

BMGT 1

Metal-mediated and metal-catalyzed coupling for incorporation of fluorine into aromatic molecules

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Fluorine-containing aromatic compounds are widespread in medicinal chemistry and material sciences, due to their unique stability, reactivity, and biological properties. Compounds containing a fluorinated aromatic ring or a trifluoromethyl group are particularly valuable, but methods to prepare these compounds under mild conditions with broad scope have been challenging to develop. During the past several years, we have sought to exploit our expertise in the synthesis of copper complexes that are intermediates in cross coupling, our expertise in palladium-catalyzed coupling reactions, and our methods to conduct C-H bond functionalization of arenes to develop methods for the conversion of aromatic compounds to aryl fluorides and aryl fluoroalkyl compounds. This lecture will describe our results on cross coupling related to the incorporation of fluorine and fluoroalkyl groups into aromatic molecules, along with a discussion of the fundamental organometallic chemistry addressed by this methods development and the mechanisms of these new classes of reactions.

BMGT 2

Metal catalyzed carbohalogenation reactions through reversible oxidative addition

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Oxidative addition and reductive elimination are two fundamental steps common to many different catalytic reactions. Insertion into C-X bonds is particularly prevalent as one of the first steps in a catalytic cycle.

Our research group at the University of Toronto has been exploring the synthetic potential associated with reversible oxidative addition into carbon-halogen bond and recently developed a palladium catalyzed carboiodination reaction.¹ This lecture will describe the scope and limitations of the reaction² including recent work that has expanded the scope to include carbobromination and carbochlorination.³

1. Newman, S.G.; Lautens, M. *Journal of the American Chemical Society* **2011**, *133*, 1778-1780.

2. Petrone, D.A.; Le, C.; Newman, S.G.; Lautens, M. *New Trends in Cross Coupling: Theory and Applications*, RSC, Colacot, T. Ed. 2014.

3. Le, C.M.; Menzies, P.J.C.; Petrone, D.A.; Lautens, M. *Angewandte Chemie International Edition* 2014, 53, xxx. doi: 201409248R1

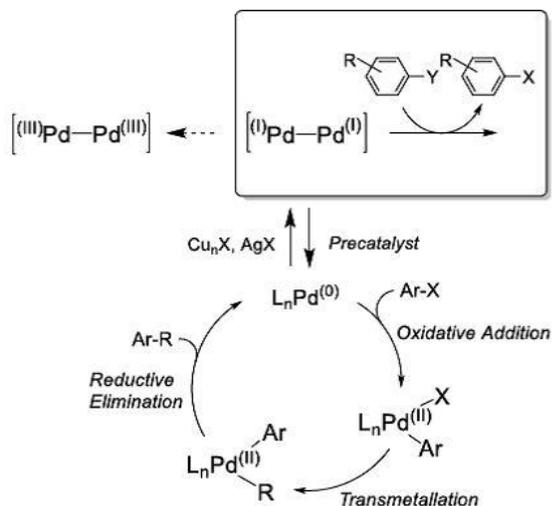
BMGT 3

Understanding and design of organopalladium reactivity with experimental and computational tools

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Detailed understanding of catalytic transformations is key to designing better catalysts. This talk will give insights on case studies and reactivity designs recently undertaken in our laboratory. A combination of experimental and computational tools were applied to study and/or predict the favored reaction mechanisms, active catalytic species, ligand and additive effects of selected transformations mediated by palladium species of the oxidation states 0, I, II and III.¹ A particular emphasis will be made on the oxidation state I. As a result of these investigations, novel reactivities have been uncovered.

(1) For a recent review, see: Bonney, K. J.; Schoenebeck, F. *Chem. Soc. Rev.* 2014, 43, 6609.



BMGT 4

Carbon-carbon and carbon-heteroatom bond forming reactions in continuous flow

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The use of microfluidic devices has recently attracted much attention from the pharmaceutical industry.^[1] This is due to the fact that these devices provide several advantages for chemical synthesis, such as enhanced heat- and mass-transfer, precise control over residence (reaction) time and scalability.

In recent years, our group has been focused on the development of more efficient cross-coupling, C–H activation and photocatalytic reactions to establish carbon-carbon and carbon-heteroatom bonds. This lecture will describe our results in this field and will provide insight information about the discovery process and the different parameters that led to success.

[1] T. Noël, V. Hessel, in *New trends in cross-coupling: Theory and applications*, T. J. Colacot Ed., RSC Catalysis series No. 21, **2015**, pp 610-644.

BMGT 5

Applications of Pd and Ni catalysis to Pfizer's portfolio

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The incorporation of Pd catalysis in the design of two commercial routes at Pfizer will be discussed. In addition, new developments in Ni catalysis research at Pfizer will be disclosed, with special emphasis on a new, stable Ni(II) precatalyst for high-throughput experimentation applications as an alternative to Ni(COD)₂.

