Catalytic Formation of C-N Bonds

ICS Symposium Honoring Wolf Prize Laureates

Stephen L. Buchwald and John F. Hartwig

May 29th, 2019

TECHNION
Israel Institute of Technology

Technion, Schulich Faculty of Chemistry, Hall 1

08:15-08:45 Gathering and Registration

08:45-09:00 Opening session

Prof. Ehud Keinan, President, Israel Chemical Society
Prof. Noam Adir, Dean, Schulich Faculty of Chemistry, Technion

Session 1 **Chair: Prof. Ehud Keinan**

09:00 **Prof. Stephen L. Buchwald** , MIT, USA
Palladium-Catalyzed Carbon-Heteroatom Bond-Forming Reactions for the Functionalization of Molecules Big and Small

09:30 **Prof. John F. Hartwig**, University of California, Berkeley, CA, USA
Catalytic Formation of Carbon-Heteroatom Bonds from C-H Bonds

10:00 **Prof. Alois Fürstner**, Max-Planck-Institut, Mülheim/Ruhr, Germany
A New Reactivity Paradigm: trans-Hydrogenation, gem-Hydrogenation and trans-Hydrometalation of Alkynes

10:30 **Dr. Seble Wagaw**, AbbVie Corp., USA
Process Development for Glecaprevir

11:00-11:30 Coffee Break

Session 2 **Chair: Prof. Doron Pappo**, Ben-Gurion University of the Negev

11:30 **Prof. Scott Miller**, Yale University, USA
Selective Catalytic Reactions in Complex Molecular Scaffolds

12:00 **Prof. Dmitri Gelman**, Hebrew University of Jerusalem, Israel
Catalysis and the modular Pincer-Platform

12:30 **Prof. Qilong Shen**, Shanghai Institute of Organic Chemistry, China
Cooperative Dual Pd/Ag Catalyst for Difluoromethylation of Aryl Bromides and Iodides

13:00-14:00 Lunch Break

Session 3 **Chair: Prof. Ilan Marek**, Schulich Faculty of Chemistry, Technion

14:00 **Prof. Lanny S. Liebeskind**, Emory University, USA
Organochalcogen-Catalyzed Aerobic Redox Dehydration

14:30 **Prof. Rubén Martin Romo**, ICIQ, Tarragona, Spain
Turning simplicity into complexity via multifaceted nickel catalysts

15:00 **Prof. David W. C. MacMillan**, Princeton University, USA
New Photoredox Reactions

15:30 Concluding remarks


Stephen L. Buchwald


John F. Hartwig


Alois Fürstner


Seble Wagaw


Scott Miller


Dmitri Gelman


Qilong Shen


Lanny S. Liebeskind


Rubén Martin Romo


David W. C. MacMillan

abbvie

Schulich Faculty of Chemistry
Technion – Israel Institute of Technology

Organizers: Ehud Keinan and Ilan Marek

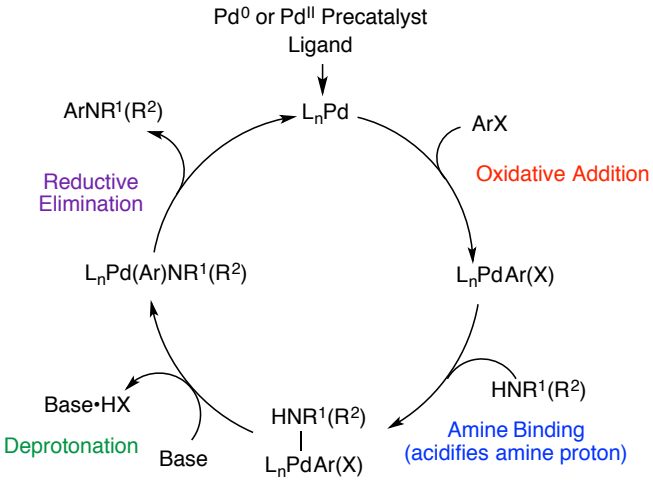
Registration: Helene Daniely <israelchemistry@gmail.com>

Palladium-Catalyzed Carbon-Heteroatom Bond-Forming Reactions for the Functionalization of Molecules Big and Small

