

RSC Catalysis Series

# New Trends in Cross-Coupling

Theory and Applications

Edited by Thomas J Colacot

Forewords by Ei-ichi Negishi, Barry M Trost  
and Gregory C Fu

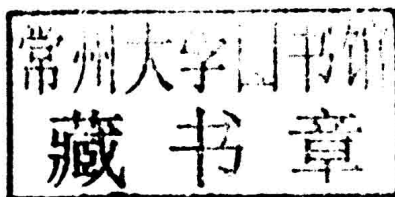


# ***New Trends in Cross-Coupling Theory and Applications***

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RSC Catalysis Series No. 21

Print ISBN: 978-1-84973-896-5

PDF eISBN: 978-1-78262-025-9

ISSN: 1757-6725

A catalogue record for this book is available from the British Library

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Published by The Royal Society of Chemistry,  
Thomas Graham House, Science Park, Milton Road,  
Cambridge CB4 0WF, UK

Registered Charity Number 207890

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Printed in the United Kingdom

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# Foreword

Transition metal-catalyzed cross-coupling involving the use of catalysts containing Pd, Ni, Cu, and other d-block transition metals has emerged as a collectively highly useful, selective, and widely applicable method for synthesizing a wide range of organic compounds through highly selective cross-coupling *via* C–C bond formation. Aside from earlier brief reviews published in the 1970s and early 1980s<sup>1</sup> a massive compilation of this important subject was first published in 2002.<sup>2</sup> Just a few years later, this publication was updated and significantly supplemented by de Meijere and Diederich in 2004,<sup>3</sup> and again in 2014 by de Meijere and his associates.<sup>4</sup> These facts simply point to the extraordinary fundamental significance of cross-coupling in organic synthesis.

We now have a welcome addition to the above-mentioned impressive and massive collection entitled “*New Trends in Cross-Coupling: Theory and Applications*”, edited by T. J. Colacot at Johnson Matthey Catalysis & Chiral Technologies, USA. He and his associates have also written the first three fundamentally important chapters.

As indicated by the title, it focuses its attention on new trends in cross-coupling, thereby distinguishing itself from the others mentioned above.

It consists of 16 chapters. Most impressively, well over 3000 references mostly on new subjects for cross-coupling are cited, making this compilation a “must” for anyone interested in learning about and using newer trends in cross-coupling. Specifically, the following topics are ably discussed: Introduction to New Trends in Cross-Coupling (Chapter 1), Prominent Ligand Types in Modern Cross-Coupling (Chapter 2), Pd-Phosphine Precatalysts (Chapter 3), Use of Pd N-Heterocyclic Carbene (Pd-NHC) Complexes (Chapter 4), Ancillary Ligand Design for Challenging Selective Monoarylation (Chapter 5), Transition Metal-Catalyzed Formation of C–O and C–S Bonds (Chapter 6), Pd(0)-Catalyzed Carboiodination (Chapter 7), Boron

Reagents in Suzuki–Miyaura Coupling (Chapter 8), The Modern Heck Reactions (Chapter 9), Palladium-Catalyzed Carbonylative-Coupling (Chapter 10), Stereospecific and Stereoselective Suzuki–Miyaura Cross-Coupling Reactions (Chapter 11), Direct Arylation *via* C–H Activation (Chapter 12), Cross-Coupling Chemistry in Continuous Flow (Chapter 13), Green Approaches to Cross-Coupling (Chapter 14), Recent Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals (Chapter 15), and Palladium Detection Technologies for Active Pharmaceutical Ingredients Prepared *via* Cross-Couplings (Chapter 16).

Inasmuch as this compilation focuses its attention on newer trends in cross-coupling, it would be useful to explicitly remind the readers of earlier compilations, such as references 1–4.

Ei-ichi Negishi

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## About Ei-ichi Negishi



Professor Negishi was awarded the 2010 Nobel Prize in Chemistry “for palladium catalyzed cross couplings in organic synthesis” jointly with Professors Richard F. Heck and Akira Suzuki. He is a distinguished Professor of Organic Chemistry & Teijin Limited Director of the Negishi-Brown Institute at Purdue University and the inventor of Negishi Coupling.

# Foreword

Helping to address the problems of society ranging from electronics to medicine is a major goal of science. What differentiates a chemist from other scientists is the ability to design a structure that one feels is desirable regardless of whether such structures exist since the chemist can go into the lab and synthesize the structure. A major obstacle is doing so in a time-efficient manner. Thus, there is a need to have a synthetic toolbox that will address such a problem. Herein is the need to improve our synthetic reactions to permit the timely synthesis of any structure regardless of its molecular complexity.