BMGT 6

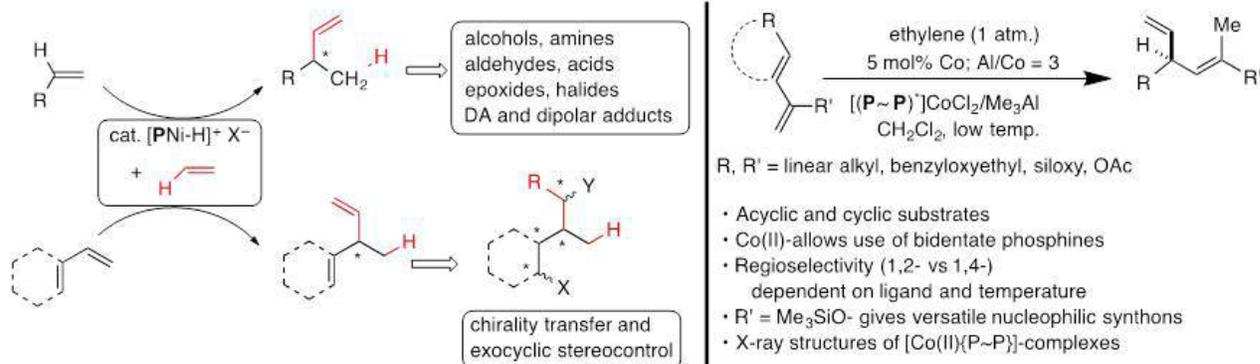
Cross-coupling without redox changes at the metal – enantioselective heterodimerization of alkenes

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One of the major challenges facing organic synthesis in the twenty first century is the utilization of abundantly available carbon sources for fine chemical synthesis. The dual problems of activation of thermodynamically stable precursors and their stereoselective incorporation pose new challenges, solutions of which may have broader implications in homogeneous catalysis, and, at a practical level, how we synthesize/manufacture chemical intermediates. In this context, we have been working on new protocols for nearly quantitative and highly selective codimerization of ethylene (and propylene), and various functionalized vinylarenes, 1,3-dienes and strained alkenes. This talk will deal with the development of various strategies for stereochemical control in enantioselective

versions of these reactions using Ni(II) and Co(II) catalysts. The products of this reaction are potentially useful for the synthesis of several classes of compounds, especially with intricately placed methyl-bearing chiral centers next to a ring or at the central carbon of a skipped 1,3-diene, the latter a ubiquitous structural motif that is potentially useful for a new approach to polyketides. This chemistry can also be used to generate all-carbon quaternary centers. Applications of this chemistry for synthesis of several biologically important compounds will be discussed.

Catalytic Enantioselective Olefin Heterodimerization Reactions



BMGT 7

Asymmetric C-C bond formation in outer sphere Pd catalyzed processes

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Pd Catalyzed C-C bond forming reactions are quite unusual in the range of mechanisms by which they occur. Particularly challenging for enantioselectivity are those C-C bond forming reactions that occur outside the coordination sphere of the metal and therefore distal to the chiral ligands attached to the metal. Creation of chiral space to impose asymmetry on such processes will be discussed.

BMGT 8

On the magical power of d-block transition metals as exemplified by ZACA (Zr-catalyzed asymmetric carboalumination of alkenes) – lipase-catalyzed acetylation – transition metal-catalyzed cross-coupling for highly enantioselective synthesis of various types of chiral organic compounds

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The discovery and synthetic applications of a widely applicable and highly enantioselective (>99% ee) protocol consisting of the ZACA reaction (Zr-catalyzed asymmetric carboalumination of alkenes), purification of the ZACA-products by lipase-catalyzed acetylation, and subsequent transformations, such as Pd-, Ni-, or Cu-catalyzed cross-coupling are discussed.

In contrast with the Sharpless epoxidation, the Noyori hydrogenation, both of which require allylic OH substituent for satisfactory asymmetric transformations, the ZACA – Lipase-catalyzed acetylation – Cross-coupling protocol in principle requires only terminal alkenes. In practice, however, the presence of a proximal hetero-functional group can be tolerated for converting terminal alkene into a wide range of chiral organic compounds including even those displaying very feeble optical rotations, such as isotopomers, as highly pure compounds of 99.9% ee or even higher!

BMGT 9

Photoinduced, copper-catalyzed coupling reaction

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The Ullmann reaction to form C–N bonds, first described over a century ago, is now a classic method in organic synthesis. During the time since its discovery, there had been no reports of a photoinduced variant. Instead, copper-mediated and copper-catalyzed processes have generally been effected with the aid of heat (e.g., at 60–120 °C). Recently, we have established that a photoinduced Ullmann C–N arylation can proceed at a temperature as low as –40 °C.

The reaction of an amine with an alkyl halide is a classic “textbook” approach to C–N bond construction. For efficient C–N bond formation, the electrophile should generally be a good substrate for an S_N2 reaction. A mild, transition metal-catalyzed N-alkylation that proceeds through a radical pathway for C–X cleavage has the potential to address important limitations of the classic S_N2 approach. In this lecture, recent efforts to address this challenge will be described.

