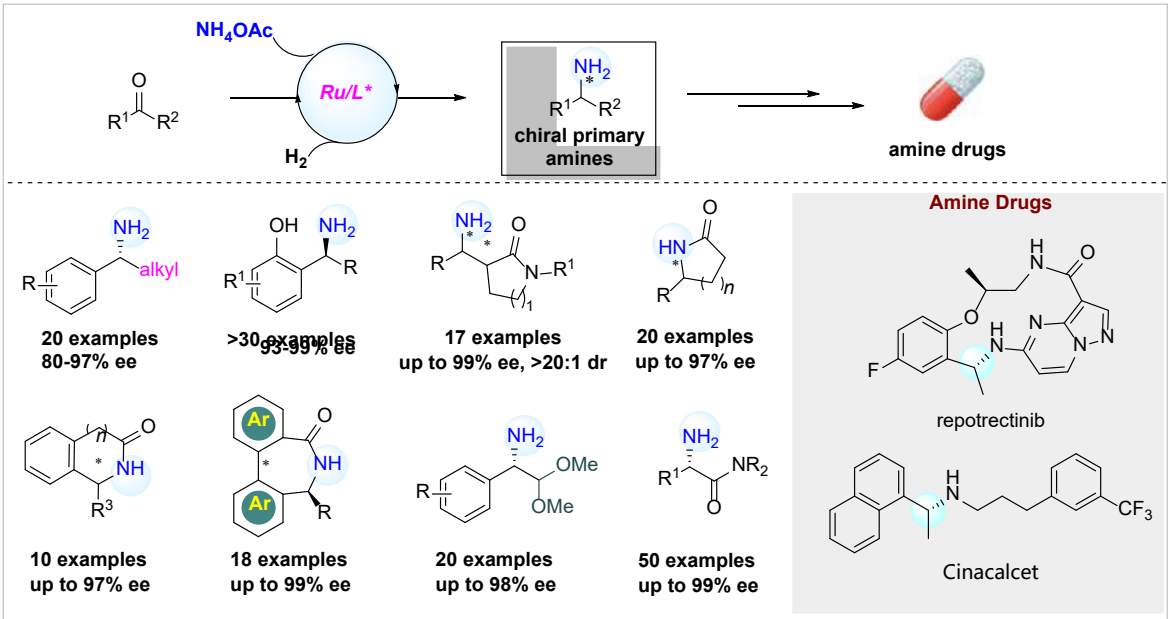

Figure 1. Summary of asymmetric reductive amination with ammonium salts from our team.

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Gold(I)-Mediated Cyclizations of Triene-Yne Systems: An Easy Access to Cyclopenta-fused Anthracenes

Rebeka Eshagh Saatlo[a], Jan P. Matiba[a], Matthias Rudolph[a], Frank Rominger[a], A. Stephen K. Hashmi[a]

[a]Organisch-Chemisches Institut, Heidelberg University, Im Neuenheimer Feld 270, 69120 Heidelberg

Email: rebeka.eshagh@oci.uni-heidelberg.de

The field of organic materials is expanding and the interest in synthesizing novel, suitable structures is increasing.[1] PAHs (polycyclic aromatic hydrocarbons), especially cyclopenta-fused PAHs (CP-PAHs) are known for being potential candidates in the application of OFETs (organic field effect transistors) or OLEDs (organic light emitting diodes).[2] We reported on the synthesis of various PAHs[3] and also on the cyclization of 1,8-diyne systems towards indenophenalene derivatives containing the CP-PAH subunit.[4] Based on the ongoing interest of obtaining novel (CP-)PAH structures, we present the gold(I)-catalyzed[5] cyclization of novel triene-yne systems performing a formal [4+2] cycloaddition (Figure 1). Both, the substrate and the target molecules, are first time reported and easily available in 3- to 4-steps synthesis using mild conditions. Besides the application in organic electronics, the target molecules can be implemented in biological research based on cancer risks.

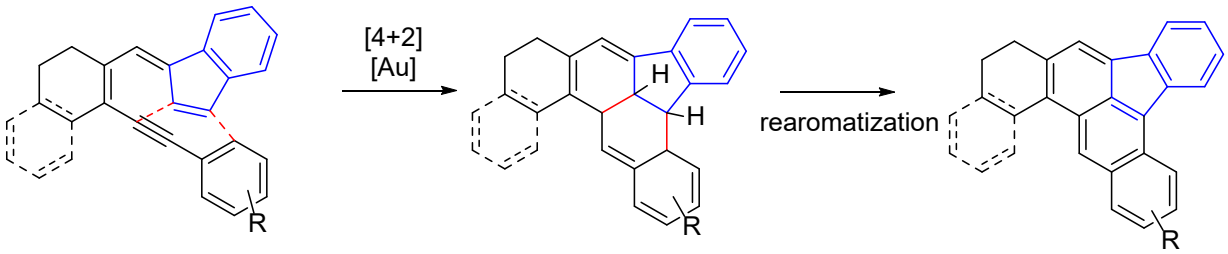

Figure 1. Gold(I)-catalyzed cyclization of triene-yne systems bearing a benzofulvene moiety.

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Modular Ferrocene Ligand: A New Strategy to Control Hydroaminoalkylation Catalysis

Sheila G. Curto, Laurel L. Schafer*
Department of Chemistry, University of British Columbia, Vancouver, Canada.

Email: sheilagc@chem.ubc.ca; schafer@chem.ubc

Amines are a family of chemical compounds of great importance due to their applicability in very diverse fields such as the purification of industrial gases or pharmaceutical products.[1] The development of efficient green chemistry methods for their syntheses is important and of industrial relevance. Hydroaminoalkylation is an atom-economic method to produce new amine species via the functionalization of *α* C-H bond of amines by reacting with alkenes (Figure 1).

Knowledge of the mechanism of this reaction is the clue to controlling and improving the regio- and diastereoselectivity of this process. Early transition metals can be exploited to realize enhanced reactivity and exquisite control.

N,*O*-chelated early transition metals are state-of-the-art hydroaminoalkylation catalysts known to promote reactivity via the hemilability of the ligands.[2] Ferrocene complexes offer modular ways to change their steric and electronic properties as well as high thermal stability.[3] This work explores the synthesis, structure and reactivity of new ferrocene substituted *N*,*O*-chelated ligands and their early transition metal complexes for realizing advances in enhanced and selective reactivity.

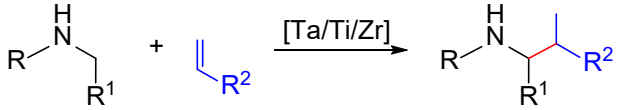

Figure 1. Hydroaminoalkylation reaction mediated by early transition metals.

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[5 + 3] Cycloaddition of N-Aromatic Zwitterions by Switching Regioselectivity of Metal-Allyl Species

Sumin Lee,† Sekwang Baek,† Eun Jeong Yoo*
† These authors equally contributed to this work
Department of Applied Chemistry, Kyung Hee University, Yongin 17104, Republic of Korea
Email: lsm0760@khu.ac.kr; tprhkd96@khu.ac.kr; ejyoo@khu.ac.kr

Compared to synthetic approaches for typical cyclic systems, methods for constructing medium-sized cyclic compounds, especially eight-membered cyclic compounds, have been less explored due to unfavorable thermodynamics. Although eight-membered heterocyclic compounds are prevalent in natural products, biologically active molecules, and functional materials, their synthesis often requires tedious and complex stepwise reactions, rather than modular methods. Previously, we developed a new type of reactant, N-aromatic zwitterions, for the construction of medium-sized heterocyclic compounds in a modular manner. In addition, we demonstrated that N-aromatic zwitterions can undergo regiodivergent cycloadditions, depending on the nature of the reaction partners. Specifically, when the zwitterion reacts with LUMO-controlled amphiphilic reactants, it undergoes [5 + n] cycloadditions, whereas, in the presence of HOMO-controlled dipolar species, regiodivergent [m + 2] cycloadditions occur[1, 3]. For example, the reaction of N-aromatic zwitterions with Pd-TMM underwent a [3 + 2] cycloaddition reaction via regioselective 1,4-dearomative addition of Pd-TMM[2].

In this symposium, we introduce a new strategy for a [5 + 3] cycloaddition of N-aromatic zwitterions and π-allyl precursors in the presence of palladium catalyst, which ensures diversity that differs from previous reports. Under the typical reaction conditions for the generation of Pd-allyl species, the additional use of zinc salt resulted in a transmetallation, affording the Zn-allyl intermediate. It readily chelated with the N-aromatic zwitterion, switching its regioselectivity which resulted in [5 + 3] cycloaddition, not [3 + 2] cycloaddition. The key intermediate was isolated and fully identified, proving the reaction mechanism involved in the formation of the Zn-allyl complex. In addition, we demonstrated the potential of this strategy for synthesizing large cyclic compounds, otherwise difficult to construct.

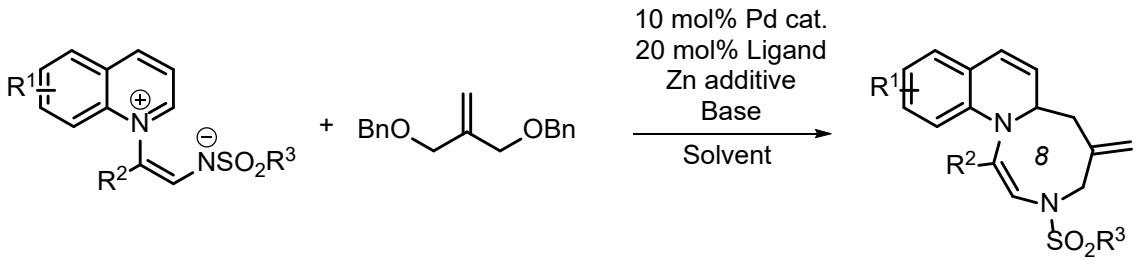

Figure 1. Regioselective cycloadditions of N-aromatic zwitterions and π-allyl species.

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Photoredox/Cobalt-Catalyzed Markovnikov Selective Hydrohalogenation of Alkene

Shotaro Shibutani,[a] Kazunori Nagao,[a] Hirohisa Ohmiya*[a]
[a]Institute for Chemical Research, Kyoto University

Email: shibutani.shotaro.62u@st.kyoto-u.ac.jp; ohmiya@scl.kyoto-u.ac.jp

Alkyl halides are known as important and versatile compounds in synthetic chemistry because they are not only synthetic intermediates for synthesis of pharmaceuticals and functional materials but also are themselves found in the structure of pharmaceuticals and natural products. Hydrohalogenation of alkenes using hydrogen halides has been known as a straightforward and atom-economical approach to alkyl halides. Due to the strong acidic conditions originated from hydrogen halides, conventional methods suffered from low functional group compatibility. As a strong acid-free method, Carreira and a coworker reported cobalt-catalyzed hydrochlorination of alkenes using hydrosilane and tosyl chloride as hydrogen and chloride sources, respectively.[1] The reaction involvles cobalt hydride-mediated metal hydride hydrogen atom transfer to an alkene and chlorination of the resultant alkyl radical by tosyl chloride. While the reaction proceeds under mild and strong acid-free conditions, it requires stoichiometric amounts of reductants and oxidants, resulting in low atomic efficiency. Herein, we report a photoredox/cobalt dual catalysis[2] enabling Markovnikov selective hydrohalogenation of alkenes under blue LED irradiation conditions (Figure 1). Since this protocol allows to use 2,4,6-collidine hydrogen halide as hydrogen and halide sources, strong-acid free and mild reaction conditions are achieved. The cooperativity of photoredox and cobalt catalyst enables to deliver a hydrogen atom to alkene and oxidize the alkyl radical to carbocation equivalent. Modification of counter anion of 2,4,6-collidine hydrogen salt leads to introduce various halogen atoms, such as fluorine, chlorine and bromine to alkene, producing highly functionalized alkyl halides. Acid-sensitive functional groups including methoxymethyl, ester, silyl ether, and carbamate are tolerated.

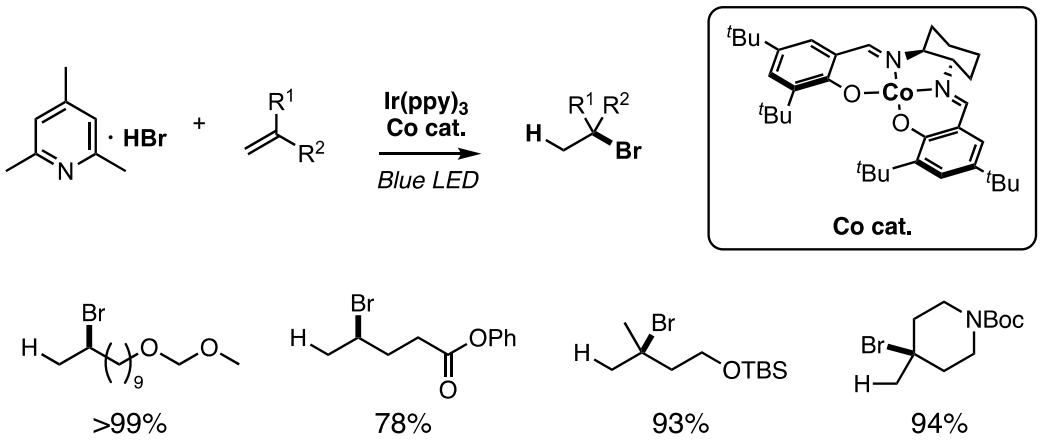

Figure 1. A photoredox/cobalt dual catalysis enabling hydrobromination of alkenes

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Iron-Catalyzed 1,4-Alkylarylation of 1,3-Enynes with Arylborates and Unactivated Alkyl Electrophiles

Siming Lu[a,b], Litian Chen[a,b], Satsuki Nomura[c], Katsuhiro Isozaki[a,b], Masaharu Nakamura*[a,b]

[a]Institute for Chemical Research, [b]Graduate School of Engineering, Kyoto University, [c]School of Chemistry, University of Edinburgh

Email: lu.siming.82u@st.kyoto-u.ac.jp

Allene is a versatile building blocks to construct complex molecular scaffolds in natural products and pharmaceuticals.[1] In recent years, transition metal-catalyzed 1,4-alkylarylations of 1,3-enynes have been proved a powerful strategy for the efficient synthesis of multi-substituted allenes.[2] Kambe and Terao reported the first nickel-catalyzed regioselective three-component coupling of alkyl halides, 1,3-enynes, and dialkylzinc reagents in 2009.[2a] In 2019, Bao and coworkers reported a copper-catalyzed radical 1,4-alkylarylation of 1,3-enynes using peroxides additive to trigger the generation of the corresponding radical species.[2c] Although the first-row transition metal catalysts improved and complemented this reaction based on the single electron transfer process, only a few reports have been published to this date.[3] Herein, we report the first iron-catalyzed radical 1,4-alkylarylation of 1,3-enynes with arylborates and unactivated alkyl electrophiles to afford multi-substituted allenes (Scheme 1).

The three–component coupling reaction proceeds smoothly under mild conditions in the presence of catalytic amounts of iron–NiXantphos complex and magnesium bromide, providing the corresponding multi-substituted allenes in good to excellent yields (Figure 1). Investigation on the substrate scope revealed the tolerance of a wide range of arylborates with various functional groups and sterically hindered substituents. Especially, some heterocyclic groups such as 2–thienyl also participated in this reaction, furnishing the allene product in excellent yield. Screening of alkyl electrophiles clarified that tertiary alkyl halides gave higher yields than secondary and primary alkyl halides. This result suggests that the stability of the alkyl radical has great impact on the reaction yields. Various alkyl and silyl substituented 1,3-enynes take part in the reaction to give high yields of the corresponding allene products albeit poor yields with the aryl substituents. Mechanistic studies using radical scavengers and radical clock substrates proved that this reaction proceeds with radical chain pathway started from alkyl radical intermediates. We will report detailed ligand screening, scope of substrates, and discuss the possible reaction mechanism in the poster presentation.
(311 words)

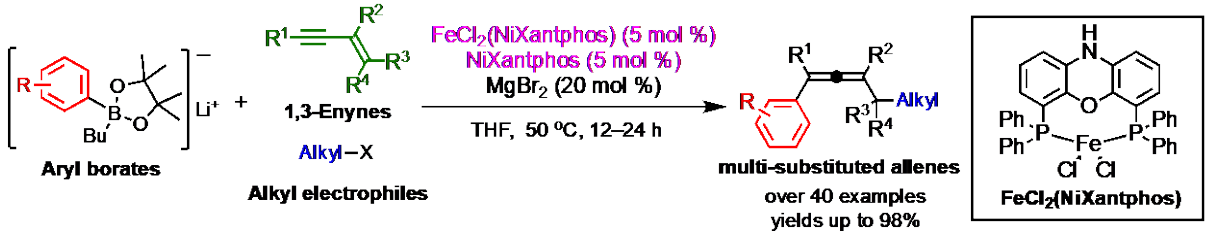

Figure 1. The first iron-catalyzed 1,4-alkylarylation of 1,3-enynes with arylborates and alkyl halides.

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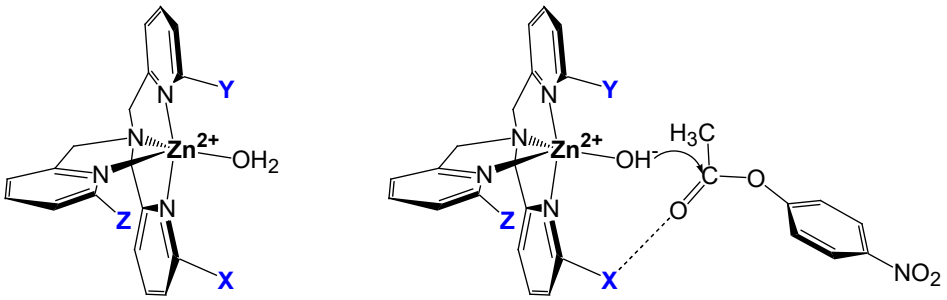
The Catalytic Carboxyester Hydrolysis by Zn(II) Complexes of 6-Hydroxymethyl Substituted Tris(2-Pyridylmethyl)Amine

Ji Yoon Lim,[a] Soo Suk Lee*[a]
[a] Department of Pharmaceutical Engineering, Soonchunhyang University, Asan, 31538, Republic of Korea.

Email: sslee0810@sch.ac.kr

Developing efficient artificial catalysts comparable to the biocatalysts such as enzymes has been a difficult challenge for studying enzyme mimics. The studies reported here are related to the design, synthesis, structural analysis by X-ray crystallography and kinetic studies of Zn(II) complexes designed to catalyze the hydrolysis of p-nitropheyl acetate (pNPA), and the identification of the mechanism of the carboxyester hydrolysis reaction. The fact that the introduction of a 6-hydroxymethyl substituents to a tris(2-pyridylmethyl)amine (TPA) ligand leads to an increase or loss of reactivity was explained in relation to the coordination structure of the Zn(II) complex. Actually, when the 6-hydroxymethyl substituent was coordinated to the Zn(II) ion or not, the effect on pNPA hydrolysis was very large. In the case of the presence of one 6-hydroxymethyl substituent, about 150-fold increase in pNPA hydrolysis rate was shown. We analyze the structure of Zn(II) complexes according to the number of 6-hydroxymethyl substituents and explain the pNPA hydrolysis mechanism. This work proposes a new strategy for the development of more efficient metal ion-based artificial catalysts and suggests possible modes of action for metalloenzymes.



X, Y, Z = H or CH_2OH

Figure 1. Zn(II) complexes of TPA and 6-hydroxymethyl substituted TPA and their pNPA hydrolysis.

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Selective Metal Nitrenoid Transfer for the Medium-Sized Ring Formation via Control of Mechanistic Pathways

Suhyeon Kim,[a,b] Se Lin Song,[a,b] and Sukbok Chang*[b,a]
[a]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea
[b]Center for Catalytic Hydrocarbon Functionalization, Institute for Basic Science (IBS), Daejeon 34141, Korea.

Email: suhyeon@kaist.ac.kr; sbchang@kaist.ac.kr

Controlling regio- and stereoselectivity of transition metal-catalyzed nitrenoid transfer reactions is highly desirable, especially in C–H functionalization reactions.[1] Herein, we report the development of a new chiral catalyst system toward intramolecular C–H nitrene insertion of dioxazolones to afford medium-sized cyclic amides, thus affording a wide range of lactam molecules with high regio- and enantioselectivity. Mechanistic investigations revealed that the new catalyst system plays a crucial role in both regio- and enantioselectivity-determining steps. Additionally, we demonstrated the synthetic values of this protocol through the implementation of concise routes for the total synthesis of natural products and drug molecules.

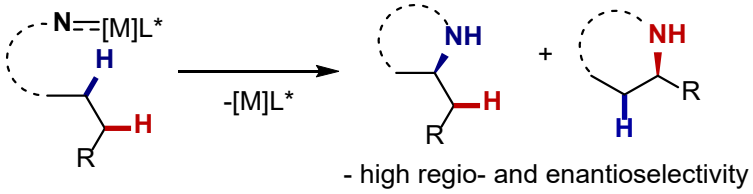

Figure 1. Intramolecular regio- and enantioselective nitrene transfer

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Synthesis of Spiropentanes and Alkylidenecyclopropanes by a Chromium Carbide

Takashi Kurogi,*[a] Asato Inoue,[a] Hideki Yorimitsu[a]
[a]Department of Chemistry, Graduate of Science, Kyoto University.

Email: kurogi@org.kuchem.kyoto-u.ac.jp

Metal carbides are special organometallic species bearing only metal–carbon bonds on the carbide center and expected to show various reactivities due to the unique structure. Reduction of carbon tetrabromide with chromium(II) bromide in THF resulted in formation of a dinuclear chromium carbide complex.[1] Treatment of terminal alkenes as well as cyclic 1,3-dienes with the chromium carbide resulted in double-cyclopropanation to afford spiropentanes, implying the chromium carbide to have a double-carbene character. In contrast to the double-cyclopropanation reactivity of the chromium carbide with alkenes, reaction of the carbide complex with alkynes afforded mononuclear cyclopropenylidene complexes, which have been characterized by X-ray analysis and IR spectroscopy. Akin to the formation of the cyclopropenylidene species from the chromium carbide and alkyne, the cyclopropylidene species could be formed via monocyclopropanation of the chromium carbide and alkene. Trapping the cyclopropylidene intermediate by treatment with aldehyde and ketone yielded alkylidenecyclopropanes.

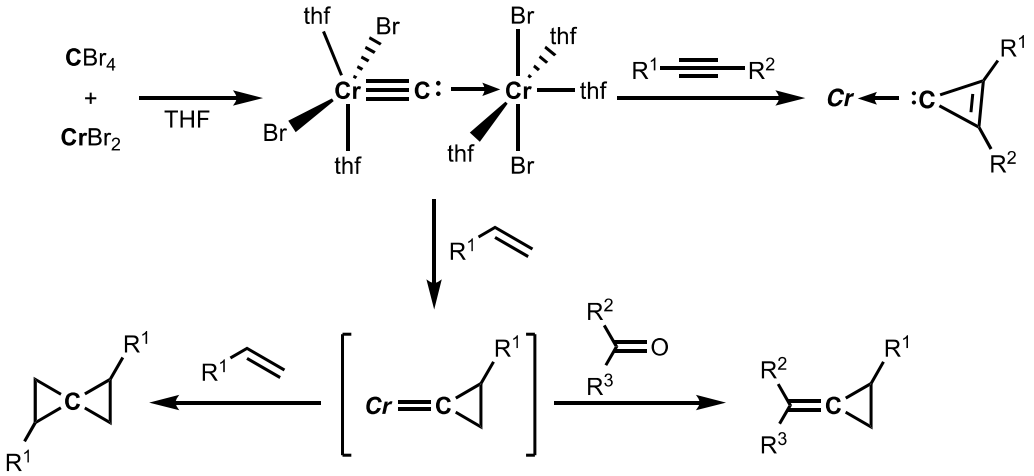

Figure 1. Generation of a Chromium Carbide and Double-Carbene Reactivity.

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A-Amino Acid and Peptide Synthesis using Catalytic Cross-Dehydrogenative Coupling

Taro Tsuji,[a] Kayoko Hashiguchi,[a] Mana Yoshida,[a] Tetsu Ikeda,[a] Yunosuke Koga,[a] Yusaku Honda,[a] Tsukushi Tanaka,[a] Suyong Re,[b] Kenji Mizuguchi,[b,c] Daisuke Takahashi,[a] Ryo Yazaki,[a] Takashi Ohshima*[a]

[a] Kyushu University. [b] NIBIOHN. [c] Osaka University.

Email: tsuji.taro.355@s.kyushu-u.ac.jp; ohshima@phar.kyushu-u.ac.jp

Ionic or radical α-amino Schiff base methods are well known for the synthesis of α,α-disubstituted α-amino acids.[1–4] However, the incorporation of sterically demanding groups is challenging with ionic methods, and radical methods require prefunctionalization of the substrates.

We have developed a dehydrogenative coupling process of α-amino acid Schiff bases with hydrocarbon feedstocks for the synthesis of α,α-disubstituted α-amino acid derivatives (Figure 1).[5] These α-amino acid derivatives were transformed into *C*- and *N*-protected amino acids, which could be easily incorporated into peptide synthesis. A range of α-amino acid derivatives could be readily accessed, which includes, notably, those that bear contiguous quaternary centers. Circular dichroism measurements show that the helical peptide structure is stabilized by the highly sterically congested unnatural α-amino acid. Mechanistic studies revealed that deprotonation of the α-amino acid Schiff base is a turnover-limiting step.

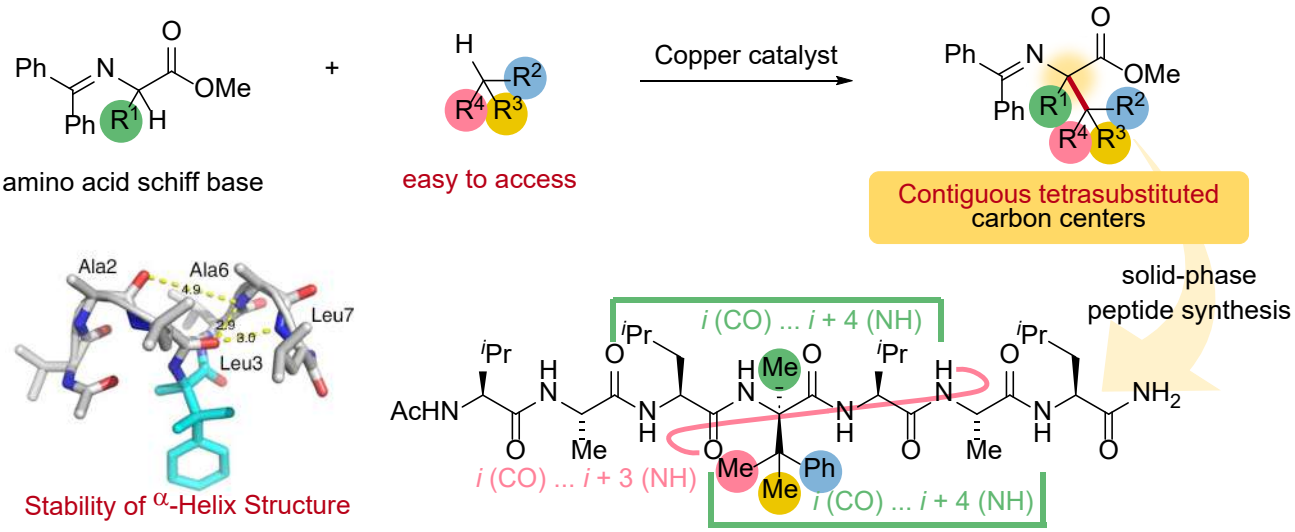

Figure 1. Summary

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Carbones with its Elusive Bonding Description and Broad Implication Complementary to NHC-Carbenes

Wen-Ching Chen,[a] Ting-Hsuan Wang,[a] Cheng-Han Yu,[a] Tiow-Gan Ong,[a,b*]
[a]Institute of Chemistry, Academia Sinica, Taipei, Taiwan, ROC. [b] bDepartment of Chemistry, National Taiwan University, Taipei, Taiwan, ROC.
Email: tgong@gate.sinica.edu.tw

Carbones (L→C←L) have emerged recently as a new class of organic molecules featuring carbon(0) directly stabilized by two electron-rich groups (L) through Lewis donor-acceptor interaction.[1] Other mesomeric features can also be understood in terms of allenic or zwitterionic form (see **Figure 1**). Owing to the peculiar bonding situation and the zero-valent nature of the central atoms, carbones have attracted much attention in the chemical community as NHC alternatives because their strong σ-donating ability broadly impacts transition-metal coordination, small molecule activation, main-group chemistry, redox non-innocent coordination, and catalysis.[2] This presentation will describe the synthetic preparation and chemical properties of the carbone as well as its application toward supporting metallic complexes for catalysis in tandem photoredox, cross-coupling reaction via tandem C-H and C-O bond activation and a new spin in diversifying FLP reactivity with co-modulator benzyl alcohol.

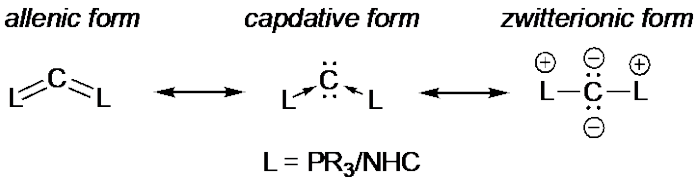

Figure 1. Mesomeric form: bonding situation of carbones.

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Synthesis of Anilides by the Aminolysis of Unactivated Esters using $MnCl_2$ in Combination with Strong Bases as Catalyst

Tobias Vollgraff,[a] Nadja E. Niggli,[a] Christian Winter,[b] Desislava Slavcheva Petkova,[b] Stefan Benson,[b] Roland Götz,[b] A. Stephen K. Hashmi,[a,c] Thomas Schaub*[a,b]

[a]CaRLa – Catalysis Research Laboratory, Im Neuenheimer Feld 584, D-69120 Heidelberg, Germany.

[b]BASF SE, Carl-Bosch-Straße 38, D-67056 Ludwigshafen, Germany.

[c]Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany.

Email: tobias.vollgraff@carla-hd.de; thomas.schaub@basf.com

Amides are omnipresent in our daily life and can be found in pharmaceuticals, natural products, and active ingredients in crop protection.[1] The direct synthesis of the amide bond, especially with the less nucleophilic aniline derivatives are still scarce. A novel, atom-economic protocol for Lewis acid catalyzed synthesis of anilides is presented, using a readily available and inexpensive base and earth abundant Lewis acid catalysts (e.g. ($MnCl_2$, $ZnCl_2$, $BiCl_3$) at low loadings – without the need of an additional ligand. A broad range of electronically diverse anilines was reacted with a variation of unactivated benzyl and alkyl ester in moderate to good yields. The shown reaction can be successfully scaled up to 50 mmol without loss in efficiency.

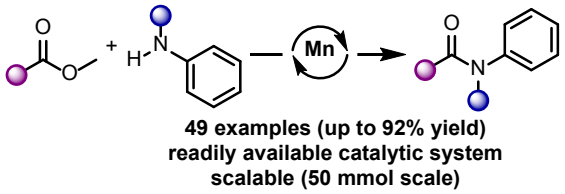

Figure 1. Mn-catalyzed Amidation of Unactivated Methyl Esters by Aminolysis.

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Recent Advancement in Gold Redox Chemistry: New Transformations and Asymmetric Catalysis

Xiaodong Shi
Department of Chemistry, University of South Florida, Tampa, FL 33620, USA
Email: xmshi@usf.edu

The recent discovery of gold(I)/gold(III) redox chemistry greatly transcends cationic gold chemistry from simple π-acid catalysis, which serves a powerful tool for C-C or C-X bond construction. However, with the high oxidation potential between Au(I) and Au(III), ca. ~1.4 eV, gold redox catalysis required the application of strong oxidants with at least stoichiometric amount. Therefore, to achieve gold redox catalysis under mild conditions, with low cost and mild oxidants, is highly desired to make the overall process practical with improved functional group tolerability. Herein, we disclosed novel approaches to facilitate oxidation of Au(I) to Au(III) through 1) Aryldiazonium salts as the mild coupling partner/ oxidant, gold catalyzed cross-coupling reactions are accomplished without any external oxidants under photocatalyst-free condition. 2) Employing sulfonium or diselenium cation as mild oxidants for the alkyne functionalization. 3) Electrochemical approach in promoting gold-catalyzed oxidative coupling.[1] These approaches open an opportunity for gold redox catalysis.

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TM-catalyzed Hydroelementation (E = B or Si) of C-C Multiple Bonds – Synthesis of New Building Blocks for Organic and Material Chemistry

Tomasz Sokolnicki,[a,b] Adrian Franczyk,[a] Jakub Szyling,[a] Bartłomiej Janowski,[c] Jędrzej Walkowiak*,[a]

[a] Center for Advanced Technology, Adam Mickiewicz University, Uniwersytetu Poznańskiego 10, Poznan, Poland

[b] Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, Poznan, Poland

[c] Synthos S.A., Chemików 1, Oświęcim, Poland

Email: tomasz.sokolnicki@amu.edu.pl

Organometalloids with boryl or silyl moieties are valuable building blocks in organic chemistry, due to their great reactivity in C-C bond-forming couplings, and other demetallation reactions.[1] On the other hand, organofunctional silanes bearing silicon atoms with readily hydrolyzable groups play a pivotal role in material chemistry. Such reagents can form stable bonds with both polymers and inorganic substances and thus are applied as dispersing agents, adhesion promoters, and silane coupling agents (SCAs).[2] The SCAs' global market is projected to reach USD 1.6 billion by 2026, emphasizing their importance for various sectors of industry (coatings, adhesives, rubbers, etc.). The addition of a filler-silane system along with carbon black to elastomers significantly improves rolling resistance and wet grip properties of tire rubbers, which is manifested in reduced fuel consumption, lower CO_2 emissions to the atmosphere, and higher driving safety. Therefore, new sustainable methodologies for the synthesis of organometalloids are sought by organic and material chemists.

Hydroelementation (hydroboration, hydrosilylation) of unsaturated substrates represents a straightforward, and reproducible way to synthesize a wide array of organoboranes and organosilanes with 100% atom economy. Traditionally, these transformations are carried out in the presence of transition metal catalysts, which ensure the formation of products with high yield and selectivity.[3]

Herein, we would like to present three catalytic hydroelementation protocols leading to novel organometalloid reagents (M = B or Si). Ru-catalyzed monohydroboration of 1,4-diarylbuta-1,3-diynes was developed to be efficient in the synthesis of stereodefined boryl-substituted enynes, applicable as substrates in Suzuki coupling or polymerization reactions.[4] Other two works focused on the synthesis of a library of 45 bio-based bifunctional organosilanes *via* Ir-catalyzed regio- and chemoselective hydrosilylation of naturally-occurring terpenoids.[5-6] Catalyst screening, the scope of substrates, and application tests as coupling agents in the synthesis of tire rubber composites will be demonstrated within this communication. Synthesized products with boron and silicon groups might be considered versatile reagents in organic and material chemistry.

This work was financed by the National Science Centre in Poland (grants no. UMO-2019/35/N/ST4/02594, UMO-2018/31/G/ST4/04012) and by the National Centre for Research and Development in Poland, no. POWR.03.02.00-00-I026/16, co-financed by the EU through the European Social Fund under the Operational Program Knowledge Education Development. The authors acknowledge financial support from Synthos S.A.

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Catalyst-Controlled Divergent Functionalization of C(sp^3)–H and C(sp^2)–H Bonds in Metal-Carbenoid Insertion of α-Diazoamides

Yu Lim Lee, Kyu In Choi, and Sang-gi Lee*
Department of Chemistry and Nanoscience, Ewha Womans University, Seoul 03760, Korea
Email: lur0610@naver.com; sanggi@ewha.ac.kr

Transition-metal catalyzed functionalization of C–H bonds has been one of the most efficient and reliable synthetic tools for the formation of C–C bonds.[1] In particular, controlling the chemo-, stereo-, and regioselectivities over the sites of functionalization is a highly challenging yet important goal, wherein the reaction pathway could be precisely controlled to result in structurally different products from the same reactant(s). Herein, we present the first example of catalyst-controlled divergent functionalizations of C(sp^3)–H/C(sp^2)–H bonds in intramolecular metal-carbenoid insertion reactions of α-diazoamides having an ester group (Figure 1). In the presence of a rhodium catalyst, the in situ generated rhodium-carbenoid undergoes insertion into the C(sp^3)–H_a bond to furnish β-lactams. In contrast, in the presence of a palladium catalyst, the functionalization of aromatic C(sp^2)–H_b bond is dominantly occurred to afford indolin-2-one derivatives. Moreover, it was found that the selectivity is largely be determined by the presence of an ester group within diazoamides. DFT calculation provided insight into the role of ester functionality in such selectivity.