This monograph relates to the explicit role that a subset of Pd-catalyzed reactions, notably with homogeneous catalysts, is having on meeting the above goal. It is instructive to examine how we got here. To begin, let's examine a brief overview of the early days in the discovery of precious metals. At the start, individuals involved with isolation of precious metals frequently spanned a broad range of aspects of the science, from the initial discovery all the way to creating a market. Let me make this point with respect to palladium, the topic of this work. Historically, around the year 1700, miners in Brazil were aware of a metal which they referred to as "ouro podre" or worthless gold, a native alloy of Pd and Au, today known as one of the forms of white gold. It was, however, through the mining of Pt that ultimately led to the actual refining of Pd. By the eighteenth century Pt had found numerous uses, and Percival Norton Johnson, son of assayer John Johnson, played a major role through his company which he co-founded in 1817. In 1838, George Matthey, a banker, joined and led to what is known today as Johnson Matthey. It was the purification of Pt by William Wollaston that led him to find a way to remove a pesky impurity. He ultimately isolated the "impurity" which he believed was a new metal. He called this new material "palladium" after a new asteroid named "Pallas", named so after the Goddess of

Wisdom. Incidentally, he also discovered rhodium. Believing there was commercial value in palladium as a metal, he anonymously announced the properties of this new metal and made it available for sale but refused to reveal the process for making it until shortly before his death in 1826. Since Pd was obtained as a by-product of Pt production, its quantities increased but, unfortunately with no market for the growing supplies. It wasn't until the 1930's that a German company developed and patented alloys of palladium and gold or silver for use in dentistry.

In 1959, the use of the “noble” metals in catalysis was virtually only taught with respect to heterogeneous hydrogenation. The first industrial process other than hydrogenation involving Pd was the Wacker process which came about in 1956 with the conversion of ethylene to acetaldehyde. Such discoveries stimulated studies into how ligands bind to metals and effect their chemical behavior, thus creating a steep growth spurt. With respect to Pd, the Wacker oxidation allowed the conversion of cheap, readily available hydrocarbons to higher value added “oxidation” products wherein useful oxygen functionality in the form of simple reagents like water and acetic acid was installed via olefinic bonds. This type of Pd process constitutes one of the important fundamental transformations in catalysis which has morphed into a host of synthetic reactions that elaborate olefins into many types of higher value products. Indeed, it was the study of the mechanism of this process that led Richard Heck, then at Hercules Chemical Co. in Wilmington, DE to invent by design what we now call the Heck reaction. In a tour-de-force, Heck disclosed these studies in a series of seven papers of which he was the sole author published back to back in the *Journal of the American Chemical Society* in 1968. Heck's reports revealed a type of chemical reactivity that heretofore did not exist, the direct addition of a carbon-metal bond to a non-activated carbon-carbon  $\pi$  bond. The only synthetic problem for its use was that the reaction required stoichiometric amounts of palladium. In 1968, Fitton discovered that tetrakis(triphenylphosphine)palladium underwent a stoichiometric reaction with iodobenzene to form a stable phenylpalladium iodide complex. Armed with this information, Heck published a catalytic version of his reaction about 4 years later in 1972 and the rest is history – his sharing of the Nobel Prize in 2010.

During this time, another type of reactivity of Pd(+2) species was reported by Professor Arthur Cope at MIT, best known for reactions like the Cope elimination and Cope rearrangement, who also played with the organic chemistry of Pd. In 1965, he demonstrated what I believe is the first example of an unactivated C-H insertion by a Pd(+2) salt upon reaction with azobenzene to give an isolable organometallic. This process revealed that appropriate coordination to an organic molecule can direct the resultant complex to facilitate the insertion of the Pd into a proximal C-H bond, a type of reactivity that has proven invaluable on the types of Pd catalyzed reactions described in this monograph.

In 1976, Ishikawa noted that the palladium complex of Fitton catalyzed the cross-coupling of aryl Grignard reagents with aryl iodides. A major drawback of this method and related nickel catalyzed reactions was the lack

of chemoselectivity associated with the use of Grignard reagents. That same year, Negishi began examining the prospect of using more chemoselective nucleophilic partners such as organoalanes and organozirconium complexes in palladium (as well as nickel) catalyzed vinyl-vinyl cross-coupling processes. Shortly thereafter Negishi noted that *in situ* generated organozinc compounds participated in chemoselective cross coupling and gave higher yields than Grignard reagents or organoalanes. It is interesting to note that Negishi reports the failure of organoboranes in such processes. In 1979, the landscape changed when Suzuki reported conditions that allowed organoboranes to be used. The grandfather of metal-promoted coupling, the Ullman reaction, morphed from a very limited process stoichiometric in metal into a widely divergent carbon-carbon bond forming process that had the characteristics of nearly perfect selectivity. Correspondingly, palladium has moved from being an esoteric metal of no known use to one of being among the most versatile type of transition metal homogeneous catalyst of any metal known to date. Thus, Negishi and Suzuki joined Heck in the recognition of these pioneers by their receipt of the Noble Prize in 2010.