Stephen L. Buchwald

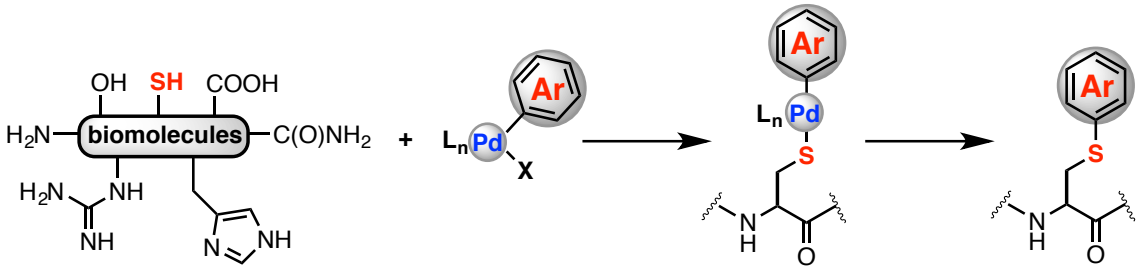
Department of Chemistry, MIT

Cross-coupling methodology is an indispensable part of the everyday repertoire of synthetic organic chemists. Among the many possibilities, we have focused a great deal of attention on the Pd-catalyzed formation of C-N bonds (*Chem. Rev.*, **2016**, *116*, 12564); a mechanistic pathway for this transformation is shown below. This methodology has been widely utilized throughout academia and industry.



Crucial to our success in the development of new and more generally applicable methods has been our discovery and use of biaryl monodentate phosphine ligands. These have been licensed for manufacture on large scale to eight companies and are available, in many cases, on very large scale (100's of Kg produced).

More recently, we have begun to apply related methodology to the functionalization of biomolecules including peptides, proteins and antibodies (*Nature*, **2015,** *526*, 687, *J. Am. Chem. Soc.* **2018**, *140,* 3128).



"transmetalation"

reductive elimination

This lecture will include: 1) An introduction to palladium-catalyzed carbon-heteroatom bond-forming reactions. 2) A description of ligand and catalyst development employing biarylphosphines. 3) Applications of these catalysts to the functionalization of heterocycles and the preparation of compounds of interest to medicinal chemists. 4) Applications of these catalysts to problems in bioconjugation. This section will describe our work on the functionalization of peptides, proteins and antibodies as well as the ligation of proteins.

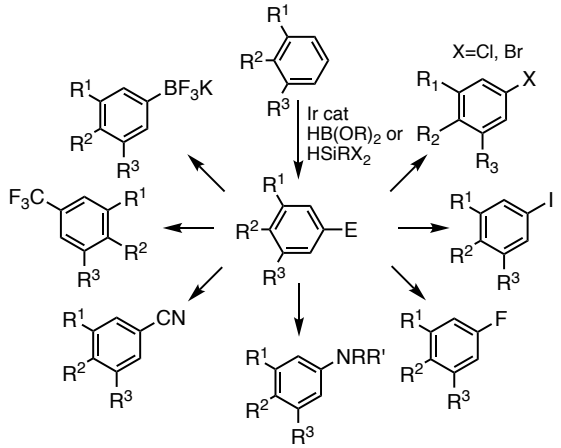
Formation of Carbon-Heteroatom Bonds from C-H Bonds

John F. Hartwig

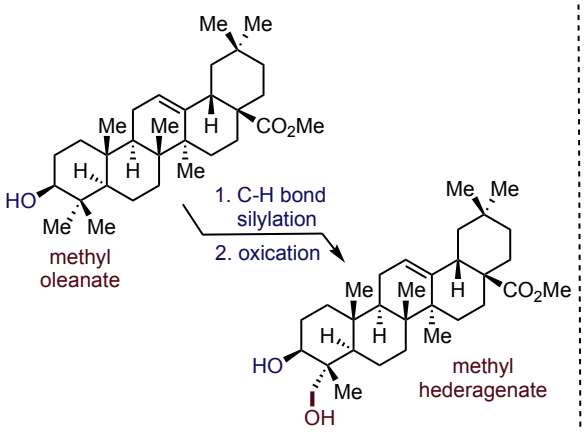
University of California, Berkeley, CA 94720 (USA) and
Division of Chemical Sciences, and Lawrence Berkeley National Laboratories, Berkeley, CA.
Email: jhartwig@berkeley.edu