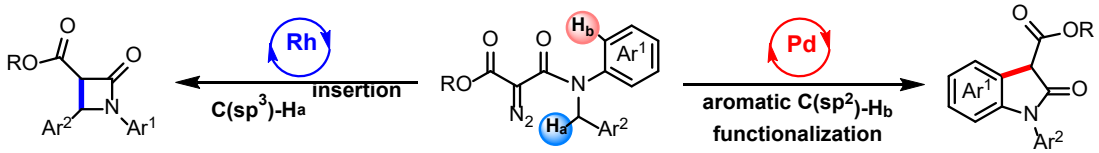

Figure 1. Catalyst-controlled Divergent C–H Bond Functionalization of α-Diazoamides

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Copper-Catalyzed Regioselective Allylation of 1-Trifluoromethylalkenes

Yuki Kojima and Koji Hirano*
Department of Applied Chemistry, Graduate School of Engineering, Osaka University
Suita, Osaka 565-0871, Japan
Email: k_hirano@chem.eng.osaka-u.ac.jp

Since the introduction of fluorine atom into organic molecules improves their lipophilicity, metabolic stability, and biological activity, organofluorine compounds have attracted significant attention in the design of pharmaceuticals and agrochemicals. In particular, trifluoromethyl group (CF_3) is frequently found in biologically compounds. Therefore, the development of efficient synthetic methods for CF_3-containing organic molecules is highly desired. We recently achieved the synthesis of *α*-trifluoromethylamines by the copper-catalyzed regioselective hydroamination of 1-trifluoromethylalkenes with hydrosilanes and hydroxylamines (Figure 1a).[1] In this reaction, the judicious choice of ligand and base selectively promoted the hydroamination reaction even with the possibility of undesired *β*-F elimination from an *α*-trifluoromethyl organocopper intermediate.[2] Based on the aforementioned strategy, herein, we disclose the copper-catalyzed regio- and enantioselective hydroallylation of 1-trifluoromethylalkenes with hydrosilanes and allylic chlorides (Figure 1b).[3] Also in this case, the appropriate choice of base can suppress the *β*-F elimination from *α*-CF_3 organocopper intermediate, giving the corresponding hydroallylation product in a good yield. Additionally, the regio- and stereoselective allylboration of 1-trifluoromethylalkenes is also achieved by using bis(pinacolato)diboron instead of hydrosilanes (Figure 1c).[4] The addition of in situ generated boryl copper species and subsequent trapping with the allyl chloride can introduce two functional groups into the 1-trifluoromethylalkene simultaneously.

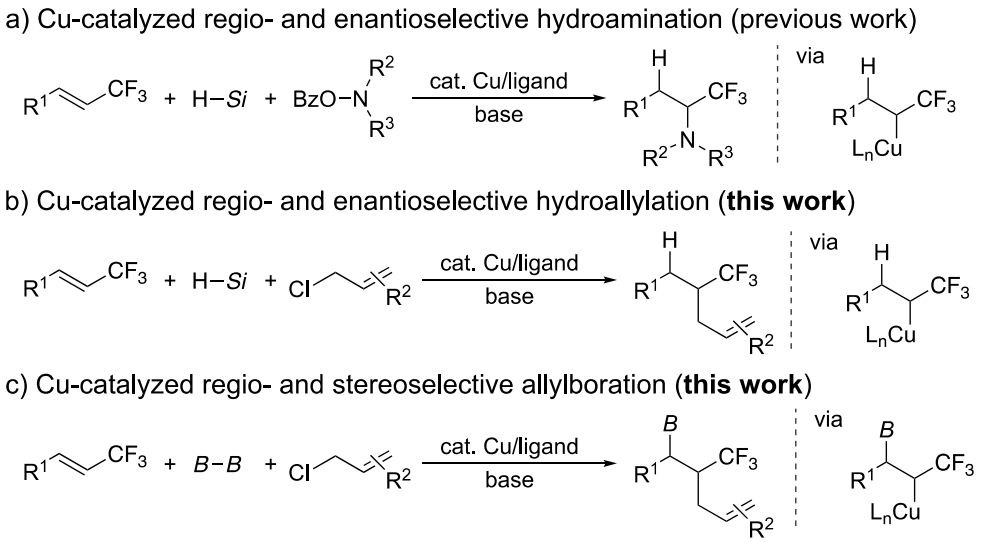

Figure 1. Catalytic functionalization of 1-trifluoromethylalkenes

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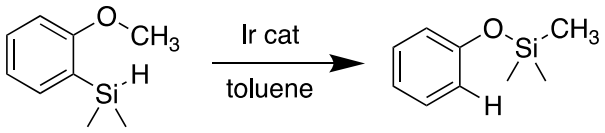
Iridium-Catalyzed Intramolecular Silylene Transfer Leading to Insertion of Silylene into C(sp^3)–O Bond

Yunhao Song,[a] Toshimichi Ohmura,*[b] Michinori Suginome*[a]
[a]Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan
[b] Faculty of Molecular Chemistry and Engineering, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan
Email: song.yunhao.84a@st.kyoto-u.ac.jp; ohmura@kit.ac.jp; suginome@sbchem.kyoto-u.ac.jp

Silylene (:SiR_2) is a divalent chemical species of silicon and is useful for the formation of two silicon-containing sigma bonds simultaneously. For the development of synthetic methods utilizing silylene, it is desirable to accumulate new findings on the efficient generation of silylene and to expand the reaction partners of silylene. We focused on triorganohydrosilanes as a new synthetic equivalent of silylene[1], because these are thermally stable and easy-to-handle compounds.

Herein, we report an iridium-catalyzed intramolecular transfer of silylene generated from triorganohydrosilane. We found that 2-(dimethylsilyl)methoxybenzene (**1**) was converted to (trimethylsilyl)oxybenzene (**2**) efficiently in heated toluene in the presence of an iridium catalyst. In this conversion, dimethylsilylene (:$SiMe_2$) was released from the hydrodimethylsilyl group, and the sp^3 carbon–oxygen bond of the methoxy group underwent insertion of the silylene. In this presentation, we will discuss in detail the catalytic conditions under which the reaction proceeds efficiently, the scope of substrates, and findings on the reaction mechanism.



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Iron Catalysis of C(sp^3)−H Azidation Using a Heteroarene Radical Cation Strategy

A Young Ji,[a] Yuri Kim,[a] and Eun Joo Kang*[a]
[a] Department of Applied Chemistry, Kyung Hee University, Yongin 17104, Korea
Email: rimyuri@khu.ac.kr; ejkang24@khu.ac.kr

C(sp^3)−H bond functionalization has received considerable attention as an atom-economical method for increasing the molecular complexity with simple modifications.[1] Although the selective activation of C(sp^3)−H over other ubiquitous C−H bonds is highly challenging, the benzylic C(sp^3)−H bond exhibits potential for the generation of reactive radical intermediates because of its smaller bond dissociation energy.[2] Based on this, precisely predicting the reaction regioselectivity, particularly for complex arenes and heteroarenes bearing benzylic-type C(sp^3)−H bonds, is difficult.

This work represents the first use of a $Fe^{III}(phen)_3$ complex for single-electron oxidation to afford an arene radical cation in which N-heteroarenes and benzene derivatives were differentiated according to their oxidation potential.[3] The stability of the radical intermediate originates from the captodative effect of the electron-donating N-heteroarene and electron-withdrawing carbonyl groups. This strategy exhibits a difference in reactivity between N-heteroarenes and benzene, which is difficult to achieve via direct hydrogen abstraction approaches. We anticipate that this sustainable Fe(II) redox catalysis will be applicable in future diverse synthetic strategies, and the late-stage functionalization is expected to promote new protocols in Fe catalysis.

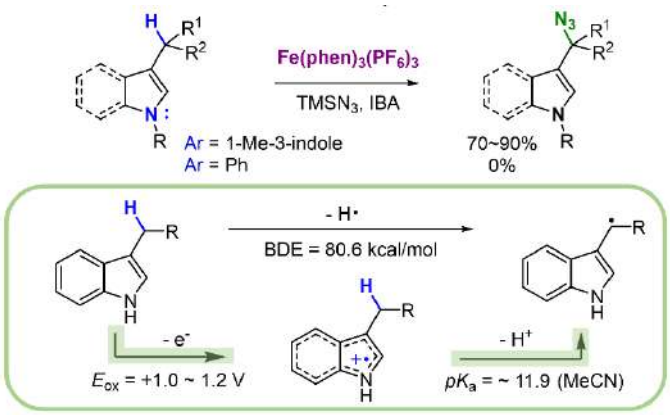

Figure 1. Chemoselective azidation by indole radical cation

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Molecular Design of Film-Forming Additives for Lithium-Ion Batteries – the Impact of Molecular Substrate Parameters on the Cell Performance

Ankita Das,[a,b] Linda Quach,[a,b] Egy Adhitama,[b,c] Valentin Göldner,[b,d] Feleke Demelash,[c] Martin Winter,[c] Uwe Karst,[d*] Tobias Placke,[c*] Frank Glorius[a*]

[a]Institute of Organic Chemistry, University of Münster, Corrensstr. 36, 48149 Münster, Germany.

[b]International Graduate School for Battery Chemistry, Characterization, Analysis, Recycling and Application, University of Münster, Corrensstr. 40, 48149 Münster, Germany.

[c]MEET Battery Research Center, Institute of Physical Chemistry, University of Münster, Corrensstr. 46, 48149 Münster, Germany.

[d]Institute of Inorganic and Analytical Chemistry, University of Münster, Corrensstr. 48, 48149 Münster, Germany.

Email: ankita.das@uni-muenster.de; glorius.uni-muenster.de

Li-ion Batteries (LIBs) have revolutionized the portable electronics market and are now aiding the electrification of vehicles. Film-forming electrolyte additives are crucial for establishing high-energy lithium-ion batteries (LIBs) to the market. Electrolyte additives that aid the formation of SEI are one of the popular strategies to enhance the overall performance and safety features of the battery. Our group, joint with the MEET (Münster Electrochemical Energy Technology), established a class of electrolyte additive: the “N-carboxy anhydrides” (NCAs) that shows great improvement in overall battery performance[1]. In this work, several derivatives of *N*-carboxyanhydrides were synthesized to distinguish relevant substrate parameters crucial for polymerization and film formation and evaluated in $LiNi_{0.8}Co_{0.1}Mn_{0.1}O_2$ || Si/graphite cells. Electrochemical performance and laser desorption/ionization mass spectrometry analysis are conducted to elucidate underlying decomposition mechanisms and dependency on functional moieties. Using this study, structural understanding of electrolyte additives can be improved and it will aid in the systematic design of additives in future.

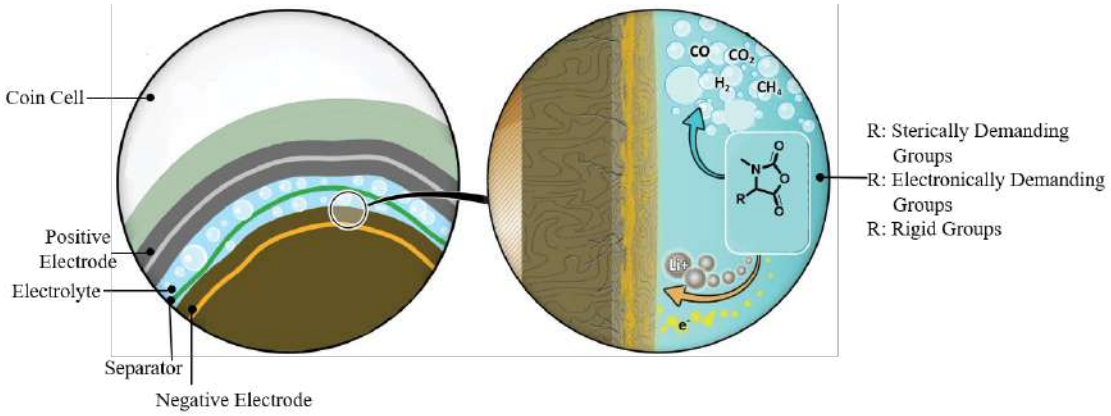

Figure1.Effect of different structural features of N-Carboxy Anhydride on the performance of Li-ion battery

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Accelerated Hydrogen Generation due to a Direct Methyl Formate Dehydrogenation Pathway

Rui Sang,[a] Zhihong Wei,[b] Elisabetta Alberico,[a,c] Haijun Jiao,[a] Henrik Junge,[a*] and Matthias Beller[a]

[a]Leibniz-Institut für Katalyse e.V., Albert-Einstein-Str. 29a, 18059 Rostock, Germany, [b]Institute of Molecular Science, Key Laboratory of Materials for Energy Conversion and Storage of Shanxi Province, Shanxi University, 030006 Taiyuan, P. R. China, [c]Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, tr. La Crucca 3, 07100 Sassari, Italy, Email: henrik.junge@catalysis.de

The use of renewable energy is central for the realization of a circular economy and will constitute the basis for further global economic development. In this respect, the implementation of a green hydrogen economy is intensively investigated. In a future hydrogen economy, also CO_2-based hydrogen storage materials and technologies play an important role.[1] In this context, we propose the previously overlooked, industrially available bulk chemical methyl formate (MF) as a new hydrogen carrier. Surprisingly, the ruthenium pincer complex ([Ru(H)(CO)Cl(PNP^{Ph})])-catalyzed aqueous phase MF dehydrogenation proceeds at a much higher rate compared to established hydrogen energy carriers and ester ingredients methanol (20 times) and formic acid (5 times, Figure 1) under identical mild conditions. [2]

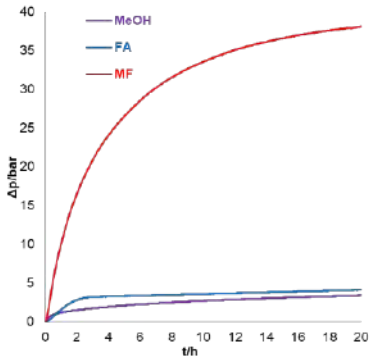

Figure 1. Comparison of MeOH, FA and MF dehydrogenation.

These unexpected results prompted us to conduct a more in-depth study on the mechanism of MF dehydrogenation including NMR-investigation, X-ray analysis of the key species as well as DFT calculations. The dehydrogenation of MF might occur *via* two routes: (a) direct MF dehydrogenation or (b) by MF hydrolysis followed by dehydrogenation of formic acid and methanol. Mechanistic investigations including KIE measurements, DFT calculations, synthesis and crystallization of intermediate species, NMR studies, and time-resolved product analysis proof a direct MF dehydrogenation pathway including [Ru(H)(CO)OCOOCH$_3$(PN^{K}P^{Ph})] as key intermediate. Additionally, the generation of up to four moles of hydrogen and two moles of CO_2 was proven and long-term experiments resulted in remarkable pressures of 70 bar (2 h) and 128 bar (10 h), as well as catalyst turn-over numbers TON(H_2) >107,000 and frequencies TOF(H_2)$_{max}$ >44,000 h^{-1}.

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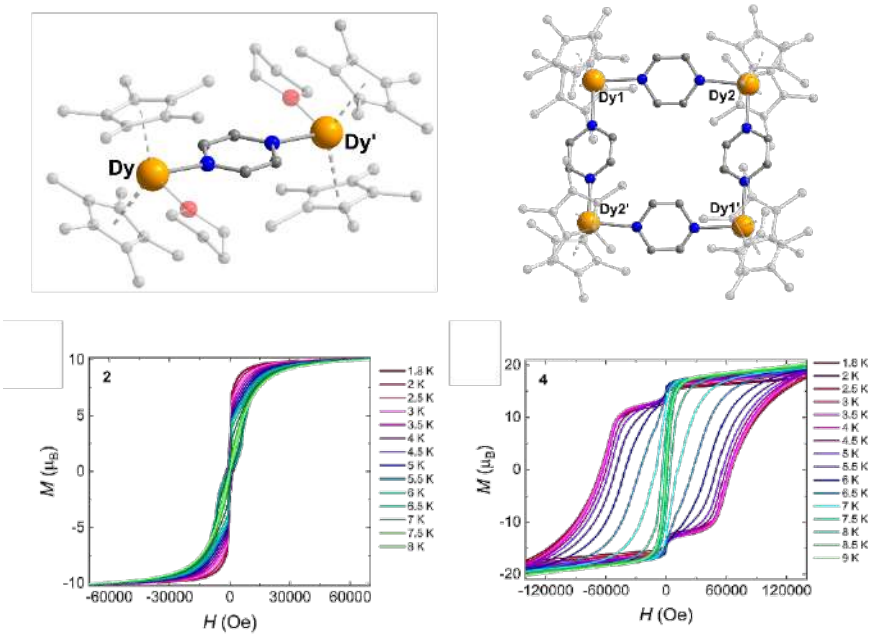
Slow Magnetic Relaxation and Strong Magnetic Coupling in Lanthanide Radical Bridged Metallocenes

Neha Bajaj, Niki Mavragani, Alexandros A. Kitos, Akseli Mansikkamäki and Muralee Murugesu*

Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario, K1N695
Email: nbaja043@uottawa.ca; m.murugesu@uottawa.ca

Promoting magnetic interactions in lanthanide-based single-molecule magnets (SMM) is an ongoing challenge in the field of molecular magnetism. To overcome the lack of strong magnetic communication between Ln(III) ions, which stems from the core-like electron density of the 4f orbitals, employment of paramagnetic bridging ligands as a direct exchange pathway is a promising avenue.[1,2] With the aim to synthesize such strongly coupled complexes, we sought to utilize for the first time in lanthanide metallocene complexes, pyrazine (pyz) as a bridging ligand. Due to its redox active sixmember ring, incorporation of the radical pyz•- in lanthanide metallocenes afforded a dinuclear family of lanthanide metallocenes [Cp*2Ln)2(pyz•-)(THF)2][BPh4] (Cp* = pentamethylcyclopentadienyl; THF= tetrahydrofuran; Ln = Gd; (1), Dy; (2)) which upon removal of the coordinated THF served as a building block for isolating the tetranuclear family [(Cp*2Ln)4(pyz•-)]·5THF (Cp* = pentamethylcyclopentadienyl; Ln = Gd; (3), Dy; (4)). Strong magnetic exchange coupling was observed in 1 where JGd-rad = -22.2 cm-1, which to this day is the highest exchange coupling in Gd complexes mediated by an organic monoanionic radical. This in combination with the high performing [Cp2*Dy] + units of in 2 and 4 led to zero-field SMM behaviour with an energy barrier of Ueff = 111 cm-1 and 140 cm-1 respectively. Hysteresis measurements of 4 showed a giant coercive field of 65kOe. To the best of our knowledge this is the highest coercive field, yet reported, for any Dy-based radical-bridged metallocene.



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Novel $C_{(Nhc)}Cc_{(Nhc)}$-Nhc Gold Pincer Complexes and Study Of Their Catalytic Activities

Hugo Valdés,* Xavi Rivas
Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Campus de Montilivi, Girona E-17003, Catalonia, Spain.

Email: hugo.valdes@udg.edu

Pincer complexes have stood out as useful tools in catalysis.[1, 2] In particular, pincer ligands with N-heterocyclic carbene (NHC) fragments have exhibited some interesting features. Since NHCs are very strong donor ligands, that enhance the nucleophilicity of a metal center, thus generating very active catalysts.[3] However, in the realm of Au(I) and Au(III) chemistry, the use of NHC-pincer ligands remains scarcely explored, and only a few examples have been described.[4] Actually, in the literature there are no examples of $C_{(NHC)}$-$C_{(Aryl)}$-$C_{(NHC)}$ gold pincer complexes, for which interesting reactivity is envisioned. Probably one of the reasons is the lack of synthetic strategies to coordinate the metal fragment to such type of pincer ligands. Up to now there are two main strategies to prepare $C_{(NHC)}$-$C_{(Aryl)}$-$C_{(NHC)}$ metal-pincer complexes. The C-H or C-halogen bond activation, and the transmetalation from Zr or Li derivatives. Both strategies have drawbacks, for example the bond activation requires high temperatures, while the transmetalation reaction requires very anhydrous conditions and the use of organolithium compounds.

Here we report a new approach to obtain $C_{(NHC)}$-$C_{(Aryl)}$-$C_{(NHC)}$ gold pincer complexes (Scheme 1a). The activation of an aryl-diazonium salt (**L-N_2**) through an oxidative addition of the C-N_2 bond enabled the coordination of the pincer ligand to the gold atom. The synthesis of **L-N_2** was carried out in three steps starting from 1,3-bis(bromomethyl)-2-nitrobenzene in 64% yield. Finally, the catalytic activity of the complexes, was evaluated in the synthesis of oxazolines and phenols (Scheme 1b).

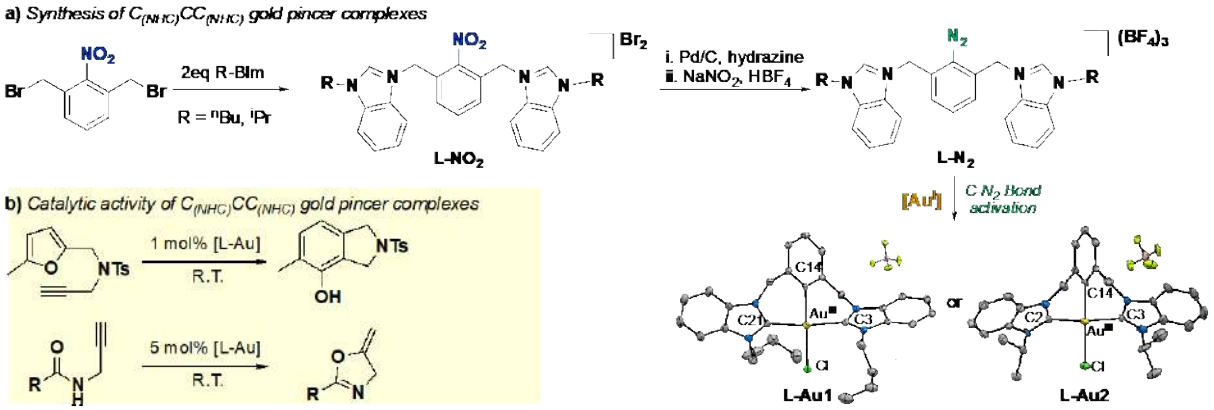

Figure 1. a) Synthesis and b) catalytic activity of $C_{(NHC)}$-$C_{(Aryl)}$-$C_{(NHC)}$ gold(III)-pincer complexes.

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A Molecular Recognition Motif for the Co-Crystallization of Two Diastereomers

Jonathan O. Bauer*[a]
[a] Institut für Anorganische Chemie, Universität Regensburg, Universitätsstraße 31, D-93053 Regensburg
Email: jonathan.bauer@ur.de

Weak intermolecular interactions are of paramount importance for the formation of certain supramolecular units in molecular crystals [1,2]. Typically, diastereomers have distinguishable chemical and physical properties and can therefore be separated by fractional crystallization making use of their different solubility. In a 1:1 co-crystallization of two diastereomers, intermolecular interactions ensure the formation of a defined molecular recognition motif [3,4]. In order to get control over crystallization processes and the separation of stereoisomers, it is therefore crucial to better understand the mechanisms of stereoisomeric co-crystallization and to identify the involved intermolecular interaction modes [5].
Fractional crystallization of a mixture of diaminocyclosilane diastereomers resulted in either a 1:1 co-crystal with both diastereomers in the asymmetric unit (Figure 1) or in the crystallization of a pure diastereomer, depending on the solvent mixture used. A molecular recognition motif was identified. It was also investigated how the substitution pattern and the solvent affects the stereoisomeric co-crystallization. The insights gained from these studies can be crucial for understanding fundamentally important nucleation processes and provide tools for the design of functional supramolecular entities.

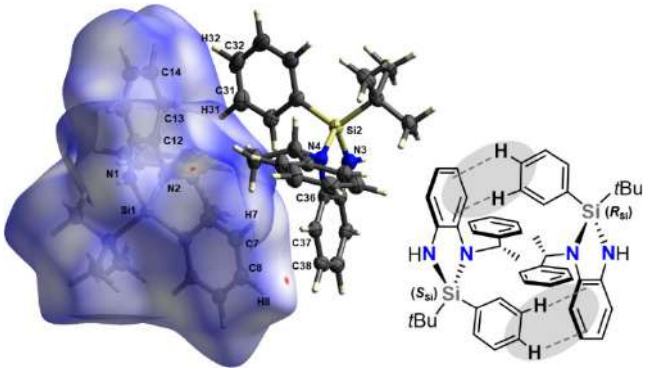

Figure 1. Identification of specific intermolecular interaction patterns responsible for the 1:1 co-crystallization of diastereomers.

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TMDSO and KO^{t}Bu Enabled Reductive Defunctionalisation and Synthesis

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

Email: pston102@uottawa.ca; Stephen.Newman@uottawa.ca

Within the past decade, 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.[1] Recently our group disclosed the TMDSO and KO^{t}Bu mediated de-trifluoromethylation of 2-trifluoromethylpyridines which proved to be chemoselective for trifluoromethyl groups located at C2.[2] Preliminary mechanistic experiments point towards a silicon-derived hydrogen atom donor, and single electron donor capable of reducing electron deficient π-systems, and vinyl arenes. Further exploitations of this unique reagent combination led to a serendipitous discovery enabling the hydroalkylation of vinyl-arenes in the presence of alkyl-halides, through what we suspect is a vinyl-arene derived nucleophilic intermediate.

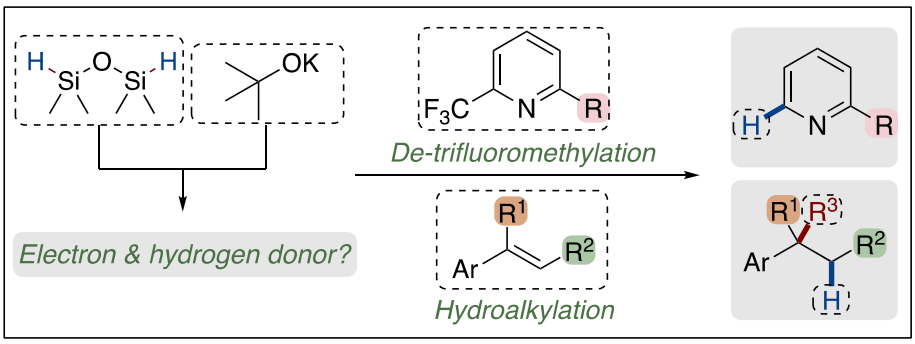

Figure 1. TMDSO and KO^{t}Bu promoted de-trifluoromethylation and hydroalkylation

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“Gold Only” Photocatalysis

Sina Witzel,[a] Elena Michel,[a] Julian J. Melder,[a] A. Stephen K. Hashmi*[a]
[a]Heidelberg University, Heidelberg, Germany
Email: hashmi@hashmi.de

The first papers showing a high increase in molecular complexity in gold-catalyzed organic reactions,[1] triggered the development of homogeneous gold catalysis to a frequently used tool in different sectors of organic synthesis, e.g. for total synthesis[2] or materials science.[3] The important influence of reactive intermediates like gold vinylidene intermediates[4] or other functionalized gold carbenes[5] on the outcome of gold-catalyzed reactions is well documented. Most of these reactions are based on polar reactivity, i.e. the reaction of nucleophiles with electrophiles.
The recent revival of photochemical conversions also led to an exploration of combinations of photoredox catalysts with other transition metal catalysts, among the latter also gold catalysts. Apart from such combinations of two catalysts, there already existed earlier work on photoredox catalysis by *dinuclear* gold(I) complexes, the first examples of “gold only” catalysis.[6]
Beyond new examples and insights into catalysis with such *dinuclear* gold(I) complexes, the contribution will also address photochemical conversions involving *mononuclear*[7] gold(I) complexes (Figure 1). This will include mechanistic studies and computational studies of these systems and reveal an exciting combination of a gold-based catalytic cycle involving two one-electron redox reactions at gold with a radical chain.

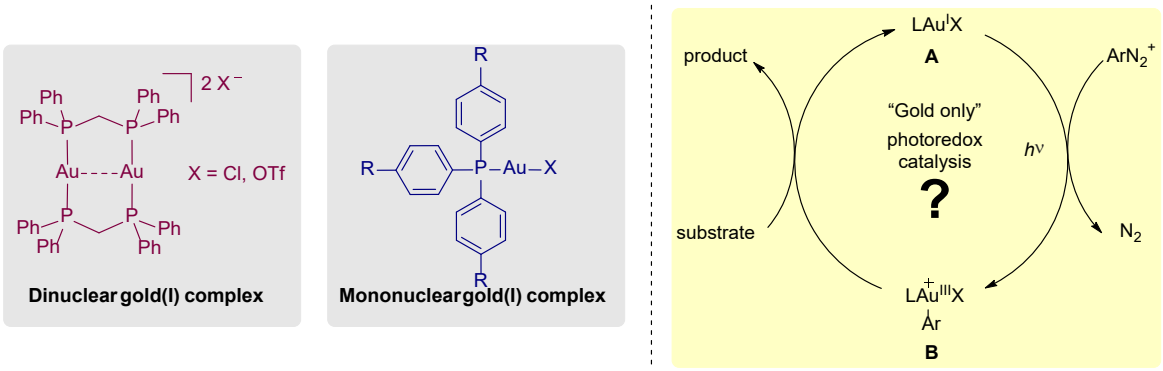

Figure 1. “Gold only” dinuclear (left) and mononuclear (middle) catalysts for photochemical reactions and the mechanistic riddle of mononuclear gold(I) photoreactions (right).

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Radical Aryl Migration: New Synthesis of GABA Drugs

Che-Chien Chang*[a]
[a] Department of Chemistry, Fu Jen Catholic University

Email: 080686@mail.fju.edu.tw

Various *N*-(2-bromo-allyl) benzamides were used as the starting materials to study vinyl radical ipso cyclization reactions. The vinyl radicals underwent ipso-cyclization, aryl migration, and recyclization, and unsaturation reactions to produce β-aryl-γ-lactams with the carbonyl group remaining intact. To further study this cascade radical reaction, vinyl radicals were generated by the addition of a tributyltin radical to alkyne moieties, followed by radical ipso-cyclization, aryl migration, recyclization, and β-scission reactions with the production of a series of α,β-unsaturated-β-aryl-γ-lactam derivatives. This new type of radical reaction was further applied to produce therapeutic agents for neurodegenerative diseases, such as rolipram and phenylpiracetam.

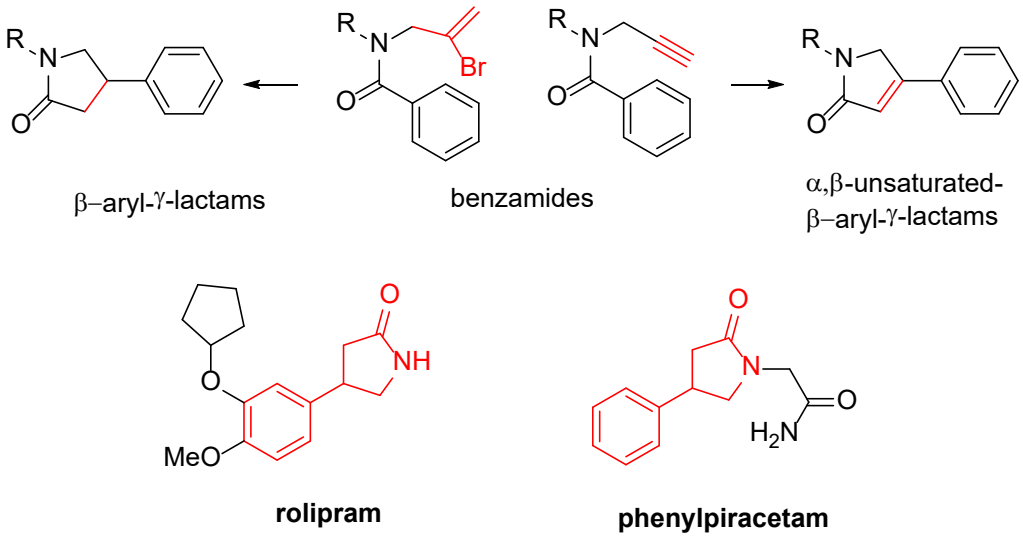

Figure 1. New synthetic methodology for GABA drugs.

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Silver/Copper Mediated Photofluorination of Aryl Halides using Visible Light

Taylor E. Spiller,[a] Karsten Donabauer,[a] Melanie S. Sanford*[a]
[a]University of Michigan Department of Chemistry

Email: tspiller@umich.edu; mssanfor@umich.edu

Fluorine is present in 43% of total registered synthetic drugs due to its favorable effect on the metabolic stability of drug molecules.[1] Its prevalence in small molecules makes fluorination method development an important area of research. However, current methods often require harsh conditions, prefunctionalized substrates, or limited functional group tolerance.[2] In this work, we are targeting aryl halides as a commercially available and synthetically ubiquitous substrates. Herein we present a room temperature, metal mediated, visible light-initiated fluorination of aryl halides. Additionally, we provide initial insight into the mechanism and scope of this transformation.

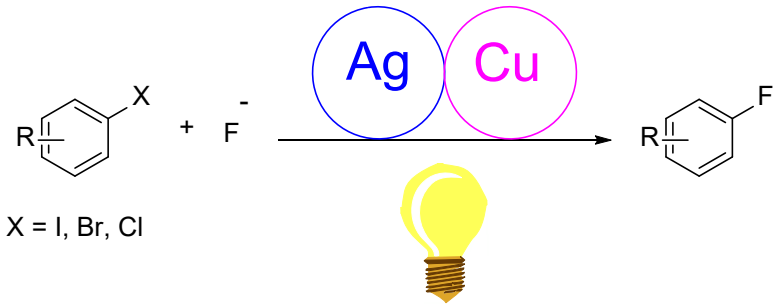

Figure 1. Photofluorination of aryl halides.

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Metalloporphyrins as Hydrogen Atom Transfer Photocatalysts for C-H to C-C Bond Conversion

Emil K. Nielsen,*[a] Mårten S. G. Ahlquist,[b] Robert Madsen[a]
[a]Technical University of Denmark, Department of Chemistry, 2800 Kgs. Lyngby, Denmark
[b]KTH Royal Institute of Technology, Department of Theoretical Chemistry and Biology, 100 44 Stockholm, Sweden.

Email: emkrni@kemi.dtu.dk

Porphyrins and metalloporphyrins have been used extensively in photochemical reactions throughout the last several years[1]. This is due to porphyrins inherent ability to act as a photosensitizer. A type of photocatalytic reaction, where porphyrins are underrepresented, is the Hydrogen Atom Transfer (HAT) reaction. By utilizing photocatalytic HAT reactions it is possible convert C-H bonds to C-C bonds. Recent studies have presented metalloporphyrins as HAT catalysts for this purpose[2]. The goal of this study has been to develop, characterize and test new metalloporphyrin complexes with transition metals. Metals used include the early d-block elements titanium, vanadium, chromium, molybdenum and tungsten. The catalysts have been investigated in test reactions and by Density Functional Theory (DFT), to evaluate the potential reaction mechanism.
This new class of photocatalysts are easily available from commercial starting materials and has the potential for providing new methods for forming C-C bonds at mild conditions in organic chemistry.

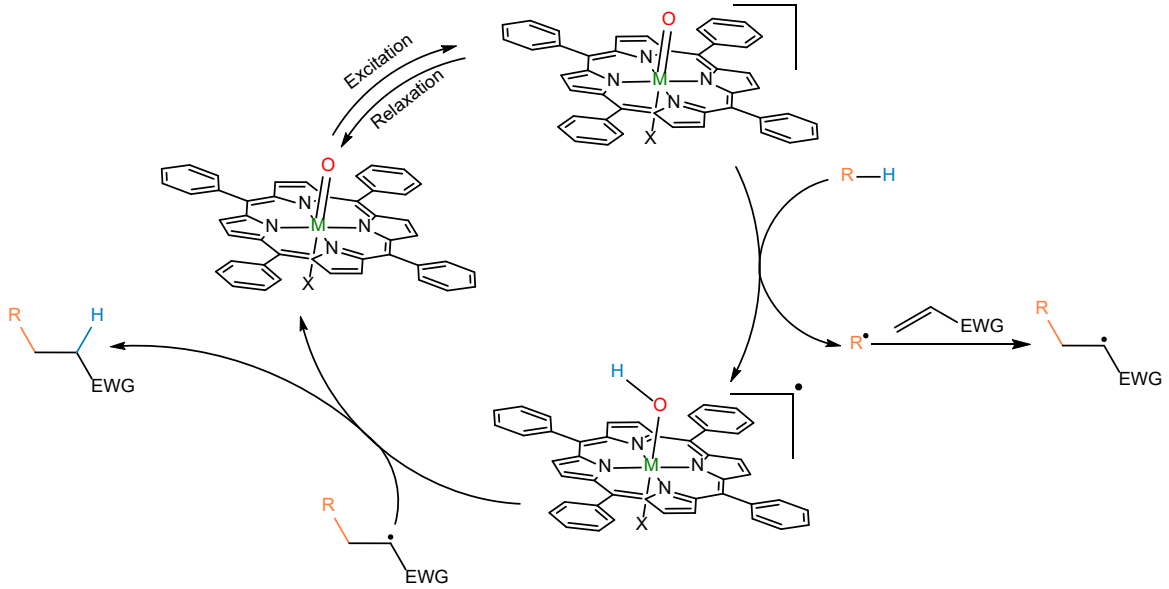

Figure 1. Illustration of proposed mechanism of C-H to C-C bond conversion using metalloporphyrins as photocatalyst. “M” is a transition metal and “X” is an arbitrary axial ligand.