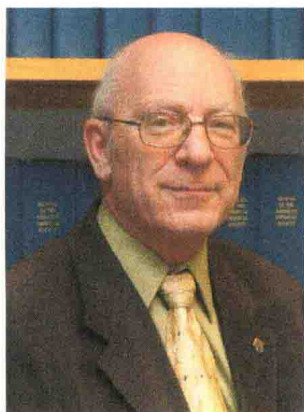
In a period of slightly more than 30 years, palladium catalysts literally changed the way complex molecules could be made. This monograph vividly illustrates the enormity of the invention. The book opens with an account of the key parameters and mechanistic characteristics of metal-catalyzed reactions in Chapter 1. Chapters 2 to 5 note the remarkable influence of ligands on the chemistry of palladium complexes. Indeed, the ability to tune any specific reaction at one's will by appropriate choice of ligand environment is both a power of this synthetic tool as well as a complication that must be realized. Key to extending the cross-coupling reaction beyond Grignard reagents is understanding how the transmetalation process works, a topic dealt with in Chapter 8. Chapters 5 and 6 demonstrate the breadth of the concept beyond C-C bond forming events to carbon-heteroatom bond forming events, with nitrogen being the most notable. The status of the Heck reaction today is dealt with in Chapter 9. An important component of selectivity in complex molecule synthesis, stereochemical control both relative and absolute, is the topic of Chapter 11. Carbon-carbon bond forming reactions extrapolating from the core Heck-Negishi-Suzuki type are illustrated in a so-called carboiodination pathway as an alternative to the Heck process in Chapter 7 and the ability to intercept an organopalladium intermediate by carbon monoxide to generate the extremely important carbonyl containing products is covered in Chapter 10. Making the reaction more atom economic by effecting such reactions by direct C-H activation is examined in Chapter 12 whereas Chapter 14 deals more broadly with making these palladium catalyzed processes "greener". A new dimension in homogeneous catalytic processes is performing them under flow conditions. The benefits of these techniques are examined in Chapter 13. In developing new synthetic tools, a critical question is the ability to scale up the processes. Chapter 15 examines this component.

This monograph vividly illustrates that these methods have rapidly gained immense impact on making truly complicated structures. But we must be

careful in coming to any conclusion about what is left to be discovered. The trite saying “you don’t know what you don’t know” is especially true in synthetic chemistry. Indeed many of these chapters show that many unimaginable processes have become real. Given the enormity of the variables, it is impossible to guess how much more can be done. It is perhaps why palladium has been referred to as the metal of the twenty-first century. This monograph is only one small step on the path toward being able to make everything imaginable. This book is invaluable to anyone involved in synthesis of organic compounds for any purpose.

Barry M. Trost

### About Barry M. Trost



Born in Philadelphia, Pennsylvania, he obtained a BA degree from the University of Pennsylvania in 1962 and PhD degree just three years later at the Massachusetts Institute of Technology (1965). He directly moved to the University of Wisconsin where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor in 1982. He joined the faculty at Stanford as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition, he has been Visiting Professor in Germany (Universities of Marburg, Hamburg, Munich and Heidelberg), Denmark (University of Copenhagen), France (Universities of Paris VI and Paris-Sud), Italy (University of Pisa) and Spain (University of Barcelona). He received honorary degrees from the Université Claude-Bernard (Lyon I), France (1994), and the Technion, Haifa, Israel (1997). In recognition of his many contributions, Professor Trost has received a large number of awards, a few among which are the ACS Award in Pure Chemistry (1977), the Dr Paul Janssen Prize (1990), the ASSU Graduate Teaching Award (1991), Bing Teaching Award (1993), the ACS Roger Adams Award (1995), the Presidential Green Chemistry Challenge Award (1998), the Belgian Organic Synthesis Symposium Elsevier Award (2000), the ACS Nobel Laureate Signature Award for Graduate Education in Chemistry (2002), the ACS Cope Award (2004), the Nagoya Medal (2008), the Ryoji Noyori Prize (2013), the International Precious Metals Institute's Tanaka Distinguished Achievement Award (2014), and the German Chemical Society's August-Wilhelm-von-Hofmann Denkmuenze (2014). Professor Trost has been elected a fellow of the American Academy of Sciences (1992) and a member of the U.S. National Academy of Sciences (1990).