Cross Coupling to form carbon-heteroatom bonds from carbon-halogen bonds has become a widely practiced approach to modify aromatic and heteroaromatic structures. To enable the modification of aromatic and heteroaromatic structures at positions distinct from those suitable for cross coupling, we have worked to develop reactions that form carbon-heteroatom bonds from C-H bonds. In addition, we have sought catalysts for the functionalization of aliphatic C-H bonds that would enable the formation of products containing new carbon-oxygen and carbon-nitrogen bonds at positions where coupling reactions would be challenging to conduct. This lecture will present recent directions of research in our group toward discovering selective reactions of C-H bonds catalyzed by transition metal complexes. The design and selection, as well as the intimate mechanism, of catalysts and catalytic reactions for these selective functionalization processes will be presented.

Ir-catalyzed borylation and silylation of arenes



Ir-catalyzed silylation of alkyl C-H bonds



A New Reactivity Paradigm: *trans*-Hydrogenation, *gem*-Hydrogenation and *trans*-Hydrometalation of Alkynes

Alois Fürstner

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cis-Delivery of H_2 to the π-system of an unsaturated substrate is the canonical course of metal catalyzed hydrogenation reactions. The semi-reduction of internal alkynes with the aid of [Cp*Ru]-based catalysts violates this fundamental rule and affords *E*-alkenes by direct *trans*-hydrogenation.[1-4] Detailed mechanistic studies show that this perplexing stereochemical outcome can either be reached by a concerted pathway or by a mechanism in which both H-atoms of H_2 are delivered to one and the same C-atom of the triple bond in the first place. This net *geminal* hydrogenation leads to the formation of discrete metal carbene complexes. Some implications of this fundamentally new transformation will be discussed.

Moreover, it will be shown that catalytic *trans*-hydrogenation is by no means a singularity: rather, the underlying principle is also manifest in *trans*-hydroboration, *trans*-hydrosilylation, *trans*-hydrogermylation and *trans*-hydrostannation, which are equally paradigm-changing processes.[5,6] These robust reactions are distinguished by excellent functional group tolerance and have already stood the test of target-oriented synthesis in a number of demanding cases.[7,8]

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8. A. Fürstner, *J. Am. Chem. Soc*. **2019**, *141*, 11.

Process Development for Glecaprevir

Seble Wagaw

Development Sciences, AbbVie, 1 N Waukegan Road, North Chicago, IL 60064

The hepatitis C virus (HCV) is a blood borne disease estimated to affect between 71 and 185 million people worldwide.[1] Persons infected with HCV can remain asymptomatic for decades; left untreated HCV can lead to liver failure, liver cancer and death. One of the challenges in developing treatments is the genetic heterogeneity of HCV, with six major genotypes identified. Fortunately, the development of combinations of direct acting antiviral agents in recent years has resulted in multiple treatment options that represent a curative therapy for all major HCV genotypes.[2] Glecaprevir was identified as a potent HCV NS3/4A protease inhibitor with pan-genotypic activity.[3] Glecaprevir was developed in combination with Pibrentasvir, an NS5A inhibitor also with pan-genotypic activity. The combination of Glecaprevir and Pibrentasvir was approved for the treatment of chronic hepatitis C virus genotypes 1–6 and is marketed as Mavyret®.[4]

Two synthetic routes to Glecaprevir were utilized during the course of development; the enabling synthesis was used to support the pre-clinical toxicological evaluation and subsequent Phase I clinical trials, and the optimized synthesis which was used to support the late stage clinical trials and commercial launch. Development work towards the enabling route and the commercial process will be presented.

1. (a) World Health Organization. *Global Hepatitis Report 2017*. (WHO, Geneva, 2017). (b) Martinello, M.; Hajarizadeh, B.; Grebely, J.; Dore, G. J.; Gail V. Matthews, G. V. Management of acute HCV infection in the era of direct-acting antiviral therapy. *Nat. Rev. Gastroenterol. Hepatol*. **2018** *15*, 412. https://doi.org/10.1038/s41575-018-0026-5 (c) Messina, J. P.; Humphreys, I.; Flaxman, A.; Brown, A.; Cooke, G. S.; Pybus, O. G.; Barnes, E. Global Distribution and Prevalence of Hepatitis C Virus Genotypes. *Hepatology* **2015**, *61*, 77. https://doi.org/10.1002/hep.27259 (d) Hajarizadeh, B.; Grebely, J.; Dore, G. J. Epidemiology and natural history of HCV infection. *Nat. Rev. Gastroenterol. Hepatol*. **2013**, *10*, 553. https://doi.org/10.1038/nrgastro.2013.107