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Iminopyridinium Derivatives as Iminyl Radical Precursors in Visible-light Photochemistry

Gyuri Han,[a] Jihyun You,[a] Eun Joo Kang*[a]
[a]Department of Applied Chemistry, Kyung Hee University, Yongin 17104, Korea
Email: haco0303@khu.ac.kr; ejkang24@khu.ac.kr

Iminyl-radical-triggered C–C bond cleavage of cycloketone oxime derivatives[1] provides a practical route to access distal cyano-substituted alkyl radicals, which has given chemists a new radical reaction platform for the synthesis of diverse alkyl nitriles. Various redox-active cycloketone oximes have been explored to generate iminyl radical intermediates through polarized homolytic N-O bond cleavage, employing transition-metal reductive catalysis (Fe, Cu and Ni) and photocatalysis (reductive or oxidative single-electron-transfer). In this work, a unique substrate introducing iminyl radical through homolytic N-N bond cleavage was developed. Electron poor iminopyridinium salts undergo the single-electron-transfer(SET) reduction to generate pyridine radicals, which lead to the bond homolysis. The visible-light-induced SET reaction is induced by the formation of a supramolecular electron donor-acceptor (EDA) complex[2] between carbonate or Hantzsch ester and iminopyridinium substrate. The corresponding iminyl radical proceed ring fragmentation to deliver cyanoalkyl radical, which subsequently added to electron-deficient alkene. Photophysical and electrochemical studies support an electron-transfer mechanism and this strategy can also applied to the late-stage functionalization of biorelevant alkenes, highlighting the usefulness of this mild and practical photochemistry.

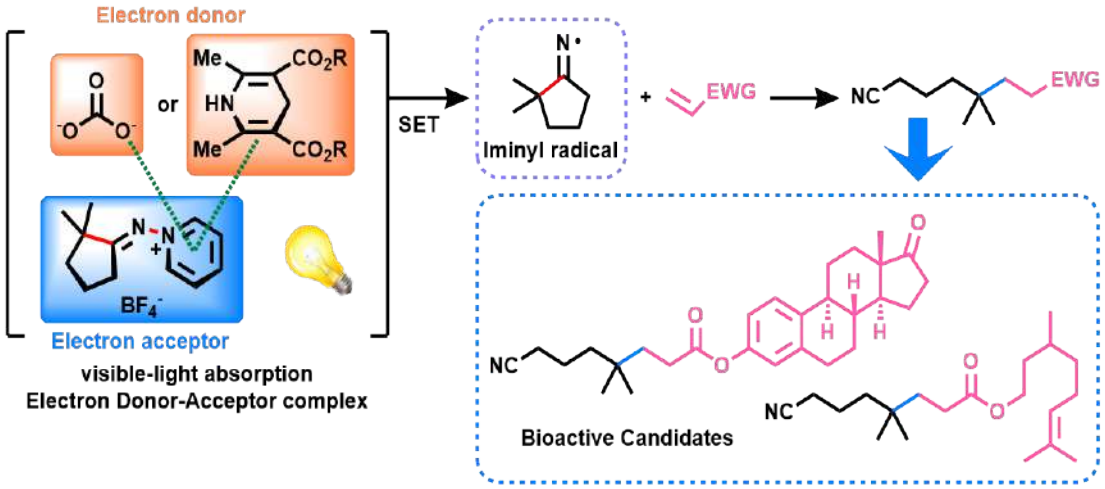

Figure 1. Iminyl radical-mediated C-C bond cleavage and addition reaction

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Direct Difunctionalization of Tricyclo[1.1.1]pentane; Radical Cyanoalkylation and Pyridylation

Jun Hyeon Choi[a] and Eun Joo Kang*[a]
[a] Department of Applied Chemistry, Kyung Hee University, Yongin 17104, Korea
Email: cjh0827@khu.ac.kr; ejkang24@khu.ac.kr

Recently, functionalization of tricyclo[1.1.1]pentane(TCP) is significantly spotlighted because bicycle[1.1.0]pentane(BCP) scaffolds from TCP are able to replace functional groups such as alkyne, arene and tert-butyl group in various pharmaceuticals and natural compounds with enhanced chemical and pharmacological properties. Therefore, a plenty of researches on BCP functionalizations are actively on going,[1] however direct C(sp3), C(sp2)-difunctionalization of TCP is still in the dark side. Herein, we designed novel iminopyridinium electrophore which can generate iminyl radical under visible-light-induced single electron transfer by electron donor-acceptor complexation. Cycloalkane iminyl radical undergo ring fragmentation to form cyanoalkyl radical by β-scission,[2] which react with TCP followed by a minisci-type reaction to finally afford the cyanoalkyl and pyridyl-functionalized BCP product. The whole reaction process is found to proceed under radical chain process and subsequent mechanistic studies are still on going.

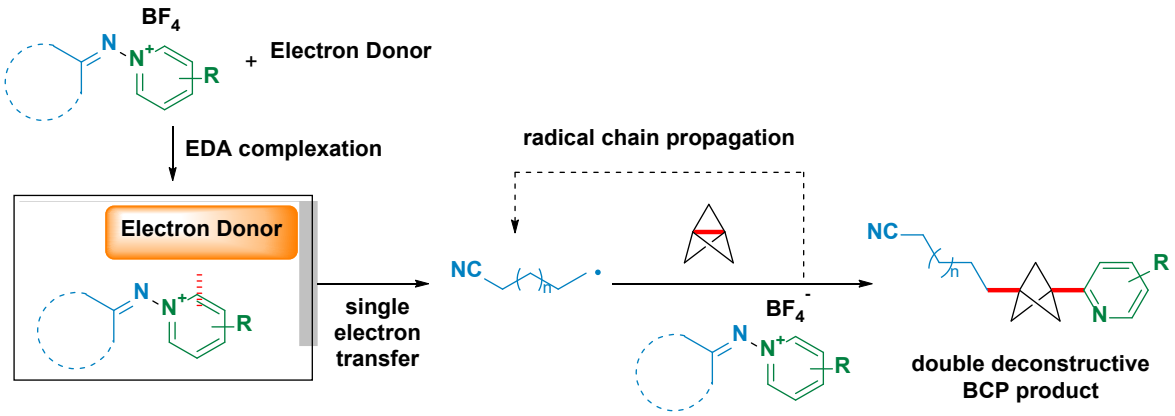

Figure 1. Difunctionalization of BCP via Visible Light-induced cyanoalkyl radical and subsequent Minisci reaction.

Acknowledgement

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New Methods for Valorization of Glycerol

Kassem El-Chami,[a] Robert Madsen*[a]
[a]Technical University of Denmark, Department of Chemistry, 2800 Kgs. Lyngby, Denmark.

Email: kelch@kemi.dtu.dk

Biodiesel is an ester of fatty acids obtained from vegetable oil or animal fat. However, the cost of biodiesel is 1.5 – 3.0 times higher than that of petroleum-derived diesel fuel. The main reason is the large amount of glycerol produced as a co-product.[1]

Glycerol can form carbon-centered radicals. A challenge during the generation of the radical on glycerol is to avoid the elimination of water, given that a more stable α-carbonyl radical will be generated.

The purpose of the project is to develop new methods for forging C-C bonds on glycerol by employing radical reactions and hereby convert glycerol into a variety of new bio-based molecules with potential high-value applications. Via photoredox catalysis it is possible to functionalize glycerol at the C2 position with electron deficient Michael acceptors.

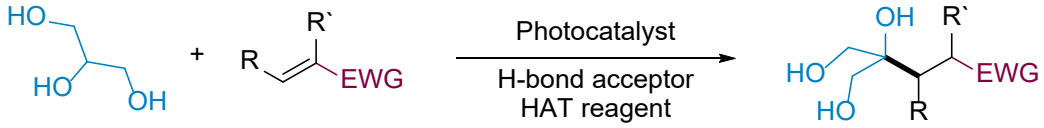

Figure 1. Photocatalytic valorization of glycerol towards Michael acceptors.

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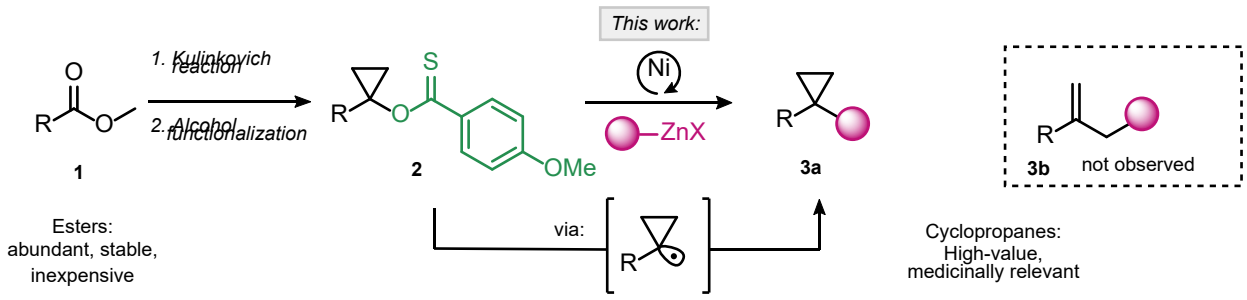
New Redox Active Leaving Groups for the Deoxygenative Cross-Coupling of Cyclopropanols

Katerina Scotchburn, Sophie Rousseaux*
University of Toronto, Toronto, Canada.

Email: katie.scotchburn@mail.utoronto.ca; sophie.rousseaux@utoronto.ca

The addition of cyclopropane rings to drugs is an attractive strategy to increase sp^3 character of a potential drug without dramatically increasing molecular weight, which can improve the pharmacokinetic/dynamic properties of a drug molecule.[1] One interesting way to generate cyclopropanes is the Kulinkovich reaction, which forms cyclopropanols from esters and alkyl Grignards.[2] While alcohols can usually be activated for cross-coupling by transformation into an appropriate leaving group (-OMs, -OTs, etc.), cyclopropanols are not compatible with traditional cross-coupling strategies. When leaving groups typically associated with 2-electron (or polar) reactivity are used, only the ring-opened product (**3b**) is obtained. To access the ring-retained product, it is necessary to generate a cyclopropyl radical intermediate via C–O bond scission. The Rousseaux lab has recently been active in the development of thiocarbonyl-containing leaving groups which achieve the deoxygenative cross-coupling of alcohols via 1-electron (or radical) reactivity.[3,4] Thionoester **2** has been discovered as a uniquely active leaving group for this chemistry, and an effective method allowing the coupling of alkyl cyclopropanols to a variety of aryl zinc coupling partners has been developed. This poster will highlight our discoveries in this area, focusing on the synthesis of thionoesters,[5] reaction optimization for the Ni-catalyzed cross-coupling, and selected scope examples.



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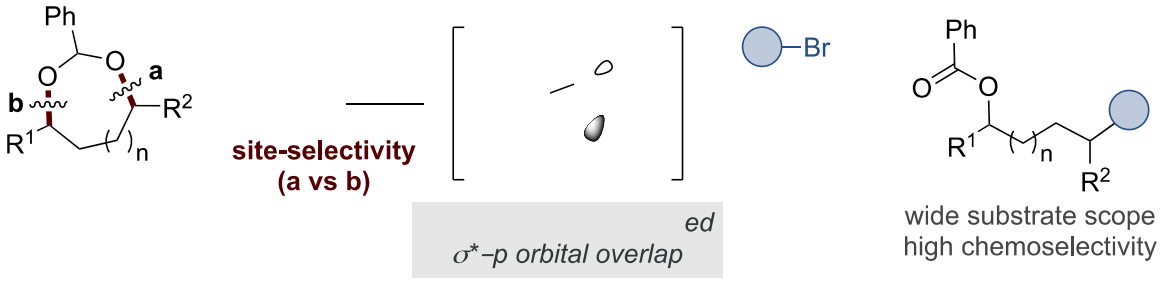
Conformational Flexibility as a Tool for Enabling Site-Selective Functionalization of Unactivated *sp*^{3} C–O Bonds in Cyclic Acetals

Ciro Romano,[a, †] **Laura Talavera** [a,b, †] **Enrique Gómez-Bengoa**[c] **and Ruben Martin**[a,d*]
[a]*Institute of Chemical Research of Catalonia (ICIQ);* [b]*Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili;* [c]*Department of Organic Chemistry I, Universidad País Vasco;* [d]*Catalan Institution for Research and Advanced Studies (ICREA);* †*Equal contribution*
Email: ltalavera@iciq.es; rmartinromo@iciq.es

In recent years, metallaphotoredox scenarios have offered new conceivable pathways to challenging transformations under exceptionally mild conditions.[1] Driven by this observation, we wondered whether we could harness cyclic acetals as vehicles to enable site-selective functionalization of strong σ alkyl *sp*^{3} C–O bonds. Unlike the elegant advances realized with symmetrical acyclic acetals,[2] the utilization of cyclic congeners not only would improve the atom economy of the overall transformation by preserving the integrity of the organic skeleton but also offer the possibility to discriminate between three similar *sp*^{3} C–O sites, thus constituting a worthwhile endeavor for chemical invention.

We hypothesized that a light-driven hydrogen atom transfer (HAT) would occur selectively at the weak acetal *sp*^{3} C–H bond. A subsequent β-fragmentation would take place via an appropriate σ*–p orbital overlap prior to C–O cleavage to deliver a carbon-centered radical. The subsequent C–C cross-coupling of the carbon-centered radical with the aryl/alkyl bromide would occur in the presence of nickel catalysis. The key β-fragmentation would only be accessible if a certain degree of conformational flexibility is granted. The protocol is characterized by its excellent chemoselectivity profile, broad scope across wide number of cyclic acetals and aryl/alkyl halides, thus offering a novel avenue to C-C bond formation.[3]



Scheme 1. Site-Selective *sp*^{3} C-O Arylation and Alkylation of Cyclic Acetals

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Umpolung Reductive Functionalization of Amides via a Tandem Hydrosilylation/Photocatalytic Strategy

Tatiana Rogova,[a] Pablo Gabriel, Stamatia Zavitsanou, Jamie A. Leitch, Fernanda Duarte, Darren J. Dixon*[a]

[a] Department of Chemistry, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, United Kingdom

Email: tatiana.rogova@rwth-aachen.de; darren.dixon@chem.ox.ac.uk

α–Functionalized amines and their derivatives are integral fragments of a vast array of pharmaceutical agents, agrochemicals and natural products.[1] Therefore, the development of a novel and efficient strategy to access these functionalities would be highly relevant for both academic and industrial applications. Within the scope of recently developed methodologies, the reductive functionalization of tertiary amides provides a synthetically useful access point towards a wide range of α–branched amine structures. In particular, the use of Vaska's complex ($IrCl(CO)(PPh_3)_2$), in conjunction with a siloxane-based reductant, has come to the forefront as an effective system for chemoselective activation of these notoriously robust and ubiquitous building blocks.[2] Traditionally, using these mild hydrosilylation conditions, tertiary amides can be converted *in situ* into reactive iminium ion intermediates that can be further intercepted with a variety of nucleophilic entities.[2] It was envisioned that through further transformation of the iminium ion into a nucleophilic α-amino radical species using a photocatalytic approach, it would be possible to venture into a previously inaccessible area of chemical space.[3]

To address this outstanding synthetic challenge, a streamlined one-pot procedure for mild generation of α-amino radicals from tertiary amide building blocks has been developed.[3] The free radical species were successfully coupled to the electrophilic dehydroalanine acceptor to produce an array of novel, α-functionalised amine derivatives. Furthermore, this strategy was applied towards reductive secondary amide functionalisation, as well as intramolecular examples that yielded substituted *N*-heterocycles. In addition to the experimental investigations, Density Functional Theory (DFT) analysis was utilised to gain further insight into the reactivity and physical properties of the reaction. Finally, to demonstrate the versatility and modularity of the developed dual catalytic, reductive functionalization approach, this concept was adapted to access enantioenriched products from feedstock starting materials, with the preliminary findings of this investigation disclosed herein.

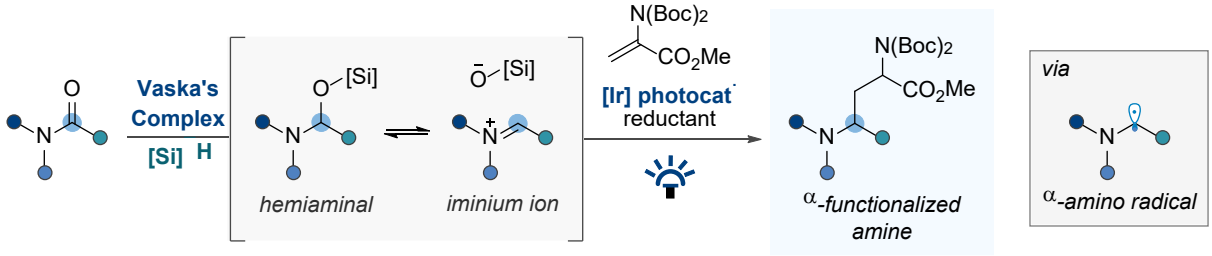

Figure 1. General strategy for umpolung reductive functionalization of tertiary/secondary amides.

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Photo-Mediated Deuterodecarboxylation and Transition Metal-Catalyzed CO_2 Valorization

Thea S. Mayer,[a] Tobias Taeufer,[a] Matthias Beller,*[a] Jola Pospech*[a]
[a]Leibniz Institute for Catalysis, Albert-Einstein-Straße 29a, 18059 Rostock, Germany.

Email: thea.mayer@catalysis.de; jola.pospech@catalysis.de

The synergy of transition metal catalysis and photocatalysis offers versatile opportunities for the development of new, highly effective synthetic methods under mild reaction conditions.

The heteroaromatic pyrimidopteridine (PPT) catalysts and their corresponding N-oxides (PPTNOs) have already been applied in additive-free photo-mediated C−N, C−C, and C−O bond formations.[1-3] Here, we present a strategy for the formation of C−H and C−D bonds in the context of photo-mediated hydro- and deuterodecarboxylation.[4] Under optimized reaction conditions, the conversion of commercially available nonsteroidal anti-inflammatory drugs (NSAIDs) in tablet form and on gram-scale was realized. This decarboxylation method not only deactivates drug residues, e.g., in wastewater, but at the same time also generates stoichiometric amounts of CO_2.

Although converting CO_2 into value-added substrates by using transition metal catalysis or photoredox catalysis remains challenging[5], our expertise in photoredox catalysis and rational ligand design enables the development of robust co-catalytic systems for stoichiometric carbon dioxide activation.

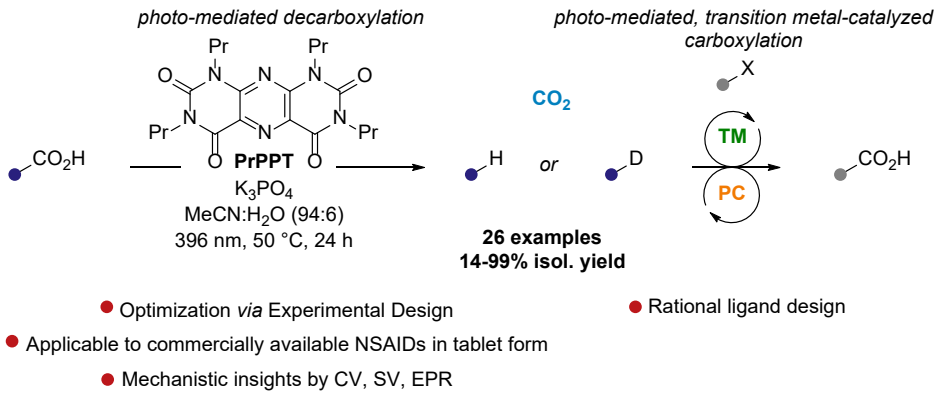

Figure 1. Photo-mediated deuterodecarboxylation and transition metal-catalyzed CO_2 valorization.

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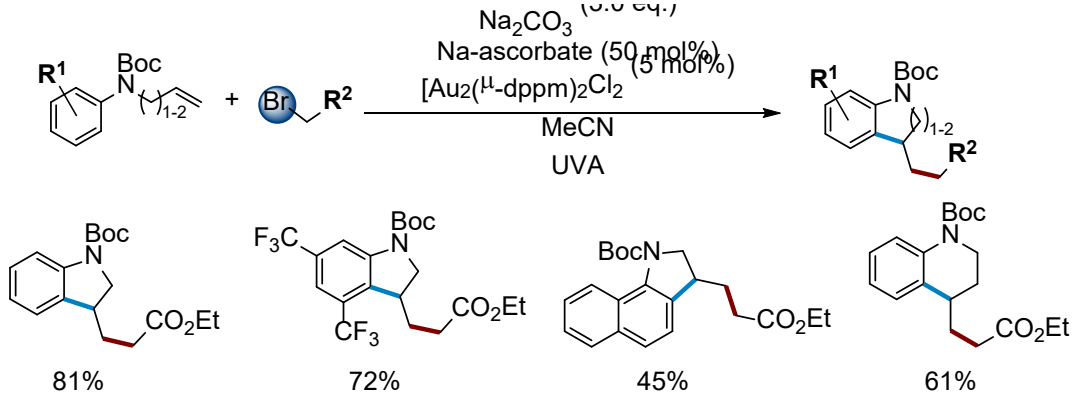
An Easy Access to Functionalized Indolines and Tetrahydroquinolines via a Photochemical Cascade Cyclization Reaction

Julian J. Melder,[a] A. Stephen K. Hashmi*[a]
[a] Organisch-Chemisches Institut, Heidelberg University, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Email: julian.melder@stud.uni-heidelberg.de; hashmi@hashmi.de

Since the first application of the di-nuclear gold complex $[Au_2(\mu\text{-dppm})_2]Cl_2$ for the reductive cleavage of alkyl and aryl bromides,[1] the complex and its derivatives has been studied intensively.[2] In this poster we present a fundamentally new synthetic approach utilizing $[Au_2(\mu\text{-dppm})_2]Cl_2$ for the preparation of indolines starting from un-activated alkyl bromides (Scheme 1). The methodology gives facile access to highly functionalized indoline derivatives from easy-to-access Boc-protected N-allylanilines. Due to its appearance in various pharmaceuticals and naturally occurring compounds the indoline scaffold represents one of the privileged motives in synthetic chemistry.



Scheme 1. Selected scope for the light-mediated indoline and tetrahydroquinoline synthesis.

The applicability of the synthetic protocol was further corroborated by the synthesis of a precursor for anti-inflammatory agent **AN669**. The synthetic procedure was carried out in three reaction steps in a very good overall yield of 65%, starting from readily accessible 4-(allylamino)phenol.

Based on the possibility for further functionalization, as well as the mild reaction conditions, we anticipate that this method will become a useful tool for the synthesis of building blocks for important target molecules. Beyond, we are currently working on an enantioselective variant of the featured protocol, which should extend the scope of application even further.

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Visible-light-promoted Radical Functionalization of Small Molecules to Synthesize Unsymmetric Diphosphine Ligands: Physical Properties and Catalytic Activity of Their Metal Complexes

Tsuyoshi Mita,*[a,b] Hideaki Takano,[a,b] Hitomi Katsuyama,[a,b] Hiroki Hayashi,[a,c] Miyu Harukawa,[c] Makoto Tsurui,[c] Sunao Shoji,[a,c] Yasuchika Hasegawa,[a,c] Wataru Kanna,[d] Yu Harabuchi,[a,b,d] and Satoshi Maeda,[a,b,d]

[a]Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Japan. [b]JST, ERATO Maeda Artificial Intelligence in Chemical Reaction Design and Discovery Project. [c]Faculty of Engineering, Hokkaido University, Japan. [d]Faculty of Science, Hokkaido University, Japan.

Email: tmita@icredd.hokudai.ac.jp

Diphosphines are ubiquitous ligands in organic synthesis due to their facile coordination to transition-metal salts. Arguably most prominent among the hitherto reported diphosphines is the structural motif of the diphosphinoethane ($R_2P–CH_2–CH_2–PR_2$) as a bidentate chelating ligand to create stable five-membered metallacycles with transition metals, which promote a variety of catalytic transformations. Straight-shaped diphosphine ligands have also been extensively studied, because they have shown unique structural and physical properties in supramolecular chemistry. In this context, bicyclo[1.1.1]pentane (BCP)-based diphosphine ligands would be promising candidates that can be synthesized from [1.1.1]propellane via radical difunctionalization. We herein disclose visible-light-promoted diphosphination reactions of ethylene and [1.1.1]propellane to produce symmetric and unsymmetric DPPE and BCP-diphosphine derivatives (Figure 1). Furthermore, we disclose the physical properties and catalytic activity of their transition-metal complexes.

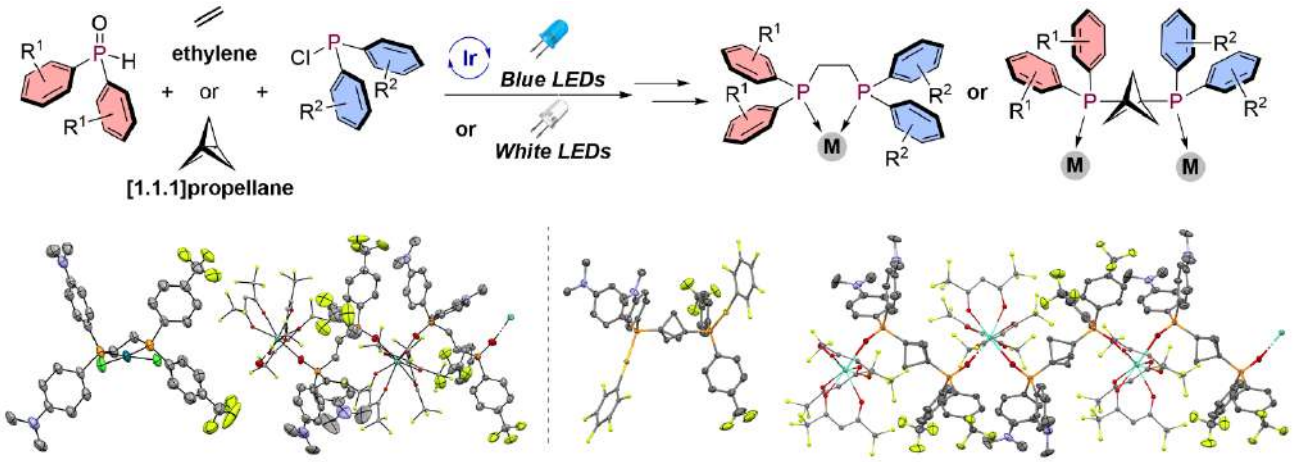

Figure 1. Visible-light-promoted diphosphination of small molecules.

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Energy Transfer Induced [3+2] Photocycloadditions of Pyridinium Ylides

Wooseok Lee[a,b], **Sungwoo Hong***[b,a]
[a]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea
[b]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Korea
Email: leews96@kaist.ac.kr

Photocycloaddition is a powerful strategy to synthesize the high-value synthetic materials that are normally difficult to obtain under thermal conditions. We design a new and efficient method for producing pyridyl lactams, which are useful for pharmaceutical applications, using a photoinduced [3+2] cycloaddition reaction (Figure 1)[1]. We utilize the unique reactivity of N–N pyridinium ylides in the presence of a photosensitizer to generate a triplet diradical intermediate, which undergoes a stepwise reaction with alkenes. This method is highly effective, selective, and tolerant of functional groups, making it a valuable tool for the synthesis of complex organic molecules in the pharmaceutical industry.[2] In this study, we use experimental and computational methods to understand the energy transfer process involved in this reaction.

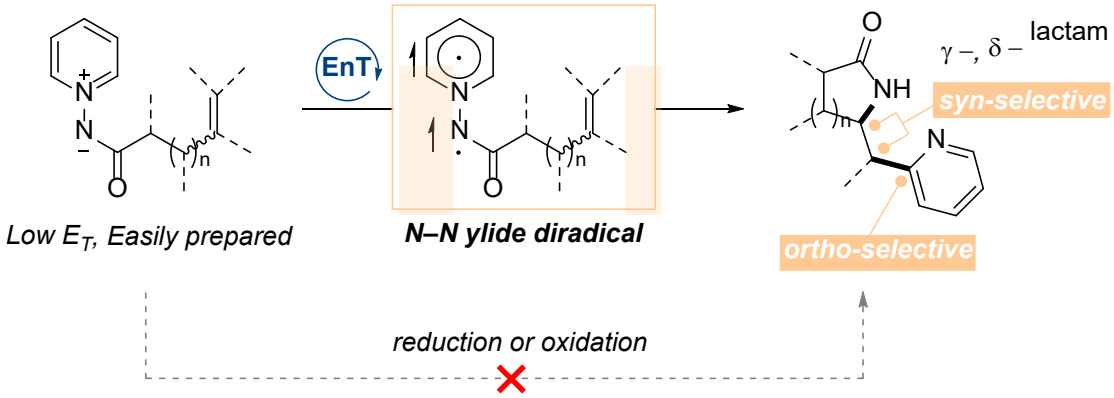

Figure 1. EnT induced [3+2] photocycloaddition

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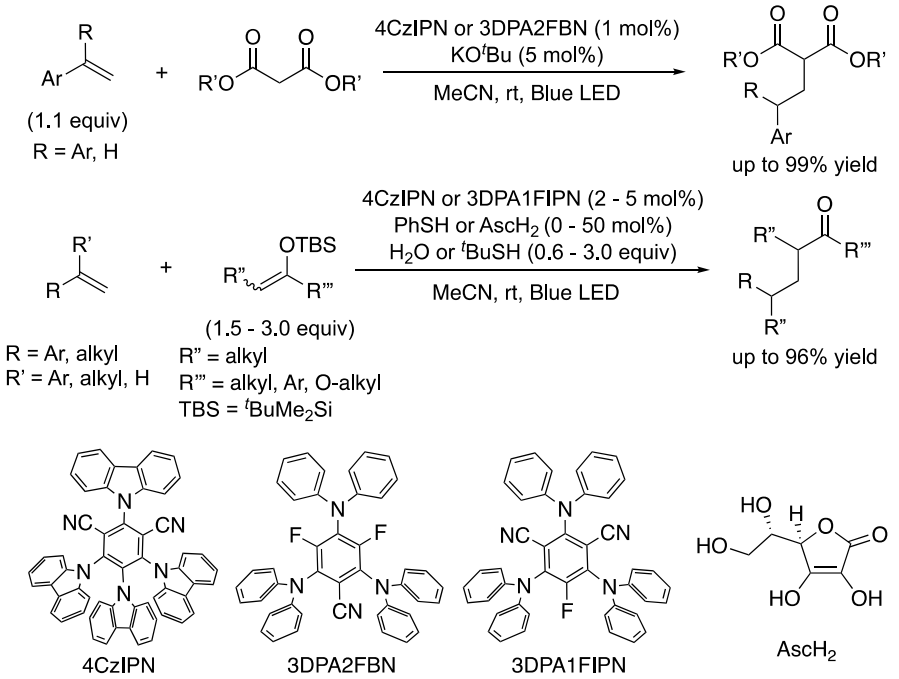
Development of Photoinduced α-Alkylation Reactions of Carbonyl Compounds with Alkenes

Yasuhiro Yamashita*[a]

[a] Department of Chemistry, School of Science, The University of Tokyo
Hongo, Bunkyo-ku, Tokyo, Japan, 113-0033.
Email: yyamashita@chem.s.u-tokyo.ac.jp

α-Alkylation reactions of carbonyl compounds are a fundamental methodology for carbon–carbon bond formation to construct basic molecular frameworks. Compared to alkylation reactions with alkyl halides in substitution fashion, the alkylation reactions with alkenes in addition fashion are more atom economical methodology; however, available alkenes are limited to activated alkenes such as Michael acceptors. Here, we developed photoinduced α-alkylation reactions of carbonyl compounds with alkenes without electron-withdrawing groups as electrophiles. First, we investigated alkylation reactions of malonates with styrene derivatives using a 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) or 2,4,6-Tris(diphenylamino)-3,5-difluorobenzonitrile (3DPA2FBN) /KO^{t}Bu catalyst system via formation of a catalytic amount of malonate radical by single electron oxidation of the corresponding malonate anion, and it was found that the desired alkylation reactions proceeded smoothly under blue light irradiation.[1] On the other hand, photoinduced α-alkylation reactions of ketones and esters, which are less acidic carbonyl compounds, were realized by using their corresponding silicon enolates as precursors for α-carbonyl radicals.[2] The silicon enolates were oxidized by organo-photocatalysts into radical cation species, which reacted with protic additives to form α-carbonyl radicals, and the desired reactions proceeded smoothly. The use of appropriate protic additives and hydrogen atom transfer (HAT) catalysts was a key to achieve high yields. Those reactions are one of desired α-alkylation reactions of carbonyl compounds. In this presentation, we will report our recent research results on the alkylation reactions via α-carbonyl radical formation.



Scheme 1. Photoinduced α-alkylation reactions of carbonyl co mpounds with alkenes

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Generation of Alkyl Radical through Direct Excitation of Alkylborate

Yukiya Sato,[a] Yuto Sumida,[b] Hirohisa Ohmiya*[a]
[a]Institute for Chemical Research, Kyoto University, [b]Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University
presenting author: sato.yukiya.62p@st.kyoto-u.ac.jp,
corresponding author: ohmiya@scl.kyoto-u.ac.jp

Recently, visible-light-driven generation of C(sp^3)-centered radicals under mild conditions has emerged as a powerful tool for chemical reactions. The process proceeds through a single electron transfer (SET) event between the excited-state photoredox catalyst and radical precursors which have been widely explored. This photochemical reaction exploits the nature of C(sp^3)-centered radicals, thus allowing for the introduction of sterically hindered C(sp^3) fragments such as tertiary or secondary alkyl groups to organic molecules. Despite remarkable progress achieved in this area, the oxidation/ reduction steps of the photoredox catalyst often complicate the reaction and require the use of expensive transition metal catalysts such as Ir or Ru photoredox catalysts. In this context, the direct excitation of a radical precursor, which enables circumventing the redox cycle of the photocatalyst, has emerged as an alternative approach for the generation of a C(sp^3)-centered radical. For example, the formation of charge-transfer complexes based on electrostatic interactions between substrates allows for SET and the generation of the corresponding radical species, but this approach is limited in the available substrates because the formation of the complex is essential. Also, more straightforward method for generating radical species by direct photoexcitation of the 4-alkyl-1,4-dihydropyridines (alkyl-DHPs) has been reported. The excited state of them acts simultaneously as a strong SET reductant and as an alkyl radical source. However, the generation of a sterically hindered tertiary alkyl radical by direct visible-light excitation remains underdeveloped.

In this presentation, we describe that the direct visible-light excitation of 8,9-dioxa-8a-**bora**benzo[*fg*]tetra**cene** (boracene)-derived organoboron-ate complex generates alkyl radicals without the need for an external photoredox catalyst (Figure 1).[1] The photoexcitation of the borates is applicable to decyanoalkylation, Giese addition, and nickel-catalyzed carbon−carbon bond formations such as alkyl−aryl cross-coupling or three-component vicinal alkylarylation of alkenes, thus enabling the introduction of various C(sp^3) fragments to organic molecules. Boracene was reacted with organolithium or Grignard reagents to produce organoboron complexes that can be handled in air or water. The direct excitation of the borates by visible light enables the generation of methyl, primary, secondary, and tertiary alkyl radicals. Various spectroscopic and electrochemical measurements suggest that the borates derived from boracene exhibit very strong reduction ability upon direct excitation. Therefore, the organoboron-ate complexes could be applied to various catalytic reactions because they function as strong single electron reductants and organic radical precursors upon visible light irradiation. Boracene could be recovered and reused after the catalytic reaction.

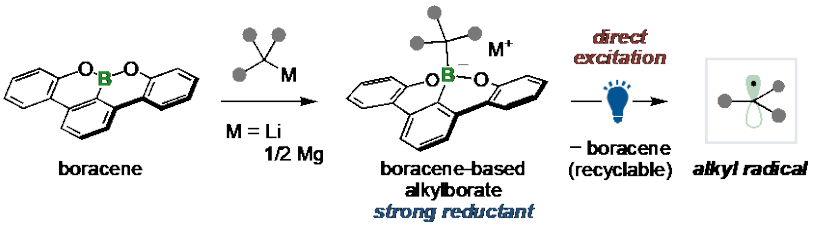

Figure 1. Alkyl radical from direct excitation of boron-based precursors.

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Organic Photoredox-Catalyzed Silyl Radical Generation from Silylboronate

Yuto Sumida,[a] Naho Takemura,[a] Hirohisa Ohmiya*[b]
[a]Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University [b]Institute for Chemical Research, Kyoto University

Email: sumida@p.kanazawa-u.ac.jp; ohmiya@scl.kyoto-u.ac.jp

Silicon-centered radicals provide a potent tool for enabling regio- and chemoselective silylation, different from the two-electron reaction due to the reactivity of the open-shell species. Silyl radical species have been extensively studied in structural complex chemistry for decades, and their characteristic reactivities have led to many synthetic applications. In this context, this species serves an important role in broad areas including materials science, polymer chemistry, and industry. While synthetic chemists have developed diverse generation methods for silyl radicals and their synthetic applications, recently, photoredox chemistry has emerged to achieve silyl radical generation under mild conditions. Photoredox-catalyzed hydrogen atom transfer (HAT) of Si−H serves as a versatile alternative for silyl radical generation, which classically required strong oxidants such as *tert*-butyl hydroperoxide. While the light-driven HAT-based silyl radical generation has quickly grown in organic synthesis, this system often complicates the reaction pathway due to the requirement of an external HAT reagent and the harmonization of the HAT process with photoredox catalysis.