# Foreword

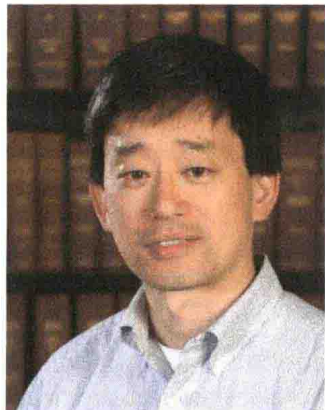
The relative difficulty of achieving the direct formation of  $C_{sp^2}-C_{sp^2}$  bonds through “conventional” organic chemistry was well-appreciated at the time that pioneering studies of cross-coupling reactions began to emerge about 40 years ago. Nevertheless, the chemistry community was surprisingly slow to embrace the seminal discoveries of Heck, Negishi, and Suzuki (along with so many other important early contributors).

During the past 15 years, that situation has changed dramatically, as evidenced by the recognition of the field with the Nobel Prize in Chemistry in 2010. Thus, more versatile and active catalysts have been developed for the classic bond-forming processes of Heck, Negishi, Suzuki, and others, and these have now been applied across many disciplines (*e.g.*, biology, chemistry, and materials science) and in large-scale manufacturing. Equally importantly, others areas of investigation have emerged: couplings that achieve the formation of C–N (Buchwald–Hartwig reaction) and other C–heteroatom bonds, as well as cross-couplings of alkyl electrophiles, direct arylations of C–H bonds...the list goes on.

Books such as the present one, *New Trends in Cross-Coupling: Theory and Applications*, can play a critical role by assessing where the field currently stands and by pointing to the unsolved challenges that represent the future of the field. In this monograph, Dr Colacot has assembled leaders who do exactly that, describing not only the remarkable progress that has been achieved to date, but also the wealth of exciting opportunities that lie ahead.

Gregory Fu

## About Greg Fu



After earning a PhD from Harvard in 1991 under the guidance of Prof. David A. Evans, and post-doctoral fellowship with Prof. Robert H. Grubbs at Caltech, in 1993, Greg Fu joined MIT, as a faculty member. In 2012, he was appointed the Altair Professor of Chemistry at the California Institute of Technology.

Greg received the Corey Award of the American Chemical Society in 2004, the Mukaiyama Award of the Society of Synthetic Organic Chemistry of Japan in 2006, and the Award for Creative Work in Synthetic Organic Chemistry of the American Chemical Society in

2012. He is a fellow of the Royal Society of Chemistry, the American Academy of Arts and Sciences, and the National Academy of Sciences. Greg serves as an associate editor for the *Journal of the American Chemical Society*. His current research interests include metal-catalyzed coupling reactions and the design of chiral catalysts. His work on “bulky, electron-rich” in 1998 was an important milestone the area of cross-coupling.

# Preface

Although the major seminal discoveries in cross-coupling occurred during the 1970s, the importance of this technology has been realized only during the last two decades. Since then, the field has experienced rapid growth, ultimately leading to the award of the 2010 Nobel Prize in Chemistry.<sup>1</sup> The original pioneers may not have anticipated during that time that this area would become such a force in industry and academia, revolutionizing the way we think about organic synthesis, be it for a small molecule or a complex drug molecule or natural product. In fact, Prof. Heck in a BBC interview after he shared the 2010 Nobel Prize with Prof. Suzuki and Prof. Negishi, commented that he “did not make a dime out of this technology”, while Prof. Negishi commented that he was “lucky enough to be alive” to receive the award. I heard Prof. Suzuki speaking at a conference that he had difficulties in publishing his pioneering work in top-rated journals as the reviewers were “not so nice”. However, in the above-mentioned BBC interview, he joked that his hypertension is well controlled by one of the *sartans* developed using the Suzuki–Miyaura coupling technology – an ultimate satisfaction for any inventor to reach the climax.