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Dr. *Seble Wagaw is an employee of AbbVie and may own AbbVie stock. AbbVie sponsored and funded the study; contributed to the design; participated in the collection, analysis, and interpretation of data, and in writing, reviewing, and approval of the final publication. We acknowledge to contributions of Enanta Pharmaceuticals to the Discovery and Development of Glecaprevir.*

Selective Catalytic Reactions in Complex Molecular Scaffolds

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This lecture will describe recent developments in our efforts to develop low-molecular weight catalysts for asymmetric reactions. Over time, our view of asymmetry has ebbed and flowed, with foci on enantioselectivity, site-selectivity and chemoselectivity. In most of our current work, we are studying issues related to enantioselectivity as a prelude to extrapolation of catalysis concepts to more complex molecular frameworks wherein multiple stereochemical issues are presented within a singular substrate. Moreover, we continuously examine an interplay between screening of catalyst libraries and more hypothesis-driven experiments that emerge from screening results. Some of the mechanistic paradigms, and their associated ambiguities, will figure strongly in the lecture.

Catalysis and the modular Pincer-Platform

Dmitri Gelman

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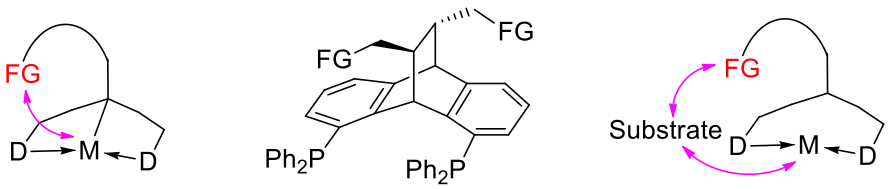
Small-molecule catalysts, equipped with a supplementary coordination sphere, have already proved themselves highly efficient in many important chemical transformations. It was previously demonstrated that attractive interactions between the secondary coordination environment and the substrate largely govern stereoselectivity and the reactivity of the primary catalytic site. This approach may become truly practical if divergent synthesis of libraries of such multifunctional catalysts is available, thus allowing facile shuffling of functional groups in the primary and secondary coordination spheres.

In this lecture, we will describe our efforts to develop modular 3-D ligands as a universal platform to examine catalytic reactions guided by secondary coordination sphere-substrate attractive interactions.



Cooperative Dual Pd/Ag Catalyst for Difluoromethylation of Aryl Bromides and Iodides

Qilong Shen

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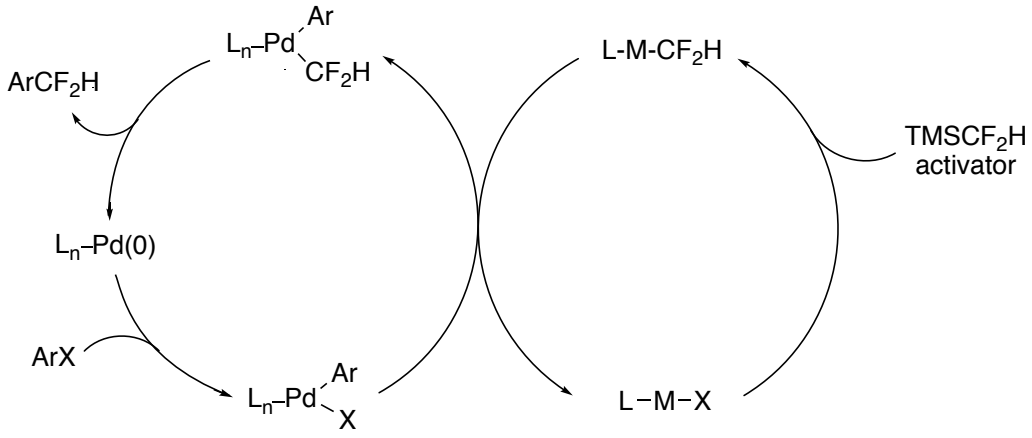
The difluoromethylated arenes are one of the privileged structural motifs that are important for fine-tuning the biological properties of drug molecules. No general catalytic method exits for the formation of difluoromethylarenes. Previous method for the preparation of difluoromethylarenes typically required harsh conditions, multiple steps or stoichiometric amount of catalysts. Here we report a cooperative dual palladium/silver catalyst system for direct difluoromethylation of aryl bromides and iodides under mild conditions. We developed the system by first preparation of the putative intermediates in the dual catalytic cycles, followed by studying the elemental steps to demonstrate the viability of the proposed cooperative catalytic cycle. The reaction was compatible with a variety of functional groups such as ester, amide, protected phenoxide, protected ketone, cyclopropyl, bromide and hetearyl subunit such as pyrrole, benzothioazole, carbazole or pyridine.