Because silylboronic acid pinacol esters ($R_3SiBpin$) have become common reagents, the use of silylboronates in organic synthesis has increased exponentially. Considering that the recent advancements in silylboronate synthesis have made a variety of silylboronates easily accessible, versatile silyl radical precursors are now possible. However, despite the enormous amount of work done on silylboronate as a silyl anion equivalent, its use as a silyl radical is still immature. In a pioneering study, Ito et al. showed that a silylaminoboronate induces homolysis under UV irradiation, resulting in the formation of silyl and boryl radicals. We envisioned that using silylboronate for the generation of a silyl radical would eliminate the HAT process and enable the use of organic photoredox catalysts with a weak reduction potential because the photoinduced single electron-transfer (SET) oxidation of a silylboronate readily occurs in the borate form by activation with an appropriate nucleophile (Figure 1). By lowering the oxidation potential, a number of photoredox catalysts can be used, leading to the expansion of applicable transformations and substrate scopes.

In this presentation, we describe a general and efficient method for silyl radical generation from silylboronates using a versatile photoredox catalyst and applied it to N-heterocyclic carbene (NHC)-catalyzed radical relay-type three-component coupling.

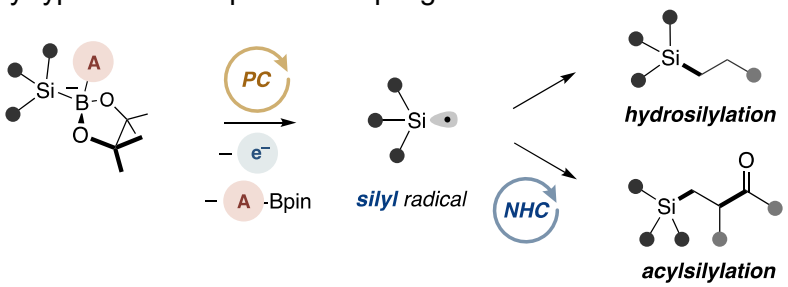

Figure 1. Silyl radical generation from silylboronate.

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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.

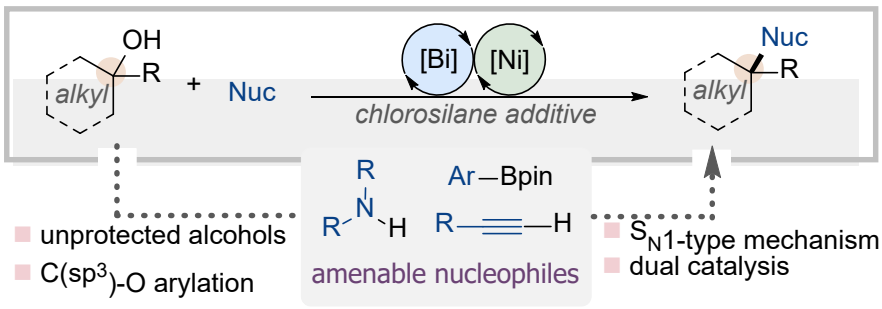

Figure 1. Employing alkyl-hybridized, unprotected alcohols as electrophiles in cross-coupling reactions

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Distal Meta-Alkenylation of Formal Amines Enabled by Catalytic use of Hydrogen-Bonding Anionic Ligands

Nupur Goswami,[1,3] Soumya Kumar Sinha,[1,3] Partha Mondal,[2] S. Adhya,[1] Ayan Datta,[2,*] and Debabrata Maiti[1,*]

[1]Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India [2]School of Chemical Sciences, Indian Association for the Cultivation of Science, Kolkata, West Bengal 700032, India

[3]These authors contributed equally

Email: goswami.nupur07@gmail.com; spad@iacs.res.in; dmaiti@iitb.ac.in

Pd-catalyzed distal C–H activation using covalently attached directed groups (DG) is well explored. However its limitation lies in the pre-installation and post-functionalization detachment of the DG. Additionally, the stoichiometric amount of transient DG employed in distal C–H activation, further hinders the efficacy. In an attempt to overcome these challenges, we have utilized the catalytic use of directing ligands to promote such distal *meta*-C–H activation. Non-covalent interactions are a ubiquitous process that promotes the spontaneity of various natural and biological transformations, thus playing a prominent role in controlling the regioselectivity and site selectivity of various organic transformations. However, the primary requirement of employing such non-covalent interactions is the presence of milder reaction conditions. Consequently, its involvement in transition-metal catalysis has, to date, remained in the infant stage. Non-covalent interactions among a target, a suitably designed directing ligand and palladium can establish an optimum arrangement that allows selective distal C–H activation of arenes. The catalytic use of directing ligands, through H-bonding interaction with the substrate helps us to achieve site-selective Pd-catalyzed distal C–H activation. The current protocol illustrates a series of directing ligands that enables selective *meta*-alkenylation of aromatic amines with varying chain lengths, signifying the generality of the work developed.

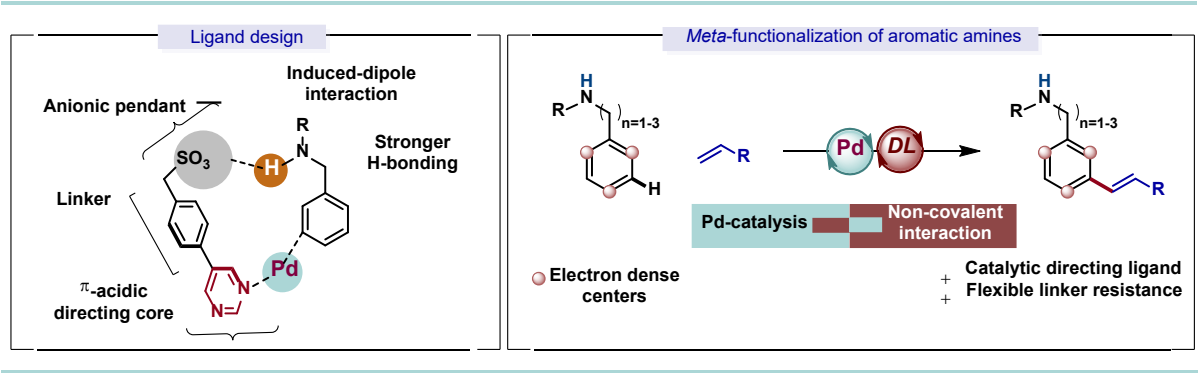

Figure 1: This Work- Non-covalent interactions to promote Pd-catalyzed distal *meta* C-H activation

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Heterogeneous Pd-polysaccharide catalysts for aerobic oxidation of benzylic alcohols.

Adi Wolfson,*[a] **Oshrat Ontman**[a]
[a]Department of Chemical Engineering, Sami Shamoon College of Engineering, Basel/Bialik Sts., Beer-Sheva 8410001, Israel.
Email: adiw@sce.ac.il

The aerobic oxidation of alcohols may proceed with many catalysts, among which are the catalysts of palladium. To that end, using heterogeneous catalysts has drawn much attention in the last decade, whereas supports that originate from a biological and renewable source that is also nontoxic and biodegradable were found to be superior.
In the present research, we were immobilizing palladium complexes with the TPPTS ligand (3.3',3"-Phosphanetriyltris (benzenesulfonic acid) trisodium salt), in the xerogels and hydrogels of various polysaccharide. The new heterogeneous catalysts were successfully used in the
aerobic oxidation of benzylic alcohols, yielding similar or even increase in activity with each subsequent reuse.[1] Furthermore, both, the heterogenozation procedure and the type of the polysaccharide, effected the reaction performance.
The new heterogeneous catalysts were characterized by FTIR, SEM-EDS, XPS, DLS, TEM and zeta potential analyses, raveling the formation of new bond between the polysaccharide and TPPTS and dispersion of the palladium in the support, whereas in alcohols the palladium was reduced and nanoparticles were formed during the reaction.
At last, for the xerogel-based catalyst, it was found that mixing the catalyst in ethanol for up to 24 hours before executing the reaction led to an increase in conversions, though, over a longer duration of mixing, conversions were decreased (Figure 1).[2] Both the HR-TEM and theDLS analyses of the various catalysts showed that, indeed, the longer the mixing time in ethanol up to 24 hours, the greater the number of nanoparticles produced; however, longer mixing periods (beyond 24 hours) produced aggregates, that might explain the maximal conversion at 24 hours in ethanol.

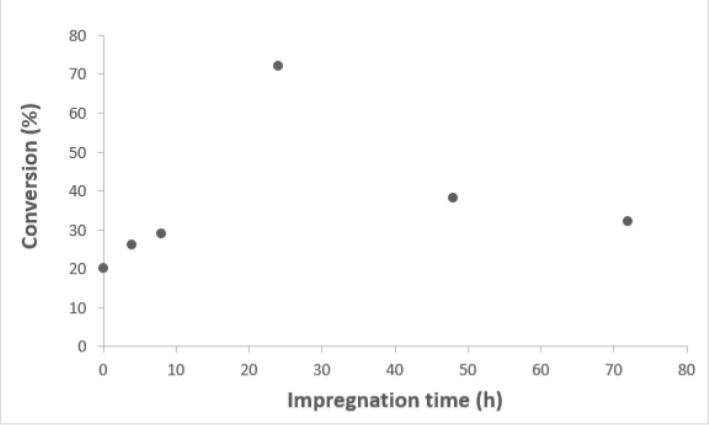

Figure 1. Effect of catalyst impregnation time on catalytic activity.

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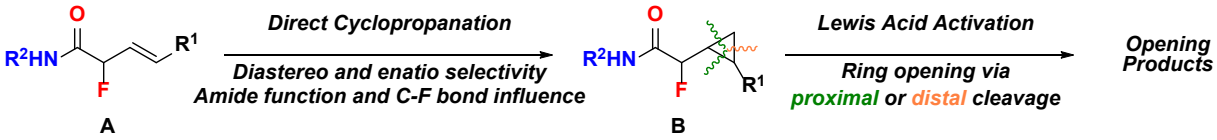
Direct Cyclopropanation of Allylic Fluorides and Opening of Cyclopropanes via C-F Bond Activation

Thomas Larribeau[a,b], **Alexandre Gagnon**[b], **Samir Bouzbouz***[a]
[a]Université de Rouen, [b]Université du Québec à Montréal.
Email: larribeau.thomas@courrier.uqam.ca ; gagnon.alexandre@uqam.ca ; samir.bouzbouz@univ-rouen.fr

The need to develop new molecular architectures still poses a major challenge for chemists. The development of chemo, regio and stereoselective reactions operating under simple and environmentally friendly conditions is crucial for the synthesis of complex molecules. Our group recently reported an addition reaction of boronic acids on allylic fluorides type **A** catalyzed by a complex of Rh(III) and Ir(III)[1, 2] and showed that the role of the C-F bond is very important in the progress of the reaction. In this project, we aimed to understand what the reactivity of this particular C-F bond would be in the homologous alpha-fluoro cyclopropyl system of the type **B**. The role of the amide function in this scaffold is determinant as it participates in the activation of the C-F[3, 4] bond thus inducing a regioselective opening of the cyclopropane ring[5] on the proximal or distal bond. The diversity of ring opening products provide access to several molecular motifs.



We report in this work the direct cyclopropanation of racemic and chiral allylic fluorides. We will show the role of the fluorine atom on the reactivity of the double bond and its control on the stereoselectivity from racemic and chiral products. Then we will discuss the opening of these cyclopropanes using Lewis acids via the activation of the C-F bond.

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Transition-metal Catalyzed Decarbonylative Isotopically-Labeled Cyanation of Carboxylic Acid Derivatives

Alexander W. Bunnell, Mami Horikawa,[a] Xia Shao,[b] Peter J. H. Scott,*[b] and Melanie S. Sanford*[a]

[a]University of Michigan. [b]Michigan Medicine

Email: abunnell@umich.edu; mssanfor@umich.edu

Reactions involving the incorporation of a nitrile group into organic molecules are valuable, as the moiety serves as a building block for further derivatization and finds usage in numerous pharmaceuticals and agrochemicals. However, common reactions for the synthesis of aryl nitriles, such as the Sandmeyer or Rosenmund-von Braun reactions, either employ potentially hazardous starting materials, like aryldiazonium salts, or forcing conditions for the reaction to occur. Recently, numerous groups have developed methods for decarbonylative cyanation, which employ readily available carboxylic acid derivatives as electrophiles. Isotopically-labelled cyanation via a decarbonylative route would allow for the interchange of ^{12}C for ^{13}C or ^{11}C, which can be used for mechanistic investigations or in positron emission tomography (PET) scans. Yet, methods for integration of isotopically-labelled nitriles via decarbonylation lack, due to long reaction times, catalyst poisoning, and use of incompatible cyanide sources.[1] This works explores ^{13}CN and ^{11}CN incorporation by addressing the aforementioned issues.

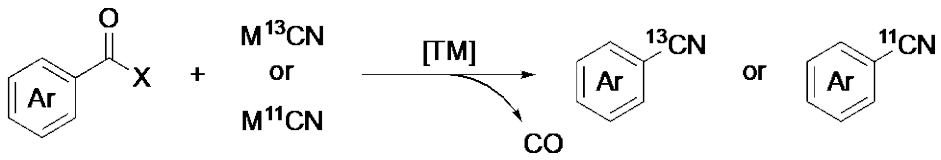

Figure 1. General scheme for decarbonylative isotopically-labeled cyanation.

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Ni-Catalyzed Reductive Cross-Coupling of Cyclopropylamines and Other Strained Ring NHP Esters with (Hetero)Aryl Halides

Alexis L. Gabbey,[a] Michael S. West,[a] Malcolm P. Huestis,[b] Sophie A. L. Rousseaux*[a]
[a]Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 2H6, Canada. [b]Discovery Chemistry, Genentech Inc., 1 DNA Way, South San Francisco, California 94080, USA.

Email: alex.gabbey@mail.utoronto.ca; sophie.rousseaux@utoronto.ca

1-Arylcyclopropylamines are useful bioisosteres for benzylamines and are an increasingly common motif in biologically active molecules.[1] Traditional strategies to access 1-arylcyclopropylamines typically require either stoichiometric organometallic[2] or azide reagents,[3] which are air and moisture sensitive and/or require specific safety precautions (Fig. 1a). The use of highly reactive reagents generally precludes application of these methods to the synthesis of complex pharmaceuticals, which often bear sensitive functional groups. The lack of a building block approach to access 1-arylcyclopropylamines, using bench stable and commercially available starting materials, limits the ability of medicinal chemists to easily explore this compound class.

We now report that 1-arylcyclopropylamines can be accessed via a modular cross-coupling approach between aryl halides and the redox-active esters of commercially available 1-aminocyclopropanecarboxylic acids. The methodology proceeds under mild conditions and the starting materials are bench stable compounds which can be prepared in a single step with minimal purification. The mild conditions of this strategy are exemplified by the presence of sensitive functional groups in the substrates, such as enolizable carbonyls, free alcohols, and base-sensitive stereocenters. Both (hetero)aryl iodides and bromides may be employed in this chemistry, and the reaction is also compatible with other α-amino strained rings. This presentation will detail reaction optimization, scope, substrate synthesis, and mechanistic hypotheses.

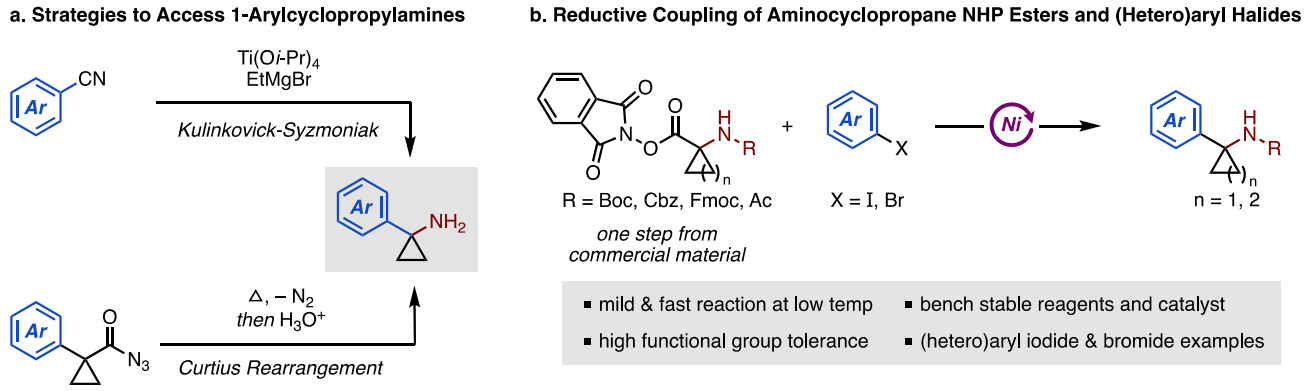

Figure 1. Synthesis of 1-arylcyclopropylamines using traditional methods vs. this method.

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Access to Chiral 1,3-Aminoalcohols by Copper-Catalyzed Protoboration of Allylic Amines

Arthur Flaget, Clément Mazet*
University of Geneva, Geneva, 1211, Switzerland.
Email: arthur.flaget@unige.ch; clement.mazet@unige.ch

Although less prevalent than 1,2-amino alcohols, 1,3-amino alcohols are ubiquitous structural motifs found in natural products and biologically active molecules.[1,2] Their use as chiral ligands, phase transfer catalysts, resolving agents or platforms for synthesis of pharmaceuticals is also documented.[1,3] Access to these important chiral building blocks by means of catalytic enantioselective methods is an area of growing interest.[4-6]

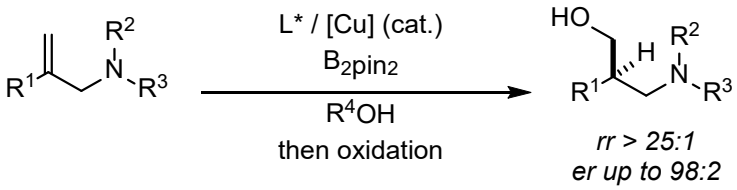

Figure 1. Regio- and enantioselective protoboration of allylic amine.

Herein, we disclose our efforts toward the development of a Cu-catalyzed enantioselective protoboration of 1,1-disubstituted allylic amines to access 1,3-amino alcohols (Figure 1).

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Investigation of the Palladium-Catalyzed Aminocarbonylation of 3-Iodochromone

Sami Chniti,[a] László Kollár,[a,b,c] Attila Takács*[b,c]
[a] Department of General and Inorganic Chemistry and János Szentágothai Research Centre, University of Pécs, Ifjúság útja. 6., H-7624 Pécs, Hungary
[b] ELKH-PTE Research Group for Selective Chemical Syntheses, Ifjúság útja 6., H-7624 Pécs, Hungary
Email: takacsattila@gamma.ttk.pte.hu; samichniti@yahoo.fr

Since the seminal research of Heck et al.[1] the palladium-catalyzed aminocarbonylation of (hetero)aryl- and alkenyl halides has been demonstrated to be an effective synthetic approach for the selective synthesis of carboxamides with various structures.[2] The amide moiety, synthesized in these reactions, represents a ubiquitous functional group in a wide range of biologically important compounds,[3] and can be found in pharmaceutically relevant heteroaryl skeletons.[4]
In this work, the palladium-catalyzed aminocarbonylation of 3-iodochromone, as an oxygen containing model substrate, was investigated using various amines (Figure 1). Detailed optimization study was performed in the presence of a secondary amine: *N,O*-dimethylhydroxylamine, chosen as *N*-nucleophile model, showed that under optimized circumstances the chromone-3-carboxamide was, selectively, formed *via* classical aminocarbonylation process. Howbeit, the use of primary amine such as *O*-methylhydroxylamine, led exclusively to the chromane-2,4-dione counterpart, instead of the expected carboxamide, through a different and unprecedented synthetic pathway. The scope of the reaction employing various primary and secondary amines, under the same experimental conditions, revealed the applicability of these experimental protocols, able to access a large library of structurally enriched chromone-3-carboxamides (8 derivatives) and functionalized chromane-2,4-diones (18 derivatives). All compounds were synthesized, isolated, and fully characterized by means of NMR and HRMS analyses. The structures of two different products have been established by single-crystal XRD study. A plausible mechanism was also proposed to explain the influence of the amine on the course of the reaction and on the chemoselectivity of the carbonylation processes.

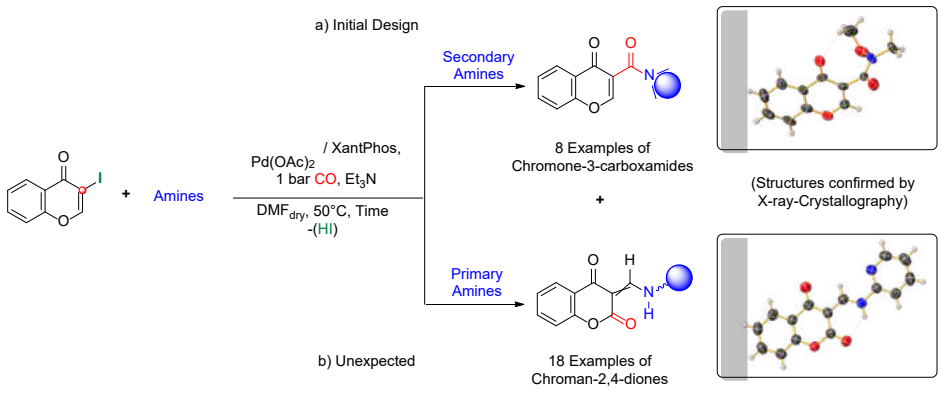

Figure 1. Palladium-catalyzed aminocarbonylation of 3-iodochromone

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1,2-Redox Transpositions of Tertiary Amides

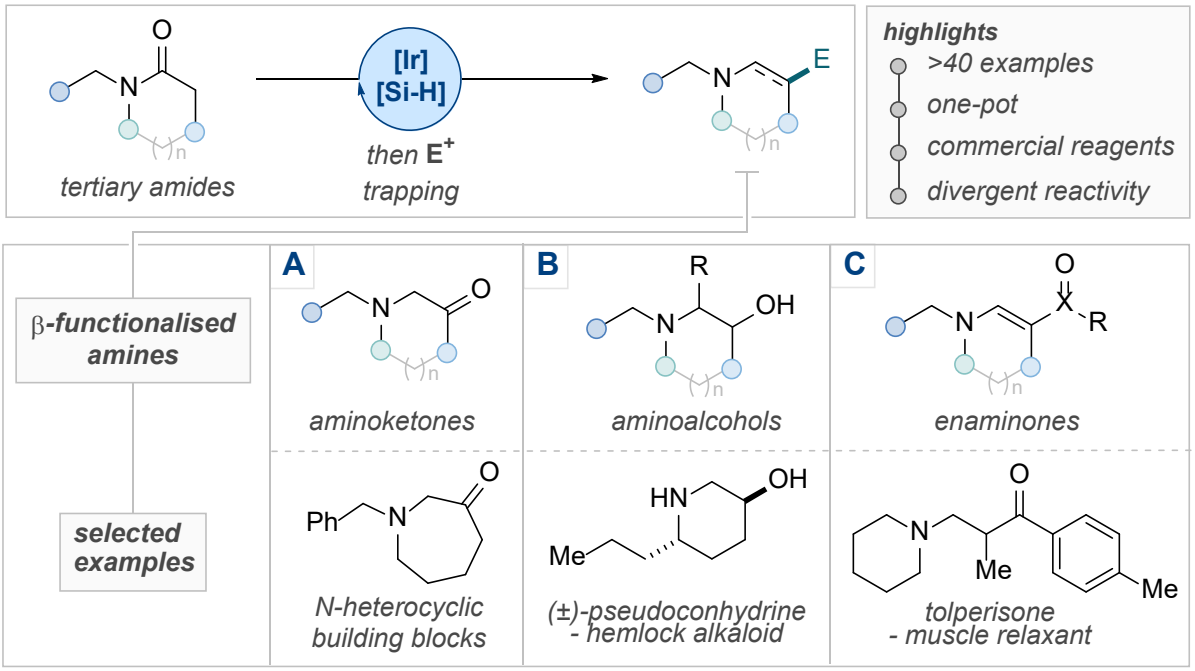
Benjamin Shennan,[a] Sergio Sánchez-Alonso,[a] Darren Dixon*[a]
[a] Department of Chemistry, University of Oxford
Email: benjamin.shennan@chem.ox.ac.uk; darren.dixon@chem.ox.ac.uk

Redox transpositions, i.e the transposition of the oxidation levels of carbon atoms, represent a po werful yet underexplored paradigm for editing a molecule's reactivity profile, circumventing challen ging functional group manipulations and expediting multi-step synthetic sequences.[1] This work inv estigates such a strategy in the direct 1,2-transposition of functionality in tertiary amides, enabling the synthesis of aminoketones, aminoalcohols, enaminones and diverse functionalized N-heteroc ycles.

Employing an iridium-catalyzed reduction,[2] transiently-formed silylated hemiaminals were convert ed cleanly to the corresponding enamines, which reacted efficiently with numerous electrophiles. Most notably, when treated with the oxidant *m*CPBA, the enamine converted to the desired amino ketone, constituting a formal carbonyl transposition.

The scope of this transformation, and related reactions with alternative electrophiles, has been ex plored to enable the synthesis of β-functionalized amines. The carbonyl transposition was scaled t o 5 mmol and the product aminoketones were shown to be valuable synthetic intermediates.

It is hoped that this work will stimulate further development of such redox-editing approaches.



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Modular Synthesis of Unnatural Peptides via Rh(III)-Catalyzed Diastereoselective Three-Component Carboamidation Reaction

Christopher W. Lamartina,[a] Cassandra A. Chartier,[a] Sumin Lee,[a] Neel H. Shah,*[a] and Tomislav Rovis*[a]

[a]Department of Chemistry, Columbia University, New York, New York 10027, United States.

Email: cwl2141@columbia.edu; tr2504@columbia.edu

Herein we report a modular peptide ligation methodology that couples dioxazolones, arylboronic acids, and acrylamides to construct amide bonds in a diastereoselective manner under mild conditions, facilitated by Rh(III) catalysis.[1] By converting the C-terminus of one peptide into a dioxazolone and the N-terminus of a second peptide into an acrylamide, the two pieces can be bridged by an arylboronic acid to construct unnatural phenylalanine, tyrosine, and tryptophan residues at the junction point with diastereoselectivity for their corresponding D-stereocenters. The reaction exhibits excellent functional group tolerance with a large substrate scope and is compatible with a wide array of protected amino acid residues that are utilized in Fmoc solid phase peptide synthesis. The methodology is applied to the synthesis of six diastereomeric proteasome inhibitor analogs, as well as the ligation of two 10-mer oligopeptides to construct a 21-mer polypeptide with an unnatural phenylalanine residue at the center.

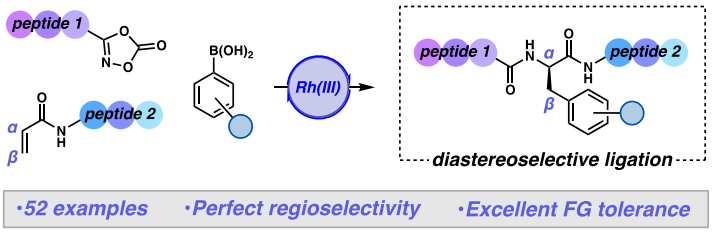

Figure 1. Modular Synthesis of Unnatural Peptides via Rh(III)-Catalyzed Diastereoselective Three-Component Carboamidation Reaction.

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Catalytic Asymmetric Dehydrogenative Coupling toward Silicon-Stereogenic Silanes

Chuan He*[a]
[a]Shenzhen Grubbs Institute and Department of Chemistry, Southern University of Science and Technology, Shenzhen, Guangdong 518055, China
Email: hec@sustech.edu.cn

Chiral molecules play significant roles in areas ranging from life, biology, medicine to materials science. Compared to the extensive studies of chiral compounds with carbon-stereogenic centers, synthesis and application of silicon-stereogenic silanes have been much less explored. Due to the inherent properties of the silicon atom, construction of enantioenriched chiral organosilanes bearing a stereocenter at silicon has always been challenging.[1]

During the last five years, our group has developed a series of catalytic asymmetric dehydrogenative coupling reactions for the synthesis of silicon-stereogenic silanes (**Si-CADC**) with high efficiency (Figure 1).[2] Key to the success is the use of Rh(I) catalysts equipped with bulky and rigid chiral diphosphine ligands for the discrimination of the enantiotopic Si-H bonds of dihydrosilanes. This general Si-CADC strategy unlocks a facile platform toward diverse Si-stereogenic silanes, that could find various applications in many areas.

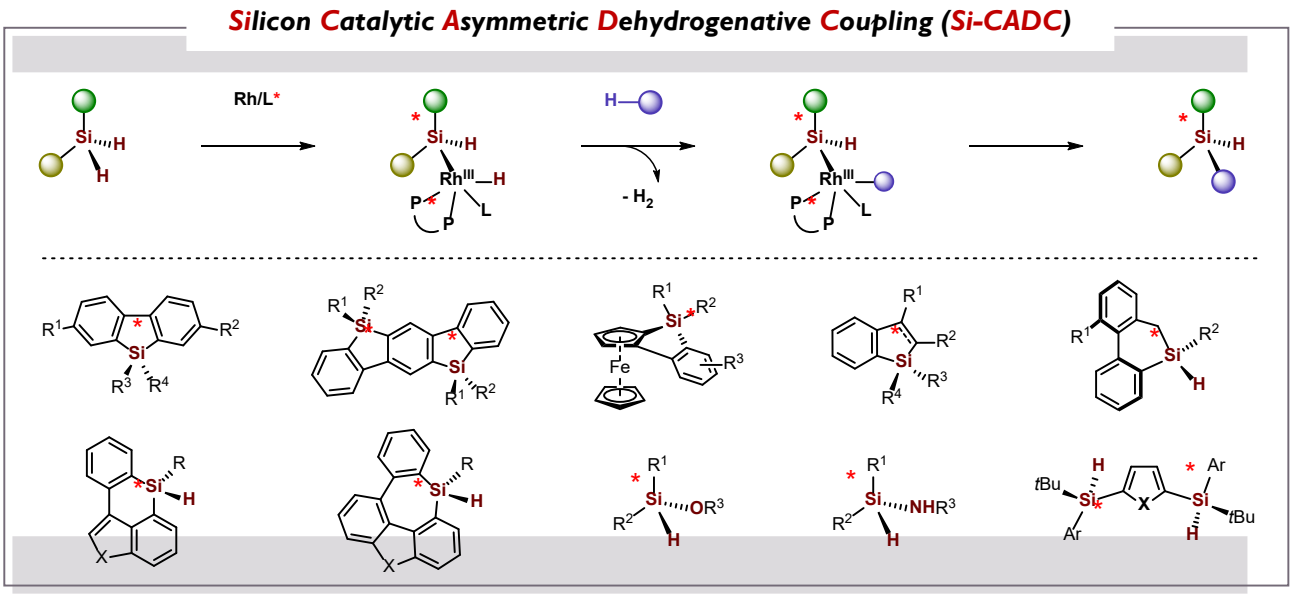

Figure 1. Si-CADC strategy

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Ir(III)-Catalyzed C–H Amidation of 2-Aryl Azlactones and Application to Chiral *N*-Amidobenzoyl Amino Acids

Eunjae Chung[a] Jeonghyun Min,[a] Hyungjin Shin,[a] In Su Kim*[a]
[a]School of Pharmacy, Sungkyunkwan University(SKKU), Republic of Korea
Email: rupeunjae@skku.edu; insukim@skku.edu

In past decades, the synthesis and modification of amino acid derivatives emerged as important research areas in organic and medicinal chemistry. In particular, functionalized natural and unnatural amino acids proved valuable in drug development, as they often exhibit enhanced bioactivity and pharmacokinetic properties. In this context, azlactones (masked amino acids) have been widely utilized for the synthesis of natural and unnatural amino acid derivatives.[1]

In this study, we examine the site-selctive iridium(III)-catalyzed C–H amidation between 2-aryl azlactones and acyl azides.[2] This transformation produces a range of *ortho*-amidated azlactones, which act as precursors for the synthesis of chiral amino acids via organocatalyzed ring-opening reactions. To test its effectiveness we conduct the azlactone-assisted Ir(III)-catalyzed C–H amidation using acyl azides. Furthermore, we isolate an iridacycle species that supports a proposed reaction pathway. In addition, we highlight the application of this method to the late-stage C–H amidation of complex drug molecules. Importantly, the synthesized adducts are readily converted into chiral amino acids via urea-catalyzed ring-opening reactions[3] (Figure 1).

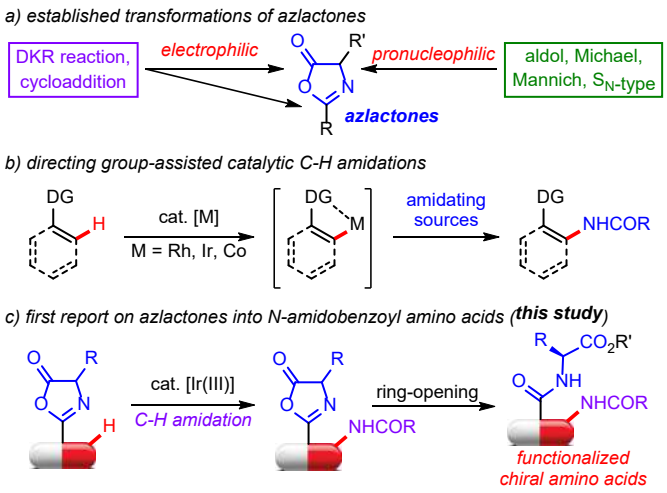

Figure 1. C–H amidation and transformation using azlactones

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Palladium-Catalysed Hydroaminocarbonylation of Olefins with Aliphatic Amines without Additives

Fanni Bede[a], László Kollár[a,b], Nándor Lambert[c], Péter Huszthy[d], Péter Pongrácz[a]*

[a]Department of Inorganic Chemistry, University of Pécs and János Szentágothai Research Centre, H-7624 Pécs, Hungary. [b]ELKH-PTE Research Group for Selective Chemical Syntheses, H-7624 Pécs, Ifjúság u. 6., Hungary. [c]MTA–PTE Molecular Interactions in Separation Science Research Group, Ifjúság útja 6, H-7624 Pécs, Hungary. [d]Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary.

Email: bedef@gamma.ttk.pte.hu; pongracz@gamma.ttk.pte.hu

A new palladium-catalyzed hydroaminocarbonylation protocol of olefins, using aliphatic amines under carbon-monoxide atmosphere is disclosed. Previously reported protocols have revealed, that the strong basicity of the nucleophiles requires the addition of acid in order to facilitate the reaction. This work represents an additive-free approach of the synthesis of hydroaminocarbonylated compounds in moderate to good isolated yields. Styrene, oct-1-ene and isoprene were transformed under optimized reaction conditions in the presence of various aliphatic amines to obtain the corresponding amide isomers. The effect of chiral diphosphine ligands on product distribution, and enantiomeric excess, was investigated and a mechanism for the additive-free hydroaminocarbonylation reaction was proposed.

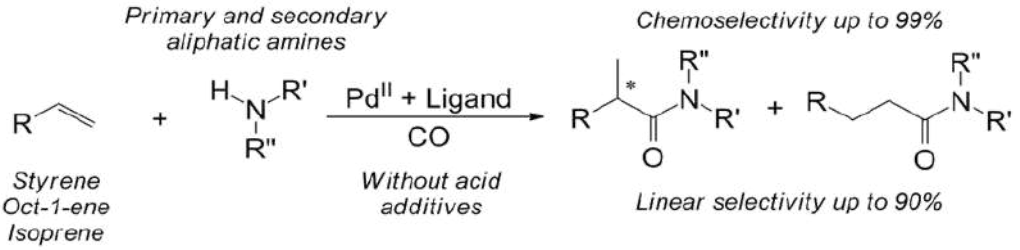

Figure 1. Palladium-catalysed hydroaminocarbonylation of olefins

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Palladium-Catalyzed Arylation of Hydantoins with Aryl Chlorides Enabled by Ylide-Functionalized Phosphines (YPhos)

Florian Papp, Daniel Sowa Prendes, Sourav Manna, Ann-Katrin Seitz, Sofiya Kostiukovska, Viktoria H. Gessner*, Lukas J. Gooßen*

Email: florian.papp@rub.de; viktoria.daeschlein-gessner@rub.de, lukas.goossen@rub.de

The hydantoin moiety is an important structural motif present in various pharmaceuticals like the anticonvulsant phenytoin. The arylation of protected hydantoins was achieved by the group of Clayden with aryl iodides applying Xantphos as ligand.[1] However, an arylation with cheap and broadly abundant aryl chlorides was not achieved. In previous work, palladium catalysts bearing highly electron-rich, bulky Ylide-functionalized phosphine (YPhos) ligands were found to efficiently promote arylations with aryl chlorides at low temperatures.[2–5] In this work[6], YPhos ligands enabled the arylation of *N*-protected hydantoins in good to excellent yields (Figure 1). By adjustment of the YPhos ligand, a selective monoarylation of a 5-unsubstituted hydantoin was achieved. This has opened up an expedient access to a wide variety of hydantoins, including derivatives of the anticonvulsant drugs phenytoin and mephenytoin, sequential diarylations and arylation-alkylation sequences in combination with stepwise deprotection strategies.