I got into the area of cross-coupling accidentally when I joined Johnson Matthey in late 1995. I originally worked in the area of process chemistry and non-precious metal-based new product development, and in my spare time I started looking at the dppf ligand based on an inquiry. Although we developed a good process, the project died. Quite frustrated, I started to read about this ligand in a book titled *Ferrocenes* by Prof. Togni and Prof. Hayashi, where the importance of the bite angle was mentioned with respect to a Kumada–Corriu coupling involving a *sec*-alkyl Grignard reagent.<sup>2</sup> Although we could not sell even gram quantities for 1–2 years, we pushed dppfPdCl<sub>2</sub> as a “magic catalyst” based on the description by Gan and Hor,<sup>2</sup> in terms of its air stability and activity/selectivity in comparison with the air-sensitive

$\text{Pd}(\text{PPh}_3)_4$ . This was during the time that Prof. Hartwig started publishing several amination reactions, where the use of the dppf ligand in conjunction with  $\text{Pd}(\text{dba})_2$  or even the preformed catalyst was highlighted, while Prof. Buchwald was using a BINAP/ $\text{Pd}_2\text{dba}_3$  combination for the same technology. We were the first group to develop a good process for both dppf and  $\text{dppfPdCl}_2$  for multi-kilogram quantities for the industry. This helped us gain an early understanding of the importance of preformed catalysts *versus in situ* in terms of selectivity, activity, scalability and ease of handling, which has become a main theme today in the area of cross-coupling. Very soon, the field began to develop rapidly – 1998 was marked as an exciting year for cross-coupling. The first book on this topic was published by Prof. Diederich and Prof. Stang.<sup>3</sup> Prof. Buchwald's work<sup>4</sup> using a novel electron-rich phosphine and Prof. Fu's work<sup>5</sup> on the use of the known "bulky electron-rich"  $\text{P}(t\text{-Bu})_3$  ligand, in conjunction with Pd, were other significant events in the new trends in cross-coupling with respect to C–C and C–N coupling, although Dr. Koie<sup>6</sup> also reported related studies for C–N coupling. Continuing on the same theme, in subsequent years many modern ligands were developed by Prof. Buchwald (biaryl ligands – 1998),<sup>7</sup> Prof. Nolan (*N*-heterocyclic carbenes – 1999),<sup>8</sup> Prof. Hartwig (Q-Phos – 2000)<sup>9</sup> and Prof. Beller (adamantyl-based ligands – 2000)<sup>10</sup> to solve many problems in cross-coupling (see Chapters 2 and 4).

Making the catalyst technology accessible to fine chemical and pharmaceutical industries all over the world and also academia to meet their needs has been my primary concern in concert with understanding the structure–activity relationships of the catalysts and substrates. Several new preformed catalysts have been developed involving the following classes of compounds:  $\text{L}_2\text{PdX}_2$ ,  $\text{L}_2\text{Pd}(0)$ ,  $(\text{L-L})\text{PdX}_2$  and precursors to  $\text{LPd}(0)$ -based catalysts, which indeed changed the landscape (Chapter 3).<sup>11</sup> New versions of the catalysts have emerged from time to time just as in the case of the iPhone™ technology, where the ever-increasing requirements of the customers such as air stability, low loading/high activity and selectivity, operating under mild reaction conditions, ease of handling, scalability of the catalyst and the coupling reactions, broader substrate scope and waste minimization have been addressed.

In spite of the new developments, demands continue to increase, broadening the scope of this technology. This was a significant driving force when I agreed to do this book, following an invitation from Dr Merlin Fox of the Royal Society of Chemistry. The initial feeling was overwhelming given my other responsibilities. Fortunately, I was very much aware of the academic push and industry expectations, and hence decided to create this book by providing the reader with a basic understanding about coupling, while discussing the modern trends from a technology and applied point of view. On behalf of the contributors, I hope that this book will serve as a textbook-cum-reference guide for both undergraduate and graduate students and also those who are experts in the area, irrespective of their academic or industrial background. It was designed to have contributions from both junior and

senior authors, who are world leaders in their field, covering a wide range of topics in 16 chapters; including the logic behind choosing the ligand and catalyst, new reactions such as carboiodination, metal detection in the APIs, flow chemistry, API synthesis, reaction mechanisms, green chemistry, *etc.*

Because of my industry background, quality was one of my prime concerns, considering the size of the book. I was fortunate enough to be able to implement a peer review process for each chapter by at least two or three subject experts. With the reputation of Royal Society of Chemistry, I promised to maintain a high quality standard in terms of the book production.

I knew how busy each author was, considering their day-to-day responsibilities. A few had to go through some personal, unforeseen difficulties after they accepted the offer. I sincerely thank them all for putting their trust in me and completing the chapters with utmost sincerity. I am sure that their contributions in this book will stimulate the area further to grow at an advanced pace. I also personally acknowledge Johnson Matthey Catalysis and Chiral Technologies, the Royal Society of Chemistry and all the reviewers for their support and help in different capacities to make this project a success. My co-workers, Dr Carin Johansson Seechurn and Dr Andrew DeAngelis, are also thanked for their assistance, and William Carole is acknowledged for assistance in the design of the cover graphic.

Thomas J. Colacot

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