Reference

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Organochalcogen-Catalyzed Aerobic Redox Dehydration

Lanny S. Liebeskind

Department of Chemistry, Emory University, Atlanta, Georgia USA

This lecture describes the discovery and development of a new organocatalytic oxidation-reduction-condensation reaction for amide/peptide and ester construction, whose origins evolved from studies of aerobic, Cu-catalyzed desulfitative coupling of functionalized thioesters with boronic acids. The reaction system relies on triethylphosphite as a stoichiometric reductant and organocatalytic chalcogenides (benzoisothiazolones, benzoisoselenazolones, functionalized diselenides) with O_2 in air as the terminal oxidant. Triethylphosphate is the easily removed byproduct. These simple to run catalytic reactions provide practical and economical procedures for the acylative construction of C—N and C—O bonds. Variations in the structure of the organocatalyst supported by mechanistic studies allowed identification of reaction systems that perform well at 2.5 mol % organocatalyst loadings near room temperature under simple aerobic conditions.

"Benzoisothiazolone Organo/Copper-Cocatalyzed Redox Dehydrative Construction of Amides and Peptides from Carboxylic Acids using $(EtO)_3P$ as the Reductant and O_2 in Air as the Terminal Oxidant" by Lanny S. Liebeskind, Pavankumar Gangireddy, and Matthew G. Lindale, *J. Am. Chem. Soc.*, **2016**, 138, 6715−6718, DOI: 10.1021/jacs.6b03168

"On the Mechanism of Acylative Oxidation-Reduction-Condensation Reactions using Benzoisothiazolones as Oxidant and Triethylphosphite as Stoichiometric Reductant" by Pavankumar Gangireddy, Vidyavathi Patro, Leighann Lam, Mariko Morimoto, and Lanny S. Liebeskind, *J. Org. Chem.,* **2017**, *82* (7), pp 3513–3529. DOI: 10.1021/acs.joc.7b00020

"Esterification by Redox Dehydration Using Diselenides as Catalytic Organooxidants" by Thomas C. Pickel, Srirama Murthy Akondi, and Lanny S. Liebeskind, *J. Org. Chem.*, **2019**, *84* in press. DOI: 10.1021/acs.joc.8b02765

Turning simplicity into complexity via multifaceted nickel catalysts

Rubén Martín Romo

Institute of Chemical Research of Catalonia (ICIQ), 43007, Tarragona, Spain

An increased utilization of feedstock materials and earth-abundant metal catalysts hold promise to revolutionize approaches in organic synthesis for preparing added-value building blocks from simple precursors. In recent years, nickel catalysis has received considerable attention as a vehicle to enable the functionalization of strong sigma bonds, carbon dioxide fixation or the valorization of (un)saturated hydrocarbons. Our research group has reported some progress in these areas of expertise, with a series of methods that are characterized by their simplicity and wide substrate scope, including particularly challenging substrate combinations.

New Photoredox Reactions

David W. C. MacMillan

Merck Center for Catalysis, Princeton University, Princeton, NJ 08544

This lecture will discuss the advent and development of new concepts in chemical synthesis, specifically the application of photoredox catalysis to organic chemistry. This new approach to visible light-driven catalysis will demonstrate the development of many new C–C and C-heteroatom bond forming reactions via an array of new reaction mechanisms. This lecture will also highlight the various applications of these new bond-forming reactions to pharmaceutical synthesis.

We will also introduce an approach to modulating organometallic catalysis using photoredox methods. This presentation will also demonstrate why a detailed understanding of the mechanistic underpinnings of these new photoredox–organometallic based processes can enable the invention and development of many transformations that are now being applied widely in the pharmaceutical and fine chemical areas.

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