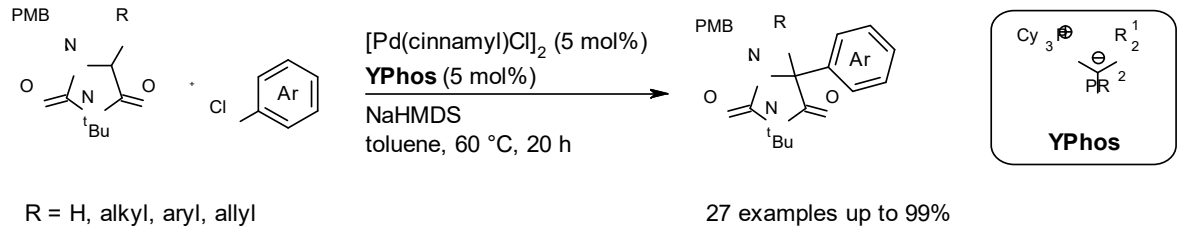

Figure 1. Pd-catalyzed Arylation of hydantoins with aryl chlorides.

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Rhodium-Catalyzed Alkenylation of Allylbenzene and Styrene Derivatives via Unstrained C–C Bond Cleavage

Shunsuke Onodera,[a] Soya Ishikawa,[a] Ryo Togashi,[a] Ryosuke Ueda,[a] Takuya Kochi,[a] Fumitoshi Kakiuchi*[a,b]

[a]Department of Chemistry, Faculty of Science and Technology, Keio University Kanagawa, Japan.

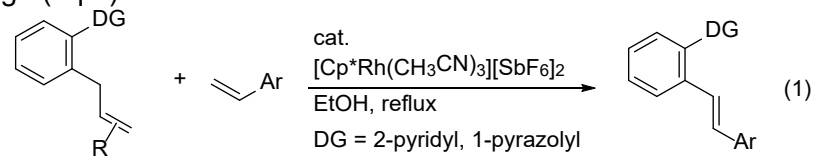
[b]JST, CREST, JPMJCR20R1, 4-1-8 Honcho, Kawaguchi, Saitama, 332-0012, Japan.

Email: kakiuchi@chem.keio.ac.jp

Catalytic, direct transformations of C–C bonds to new C–C bonds afford unique tools for organic synthesis, and various research groups have developed a variety of C–C bond formation methods. Among these methods, catalytic reactions involving cleavage of unstrained C–C bonds have been recognized as highly challenging transformations.

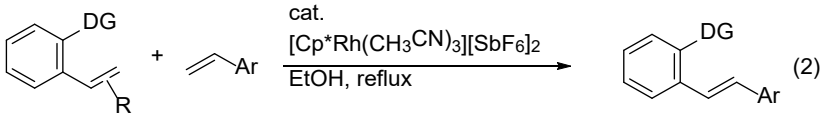
We have developed catalytic, chelation-assisted alkenylation of allylbenzene and styrene derivatives via unstrained C–C bond cleavage using rhodium catalysts. This presentation reports three types of C–C bond transformations.

When the reaction of prenylbenzene derivatives bearing a pyridyl or 2-pyridyl group with styrenes was carried out in the presence of a catalytic amount of $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ under EtOH refluxing conditions, the corresponding ortho alkenylation products were obtained in high yields via C(sp^2)–C(sp^3) bond cleavage (eq 1).[1]



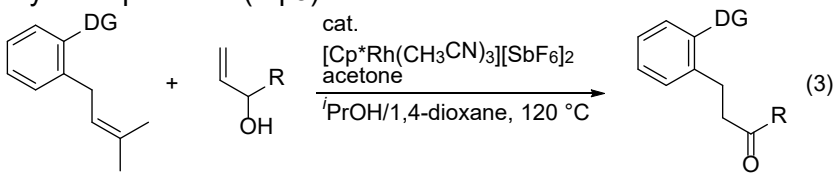
(1)

This C–C bond transformation can also be applied to the reaction of styrene derivatives having the directing group with styrenes. When isopropenylbenzene derivatives having a directing group were reacted with styrenes in the presence of the dicationic rhodium catalyst under EtOH refluxing conditions, conversion of the isopropenyl group to β-styryl groups proceeded to afford the alkenylation products in good to high yields (eq 2).[2]



(2)

The use of allyl alcohols as a coupling partner of this C–C bond transformation provided the deallylative β-acylalkylation products (eq 3).[3]



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Au-Catalyzed Reactions via N-S Bond Cleavage

Itaru Nakamura,* Hiroki Tashiro, Takato Asoh, and Masahiro Terada

Graduate School of Science, Tohoku University, Sendai, 980-8578, Japan
Email: itaru-n@tohoku.ac.jp

Au-catalyzed reactions are a powerful tool to synthesize functionalized molecules, which are inaccessible by other conventional methods, under mild conditions with high functional group compatibility. In particular, Au catalysis efficiently promotes atom efficient transformations, such as addition and rearrangement reactions, via cleavage of various kinds of σ bonds, such as not only C-H and heteroatom-hydrogen bonds but also C-C, C-heteroatom, and heteroatom-heteroatom bonds, to produce multi-substituted molecules in an atom-efficient manner. We recently developed Au-catalyzed reactions via N-S bond cleavage to efficiently synthesize organic molecules containing both nitrogen and sulfur atoms. For example, Au-catalyzed reactions of alkynyl *N*-sulfinylimines **1** were utilized to produce the corresponding 2*H*-azirines **2** that possess sulfenyl and acyl groups at the 3 position of the azirine ring, in good to excellent yields via cleavage of O-S and N-S bonds (Figure 1a).[1] In addition, Au-catalyzed reactions between terminal alkynes **3** and sulfenamides **4** proceeded via cis-insertion of alkynes into the N–S bond in sulfenamides, affording the corresponding β-sulfenylenamines **5** in yields up to 90% (Figure 1b).[2]

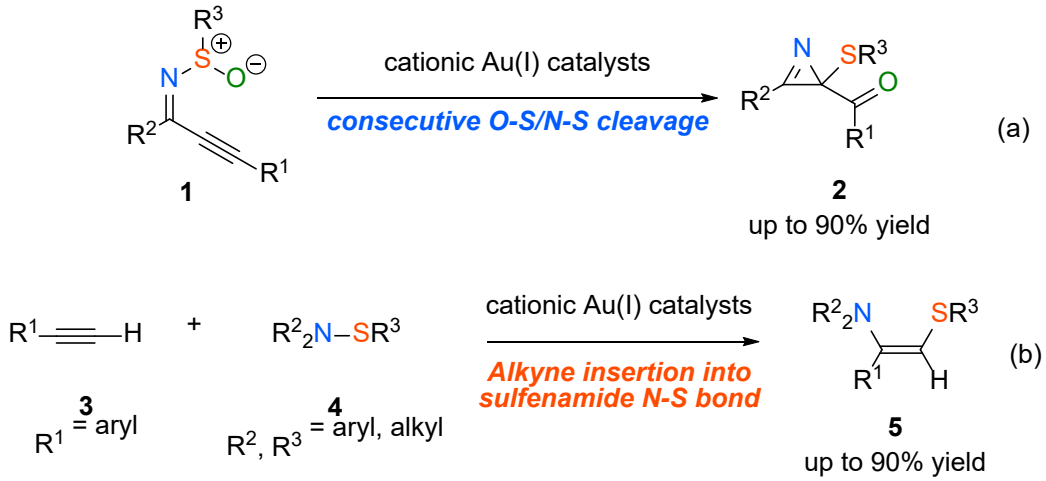

Figure 1. Au-Catalyzed Reactions via N-S Bond Cleavage

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Access to β-Lactams via Iron-Catalyzed Olefin Oxyamidation Enabled by the π-Accepting Phthalocyanine Ligand

Jeonguk Kweon,[a,b] Dongwook Kim,[b,a] Seungju Kang,[a,b] and Sukbok Chang*[,b,a]

[a] Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 34141, South Korea
[b] Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon, 34141, South Korea

Email: jeongukkweon@kaist.ac.kr; sbchang@kaist.ac.kr

Herein, we report the development of an iron-catalyzed olefin oxyamidation by utilizing tethered dioxazolones as the nitrenoid precursor to produce valuable β-lactam scaffolds. Mechanistic studies revealed that a relatively strong π-accepting ability of the phthalocyanine ligand is critical in generating the key triplet iron-imidyl radical intermediate to enable the *4-exo-trig*-lactamization with the incorporation of oxygen nucleophiles in high diastereoselectivity. This cyclization approach was readily extended to the highly efficient γ-lactam synthesis (TON > 300).

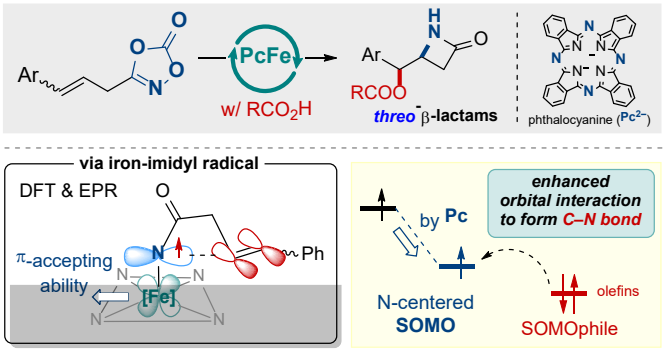

Figure 1. Phthalocyanine-Fe catalyzed oxyamidation toward β- and γ-lactams

New Methods for the Synthesis of (*E*)-Stilbenes from Alcohols promoted by KO^{t}Bu

Johanna Schichler[a], **Robert Madsen***[a]
[a] Department of Chemistry, Technical University of Denmark

Email: johkim@kemi.dtu.dk; rm@kemi.dtu.dk

Alcohols are cheap and environmentally benign substrates, which can be obtained from biomass. This makes them a sustainable source of carbon compared to fossil resources for the production of bulk and fine chemicals. The development of new methods for carbon-carbon bond formation from alcohols is therefore of great interest.[1]Olefinations are among the fundamentally important reactions in organic chemistry, which makes the formation of alkenes from alcohols an interesting target when investigating new synthetic methods with alcohols.Stilbenes are an important class of compounds as their scaffold is present in biologically active compounds as well as in materials due to their optical properties. Today, stilbenes are synthesized through various reactions, including most prominently the Wittig, Horner-Wadsworth-Emmons, and palladium catalyzed reactions.[2]The developed transition-metal-free method for the synthesis of (*E*)-stilbenes from benzyl alcohols and phenyl acetonitriles is a new route for the formation of (*E*)-stilbenes and employs only potassium tert-butoxide as a base in addition to 18-crown-6 (Figure 1). Furthermore, a two-step-one-pot coupling has been developed enabling the use of benzyl halides instead of phenyl acetonitriles as starting materials.

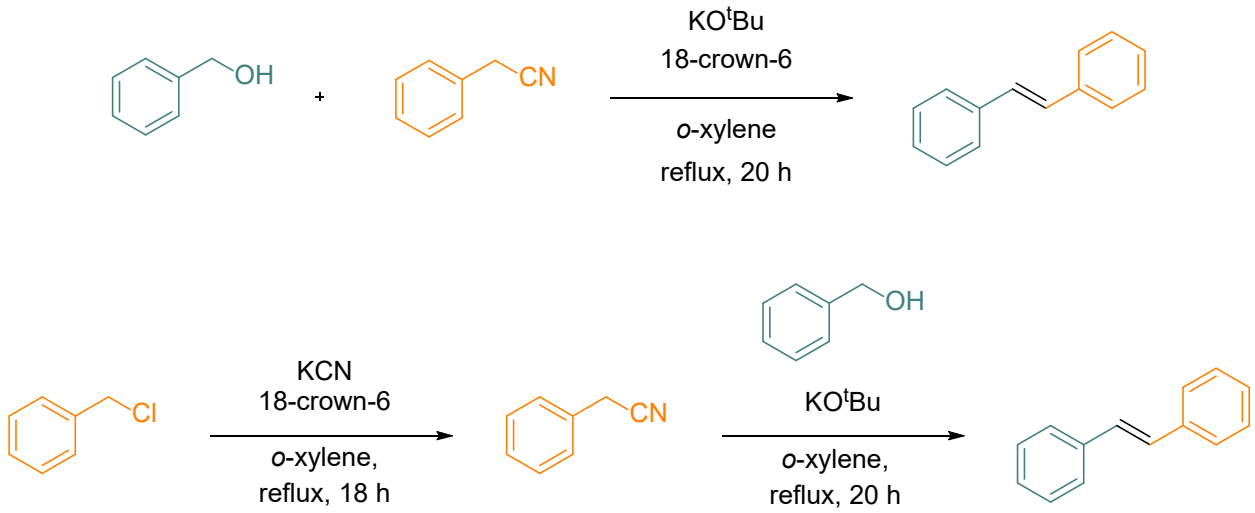

Figure 1. Reaction schemes for the coupling reaction of benzyl alcohols and phenyl acetonitriles forming (*E*)-Stilbenes and the two-step-one-pot reaction enabling the use of benzyl chlorides as starting materials.

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Manganese(I) catalyzed *ortho* C–H allylation of Benzoic Acids

J. Stemmer,[a] J. F. Goebel,[a] F. Belitz,[a] and L. J. Gooßen*[a]

Email: johanna.stemmer@rub.de, lukas.goossen@rub.de

The 3d-metal catalyst $Mn(CO)_5Br$ was found to efficiently promote *ortho* C–H allylations[1] of arenecarboxylates in the presence of neocuproine as the ligand. Despite the simplicity of directing group and catalyst system, the selectivity goes well beyond the state of the art[2] in that mono-allylated products are obtained exclusively with high selectivities for the least hindered *ortho*-position. The directing group can optionally be removed by *in situ*[3] decarboxylation, opening up a regioselective entry to allyl arenes. The preparative utility of the process and its othogonality to other approaches was demonstrated by 44 products with otherwise hard-to-access substitution patterns, including 3-bromo-allylbenzene, 3-allylbenzofuran, or 5-allyl-2-methylnitrobenzene.[4]

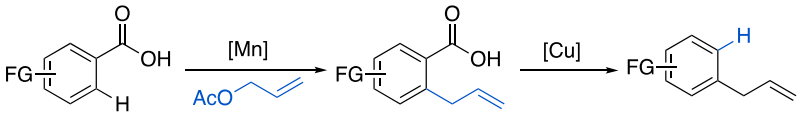

Figure 1. Mn-catalyzed allylation of benzoates with optional decarboxylation.

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Computer-Driven Development of Ylide functionalized Phosphines for Palladium-Catalyzed Hiyama Couplings

J. F. Goebel,[a] J. Löffler,[b] Z. Zeng,[a] J. Handelmann,[b] T. Gensch,[c] V. H. Gessner,*[b] and L. J. Gooßen*[a]

Email: Jonas.goebel@rub.de, viktoria.gessner@rub.de, lukas.goossen@rub.de

Palladium-catalyzed couplings of silicon enolates with aryl electrophiles are of great synthetic utility, but often limited to expensive bromide substrates. A comparative experimental study confirmed that none of the established ligand systems allows to couple inexpensive aryl chlorides with α-trimethylsilyl alkylnitriles. [1] In contrast, ylide-functionalized phosphines (YPhos) led to encouraging yields.[2] A statistical model was developed that correlates the reaction yields with ligand features. It was employed to predict catalyst structures with superior performance. With this cheminformatics approach, YPhos ligands were tailored specifically to the demands of Hiyama couplings. The newly synthesized ligands displayed record-setting activities, enabling even the eluive coupling of aryl chlorides with α-trimethylsilyl alkyl nitriles. The preparative utility of the catalyst system was demonstrated by the synthesis of pharmaceutically meaningful α-aryl alkylnitriles, α-arylcarbonyls and biaryls.[3]

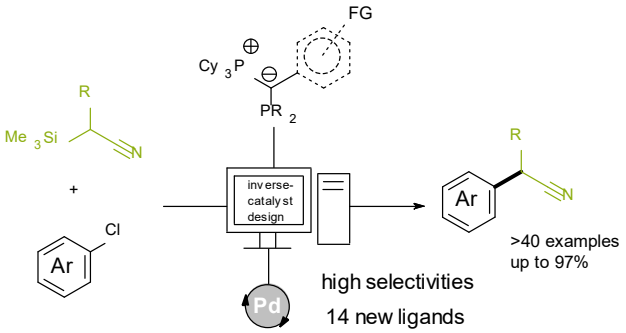

Figure 1. Computer-Driven Development of Ylide functionalized Phosphines for Palladium-Catalyzed Hiyama Couplings.

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Access to α-Chiral Olefin via Nickel-Catalyzed Enantioconvergent Cross-Coupling between β-Bromostyrenes and Secondary Grignard Reagents

Kaidi Li, Clément Mazet*
University of Geneva, Geneva, 1211, Switzerland
Email: kaidi.li@unige.ch; clement.mazet@unige.ch

Owing to the prevalence of α-chiral olefins in biologically active compounds, access to this motif has attracted continuous attention.[1] In recent years, significant efforts have been placed on the development of direct methods to forge tertiary benzylic/allylic stereocenters via Csp^2–Csp^3 bond-forming strategies.[2] Among other examples, this includes several Ni-catalyzed enantioselective reductive cross-coupling reactions,[3] photo-induced Ni-catalyzed Csp^3–H benzylic alkenylations,[4] and an enantioselective dual [Cu/Pd]-catalyzed hydroalkenylation of olefins.[5]

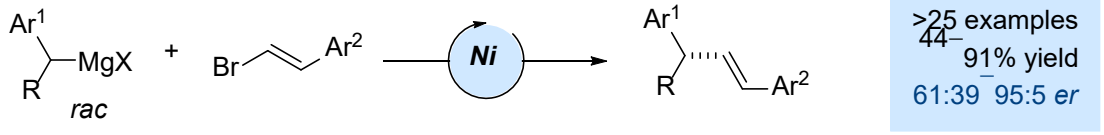

Figure 1.Nickel-catalyzed enantioselective cross-coupling between β-bromostyrenes and secondary Grignard reagents

While the Ni-catalyzed cross-coupling between vinyl bromide and rapidly epimerizing benzylic Grignard reagents is well-documented,[2,6] the corresponding reaction using β-bromostyrenes has not reached the same level of achievement.[3,6] We report herein our efforts in this direction with the identification of a general and highly enantioselective nickel catalyst supported by a chiral (P,N) ligand. Rarely explored secondary benzylic Grignard reagents were evaluated as electrophiles and showed excellent reactivity and enantioselectivity in most cases. The protocol is operationally simple, and applicable to a broad range of substrates.

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Direct Conversion of Low-Concentration of CO_2 to Carbamic Acid Esters Using Tetramethyl Orthosilicate as a Regenerable Reagent

Katsuhiko Takeuchi*,[a] Hiroki Koizumi,[a] Kazuhiro Matsumoto,[a] Norihisa Fukaya,[a] Kazuhiko Sato,[a] Masahito Uchida,[b] Seiji Matsumoto,[b] Satoshi Hamura,[b] Junya Hirota,[b] Makoto Nakashige,[b] Jun-Chul Choi*[a]

[a]*National Institute of Advanced Industrial Science and Technology (AIST).*

[b]*Tosoh Corporation*

Email: takeuchi-k@aist.go.jp; junchul.choi@aist.go.jp

In order to reduce anthropogenic CO_2 emissions, which are considered the main cause of global warming, it is effective to convert CO_2 emitted from thermal power plants into mass-produced basic chemicals. However, the energy and cost required to purify, concentrate, and compress the low-concentration and low-purity CO_2 contained in the exhaust gas from thermal power plants is significant. Therefore, it should be worthwhile to directly utilize the CO_2 in the exhaust gas from thermal power plants without going through such pretreatment processes.

In this study, we report the direct conversion of low-concentration of CO_2 (15 vol %), equivalent to CO_2 concentrations in the exhaust gas of thermal power plants, to carbamic acid esters (CAEs), which are precursors of pharmaceuticals, agrochemicals, and isocyanates (Figure 1).[1] The reaction was carried out using $Si(OMe)_4$ as a regenerable reagent and 1,8-diazabicyclo[5.4.0]undec-7-ene as a CO_2 capture agent and catalyst. As a result, various *N*-aryl and *N*-alkyl CAEs were obtained in moderate to high yields (45-77% in six cases and 84-89% in seven cases). In addition, bis CAEs (precursors of polyurethane raw materials) were successfully synthesized from simulated exhaust gas containing impurities such as SO_2, NO_2, and CO, or on a gram scale. We believe that this method avoids the use of harmful phosgene derived from fossil resources as a raw material for isocyanate production and reduces CO_2 emission.

This work was supported by the Uncharted Territory Challenge 2050 (Mitou Challenge 2050) (K.T.) from the New Energy and Industrial Technology Development Organization (NEDO).

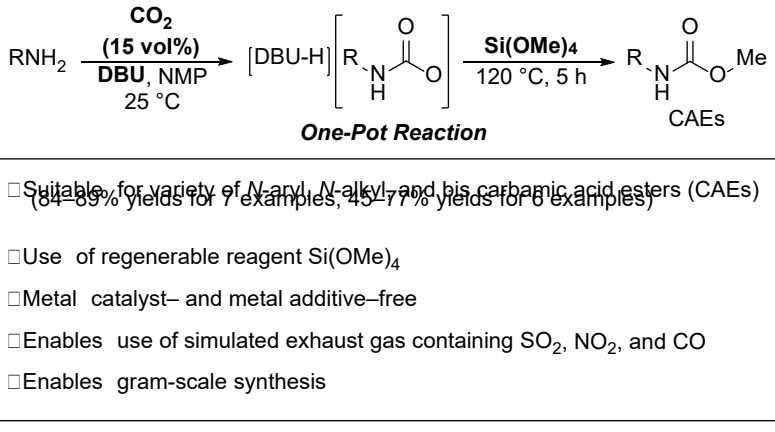

Figure 1. Overview of this work.

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Direct Suzuki–Miyaura Cross-Coupling of dan-Substituted Organoboron Compounds under Weak Base Conditions

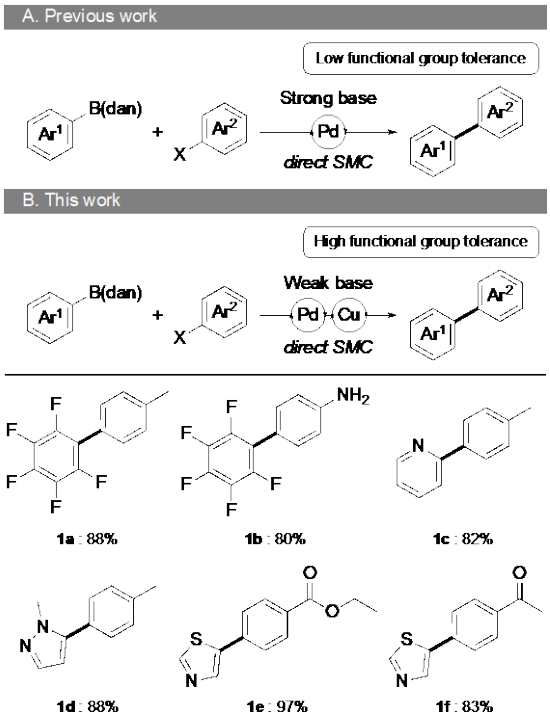
Kazuki Tomota, Masaaki Nakamoto, and Hiroto Yoshida*
Graduate School of Advanced Science and Engineering, Hiroshima University, Higashi-Hiroshima 739-8526, Japan
Email: m223325@hiroshima-u.ac.jp; yhiroto@hiroshima-u.ac.jp

Cross-coupling reactions are an extremely important tool for making carbon–carbon bonds of organic compounds. In particular, the Suzuki–Miyaura cross-coupling reaction (SMC) with organoboron reagents is the most frequently used, because of its practicality and versatility. Lewis acidic organoboronic acids and esters are generally employed for the SMC, however some of these organoboron compounds are hard to participate in the reaction, because they suffer protodeborylation under the basic and/or aqueous reaction conditions. Since the instability mainly arises from the boron-Lewis acidity, installation of a 1,8-diaminonaphthalene (dan) substituent on the boron center that diminishes the Lewis acidity has been demonstrated to significantly improve the stability.[1]

On the other hand, Lewis acidity-diminished dan-substituted organoboron compounds become reluctant toward the SMC, because it is difficult to activate the B(dan) center with a base. Hence conversion of the B(dan) moiety into $B(OH)_2$ via acidic deprotection is performed before its use for the SMC; the process is totally unsuitable for pentafluoro–B(dan) and 2-pyridyl–B(dan) being unstable in their boronic acid-forms. Under these circumstances, we have recently reported on the direct SMC of Ar–B(dan) that does not need acidic deprotection by use of a strong base (KO^tBu) as an activator, albeit at the cost of functional group tolerance (Scheme 1A).[2] Herein, we disclose that the direct SMC smoothly takes place even under weak base conditions by using a palladium/copper cocatalyst (Scheme 1B).

As depicted in Scheme 1B, the cross-coupling of pentafluorophenyl–B(dan) with *p*-bromotoluene afforded **1a** in 88% isolated yield. The weak base conditions allowed an electron-rich aryl bromide having a relatively reactive NH_2 group to be included in the direct SMC to give an 80% yield of **1b**, and furthermore, the reaction was also applicable to 2-pyridyl–, 5-pyrazolyl– and 5-thiazolyl–B(dan), being unstable in their boronic acid-forms, resulting in the efficient formation of the respective coupled products (**1c**–**1f**). It should be noted that base-sensitive ester and ketone functionalities remained intact.

Scheme 1



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Theoretical and Experimental Studies of Chain Walking of a 1,10-Phenanthroline Palladium Catalyst: Alkene Rotation as a Key, Selectivity-Determining Step

Kazuma Muto, Miho Hatanaka, Fumitoshi Kakiuchi, Takuya Kochi*
Department of Chemistry, Faculty of Science and Technology, Keio University
3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa, 223-8522, Japan.

Email: kochi@chem.keio.ac.jp

Alkene rotation around the metal–alkene bond in complexes is one of the most fundamental elementary processes in organometallic chemistry, and the energy barrier of alkene rotation has been studied experimentally[1] and theoretically[2] for various alkene complexes. There have been numerous organometallic catalytic reactions involving the alkene rotation step, especially right before migratory insertion. However, it has rarely been recognized as key steps such as turnover-limiting or selectivity-determining steps in catalytic cycles. Chain walking is a process where alkylmetal species move along aliphatic carbon chains through repetitive β-hydride elimination, alkene rotation, and migratory insertion. During the course of our theoretical and experimental studies on the catalytic reactions proceeding via nondissociative chain walking of 1,10-phenanthroline palladium catalysts, we obtained some results indicating that the alkene rotation step mostly has the highest energy barrier in the chain walking process.

Explorations of nondissociative chain walking pathways of an *n*-propylpalladium species by DFT calculation suggested that the transition states on the alkene isomerization pathways only located during the alkene rotation. Alkene dissociation from the alkene hydrido complex and associative alkene exchange were also calculated and found to be less favorable than the nondissociative chain walking pathway. Theoretical calculation of palladium complexes with longer alkyl groups also provided similar results to the propylpalladium complex. In addition, it was suggested that chain walking of the palladium center between internal carbons proceeds via palladium hydride complexes ligated to cis alkenes, although cis alkene complex is thermodynamically less stable than trans alkene complex (Figure 1). The preference of cis alkene intermediates was supported by a deuterium-labeling experiment of remote arylative substitution using a 1,10-phenanthroline palladium catalyst.[3]

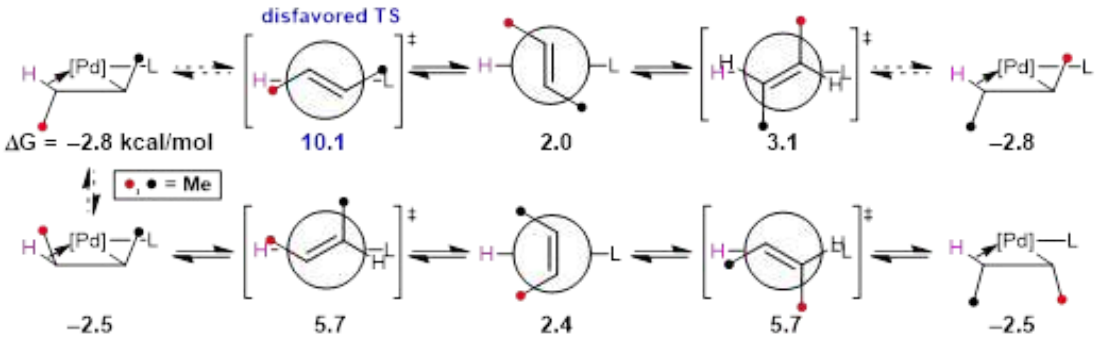

Figure 1. Energy barriers of chain walking pathways between 2- and 3-positions of 4 carbon alkyl chain.

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Catalytic Dearomative Azaspirocyclization of Bromoarenes with *N*-Tosylhydrazones and Synthesis of *Cephalotaxus* Alkaloids

Kei Muto,*[a] Yota Uwabe,[b] Junichiro Yamaguchi*[b]
[a]Waseda Institute for Advanced Study, Waseda University. [b]Department of Applied Chemistry, Waseda University
Email: keimuto@aoni.waseda.jp; junyamaguchi@waseda.jp

1-Azaspirocycles have been widely utilized not only in bioactive molecules, but also in chiral organocatalysts and ligands. Dearomative spirocyclization is one of the powerful methods to approach such skeleton because this reaction allows to build such a molecular complexity from simple and abundant arenes. Nevertheless, the majority of these methods have been limited to the conversion of phenol derivatives.[1]

In this regard, we have developed a Pd-catalyzed dearomative azaspirocyclization of bromoarenes bearing an amino alkyl chain with *N*-tosylhydrazones.[2] The key design for this reaction is the generation of benzyl-palladium intermediate, which then undergoes an unusual intramolecular C–N bond formation to give an alkylideneazaspirocycle. Under the influence of Pd/DPEphos as well as Pd/PPh_3, a variety of bromoarenes including furans, thiophenes, and naphthalenes were transformed into the corresponding azaspirocycles in a convergent manner. The spirocycles from furans were further converted to azaspirocyclopentenone by an acid-catalyzed skeletal rearrangement. Utilizing the present methodology, the first total synthesis of fortuneicyclidins, which are the *Cephalotaxus* alkaloids with a uniquely complex polycyclic skeleton,[3] has been accomplished in eight steps from commercially available compounds.

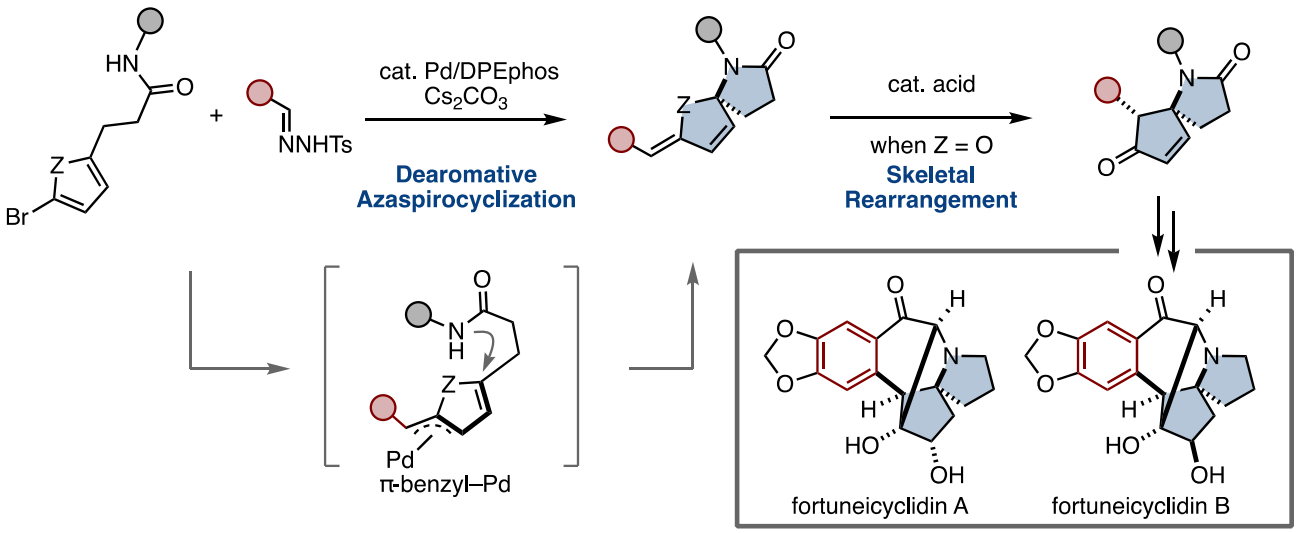

Figure 1. Pd-Catalyzed Dearomative Azaspirocyclization of Bromoarenes with *N*-Tosylhydrazones and Concise Synthesis of *Cephalotaxus* Alkaloids.

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Ir-Catalyzed Distal Functionalization of Internal Alkenes via C–H Activation and Chain-Walking Synergistic Strategy

King Hung Nigel Tang, Ryo Tokutake, Mamoru Ito, Takanori Shibata*
Department of Chemistry and Biochemistry, Graduate School of Advanced Science and Engineering, Waseda University.
Email: khntang@toki.waseda.jp; tshibata@waseda.jp

Insertion of alkene, a versatile building block in organic synthesis, to metal–carbon bond was extensively investigated. In particular, organometallic catalytic reactions manipulating hydrido-complexes generated from C–H activation is a hot topic of research. Whilst hydrofunctionalization of terminal alkenes was widely reported, coupling of internal unactivated alkenes is still challenging. In 2012, Kochi and Kakiuchi first demonstrated the use of consecutive isomerization, which is known as "chain-walking", in organic synthesis.[1] This provides a powerful tool to move double bonds along a hydrocarbon chain for the introduction of functional groups to remote positions. We hypothesized that the combination of C–H activation and chain-walking will open new possibilities to organic transformation. As of 2020, there were only two reports on the combination of C–H activation and chain-walking as means in organic synthesis.[2,3] In 2022, our group contributed one more example adopting cationic iridium catalyst to facilitate the deconjugative chain-walking C–H functionalization of substances with an imine directing group (Figure 1).[4]

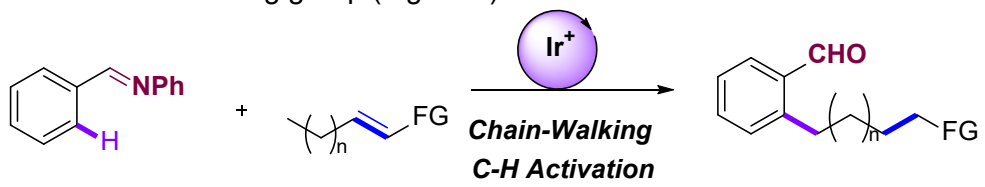

Figure 1. Imine directed C–H activation along with chain-walking.

In contrast to the previous work, we here demonstrate that branched product can be obtained using a carbamoyl directing group (Figure 2). Fine tuning of the aniline moiety and ligand realized excellent yield and excellent regioselectivity. A wide substrate scope is available with high functional group tolerance including pharmacophore and biologically active scaffold. We will discuss the mechanistic studies in the presentation.

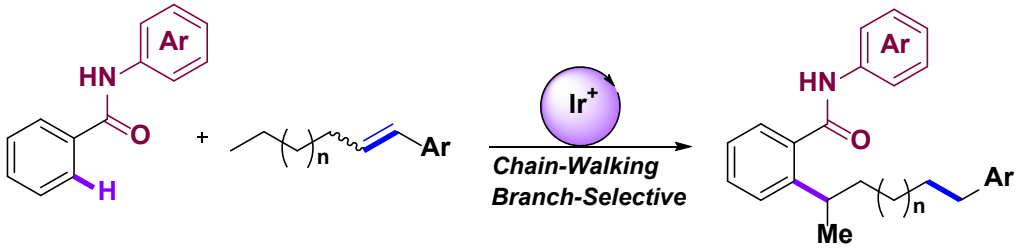

Figure 2. Branch-selective C–H hydroarylation to internal alkenes along with chain-walking.

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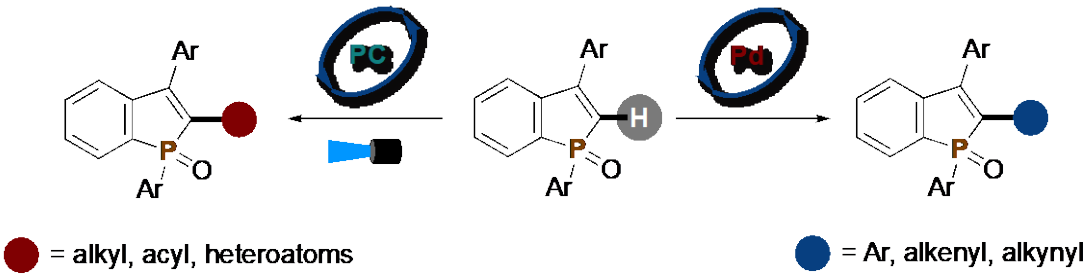
Catalytic C–H Transformations of Phospholes

Koji Hirano*, Shibo Xu, Yu Tokura, Kazutoshi Nishimura, Kosuke Saito
Department of Applied Chemistry, Graduate School of Engineering,
Osaka University, Suita, Osaka 565-0871, Japan
Email: k_hirano@chem.eng.osaka-u.ac.jp

Because of unique optical, electronical, and physical properties, benzophosphole derivatives have attracted much attention in the field of organic functional materials. Accordingly, the development of synthetic strategies for the preparation of benzophospholes, particularly, multiply substituted ones, has been one of the long-standing research subjects in synthetic community.[1] On the other hand, transition-metal-promoted C–H activation has been proven to be one of the most powerful strategies in the conversion of simple starting materials to the diverse and value-added molecules. Among them, the C–H transformations of benzoheteroles such as indoles, benzothiophenes, and benzofurans, have received tremendous attention and have made remarkable progress.[2] However, the direct catalytic C–H transformation of phosphorus analogues, benzophospholes, has not been successful so far. Here, we present Pd-catalyzed C–H arylation,[3] alkenylation,[4] and alkynylation of the phosphole nucleus. Additionally, related direct functionalizations under visible light irradiation will also be disclosed (Scheme 1).