BMGT 10

Connecting directed *ortho* metalation – transition metal catalyzed chemistries

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The common theme in our laboratories at Queen’s University is the discovery and development of new DoM aromatic/heteroaromatic chemistry, separate and linked to transition metal catalyzed processes, and their demonstration in bioactive molecule, natural product, and materials construction. A selection of these themes, including

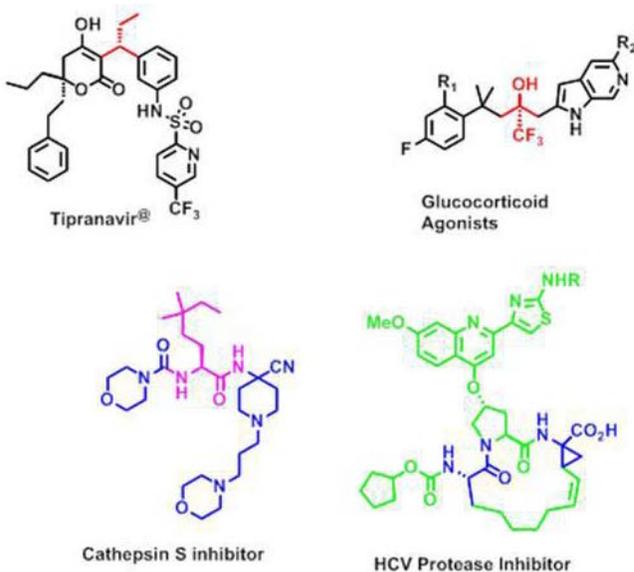
recent departures into DMG dances and Ir- and Ru-catalyzed DoM-enhancing links, will be described.

BMGT 11

Important catalytic transformations for drug development

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During the past two decades, the process research group at Boehringer Ingelheim Pharmaceuticals, Inc. has been involved in the development of truly efficient, reliable, greener and economically viable catalytic and asymmetric transformations for many drugs and drug candidates. Finding effective asymmetric methodologies in a timely manner for important drug candidates has provided many advantages to producing complex APIs rapidly for clinical development. This lecture will be centered on several highlights of these methods for the synthesis of important drug candidates.



BMGT 12

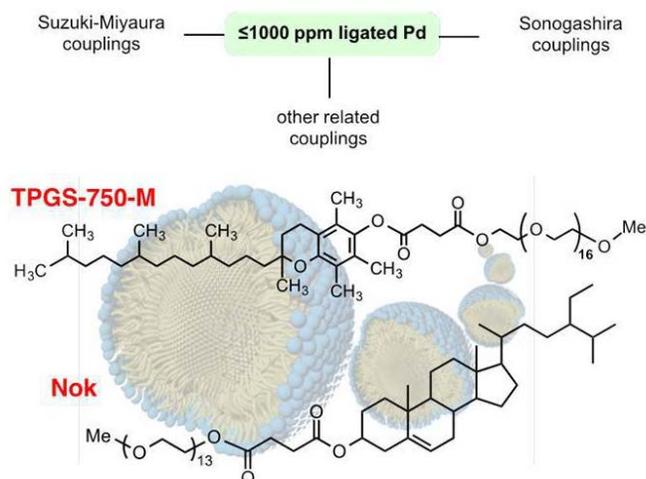
ppm-Level Pd-catalyzed cross-couplings in water at room temperature

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Several Pd-catalyzed cross-coupling reactions will be presented that can now be effected not only in water at RT,¹ but in the presence of **ppm** levels of an inexpensive source of Pd. A new ligand that leverages high substrate/catalyst concentrations found in aqueous nanomicelles, derived from either designer surfactant TPGS-750-M or Nok, is the key to these advances.

References

1. Reviews: Lipshutz, B. H.; Ghorai, S. *Green Chem.* **2014**, *16*, 3660; Lipshutz, B. H.; Isley, N. A.; Fennewald, J. C.; Slack, E. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 10952; Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta*, **2012**, *45*, 3; Lipshutz, B. H. *Platinum Metal Reviews*, **2012**, *56*, 62; Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta*, **2008**, *41*, 59.



BMGT 13

Award Address (ACS Award in Industrial Chemistry sponsored by the ACS Division of Business Development & Management and the ACS Division of Industrial & Engineering Chemistry). Story of Pd-catalyzed coupling: The reactions of the 21st century

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Pd-catalyzed cross-coupling reactions have become integral to both academia and industry over that last two decades, although the seminal contributions happened during the 1970's. These reactions constitute one of the most powerful methods for the formation of C-C and C-heteroatom bonds with direct applications in the synthesis of pharmaceuticals, agrochemicals, materials for electronic devices, and more. At Johnson Matthey, our goal has long been to provide practical yet novel catalysts for these

applications on commercial scale, while providing a theoretical understanding behind the structure activity relationship. In this regard, we have developed and introduced many exceptional precatalysts (traditional and new-generation) for several reaction types including Heck, Suzuki-Miyaura, ketone enolate arylation, Sonogashira, Buchwald-Hartwig amination, to name a few for commercial applications. Herein, we will cover the history of the development and implementation of these catalysts from an industrial perspective while understanding the role of academia, covering the past two decades.