Scheme 1. Direct C–H transformations of phospholes.

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Rapid Access to Diabetes Medicine Glitazones: Methylene Thiazolidinediones as Alkylation Reagents via Rh(III) Catalysis

Kyeongwon Moon,[a] Junhyeok Yang,[a] Taeeun Kim,[a] In Su Kim*[a]
[a]School of Pharmacy, Sungkyunkwan University(SKKU), Republic of Korea

Email: kyeongwonmoon@gmail.com; insukim@skku.edu

The straightforward and rapid incorporation of a thiazolidinedione scaffold into prefunctionalized (hetero)aromatic compounds is in demand for the development of antidiabetic glitazones and other pharmaceuticals. Herein, we report the unprecedented N- and O-directed C−H alkylation of various (hetero)arenes with methylene thiazolidinediones under rhodium(III) catalysis. The applicability of the developed protocol in challenging contexts is exhibited by the late-stage installation of a methylene thiazolidinedione moiety on the C−H bond of commercially available drug molecules.

The selective modulation of peroxisome proliferatoractivated receptor γ (PPAR-γ) is one of the central topics for the treatment of type 2 diabetes. In particular, a thiazolidine-2,4-dione (TZD) scaffold on glitazones plays a crucial role in selective receptor binding, hence leading to the stimulation of PPAR-γ.[1] A common structural feature of PPAR-γ agonists is the Ar-CH_2-TZD group. The conventional approach for generating this framework relies on the aldol condensation between nucleophilic TZD and aryl aldehydes followed by olefin hydrogenation. However, from the viewpoint of medicinal chemistry and drug development, this strategy presents intrinsic drawbacks, namely, the need for prefunctionalized aldehydes and functional group instability under hydrogenation conditions, which lead to the limited generation of synthetic derivatives. Therefore, the a new methodology for synthesizing the Ar-CH_2-TZD backbone with fewer synthetic steps is in demand. Herein, we first demonstrate the utility of methylene TZD in the C−H functionalization of various (hetero)arenes, affording (Het)Ar-CH_2-TZD. Notably, this protocol provides a valuable opportunity to rapidly access the drug candidates via PPAR-γ modulation (Figure 1).[2] Moreover, the late-stage installation of the CH_2-TZD moiety into complex drug molecules can be an alternative way to afford synergistic and complementary effects of two pharmacological groups in a single molecule.

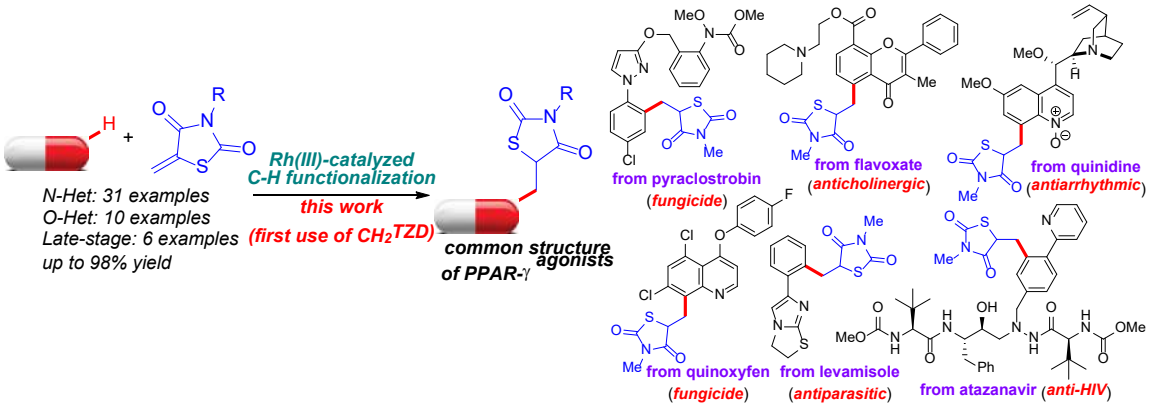

Figure 1. Catalytic approach into Glitazone scaffold and late-stage C–H functionalization

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Schlenk's Legacy – Methyllithium Put under Close Scrutiny

Jakob Lebon,[a] Alexandros Mortis,[a] Cäcilia Maichle-Mössmer,[a] Manfred Manßen,*[a] Peter Sirsch,*[a] Reiner Anwander*[a]

[a] Institut für Anorganische Chemie, Eberhard-Karls-Universität Tübingen
Auf der Morgenstelle 18, 72076 Tübingen (Germany).

Email: manfred.manssen@anorg.uni-tuebingen.de

Over 100 years ago in 1917,[1] Wilhelm Schlenk and Johanna Holtz reported on their seminal work "Über die einfachsten metallorganischen Verbindungen" comprising a series of organosodium compounds but also methyllithium, ethyllithium, *n*-propyllithium, and phenyllithium. These organolithium reagents (RLi) display key components in organic and organometallic chemistry alike.[2] Moreover, both academic and industrial interests draw upon the versatility and efficiency of these universal reagents which can act as nucleophiles, bases[3] or reducing agents,[4] but they can also act as polymerization initiators (elastomer sector).[5] However, commercially available stock solutions of organolithium reagents are inherently contaminated with lithium halide salts (up to 10%) originating from their syntheses, which can complicate certain synthesis protocols and purification processes. Here, we report the isolation of chloride-free methyllithium employing $K[N(SiMe_3)_2]$ as a halide-trapping reagent (Figure 1). The influence of distinct LiCl contaminations on the ^{7}Li-NMR chemical shift is examined and their quantification is demonstrated. The structural parameters of new chloride-free monomeric methyllithium complex $[(Me_3TACN)LiCH_3]$, ligated by an azacrown ether, are assessed by comparison with a halide-contaminated variant and monomeric lithium chloride $[(Me_3TACN)LiCl]$, further emphasizing the great effects of halide impurities.

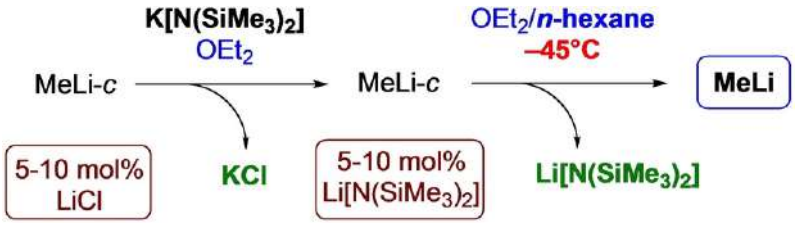

Figure 1. Isolation of pure methyllithium. MeLi-*c*=contaminated methyllithium.

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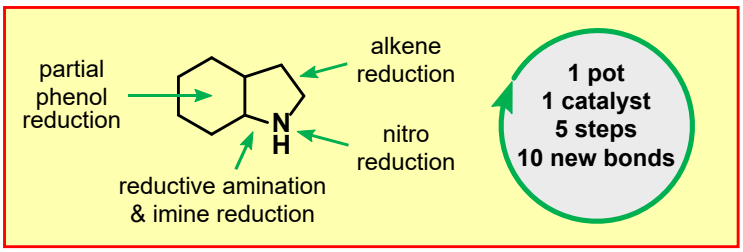
Synthesis of Saturated N-Heterocycles *via* a Catalytic Hydrogenation Cascade

Tobias Wagener,[+a] Marco Pierau,[+a] Arne Heusler,[a] Frank Glorius*[a]
[a] Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut, Corrensstraße 40, 48149 Münster, Germany.
[+] These authors contributed equally to this work.

Email: marco.pierau@uni-muenster.de; glorius@uni-muenster.de

Saturated N-heterocycles are prominent motifs found in various natural products and pharmaceuticals. Despite the increasing interest in this class of compounds, the synthesis of saturated bicyclic azacycles requires tedious multi-step syntheses. Herein, we present an one-pot protocol for the synthesis of octahydroindoles, decahydroquinolines, and octahydroindolizines through a cascade reaction.



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Cyclotrimerization Reactions with Manganese and Cobalt: Catalytic twins?

Tim Gläsel,[a] Benedikt N. Baumann,[a] Haijun Jiao,[b] Marko Hapke*[a,b]
[a]Johannes Kepler University Linz, Institute for Catalysis (INCA), Altenberger Strasse 69, 4040 Linz, Austria. [b] LIKAT Rostock, Albert-Einstein-Strasse 29a, 18069 Rostock, Germany
Email: marko.hapke@jku.at

Transition metal-catalyzed cycloaddition reactions have become particularly successful examples for high versatile and atom-efficient transformations with [2+2+2] cycloaddition reactions as a particular versatile representative. This reaction stands out as a large number of transition metals are capable to mediate or catalyze this reaction.[1] The late metals of the first row of the transition metals have been among the first, from which successful examples of catalytic cyclotrimerizations have been reported.[2] These metals, especially nickel and cobalt, exhibit interesting and unique catalytic features compared to the heavier congeners. Most recently our studies led to the discovery of a Co(II)-based catalytic process for the synthesis of phosphinines from diynes and phosphaalkynes, featuring a large substrate scope including even tolerance to nitrile groups in the substrates.[3] While our interest is focusing on developing new catalysts and exploiting different oxidation states, we are also interested in discovering the catalytic features of other 3d metals like iron and especially manganese. Except for a few (formal) examples, manganese complexes were not known to catalyze cyclotrimerization reactions so far, although the Cp (cyclopentadienyl) and CO complexes share structural similarities to those of cobalt. The presentation will discuss the development of novel manganese catalysts for [2+2+2] cycloadditions, their catalytic features and scope of substrates, including a comparison to cobalt-catalyzed transformations and reaction mechanisms, and their evolution to master new substrate challenges.

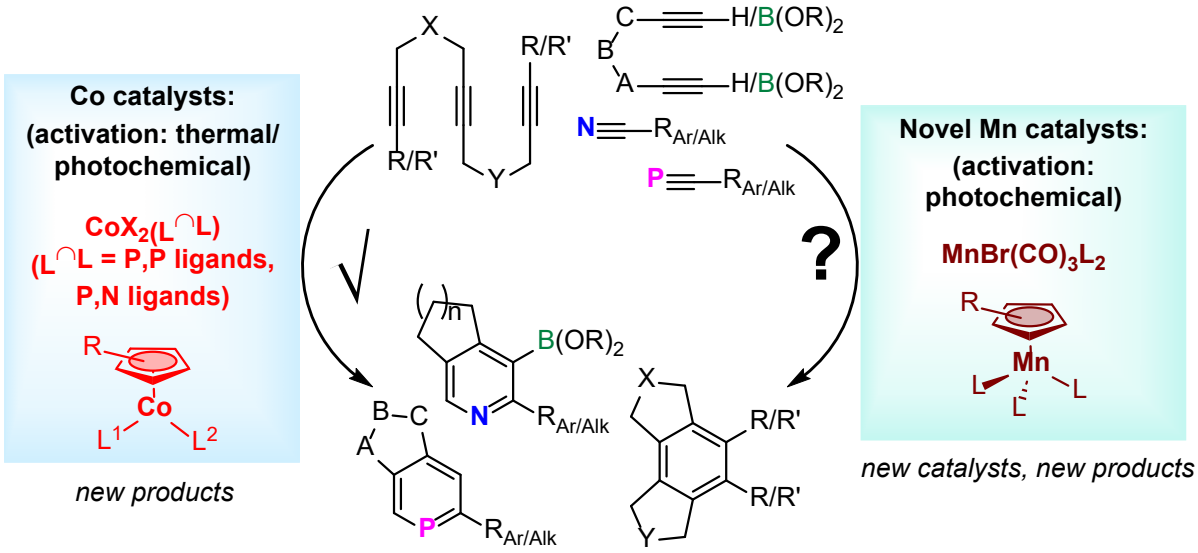

Figure 1. Novel cyclotrimerizations by manganese and cobalt catalysts.

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Make It Homogeneous: Palladium-Catalysed *O*-Arylation Enabled By a Soluble Organic Base

Martyna I. Ostrowska,[a] Dr James Morris,*[b] and Dr Liam T. Ball,*[a]
[a] School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK.
[b] Syngenta, Jealott's Hill International Research Centre, Bracknell RG42 6EY, UK.

Email: martyna.ostrowska@nottingham.ac.uk; james.morris@syngenta.com; liam.ball@nottingham.ac.uk

Metal-catalysed cross-couplings are powerful tools for the synthesis of a diverse range of agrochemicals and pharmaceuticals. Despite significant advances achieved in this area, most of these reactions are carried in a presence of insoluble inorganic bases or metal alkoxides, which leads to heterogeneous reaction mixtures and 'clumping' of the base during reactions.[1,2] This in turn leads to reproducibility issues, problematic sampling, poor isolated yields, and safety hazards associated with microwave heating. Furthermore, reaction heterogeneity results in poor scalability, an issue that is especially acute when High Throughput Experimentation (HTE) screens are translated to the synthetic laboratory. Recently, these issues have been addressed in C-N[3] and C-S[4] couplings by using milder, soluble organic base. However, the equivalent procedure for Pd-catalysed C-O cross-couplings is currently unknown.

We have developed the first Pd-catalysed *O*-arylation of phenols with aryl triflates that uses a soluble organic base. The methodology tolerates a broad range of sterically and electronically diverse coupling partners and is compatible with both microwave heating and HTE formats. We anticipate that this methodology will prove to be a useful tool in both academic and industrial discovery programmes.

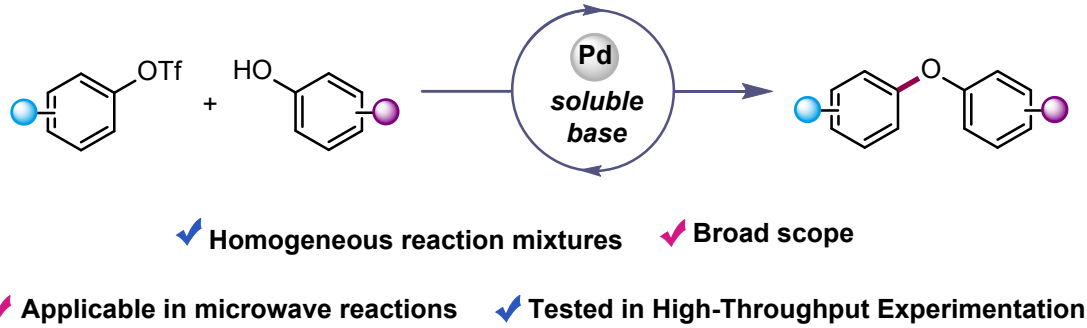

Figure 1. Soluble-base-assisted *O*-arylation.

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Exploration of the reactivity of dinuclear metal complexes

Marvin Mendel and Franziska Schoenebeck*
RWTH Aachen University, Landoltweg 1, 52074 Aachen/Germany.
Email: marvin.mendel@rwth-aachen.de; franziska.schoenebeck@rwth-aachen.de

Homogeneous metal catalysis has revolutionized modern organic synthesis. Traditionally, the vast majority of reported methods have focused on closed-shell two-electron processes involving mononuclear species, e.g. Pd(0)/Pd(II) cycles, while processes involving dimeric metal complexes in rather unusual oxidation states like Pd(I) have – by comparison – received much less attention.[1] This presentation will discuss dinuclear as well as odd oxidation state metal catalysis to address important challenges in synthesis with particular emphasis on selectivity, mildness and speed.[2] Examples of privileged reactivity of the M(I) species will be showcased also and range from fully predictable, sequential functionalization of poly(pseudo)halogenated arenes to modular and iterative synthesis to vinyl cyclopropanes and more.

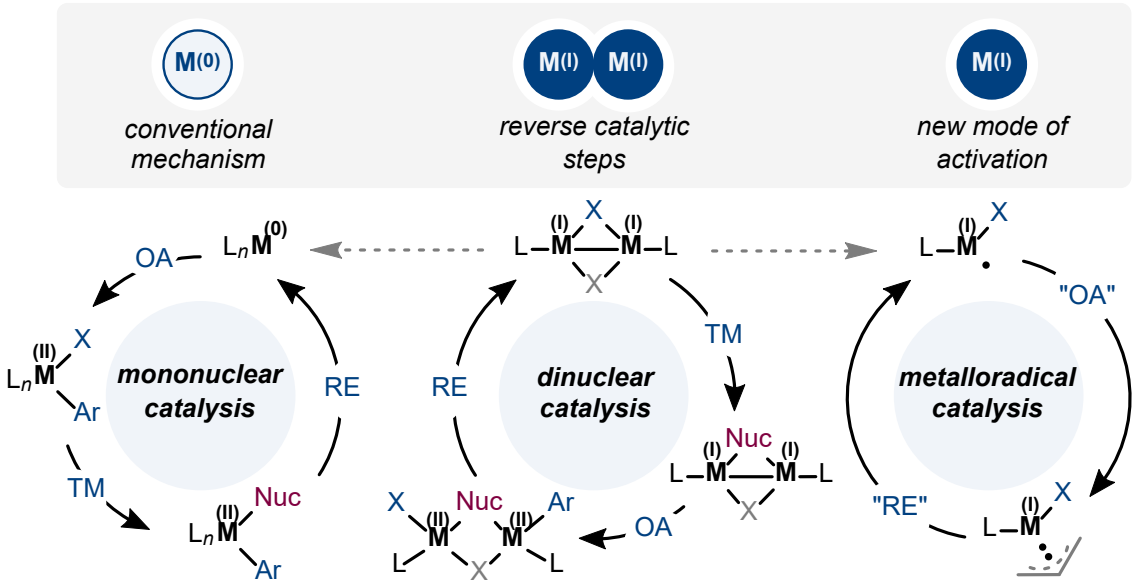

Figure 1. Application of dinuclear M(I)-M(I) scaffolds as diverse (pre)catalysts in mononuclear, dinuclear and metalloradical catalysis.

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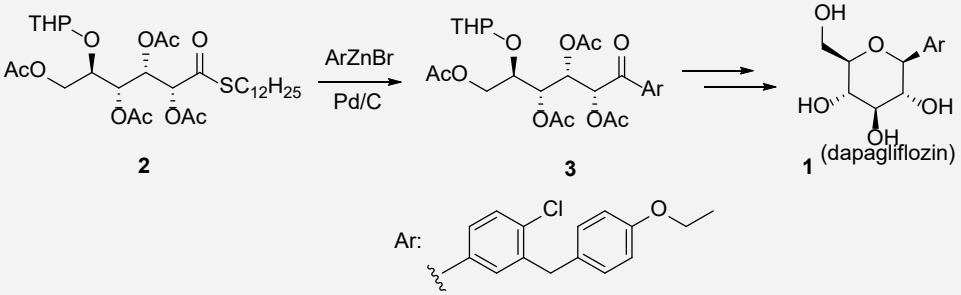
Synthesis of SGLT2 Inhibitors by Means of Fukuyama Coupling Reaction

Dr Masahiko Seki, Dr Sandeep Tapkir, Dr Maheshwara Reddy, Dr Shaheen Mulani, Prof Kazushi Mashima

Masahiko Seki*, [1, 2], Tapkir Sandeep Ramesharao,[2] Maheshwara Reddy Nadiveedhi, [2] **S**haheen Kasim Mulani[2] and Kazushi Mashima*, [2]

R&D Planning Department, Tokuyama Corporation,[1] Graduate School of Pharmaceut ical Science,
Osaka University[2]

Sodium dependent glucose transporter 2 (SGLT2) inhibitors **1** have received keen att ention as a diabetes drug due to high efficacy and safety.[1] Recent discoveries on addition al potency of those drugs for nephritis and heart failure have enhanced the importance as a therapeutic agent significantly.[2] SGLT2 inhibitors have b-C-glycoside motif as a commo n structure where sugar unit is combined with aromatic substituent by b-orientation.[3] Prev ious synthetic methods have a serious issue of need of cryogenic conditions (-78 °C) to in stall the characteristic structure itself. To address the drawback, we have developed new synthesis which can be undertaken at ambient temperature for the key step.[4] The method consists of a new ketone synthesis from **2** to **3** through Fukuyama coupling reaction. The mild conditions enable use of labile acetyl protecting group.



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Selective and Scalable Synthesis of Sugar Alcohols by Homogeneous Asymmetric Hydrogenation of Unprotected Ketoses

M. Roca Jungfer,[a] D. J. Tindall,[a] S. Mader,[b] A. Kindler,[b] F. Rominger,[c] A. S. K. Hashmi,[c] T. Schaub*[a,b]

[a]Catalysis Research Laboratory (CaRLa), Im Neuenheimer Feld 584, D-69120 Heidelberg
[b]BASF SE, Carl-Bosch-Str. 38, D-67056 Ludwigshafen
[c]Organisch-Chemisches Institut, University of Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg.

Email: thomas.schaub@basf.com

Sugar alcohols are of great importance to the food industry and are promising building blocks for bio-based polymers. Industrially, they are produced by heterogeneous hydrogenation of sugars with H_2, usually with none to low stereoselectivity. Now, we present a homogeneous system based on commercially available components, which not only increases the overall yield, but also allows a wide range of unprotected ketoses to be diastereoselectively hydrogenated.[1] Furthermore, the system is reliable on a multi-gram scale allowing sugar alcohols to be isolated in large quantities at high atom economy.

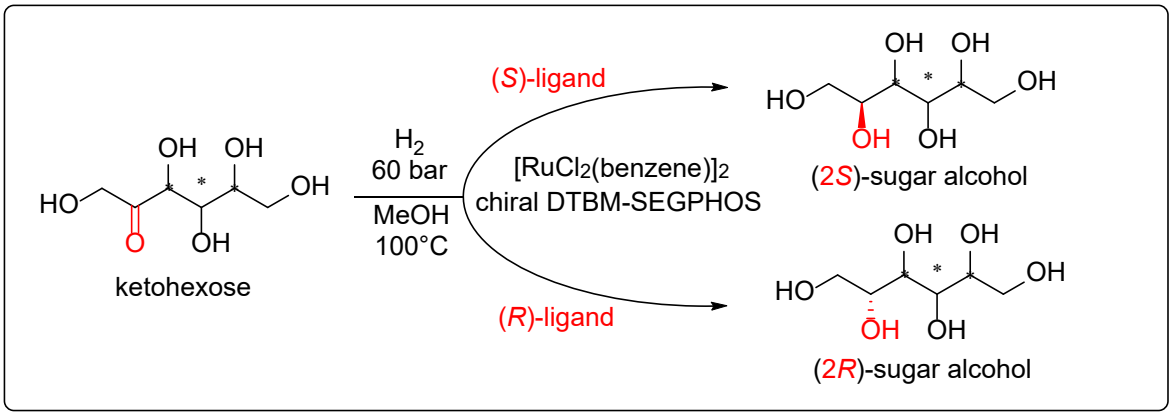

Figure 1. Diastereoselective, ruthenium-catalyzed hydrogenation of ketohexoses to the corresponding sugar alcohols with chirality transfer from the corresponding DTBM-SEGPHOS ligand.

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Nickel-Catalyzed Decarbonylative Reductive Alkylation of Acyl Fluorides with Alkyl Bromides

Myuto Kashihara,[a] Qian Chen,[b] Jingwen You,[b] Tian Tian,[b] Zhenyao Li,[b] Hiroki Mori,[a] Yasushi Nishihara*[a]

[a]Research Institute for Interdisciplinary Science, Okayama University, Okayama, Japan.
[b]Graduate School of Natural Science and Technology, Okayama University, Okayama, Japan.

Email: mkashihara@okayama-u.ac.jp

Acyl fluorides are a class of compounds containing a carbonyl–fluorine bond. They are more stable than other acyl halides, but more reactive than the corresponding esters and amides. This moderate reactivity has recently attracted attention and opened up new fields to utilize acyl fluorides as easy-to-handle electrophiles.[1,2] Another synthetically useful feature is two possible reaction modes: acyl coupling (RCOF as the RCO source) and decarbonylative coupling (RCOF as the R source). Late transition metal catalysts are especially suitable for controlling selectivity and expanding the variation of transformations.

Following our report on the alkylation of acyl fluorides with organoboron reagents,[3] we this time disclose the nickel-catalyzed cross-electrophile coupling between aroyl fluorides and alkyl bromides (Figure 1).[4] The reaction conditions using zinc as the reductant constructed C(sp^2)–C(sp^3) bonds with a relatively broad functional-group tolerance. Furthermore, investigation of the reaction mechanism revealed that the present reaction proceeds *via* the radical pathway. This reaction protocol bypasses prior preparation of organoboron compounds for classical cross-coupling, leading to efficient production of alkylarenes.

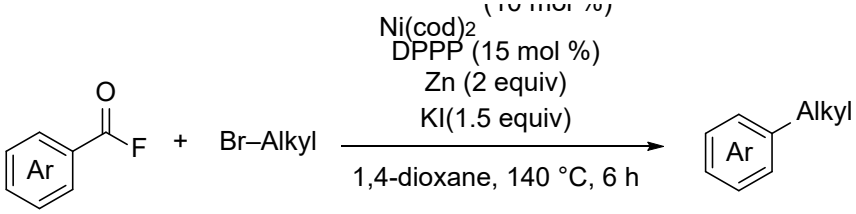

Figure 1. Nickel-Catalyzed Decarbonylative Reductive Alkylation of Acyl Fluorides with Alkyl Bromides.

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Conjugate Addition of β-CF_3-Enones with Quinoline *N*-Oxides Under Rh(III) Catalysis

Na Young Ko,[a] **Sujin Min**,[a] **Heesang Yang**,[a] **In Su Kim***[a]
[a]School of Pharmacy, Sungkyunkwan University(SKKU), Republic of Korea
Email: thenaayoung@gmail.com; insukim@skku.edu

The site-selective incorporation of trifluoromethyl group into biologically active molecules and pharmaceuticals has emerged as a central topic in medicinal chemistry and drug discovery. Tremendous progress has been made on the direct incorporation of a CF_3 group into a series of organic molecules by using trifluoromethylating agents reported by Ruppert-Praksch, Togni, Umemoto, Langlois, and MacMillan[1] (Figure 1a). Recently, β-CF_3-α,β-unsaturated ketones have been also employed in the catalytic C−H functionalizations. For example, Yu and co-workers reported the pyridinyl-directed Rh(III)-catalyzed C−H alkylation reaction of aromatic and vinylic C−H bonds with β-CF_3-substituted unsaturated ketones[2] (Figure 1b). Herein, we demonstrate the rhodium(III)-catalyzed conjugate addition of β-trifluoromethylated enones with quinoline *N*-oxides, which result in the generation of β-trifluoromethyl-β'-quinolinated ketones (Figure 1c). The reaction proceeds under mild conditions with complete functional group tolerance. The synthetic applicability was showcased by successful gram-scale experiments and valuable synthetic transformations of coupling products.

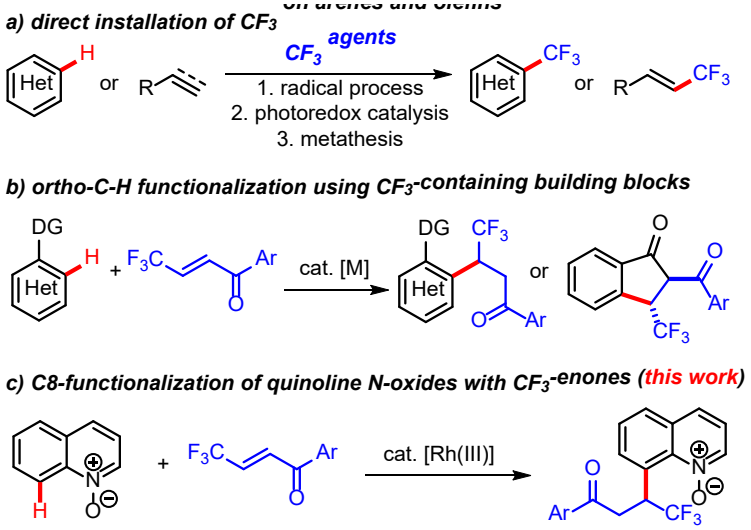

Figure 1. C8-Alkylation of quinoline *N*-oxides using β-CF_3-enones

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Bisphosphine/Nickel-Catalyzed C–O Cross-Coupling of Phenols with Chloropyridine and Related Electrophiles

Nicholas E. Bodé,[a] Ryan T. McGuire,[a] Mark Stradiotto[a]
[a]Department of Chemistry, Dalhousie University
Email: nicholas.bode@dal.ca; mark.stradiotto@dal.ca

Diaryl ethers are found in a variety of natural products and pharmaceuticals. Popular ancillary ligands have enabled efficient routes to this motif using homogeneous Pd catalysis,[1] and while Cu-mediated methods (*e.g.,* Chan-Evans-Lam,[2] along with more recently reported catalytic methods[3]) are also effective, they are typically unable to accommodate the use of inexpensive and commercially available (hetero)aryl chlorides. Ni has emerged as a promising alternative to these metals, but while ligand design and photoredox catalysis alike have enabled recent strides in Ni-catalyzed C-O cross-coupling,[4] these limitations in terms of electrophile scope remain present (Figure 1). Herein, we present a method for the synthesis of unsymmetrical (hetero)diaryl ethers from chloropyridine-type electrophiles and substituted phenols using PhPAd-DalPhos and $Ni(cod)_2$ as a catalyst system under thermal conditions.[5] Optimization of this system will be presented, along with the useful substrate scope and reactivity preferences as determined through competition experiments.

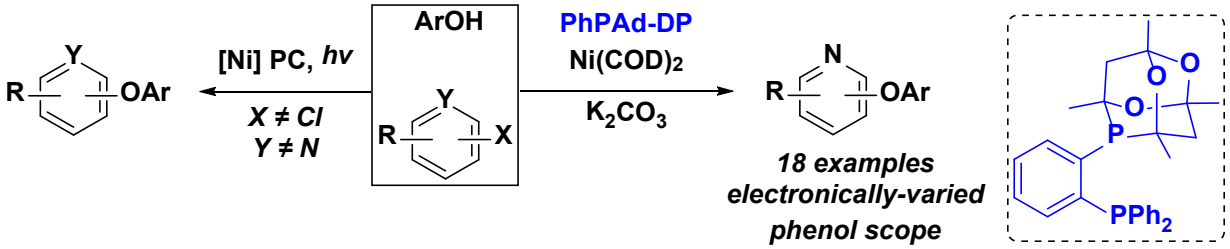

Figure 1. Ni-catalyzed synthesis of (hetero)diaryl ethers enabled by the ancillary ligand PhPAd-DalPhos.

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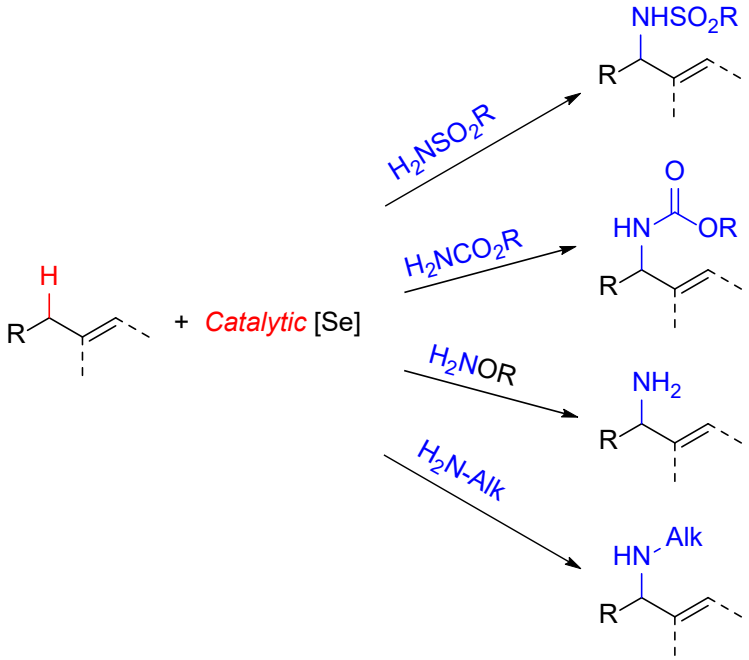
Direct Allylic C-H Amination Via Selenium Catalysis: Accessing New Nitrogen Sources

Shardon T. Morrill, **Forrest E. Michael***

Department of Chemistry, University of Washington

Email: shardont@uw.edu; michael@chem.washington.edu

Direct allylic C-H amination of alkenes allows for the regioselective formation of a new C-N bond, making it an efficient method for introducing new functionality. As such, this transformation can be valuable is functionalizing feedstock, derivatizing compounds, or within synthetic routes. We have developed a metal-free allylic C-H amination method catalyzed by selenium complexes of phosphines and N-heterocyclic carbenes. A variety of electron-poor nitrogen sources such as sulfonamides, sulfamates, and carbamates can be installed using these methods, with unique regioselectivity and no allylic transposition[1]. This regioselectivity can depend on subtle electronic factors. Direct installation of more basic alkylamino and -NH_2 groups allows subsequent functionalization and/or deprotection steps to be bypassed, providing more efficient access to these derivatives compared to prior established methods.



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Synthetic possibilities of multifunctional nucleophiles in homogeneous catalytic carbonylation reactions

László Kollár[a], Attila Takács[a], Csilla Molnár[a], Andrew Kovács[a], László T. Mika[a], Péter Pongrácz*[a]

[a]Department of Inorganic Chemistry, University of Pécs, Hungary
[b]Budapest University of Technology and Economics, Hungary
Email: pongracz@gamma.ttk.pte.hu

Homogeneous catalytic carbonylation reactions performed in the presence of various nucleophiles are excellent synthetic tools for the production of valuable fine chemicals, such like amides, esters, thioesters. Several studies have been reported for the utilization of simple amines and alcohols as model reactants, only a few works focused on the investigation of carbonylation reactions in the presence of homo- and even heterobifunctional nucleophiles. However, the application of the latter open alternative and easier synthetic routes for the construction of complex molecular structures. Our investigation was focused on the selective transformation of iodoarenes with various aminoethanols to get the corresponding amides or amide-ester derivatives. It was showed, that the substrate-nucleophile ratio and the base have crucial role on product distribution. Furthermore, interesting correlation was found between the substituents of the aryl iodides and the rate of amino/alkoxy-carbonylation reactions. Additionally, trifunctional nucleophiles were also tested with various iodobenzene amounts. Surprising results showed increased affinity on 'tricarbonylated' products, which phenomena were explained by mechanistic considerations.
Additionally, some selected aminoethanols were reacted with *ortho*-dihalogenated aromatic substrates under carbonylation conditions. Iodo- and bromo-aromatic structures showed diverse reactivity and selectivity with the selected heterobifunctional nucleophiles. As it was expected, iodobenzenes and amines were much more reactive compared to bromo analogues and O-nucleophiles, but latter structural items are also suitable coupling partners and showed interesting behaviour under the applied conditions.

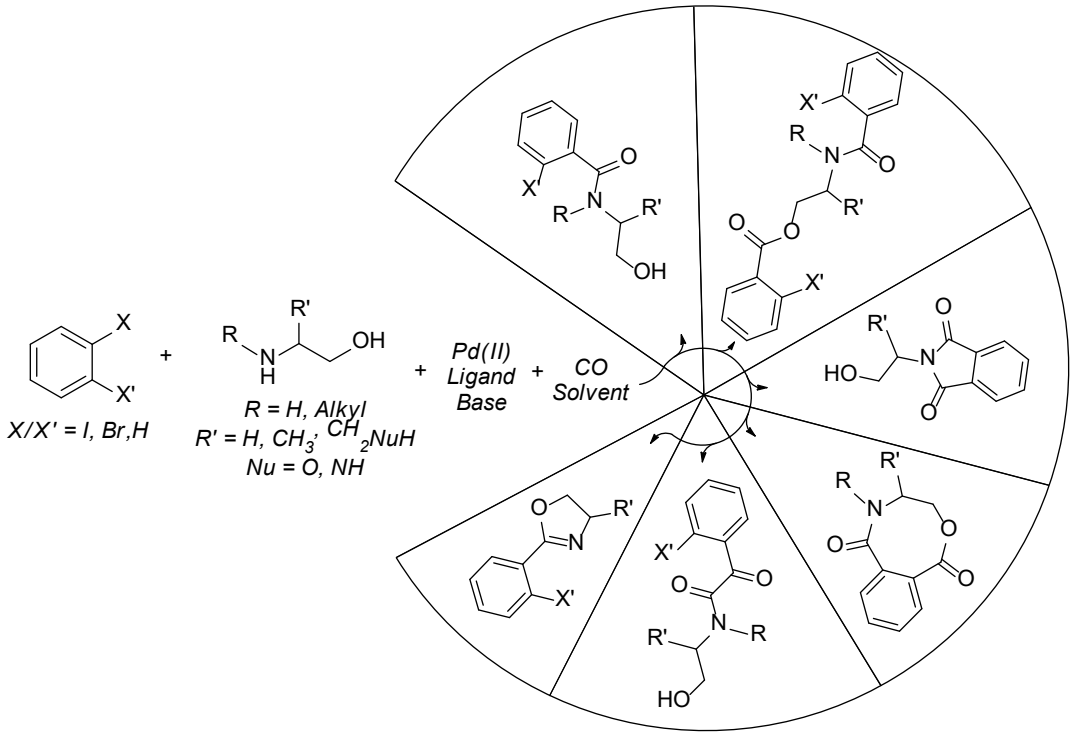


Figure 1. Carbonylation reaction of aryl halides in the presence of bifunctional N,O-nucleophiles

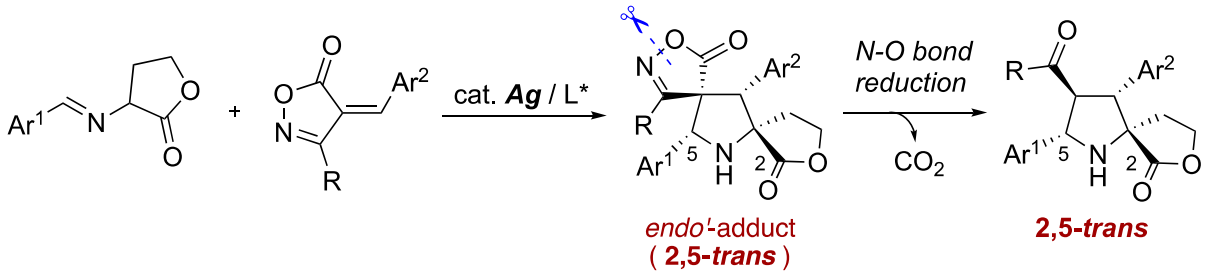
Chiral Silver Complex-catalyzed 2,5-*trans* Selective Asymmetric [3+2] Cycloaddition of Iminolactones with Ylidene-isoxazolones

Shohei Furuya, Kenji Muroi, Shin-ichi Fukuzawa*
Department of Applied Chemistry, Graduate School of Science and Engineering,
Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo, 112-8551, Japan
Email: a15.k3tk@g.chuo-u.ac.jp; orgsynth@kc.chuo-u.ac.jp

Chiral pyrrolidine scaffolds are frequently found in natural products and biologically active compounds. Paying attention to the relative configuration of these pyrrolidine derivatives, it has been known that not only 2,5-*cis*-substituted ones but also 2,5-*trans* substituted ones are used.[1] Therefore, a reliable method for efficient preparation of stereochemical divergent pyrrolidine derivatives is desired in drug discovery.

Metal complex-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with electron-deficient olefins is one of the most efficient synthetic methods for the preparation of the scaffolds and many efforts have been made to develop synthetic methods to construct these scaffolds.[2] However, this method usually affords 2,5-*cis* configuration such as *endo*- or *exo*-cycloadducts, and 2,5-*trans* configuration such as *endo´*- or *exo´*-cycloadducts are rarely obtained. In 2010, the first *exo´*-selective symmetric [3+2] cycloaddition, catalyzed by a chiral nickel complex, was reported by Arai and co-workers.[3a] This pioneering work suggested that *exo´*-diastereoselectivity was expressed by a stepwise Michael addition/Mannich pathway with bond rotation instead of a concerted 1,3-dipolar cycloaddition process. On the other hand, we have revealed that the 2,5-*trans* diastereoselectivity can be also expressed in the construction of spirocyclic pyrrolidines using ylidene-heterocycles as electron-deficient olefins. For example, we previously reported that silver complex-catalyzed *exo´*-selective asymmetric [3+2] cycloaddition of iminoesters with ylidene-2,3-dioxopyrrolidines.[3b]

In this work, we report the silver complex-catalyzed *endo´*-selective asymmetric [3+2] cycloaddition of iminolactones with ylidene-isoxazolones[4a], which efficiently afforded chiral spiro pyrrolidine scaffolds with excellent *endo´*-diastereoselectivity and high enantioselectivity. In particular, the isoxazolone moiety of the cycloadduct can be converted to ketone without loss of enantiomeric excess by the reduction of the N-O bond.[4b,c]



Scheme 1. The present work

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Palladium-Catalyzed Remote Borylative Cyclization of 1,n-Dienes via Chain Walking

Shota Kanno, Fumitoshi Kakiuchi, Takuya Kochi*
Department of Chemistry, Faculty of Science and Technology, Keio University
3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan.

Email: kochi@chem.keio.ac.jp

Remote functionalization of alkenes has attracted much attention since it enables transformations which would be otherwise difficult to achieve. On the other hand, it is still challenging to develop remote difunctionalizations, catalytic reactions to form bonds at both the alkene moiety as well as a remote position.[1] Our group has developed catalytic organic synthesis taking advantage of chain walking such as the palladium-catalyzed hydrosilylation/cyclization of 1,n-dienes with hydrosilanes.[2] In contrast, there have been scarce reports on remote difunctionalization involving a synthetically-useful C–B bond formation.[3]

Here we report palladium-catalyzed remote hydroboration/cyclization of 1,n-dienes (n = 7-9) with hydroboranes via chain walking (eq. 1).[4] In addition, we found that diborons could introduce further boryl group at the terminal position of the other alkyl chain and thus achieved remote diborylative cyclization of 1,n-dienes (n = 6-9) via chain walking (eq. 2).[5] Further transformation of the two boryl scaffolds enabled formal remote difunctionalization reactions which have been not achieved with the previous difunctionalization methods. Mechanistic studies implied that a key process in the reaction, conversion of a remote unactivated C(sp^3)–H bond to a C(sp^3)–B bond, proceeds via formal sigma bond metathesis between an alkylpalladium species and a diboron reagent.

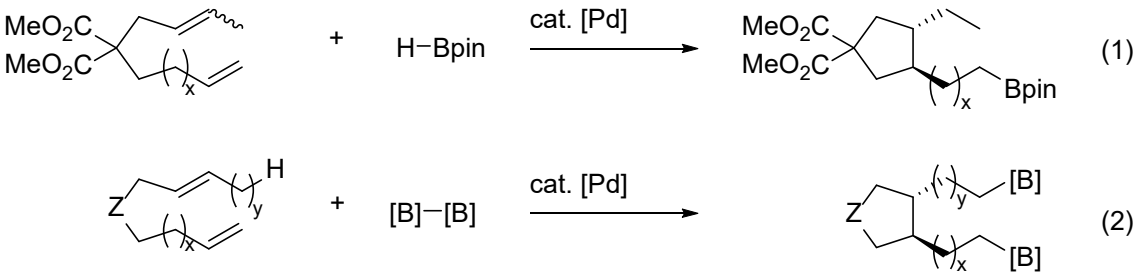

Figure 1. Palladium-catalyzed remote borylative cyclization of 1,n-dienes via chain walking.

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Planar Chiral Rhodium Complexes for Enantioselective Catalysis

Simon B. Blakey*[a]
[a]Department of Chemistry, Emory University, Atlanta, GA, USA.
Email: sblakey@emory.edu

The development of new reactions and catalysts for the oxidative cross-coupling of C-H bonds with C-H, N-H and O-H bonds will be discussed. Strategically, these reactions allow for the synthesis of complex molecules from their constituent components, minimizing the need for functional group activation and manipulation. A novel planar chiral catalyst platform for enantioselective reactions will be presented. Illustrative examples of emergent applications will be provided.

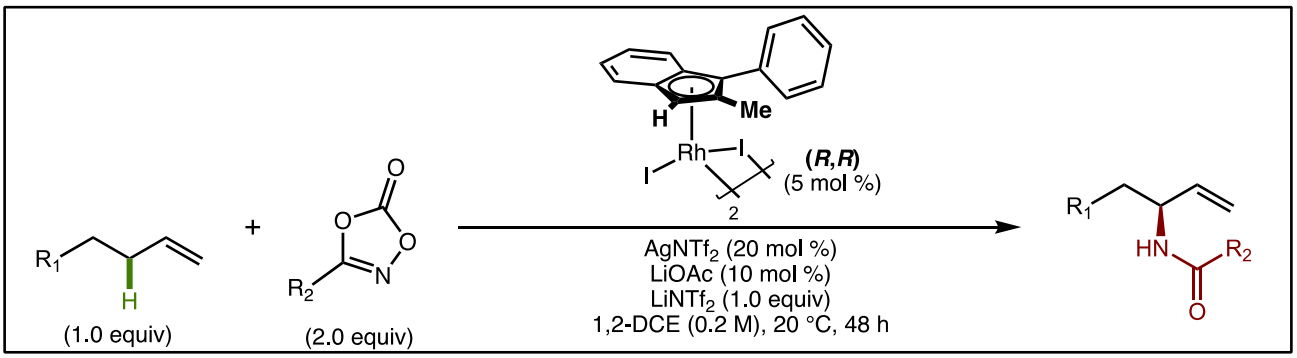

Figure 1. Illustrative enantioselective C-H amidation.

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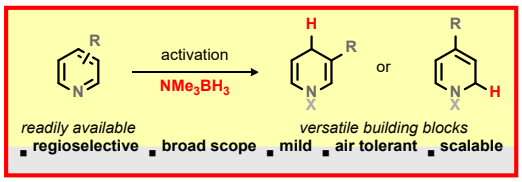
Substituted Dihydropyridine Synthesis by Dearomatization of Pyridines

Arne Heusler,[+a] Julian Fliege,[+a] Tobias Wagener,[a] Steffen Heuvel,[a] Frank Glorius*[a]
[a]Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 36, 48149 Münster (Germany)
[+] These authors contributed equally.

Email: steffen.heuvel@wwu.de; glorius@uni-muenster.de

Dearomatization is an effective method to transform readily available N-heterocycles into partially saturated motifs. Manipulation of dihydro-derivatives holds great potential and provides access to a variety of semi-saturated N-heterocyclic building blocks. However, current strategies are limited in scope and the use of sensitive reagents restricts the applicability in synthetic laboratories. Herein, we report the synthesis of a broad variety of N-substituted 1,4- and 1,2-dihydropyridines by very mild and selective reduction with amine borane for the first time.



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Iron-Catalyzed Oxidative C–H Alkenylation of Thiophenes with Enamines

Takahiro Doba,[a] Rui Shang,*[b] Eiichi Nakamura*[b]
[a]International Research Center for Elements Science, Institute for Chemical Research, Kyoto University.
[b]Molecular Technology Innovation, Department of Chemistry, The University of Tokyo.
Email: doba.takahiro.3t@kyoto-u.ac.jp;
rui@chem.s.u-tokyo.ac.jp; nakamura@chem.s.u-tokyo.ac.jp

Construction of a vinylene structure through C–H/C–H coupling provides straightforward synthetic access to functional π-conjugated organic molecules.[1] The palladium-catalyzed oxidative C–H alkenylation between an arene and an olefin, or Fujiwara–Moritani (FM) coupling presents one of the earliest examples.[2] However, the FM reaction is not applicable to electron-rich alkenes because of the difficulty in the carbometallation step and the undesired oxidation of electron-rich alkenes leading to decomposition and oligomerization. We report herein iron-catalyzed oxidative C–H alkenylation between thiophenes and enamines and its application to copolymerization of bisthiophene and bisenamine monomers using Fe(III) as an iron source, conjugated trisphosphine[3] as a ligand, $AlMe_3$ as a base, and diethyl oxalate as an oxidant. The C–H bond next to the sulfur atom of the thiophene and the terminal position of the enamine reacted with excellent regio-, linear, and *E* selectivity. The reaction includes C–H activation of thiophene via σ-bond metathesis and subsequent enamine C–H cleavage triggered by nucleophilic enamine addition to the Fe(III) center, thereby differing from the FM reaction in mechanism and synthetic scope (Figure 1). The copolymers synthesized by the new reaction possess a new type of enamine-incorporated polymer backbone.

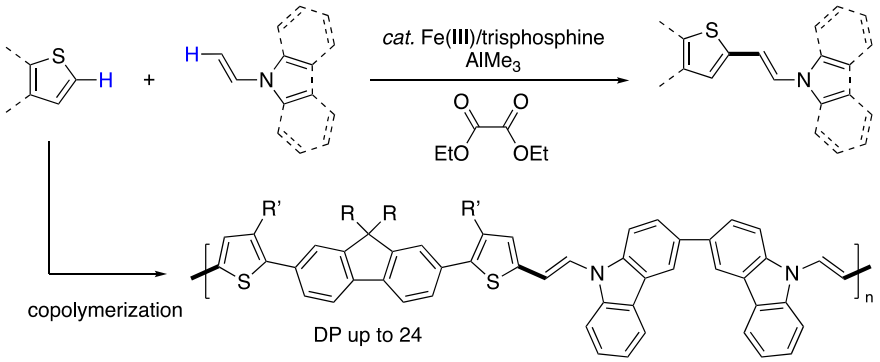

Figure 1. Oxidative C–H alkenylation of thiophenes with enamines enabled by Fe(III)/trisphosphine/$AlMe_3$/oxalate catalysis.[4]

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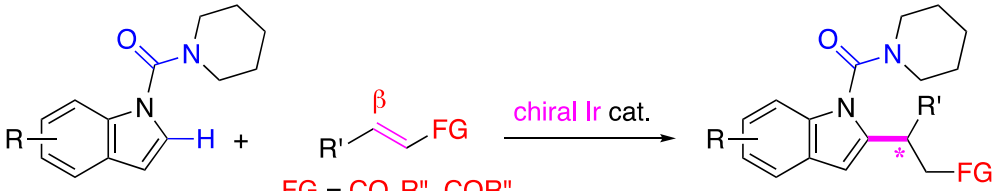
Ir-Catalyzed Transformations Initiated by C–H Activation Using Nitrogen- or Sulfur-Containing Substrates

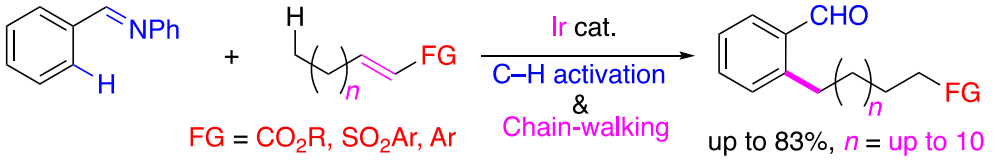
Takanori Shibata,* King Hung Nigel Tang, Haru Marumo, Ryo Tokutake, Masafumi Kojima, Kanako Uchida, Takahiro Iwaki, Mio Sasaki, Kazuki Nishihara, Mamoru Ito
Chemistry & Biochemistry, Advanced Science and Engineering, Waseda University
Email: tshibata@waseda.jp

Transition metal-catalyzed transformation initiated by C–H activation is fascinating in organic synthesis, because it can realized atom- and step-economical protocols. We comprehensively studied cationic Ir-catalyzed reactions using various heteroatom-containing substrates. We here disclose our recent results using nitrogen- or sulfur-containing directing group.

The synthetic methods of regioselective C–H functionalization of indole are strongly desired. We have focused on Ir-catalyzed C–H activation of the C2 position. When amide group was used as a directing group, highly enantioselective C–H alkylation was achieved by using functionalized alkene via formal C–H conjugate addition (Eq 1).[1] In contrast, when imino group was used, consecutive double bond isomerization (i.e., chain walking) proceeded, and the C–C bond formed at the terminal position of the alkyl chain, which means that remote functionalization is possible (Eq. 2).[2]

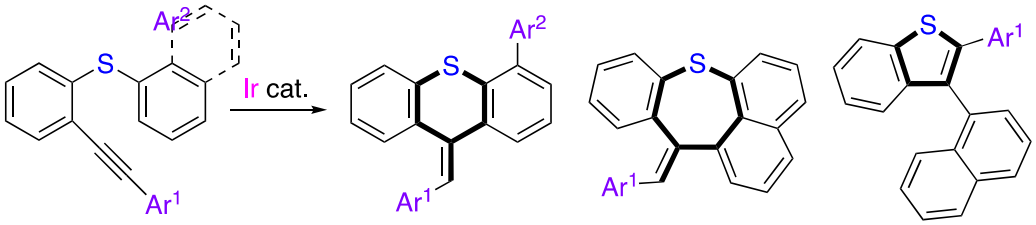


(Eq. 1)



(Eq. 2)

Examples of sulfide-directed C–H activation is limited, because the sulfide moiety often acts as a poison in transition metal catalysis. We realized Ir-catalyzed sp^2 C–H activation of 2-alkynyl diaryl thioether (Eq. 3).[3] The intramolecular reaction provides three types of sulfur-containing multicyclic compounds with 5, 6, and 7-membered system, respectively, by the choice of substituent and reaction temperature. We will demonstrate sulfide-directed sp^3 C-H activation in the presentation.



(Eq. 3)

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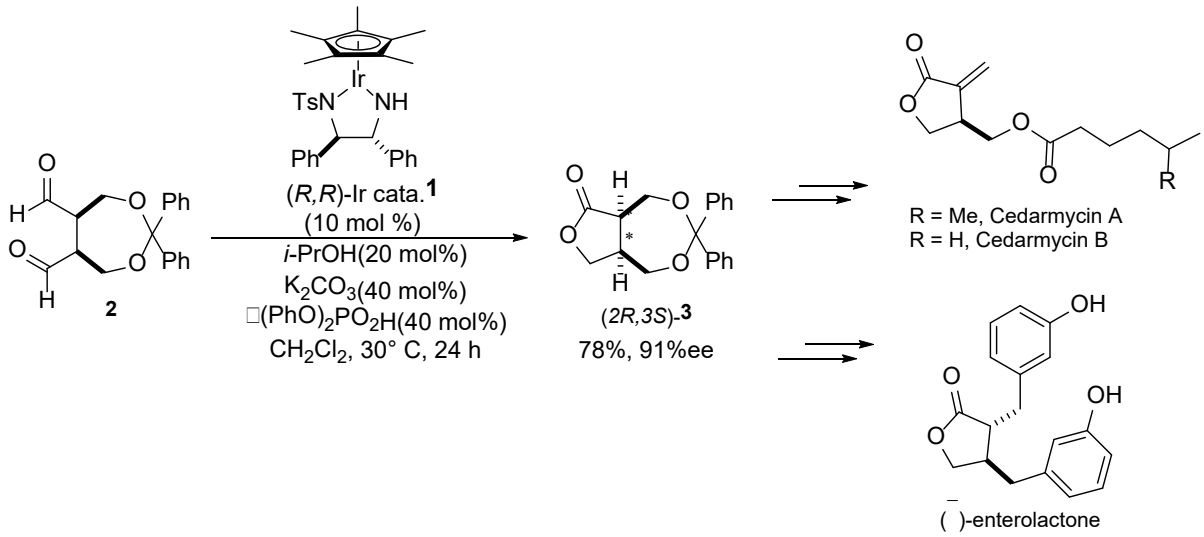
Asymmetric Tishchenko Reaction and their Application in Enantiodivergent Synthesis of Natural Products

Takeyuki Suzuki
Sanken, Osaka University, Osaka, Japan
Email: suzuki-t@sanken.osaka-u.ac.jp

The first successful example of a catalytic enantioselective intramolecular Tishchenko reaction of a *meso*-dialdehyde **2** in the presence of a chiral iridium complex **1** is described. Chiral lactone **3** was obtained in good yields with up to 91% ee (Scheme 1).[1] To compare the enantioselective intramolecular Tishchenko reaction with the enantioselective oxidative lactonization, the corresponding diol was treated with the same catalyst in the presence of acetone as an oxidant, to afford the desired lactone in 92% yield and 79% ee with the opposite configuration. The obtained enantioenriched lactones were successfully converted to (*S*)-cedarmycins A and B.

In the context of asymmetric synthesis, epimerization is usually problematic. We report the use of the epimerization of *cis*-2,3-bis(hydroxymethyl)-γ-butyrolactone which is obtained from **3** for the synthesis of enterolactones with anti-carcinogenic, anti-inflammatory, anti-angiogenic, and antioxidant activity. Selective α- or β-epimerization of a γ-butyrolactone was used for the enantiodivergent synthesis of enterolactone.[2] Theoretical and kinetic studies were performed to elucidate the epimerization mechanism.



Scheme 1. Catalytic enantioselective intramolecular Tishchenko reaction of *meso*-dialdehyde **2.**

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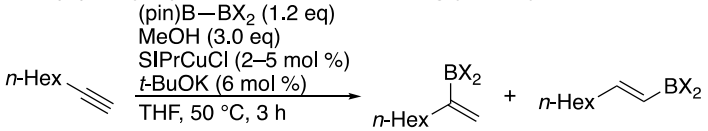
Origins of Internal Regioselectivity in Copper-Catalyzed Borylation of Terminal Alkynes

Takumi Tsushima, Masaaki Nakamoto, Hiroto Yoshida*
Graduate School of Advanced Science and Engineering, Hiroshima University, Higashi-Hiroshima 739-8526, Japan.
Email: tsushimatakumi@hiroshima-u.ac.jp; yhiroto@hiroshima-u.ac.jp

Alkenylboron compounds with defined regio- and stereochemistry are indispensable reagents in chemical synthesis, because they are efficiently convertible into invaluable multisubstituted alkenes with controlled geometry through carbon–carbon bond-forming processes including Suzuki–Miyaura coupling (SMC). Copper-catalyzed three-component hydroboration of alkynes with a diboron in the presence of an alcohol has been one of the most convenient and reliable methods for synthesizing alkenylboron compounds, whose regiochemistry is determined in addition step of a borylcopper species across a triple bond (borylcupration). In general, attachment of a boron functionality to a more substituted carbon of terminal alkynes via internal-selective borylcupration is challenging, since an inherently Lewis acidic boron moiety, in principle, favors the attachment to a terminal carbon (entry 1). On the other hand, we have already disclosed that internal-selective borylcupration is feasible by using Cu–B(dan) (dan = naphthalene-1,8-diaminato) of diminished boron-Lewis acidity (entry 2). However, the resulting alkenyl–B(dan) bonds cannot directly be utilized for SMC under standard conditions,[1] because the strongly diminished Lewis acidity of the B(dan) moiety retards transmetalation step. Thus, development of a new boron moiety that can compatibly achieve the internal-selectivity and the SMC activity is of urgent importance.

When we carried out the reaction of 1-octyne with (pin)B–B(aam) (aam = anthranilamidato) in the presence of methanol and SIPrCuCl (%V_{bur} = 50.1), internal-selective borylcupration occurred to give B(aam)-containing products in 91% yield (*b*:*l* = 89:11) (entry 3). These results strongly imply that the boron-Lewis acidity diminishment is the key to achieving the internal-selectivity, and furthermore the regioselectivity in the borylcupration correlates closely with the degree of the diminishment, which can be qualitatively determined by theoretical calculation-based AA (Ammonia Affinity).[2] In addition, the reaction with bulkier 6DippCuCl(%V_{bur} = 53.1) led to the perfect internal selectivity to furnish the branched alkenyl–B(aam) in 96% yield (entry 4).

In conclusion, we have disclosed that the key factors governing internal-selective borylcupration of terminal alkynes are “diminishment of boron-Lewis acidity” and “ligand (NHC)-derived steric bulk around a copper center”.[3]



entry	BX_2	AA(kJ/mol)[a]	NMR yield (%)	*b*:*l*
1	B(pin)	36.2	62	12:88
2	B(dan)	12.1	92[b]	>99:1
3	B(aam)	18.6	91	89:11
4[c]	B(aam)	18.6	96	>99:1

[a] DFT calculations, by means of Ph-BX_2 as model compounds, were carried out at the M06-2X/def2-31-SVP level. [b] Isolated yield. [c] 6DippCuCl and 1,4-dioxane instead of SIPrCuCl and THF.

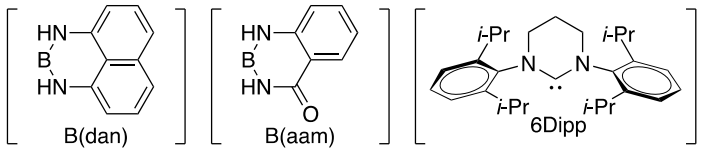


Table 1. Regioselectivities in Cu-catalyzed hydroboration of 1-octyne with diborons of varied Lewis acidity.

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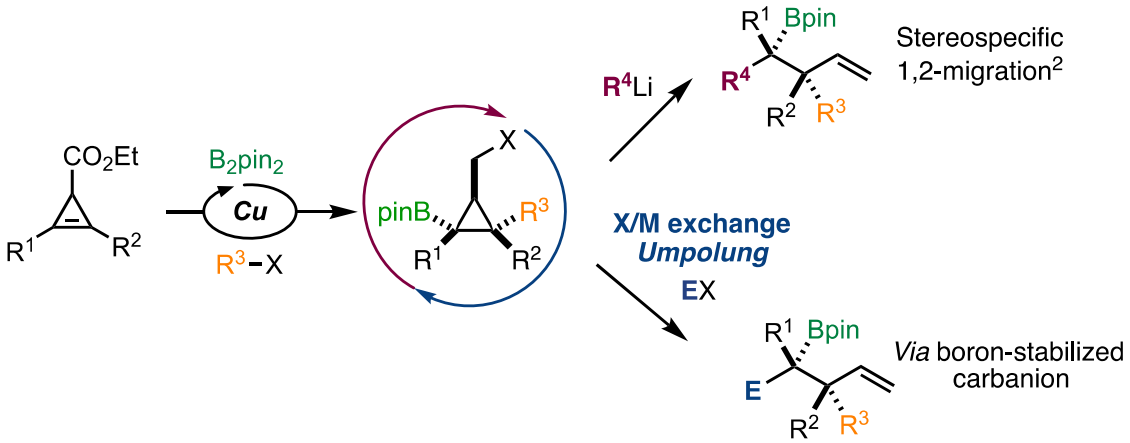
Ring Opening of Borylated Cyclopropanes: Beyond 1,2-Metalate Rearrangement

Tereza Pavlickova,[a] **Ilan Marek***[a]
[a] Schulich Faculty of Chemistry, Technion – Israel Institute of Technology, Technion City, Haifa, 3200009, Israel
Email: tereza.p@campus.technion.ac.il; chilanm@technion.ac.il

Controlled construction of congested stereogenic centers within acyclic systems represents an acute challenge in stereoselective organic synthesis. The main obstacle is the conformational flexibility of these organic frameworks compared to cyclic systems. An elegant solution to this problem involves introduction of stereocenters to cyclopropanes as highly strained carbocycles and subsequent selective ring opening.[1]
Previously, we reported synthesis and 1,2-metalate rearrangement-mediated ring opening of polysubstituted borylated cyclopropanes by various alkyl-, aryl- and alkynyllithium reagents.[2] Here, we present a selective metal-halogen exchange-mediated ring fragmentation of cyclopropyl pinacolboranes exploiting the anion-stabilizing effect of the boronic ester moiety. This *umpolung* strategy represents an original approach to boron-stabilized carbanions. Subsequent reaction of these species with electrophiles provides various acyclic frameworks with high levels of diastereoselectivity.



Scheme 1.

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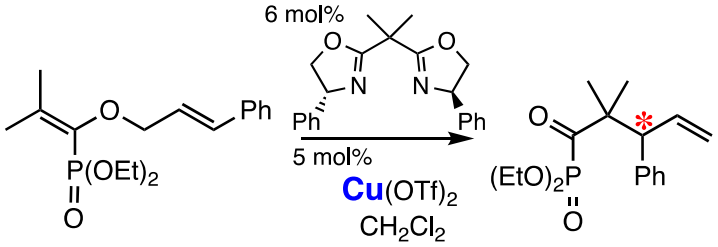
Microwave Specific Effect on Metal Catalyzed Reactions

Tohru Yamada
Department of Chemistry, Keio University, Yokohama, 223-8522 Japan

Email: yamada@chem.keio.ac.jp

We recently reported that the *atropo*-enantioselective ring-opening reactions of biaryl lactones were drastically enhanced without any loss of the enantioselectivity under microwave irradiation conditions with strict temperature control [1]. It was also observed that the racemization rate of the optically pure biaryl lactones was accelerated by microwave irradiation; at 25 °C, the half-life racemization time was 2.4 days, whereas with microwave irradiation, it was 1.6 days [2]. Catalytic enantioselective Claisen rearrangement was drastically enhanced under microwave irradiation conditions without any loss of the enantioselectivity (**Table 1**). Based on Arrhenius plots it was revealed that enantioselectivity decreased as the internal reaction temperature increased. Therefore, this reaction acceleration would NOT be caused by only a simple thermal effect [3].

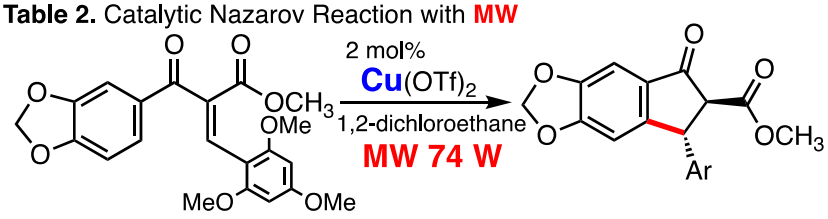
Table 1. Catalytic Asymmetric Claisen Rearrangement with **MW**



Entry	Conditions	Temp / °C	Time / h	Yield / %	Ee / %
1	Heat block	15.0±0.1	40	86	91
2	Heat block	15.2±0.1	4	55	90
3	**Microwave**	15.4±0.8	4	84	92
4	Heat block	30.2±0.4	4	83	77

A copper-catalyzed Nazarov cyclization using an aryl vinyl ketone derivative containing 1,3-dicarbonyl moiety was carried out under microwave irradiation conditions. The Nazarov cyclization was dramatically accelerated and the kinetic rate of the microwave irradiation was 5.8 times faster than that by conventional heating conditions (**Table 2**). When the asymmetric Nazarov cyclization was conducted using a chiral copper catalyst, the Nazarov reaction was subsequently enhanced by the microwave irradiation without any loss of the enantioselectivity. It is suggested that the drastic enhancement with the retention of the enantioselectivity was caused NOT by simple thermal effect, but by a microwave-specific effect on the enantioselective reaction [4].

Table 2. Catalytic Nazarov Reaction with **MW**



Entry	Temp. / °C	k_{MW} / h^{-1}	k_{HB} / h^{-1}	k_{MW} / k_{HB}
1	35	0.16 ± 0.01	0.027 ± 0.004	5.8 ± 0.9
2	40	0.23 ± 0.04	0.063 ± 0.003	3.6 ± 0.6
3	45	0.39 ± 0.03	0.16 ± 0.01	2.4 ± 0.2
4	50	0.63 ± 0.02	0.29 ± 0.02	2.2 ± 0.2

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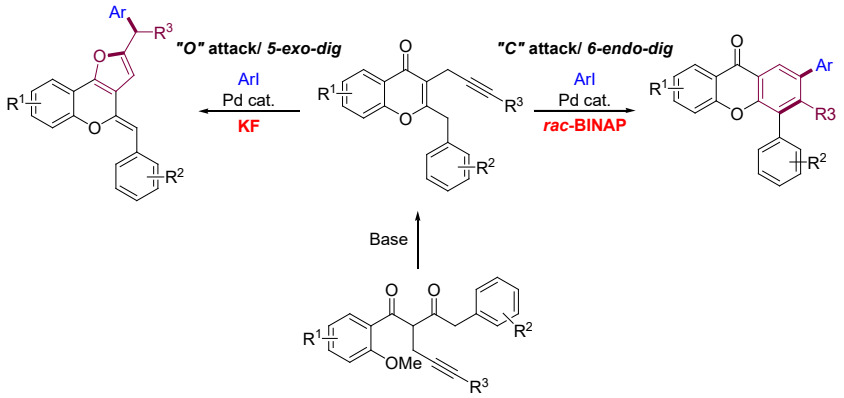
Palladium-Catalyzed Regiocontrolled Cascade Cyclization/Cross-Coupling of 2-Benzyl-3-Alkynyl Chromones with Aryl Iodides

Yi-En Liang[a] Chih-Yu Kan,[a] Balaji D. Barve,[a] and Wen-Tai Li*[a]
[a]National Research Institute of Chinese Medicine, Ministry of Health and Welfare Taipei 11221, Taiwan, R.O.C.

Email: wtli@nricm.edu.tw

Oxygen-containing heterocycles, such as xanthone and chromone, represent key structural units in many natural products and important pharmaceuticals compounds. They are also utilized as useful building blocks in synthetic chemistry.[1] As a consequence, the construction of polycyclic skeletons containing chromones and xanthones has continually attracted significant attention from synthetic chemists.

The novel Pd-catalyzed controllable regio- and chemoselective cascade approaches to synthesize 4*H*-furo[3,2-*c*]chromene and xanthone were developed. The rare examples of cascade approaches involving the intramolecular cyclization and cross-coupling reactions of 2-benzyl-3-alkynyl chromones with aryl iodides. Pd-catalyzed two modes of O- and C-nucleophilic cyclization and difunctionalization of alkynes is the key step for the cascade reactions, it could be controlled by the addition of KF or bidentate phosphine. In addition, a one-pot cascade process from γ-alkynyl-1,3-diketone was also developed through multiple cyclizations and cross-coupling reaction.[2]



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Selenium Catalyzed 1,2-Diamination of 1,3-Dienes

Victoria L. Zottarelli, Alex F. Dohoda, Forrest E. Michael*[a]
[a]Univeristy of Washington

Email: vzottare@uw.edu, fmichael@uw.edu

Due to the importance of nitrogen-containing molecules as medicinal targets and useful synthetic intermediates, development of reactions that introduce multiple C-N bonds in a single transformation remains a significant and important challenge in catalysis. We have developed a new catalytic 1,2-diamination of 1,3-dienes catalyzed by phosphine selenides, based partly on a stoichiometric diamination reported by Sharpless in 1974.[1] This original work was limited in substrate scope and reported low yields The product of a 1,2 diamination of 1,3 dienes is unique in that it contains two novel carbon-nitrogen bonds produced in one catalytic cycle. Though difunctionalization reactions of dienes can sometimes suffer from challenges in controlling regioselectivity, this new diamination is highly selective for a single 1,2-addition product. We propose that this regioselectivity is due to the unique mechanism of our selenium-catalyzed reaction. Generation of a selenium bis(imide) is followed by a [4+2] cycloaddition with the diene to afford a seleno-bicyclic species and the first new carbon-nitrogen bond. Next, [2,3] sigmatropic rearrangement forms the second carbon nitrogen bond, and subsequent oxidative turnover and aminolysis generates the diaminated product. The catalytic reaction conditions employ (diacetoxyiodo)benzene ($PhI(OAc)_2$) as a cheap and commercially available oxidant, trifluoroethylsulfamate (NH_2Tfes) as the nitrogen source, and a bulky phosphine selenide catalyst.[2] The use of NH_2Tfes as a protecting group on the nitrogen allows for facile deprotection. This reaction is effective with a variety of different 1,3-dienes, including linear and cyclic dienes, and is tolerant of a variety of functional groups.

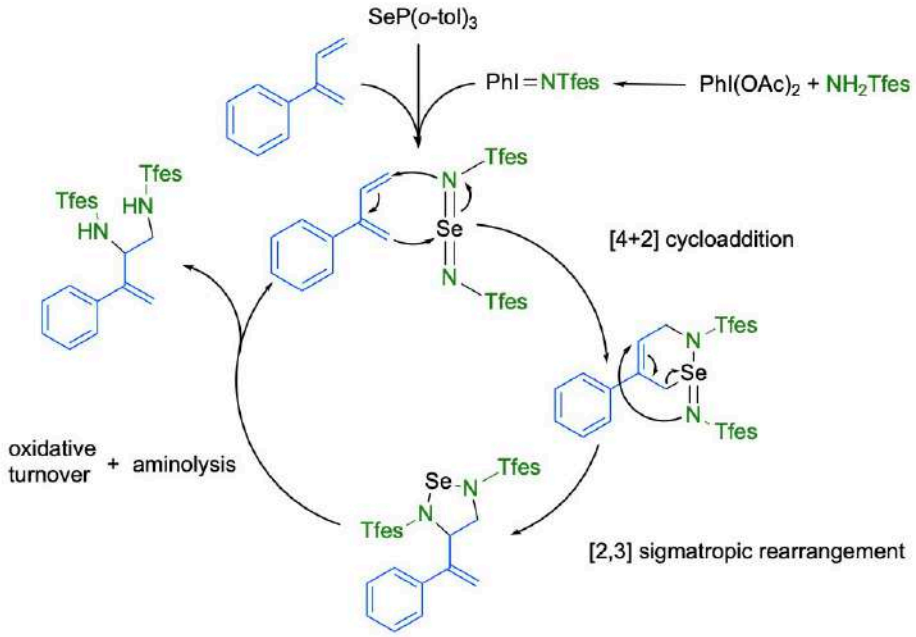

Figure 1. Proposed catalytic cycle

References

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Geometry-Controlled Enantioselective Rh-catalyzed Conjugate Arylation of 1,3-dienes

Wesley McNutt,[a] **Rylan Lundgren***[a]
[a]Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada
Email: wmcnutt@ualberta.ca; rylan.lundgren@ualberta.ca

The development of methodology to conveniently access small molecules provides a reliable tool to synthetic chemists pursuing increasingly complex targets while concomitantly decreasing synthetic difficulty and cost. The thorough investigation, typically involved in developing a general transformation, adds to our understanding of the interplay between chemical space and mechanism. Such insights will inform and inspire future innovations or applications.

Enantioselective Rh-catalyzed conjugate arylations have been well studied and applied.[1] The vinylogous variants have seen less use, but typically result in additions to the δ-position[2] unless large terminal R-groups or directing groups are applied (Figure 1A).[3]

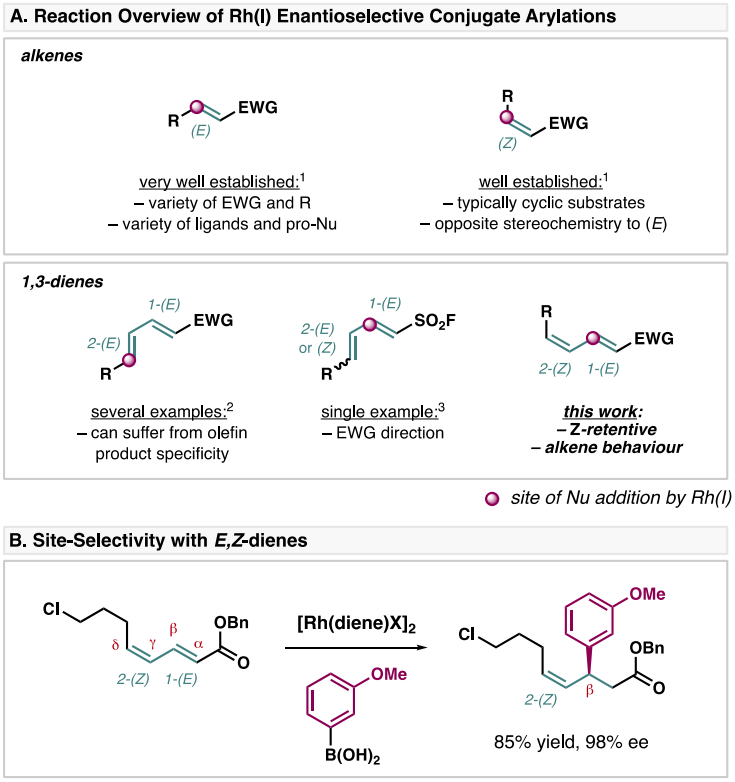

Figure 1. Site-selectivity by alkene geometry for Rh conjugate addition

This presentation will discuss a methodological campaign wherein we redirect this apparent δ-selectivity with a Rh-catalyzed β-regio- and enantioselective arylation of *E,Z*-dienes with the dominant controlling factor being the alkene geometry at the γ,δ-moiety (Figure 1B). Reaction development, scope, and mechanistic studies probing the subtle origins of reaction selectivity will be the focus of the material presented. The developed conditions provide an extension to the well-established reaction manifold. The novel substrate class highlights the significance of mild conditions on reactions with geometrically-defined products and starting materials.

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Facile Syntheses of Sulfinate Esters and Sulfinamides Mediated by Thionyl Fluoride

William P. Chappell,[a] **Marie Favie**,[a] **Glenn M. Sammis***[a]
[a]University of British Columbia
Email: wchappell@chem.ubc.ca; gsammis@chem.ubc.ca

Sulfinate esters are used in organic chemistry as synthetic intermediates[1] and in bioimaging.[2] Methods to make them are rare, and involve harsh reaction conditions and/or long reaction times.[3,4,5] The similar sulfinamide functional group is widely used as a synthetic intermediate[6] and as a catalyst.[1,7] Traditional synthetic methods often require starting from pre-installed sulfur-containing functional groups.[8,9] A recent report for the syntheses of sulfinamides allows late-stage installation of sulfur,[10] but does not facilitate access to sulfinate esters. We have developed a rapid, mild method for the syntheses of sulfinate esters, that is also applicable to sulfinamides, filling this gap in the literature.

The Sammis group has recently shown that sulfur(IV) fluoride reagents are useful for forming a variety of substrates.[11,12] Our powerful one-pot method for sulfinate ester and sulfinamide synthesis uses thionyl fluoride (SOF_2) to form a sulfur(IV) fluoride intermediate from an alcohol or an amine. This is then treated with an organozinc carbon nucleophile to form the desired product. The reactions are fast, work under mild conditions, and are applicable to a variety of substrates.

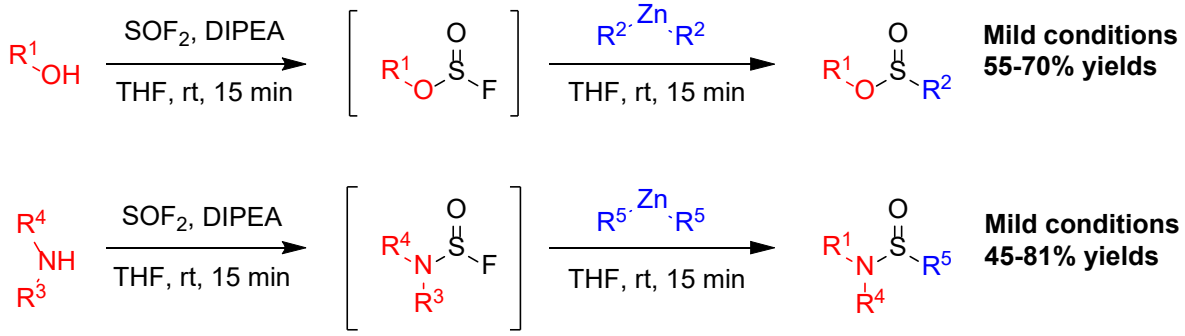

Figure 1. Syntheses of sulfinate esters and sulfinamides

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Diastereoselective Synthesis of Chiral-at-P Alkenylphosphonamidates through Ni-Catalyzed C-P Coupling of Phosphoramidites and Alkenyl Halides

Xiao-Bing Chen, Damián Padín, and Ben L. Feringa *[a]
Stratingh Institute for Chemistry, University of Groningen
Nijenborgh 4, 9747AG, Groningen (The Netherlands)
Email: xiaobing.chen@rug.nl; b.l.feringa@rug.nl

P-stereogenic compounds are widely used as ligands in asymmetric catalysis[1], and present in a myriad of bioactive compounds and pharmaceuticals[2]. Yet, their stereocontrolled preparation remains challenging[3]. Herein, we report a novel strategy towards versatile chiral-at-P alkenylphosphonamidates through a one-pot Ni-catalyzed C-P coupling/diastereoselective hydrolysis of readily available phosphoramidites and alkenyl halides. Remarkably, a diastereo- and chemodivergent behavior was observed upon subtle changes in the reaction conditions. Additionally, selective derivatizations of chiral alkenylphosphonamidates demonstrate their utility as building blocks for the synthesis of structurally diverse P-stereogenic compounds (Figure 1).

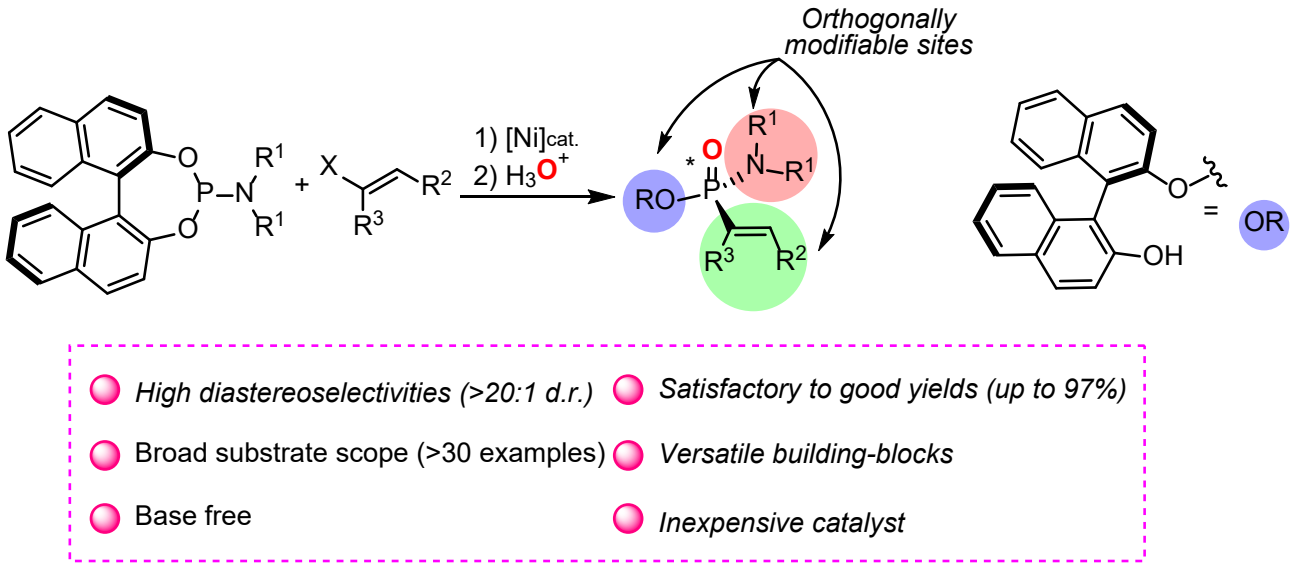

Figure 1. Strategy for the generation for chiral P- chiral alkenylphosphonamidates

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Palladium-Catalyzed Arylation of Cyclic Vinylogous Esters

Yen-Ku Wu*[a]

[a]Department of Applied Chemistry, National Yang Ming Chiao Tung University.

Email: yenkuwu@nycu.edu.tw

We recently developed the catalytic monoarylation and polyarylation of cyclic vinylogous esters.[1,2] The deprotonative arylation reactions take place at the relatively acidic α and/or γ' carbons of cyclic vinylogous esters (Figure 1). Significantly, the regioselectivity of these processes could be well controlled under customized conditions. Overall, this collection of arylation reactions have offered a unique opportunity in rapidly assembling a variety of functionalized aryl-containing scaffolds.

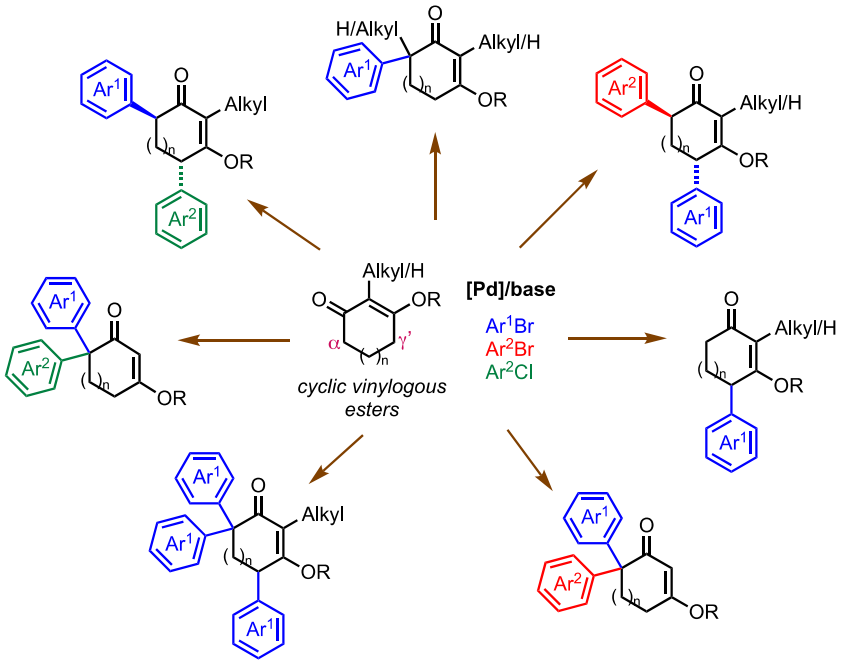

Figure 1. Arylation Reactions of Cyclic Vinylogous Esters.

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C–H Alkenylation of Pivalophenone Derivatives with Internal Alkynes by Low-Valent Iron Phosphine Complexes

Yoichi Kitazawa,[a] Takuya, Kochi,[a] Fumitoshi Kakiuchi*[a,b]
[a]Department of Chemistry, Faculty of Science and Technology, Keio University
3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa, 223-8522, Japan
[b]JST, CREST, JPMJCR20R1, 4-1-8 Honcho, Kawaguchi, Saitama, 332-0012, Japan
Email: kakiuchi@chem.keio.ac.jp

Transition-metal-catalyzed direct C–H functionalizations have become powerful synthetic tools, and especially, those using earth-abundant metal catalysts have emerged as resource-economical methods for efficient formation of C–C and C–heteroatom bonds.[1] Iron, the most abundant transition metal, has been one of the metals widely studied as active sites of C–H functionalization catalysts. Our group previously reported $Fe(PMe_3)_4$-catalyzed C–H/olefin coupling reaction of aromatic ketones and C–H homoallylation with methylenecyclopropanes.[2,3]

Here we report the $Fe(PMe_3)_4$-catalyzed reaction of pivalophenone derivatives with internal alkynes proceeds to provide C–H alkenylation products and the use of a catalytic amount of P^tBu_3 as an additive improves the product yields (Figure 1).[4] The alkenylation proceeded selectively to give a single regio- and stereoisomer in all cases. For example, when the reaction of *p*-trifluoromethylpivalophenone with 1.1 equiv of 1-phenyl-2-(triethylsilyl)acetylene was carried out using 10 mol % $Fe(PMe_3)_4$ and 33 mol % P^tBu_3 in THF at 80 °C for 48 h, the alkenylation proceeded regio- and stereoselectively to give the corresponding alkenylation product in 95% yield.

The C–H alkenylation is considered to proceed via coordination of the alkyne to the Fe center, oxidative addition of the ortho C–H bond of the ketone, 1,2-insertion of the alkyne into the Fe–H bond, and reductive elimination. $^{31}P\{^1H\}$ NMR experiments suggested that the iron-alkyne intermediate is the resting state. P^tBu_3 may donate electrons to the iron center of the iron-alkyne intermediate to facilitate the oxidative addition of the ortho C–H bond of the ketone.

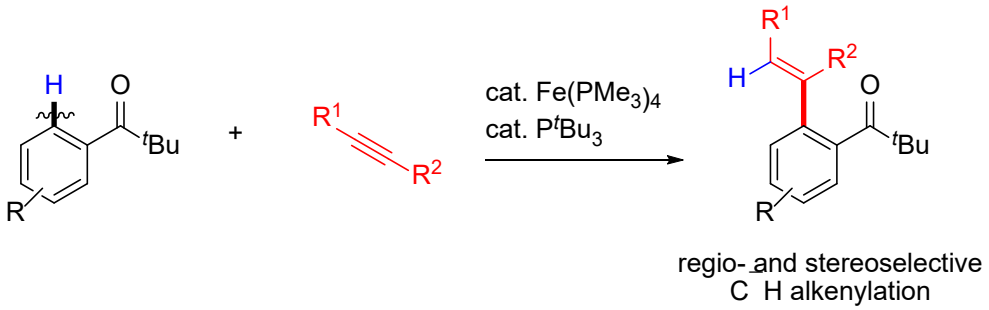

Figure 1. Iron-catalyzed C–H alkenylation using internal alkynes

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New Lewis Base Catalysts for Aromatic Halogenation

Yuji Nishii,[1]* Chandrababu Naidu Kona,[2] Rikuto Oku,[1] Shotaro Nakamura,[1] Koji Hirano,[1] Masahiro Miura[2]

[a] Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan.
[b] Innovative Catalysis Science Division, Institute for Open and Transitionary Research Initiative (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan.

Email: y_nishii@chem.eng.osaka-u.ac.jp

Haloarenes are among the most privileged chemicals in modern organic chemistry field. The versatile applications of aryl halides in pharmaceuticals, material science, and metal-catalyzed coupling reactions clearly highlight their importance. The electrophilic aromatic halogenation has been practical and straightforward synthetic method to manufacture a wide variety of haloarenes.[1] Although classical halogenation using molecular halogens (Cl_2, Br_2, I_2) and Lewis/Brønsted acid activators is still a promising protocol, it suffers from handling difficulties, low regioselectivity, and limited functional group tolerance (Figure 1a). Moreover, the late-stage halogenation of complex molecules has been regarded as a challenging task.

Meanwhile, Lewis basic molecules have also been used to catalytically activate halogenating reagents by forming halonium complexes (Figure 1b). However, the Lewis base activation is generally less powerful than the acid catalysis, and thereby is only effective for the aromatic halogenation of electron-rich substrates.[2] To overcome this limitation, we began a quest for a suitable structural platform for enhancing the reactivity of halonium species and developed new sulfide catalysts (Figure 1c). To our delight, the developed catalytic system was applicable not only to bromination but also to more challenging chlorination and iodination. Potential synthetic applications are demonstrated by late-stage halogenation of bioactive compounds and straightforward synthesis of multi-halogenated compounds.[3]

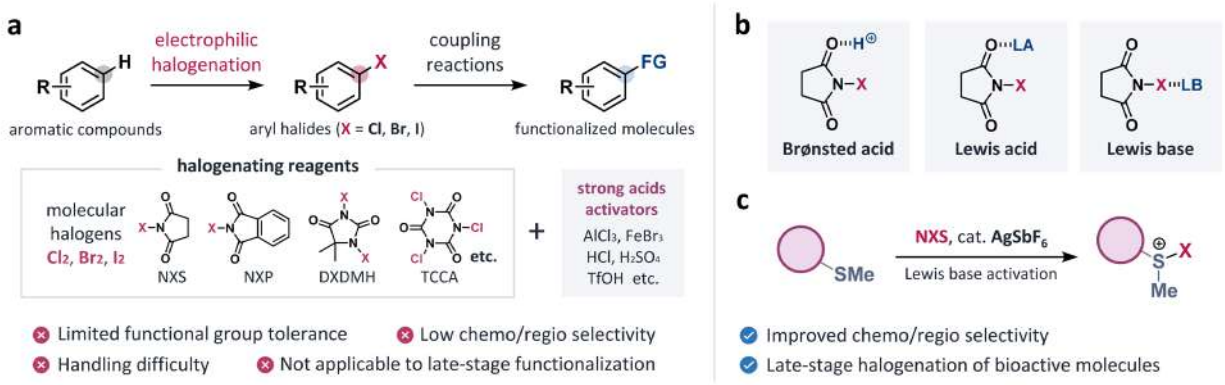

Figure 1. A schematic presentation for the electrophilic aromatic halogenation.

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Chiral Copper Complex-catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Iminoesters with α-Sulfonyl Cinnamonitriles

Yuki Sakuma, Shohei Furuya, Shin-ichi Fukuzawa*
Department of Applied Chemistry, Graduate School of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo, 112-8551, Japan
Email : a19.f6x5@g.chuo-u.ac.jp ; orgsynth@kc.chuo-u.ac.jp

1,3-Dipolar cycloaddition of azomethine ylide with activated alkene is the powerful tool for the synthesis of pyrrolidine derivatives.[1] Acrylic ester and acrylonitrile can be used as good dipolarophiles, while 3-substituted α,β-unsaturated esters and nitriles such as cinnamates and cinnamonitriles are not allowed as dipolarophiles. Arylidene esters and nitriles sometimes used as alternative dipolarophiles of plain unsaturated esters and nitriles, which give 4,4'-diester substituted pyrrolidines.[2]

α-Phenylsulfonyl cinnamonitrile has been demonstrated as a good Michael acceptor in the organocatalyzed conjugated addition.[3] The chemo- and stereospecific removal of the sulfone group from the chiral quaternary center of the cyanosulfone can afford the corresponding nitrile.

In this study, we would like to propose α-phenylsulfonyl cinnamonitrile as an alternative dipolarophile in 1,3-dipolar cycloaddition of azomethine ylide and stereoselective synthesis of 3-aryl-4-cyano-substitured pyrrolidines by the removal of the sulfone group.

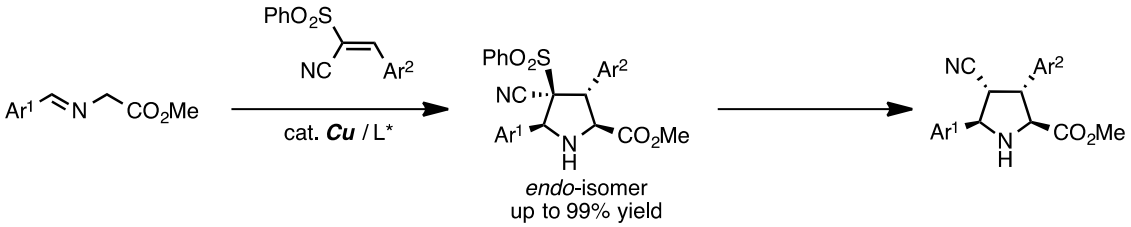

Figure 1

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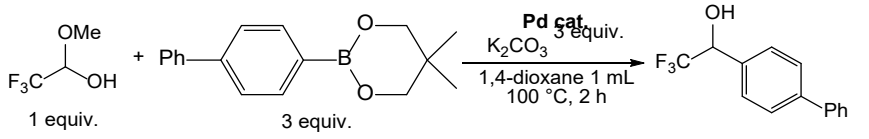
Bulky and Rigid NHC-Coordinated Palladium Complexes Catalyzed Arylation of Perfluoroacetoaldehyde Hemiacetals

Yuna Yamaguchi,[a] **Tetsuya Yamamoto***[a]
[a] Department of Materials Science and Engineering, Graduate School of Engineering, Tokyo Denki University,
Email: 22kms28@ms.dendai.ac.jp; t-yamamoto@mail.dendai.ac.jp

Perfluoroalkylated alcohols are useful synthetic building blocks for pharmaceuticals, organic electronic materials, and polyelectrolyte membranes, and are generally synthesized by three routes; nucleophilic additions of perfluoroalkyl carbanion source such as Ruppert-Prakash reagent to carbonyl compounds, reduction of fluoroalkylated ketones, and nucleophilic additions of carbanion such as Grignard reagents to fluorinated carbonyl compounds.[1] The transition metal catalyzed addition of arylboron compounds to carbonyl compounds has garnered attention as a reliable method for synthesizing alcohols with various functional groups. While the Rh-catalyzed addition of arylboronic acids to perfluoroalkyl ketones has been developed, this catalytic reaction has not been adapted to perfluoroalkyl aldehydes due to their instability in air and difficulty in handling.[2,3] In this study, we have developed palladium catalysts that enable the synthesis of perfluoroalkylated alcohols from organoboron compounds and perfluoroacetaldehyde hemiacetals. The results of the arylation of trifluoroacetaldehyde methyl hemiacetals, catalyzed by bulky and rigid NHC-coordinated palladium complexes were shown in Figure 1.



Entry	Pd catalyst	Yield[a]
1	CH_3-IPr*-CYP (0.05 mol%)	84
2	F-IPr*-CYP (0.05 mol%)	80

[a] Isolated Yield

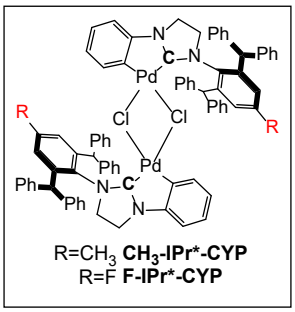


Figure 1. Pd-catalyzed arylation of trifluoroacetaldehyde methyl hemiacetal

Bulky and rigid NHC coordinated cyclometalated palladium complexes, denoted as CH_3-IPr*-CYP and F-IPr*-CYP, showed excellent catalytic activity for arylation of trifluoroacetaldehyde methyl hemiacetal in 0.05 mol% Pd catalyst loading. So, we report the scope and limitations of these catalysts for the synthesis of fluorous alcohols.

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Stereodivergency in Copper-Catalyzed Borylative Difunctionalizations: The Impact of Lewis Acidity

Bijan Mirabi,[a] Shangyu Li,[a] Justin Ching,[a] Madina Lenz,[a] Simon M. Popovic,[a] Mark Lautens*[a]

[a]Department of Chemistry, Davenport Chemical Laboratories, University of Toronto, Toronto, Ontario, M5S 3H6, Canada

Email: bijan.mirabi@mail.utoronto.ca; mark.lautens@utoronto.ca

A reagent-controlled diastereodivergent copper-catalyzed borylative difunctionalization is reported. The formation of Lewis adducts that guide selectivity is commonly invoked in organic reaction mechanisms.[1] Using density functional theory calculations, we identified BpinBdan as a sterically similar and less Lewis acidic alternative to B_2pin_2. Using a newly developed borylative aldol domino reaction as the proof-of-concept, we demonstrate a change in stereochemical outcome by a simple change of borylating reagent – B_2pin_2 affords the diastereomer associated with coordination control while BpinBdan overturns this mode of binding. We show that this strategy can be generalized to other scaffolds and, more importantly, that BpinBdan does not alter the diastereomeric outcome of the reaction when coordination is not involved. BpinBdan can be viewed as a mechanistic probe for coordination in future copper-catalyzed borylation reactions.

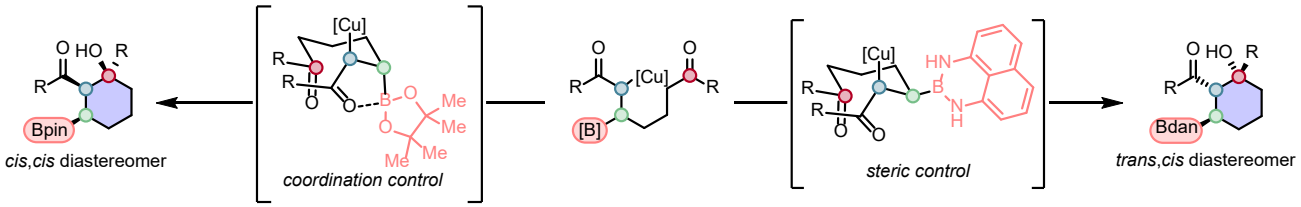

Figure 1. Reagent-controlled, stereodivergent copper-catalyzed borylative difunctionalization of π-systems

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Efficient Iridium-Catalyzed C–H Borylation of Electron-Rich Arenes Enabled by SpiroBipyridine Ligand

Yushu Jin, Boobalan Ramadoss, Sobi Asako,* Laurean Ilies*
RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan
Email: yushu.jin@riken.jp; sobi.asako@riken.jp; laurean.ilies@riken.jp

Iridium-catalyzed C–H borylation of aromatic compounds is one of the most efficient methods for the direct preparation of aryl boron compounds. However, the conventionally utilized 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) and 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) ligands show low reactivity when electron-rich arenes are used as substrates, especially with pinacolborane (HBpin) as the borylating agent.[1] In this work, we have developed a SpiroBipyridine (SpiroBpy) ligand[2] that boosts the reactivity of the iridium-catalyzed C–H borylation of electron-rich arenes.[3] This method is expected to expand the toolbox of this reaction to achieve more diverse applications.

As shown in Figure 1, when electron-rich arenes such as 1,3-diaminobenzene, 1,3-dimethoxybenzene, and 1,3-di-*tert*-butylbenzene were used as the substrate for the iridium-catalyzed C–H borylation with HBpin, the borylated products were obtained in high yields by using SpiroBpy as the ligand. In contrast, the borylation proceeded in lower yields with the commonly used ligands (dtbpy or tmphen) under similar conditions. Various other electron-rich arenes, such as anilines, anisoles, alkylbenzenes, etc., were also efficiently borylated by employing our SpiroBpy ligand to provide the corresponding borylated products in good to high yields. Notably, the SpiroBpy ligand also showed high reactivity in late-stage functionalization of pharmaceutically relevant compounds, such as Lidocaine, Phenylalanine derivatives, etc. We postulate that a potential C–H-π interaction between the arene substrate and the fluorene backbone, which only exists in SpiroBpy skeleton, may be responsible for the acceleration.

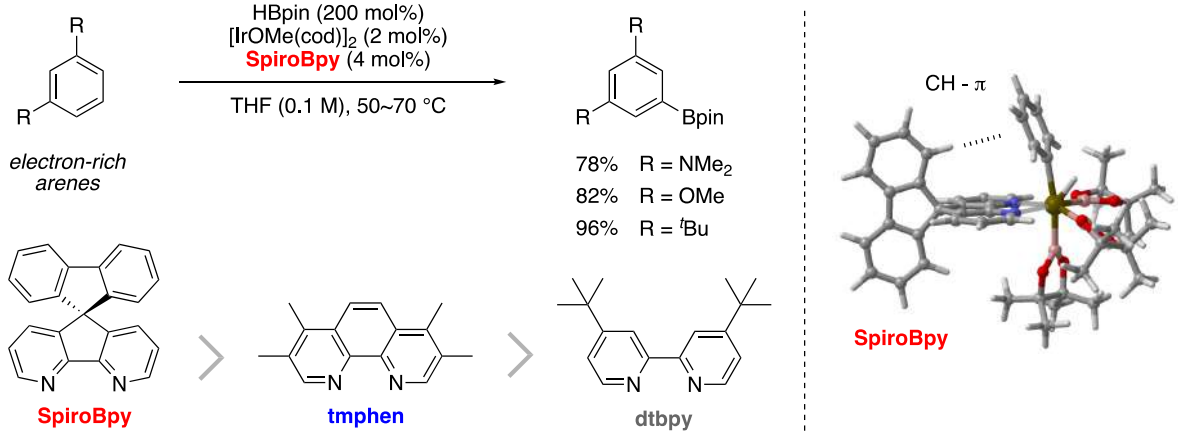

Figure 1.

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Difluorocarbene Insertion Reaction of the Fluoroalkyl Copper Complexes

Yuyang Zhou[a], Ryohei Doi*[a], Sensuke Ogoshi*[a]
[a]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan
Email: y_syu@chem.eng.osaka-u.ac.jp; rdoi@chem.eng.osaka-u.ac.jp; ogoshi@chem.eng.osaka-u.ac.jp

The development of a new synthetic strategy for perfluoroalkyl compounds earns attention because of their chemical and physical properties. Therefore, various methods for introducing perfluoroalkyl groups were invented. Use of fluoroalkyl copper complex is one of the powerful methods. However, the introduction method of perfluoroalkyl groups longer than CF_3 is limited. Specifically, only a few reports demonstrated synthetic pathways for perfluoroalkyl compounds with different functional groups on each edge. We have previously reported the synthesis of 1,1,2,2-tetrafluoroethane derivatives mediated by the fluoroalkyl copper complex (phen)$CuCF_2CF_2R$ (R = aryl)[1]. The complex was prepared by pressurizing tetrafluoroethylene to the THF solution of the aryl copper species derived from aryl boronic acid ester.

Herein, we report a homologation reaction of (phen)$CuCF_2CF_2Ph$ by using $TMSCF_3$ to fabricate new perfluoroalkyl compounds having C_3 and C_4 perfluoroalkyl chain and different functional groups on each edge (Fig. 1). This reaction didn't require any additives such as KF which is often used as an activator of $TMSCF_3$[2]. The resulting elongated fluoroalkyl copper complex reacts with various coupling partners to afford corresponding fluoroalkyl compounds in good to moderate yields. Reactions of iodoarenes carrying electron-withdrawing groups, benzyl chloroformate, benzyl bromide, and ethyl *cis*-3-Iodoacrylate proceeds smoothly with the copper complex to afford the purpose compounds. Furthermore, $C(sp^2)$−Cl, $C(sp^2)$−Br, and unprotected amino group are tolerated. The one-pot reaction, in which a fluoroalkyl copper was used without purification for convenience of experimental procedure, afforded the C_3 fluoroalkyl compounds in good to moderated yield. Our CF_2 insertion reaction is believed to proceed via α-fluorine elimination of fluoroalkyl copper complex promoted by $TMSCF_3$ acting as a Lewis acid. The selectivity for α- and β-fluorine elimination[3] would be controlled by the character of Lewis acid.

This strategy demonstrates a novel pathway for C_3 and longer perfluoroalkyl compounds and expands the scope of perfluoroalkyl copper chemistry.

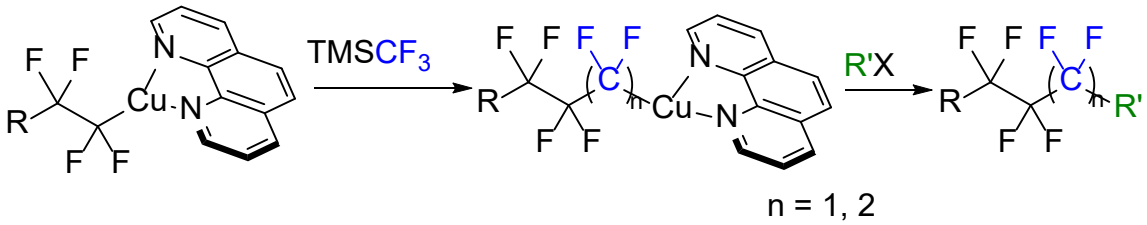

Figure 1. Difluorocarbene insertion reaction on a fluoroalkyl copper complex.

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The Development and Application of New Electrophilic Trifluoromethyl- -selenolation Reagents: Trifluoromethyl Selenoxides

Yang Li,[a] Shangbiao[a] Zhang, Zhegao Ye,[a] Yanan Wang,[a] Zheliang Yuan*[a,b]

[a] Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, Department of Chemistry, Zhejiang Normal University, Jinhua, Zhejiang 321004. [b] Department of Chemistry, Simon Fraser University, Burnaby, British Columbia V5A 1S2, Canada.

Email: zyuan88@zjnu.edu.cn; zheliang_yuan@sfu.ca

Trifluoromethylselenyl group (CF_3Se) has become an emerging fluorinated moiety in synthetic chemistry due to its high Hansch lipophilicity parameter (Hansch–Leo Parameter π_R = 1.61) and strong electron-withdrawing effect (Hammett constants σ_m = 0.44, σ_p = 0.45).[1] The trifluoromethylselenolation is hampered by limited synthetic methods and related reagents.[1] Inspired by Procter's recent work,[2] we designed and synthesized the new electrophilic trifluoromethylselenolation reagents, trifluoromethyl selenoxides, which are easy to prepare, easy-to-handle and not moisture or air sensitive (Figure 1a).[3,4] The selenoxides are successfully applied into metal-free C-H trifluoromethylselenolation of a series of (hetero)arenes and Lewis acid (Tf_2O)-promoted vicinal oxytrifluoromethylselenolation of alkenes with good functional group tolerance (Figure 1b and 1c).[3]

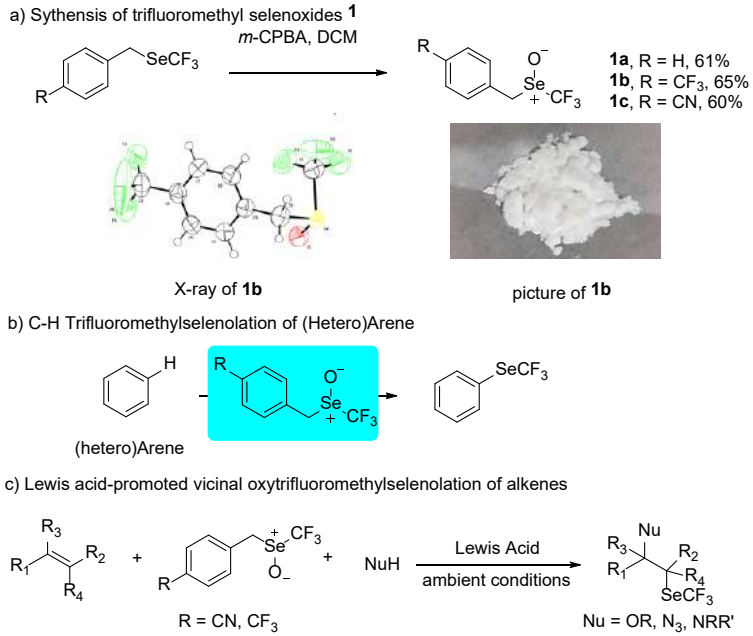

Figure 1. Synthesis and Application of Trifluoromethyl Selenoxides.

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Generation of Vinylic Lithium Species from Silyl Enol Ethers

Ziwei Zhang,[a] Fumiya Takahashi,[a] Takashi Kurogi,[a] Hideki Yorimitsu*[a]
[a]Department of Chemistry, Graduate School of Science, Kyoto University

Email: zhang.ziwei.64s@st.kyoto-u.ac.jp; yori@kuchem.kyoto-u.ac.jp

Silyl enol ethers represent stable forms of enolates and are easy to prepare from various carbonyl compounds. Because of their electron-rich nature, silyl enol ethers are typically used for nucleophilic attack or one-electron oxidation in organic synthesis. In contrast, no transformation of silyl enol ethers via one-electron reduction has been reported. Recently we have been working on the development of reductive transformations of unsaturated bonds using strong reducing agents such as alkali metals. For example, we reported alkali-metal-promoted reductive cleavage of the carbon-oxygen bond of propargylic ethers to generate allenylic lithium species[1] and vinylic carbamates to generate vinylic sodium species.[2]
Based on the previous report, we envisioned that silyl enol ethers could undergo reduction by means of a strong reductant without degradation of the robust Si−O bond and that the following elimination of the siloxide would furnish the corresponding vinylic lithium species which can be trapped by various electrophile. As expected, lithium arenides were found to promote the lithiation of silyl enol ethers to afford the corresponding allylic alcohols after trapping with carbonyl compounds in high yields. The present reaction can generate vinylic lithium species in two steps from the corresponding ketones and be regarded as an equivalent of the Shapiro reaction.

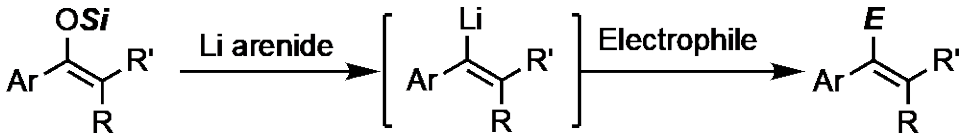

Figure 1. Generation of vinylic lithium species.

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