

## “New Trends in Cross-Coupling: Theory and Applications”

**Edited by Thomas Colacot (Johnson Matthey Catalysis and Chiral Technologies, USA), RSC Catalysis Series, No. 21, Royal Society of Chemistry, Cambridge, UK, 2015, 864 pages, ISBN: 978-1-84973-896-5, £175.00, US\$290.00, €18.75**

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This massive volume with a most appropriate title will lead the user to say: 'I read, I understand modern trends, I will apply'. After perusing it, the reader is encouraged to give a quiz to their students or colleagues: what is the largest scale Heck reaction to date? Why is a reaction in water not a fully 'green' process? What are the problems of scale up flow reactions? How much palladium may there be in the over-the-counter drug ibuprofen? What are the major caveats for a chemist using transition metal catalysis? among many other questions.

Colacot has gathered thirteen academic and industrial chemists with their respective coauthors who are at the forefront of the various reactions that comprise the cross-coupling theme to serve as a cornucopia of fundamental and practical knowledge. With forewords by three chemists, prominent in their own right in the field, this collection of chapters will bring up-to-date all those interested in teaching and practicing the chemistry which has largely superseded the classical reactions of the pre-1970 era.

Although multi-authored, a uniformity of presentation prevails, perhaps owing to the fact that all chapters have been independently reviewed by two to three experts.

Individual authors teach the reader about the breadth of the cross-coupling landscape, the still incomplete mechanistic knowledge and the important practical characteristics of new areas: the rapid acceptance of continuous flow reactions, the increasing attempts to be 'green' and the requirements of metal detection in active pharmaceutical ingredients (APIs), the latter, a humbling read for the academic researcher.

The authors ask the reader to linger on mechanistic aspects before leaping into the less cerebral-requiring synthetic data. The present reviewer ponders that since the advent of transition metal reactions, revision of retrosynthetic strategy as taught by Corey and others is required. As suggested by the Editor, this compendium will 'rejuvenate the entire area of cross-coupling'; it may be argued that 're' is not required – the area is still in its rapidly developing infancy.

### **Review of Fundamentals**

Following historically insightful brushstrokes on 'how we got here' in the foreword by Professor Barry Trost (Stanford University, USA) and in the preface by Tom Colacot, the fundamentals of the broad canvas of cross-coupling are described. In Chapter 1, Carin Johansson Seechurn (Johnson Matthey Catalysis and Chiral Technologies, UK), Andrew DeAngelis and Tom Colacot (Johnson Matthey Catalysis and Chiral Technologies, USA) define the basic terminology, such as turnover number (TON) and valence bond picture, sketch the discovery tree with due recognition,

including names of some widely unknown chemists, and set the stage for both industrial and academic chemists' palates to view the recent state (mainly the last five years) of transition metal-catalysed cross-coupling reactions and to taste the next courses of surprises in the near future.

Chapter 2 by DeAngelis and Colacot serves as a perfect primer for the rapid advances that have occurred in the last decade in the design and development of ligands that have reached sophisticated levels of application in catalytic cross-coupling reactions where Pd is king. In agreement with Crabtree (1), who perceptually taught in his textbook that 'to pick suitable spectator ligands' is the key to the art, the reader learns about steric, electronic effects and bite angle consequences (a table of 29 ligands) and is then taken on a tour (for example in industrial context, **Figure 1**) on useful modern ligands: bulky  $\text{Ar}_3\text{P}$ , chelating bisphosphines, biaryl monophosphines, *N*-heterocyclic carbenes (NHCs) and chiral ligands. Copious examples in C–C but also C–N and C–O coupling reinforce the schematically explained, mechanistically significant points.

Chapter 3 by Carin Johansson Seechurn, Hongbo Li and Tom Colacot, the last chapter of collaboration from the very able Johnson Matthey chemists, authoritatively instructs in the rapidly emerging evolution of preformed Pd catalysts (isolated, pure  $\text{L}_n\text{PdX}$  ligands). A refresher course on the 18 electron rule, with examples and exceptions is followed by a section on complex stability which is photographically illustrated by the decomposition of 'tetrakis' with time, events very familiar in practicing laboratories. Mechanistic studies, still incomplete, promise to play a crucial part in the provision of improved precatalyst procedures on large scale that will undoubtedly help process economics of

these reactions. The chapter concludes with valuable tables of recommended precatalysts and their use in specific cross-couplings.

## Ligands

In the hefty Chapter 4, Anthony Chartoire (Econic Technologies, UK) and Steven Nolan (University of St Andrews, UK) focus on the NHCs, the new kid on the block in ligands. Appreciation is gained of the influence of  $\text{p}K_a$ , sterics and electronic effects on NHCs and a journey is provided of the cross-coupling name reactions for which they are effective and those as yet little studied (Kumada-Corriu, Hayashi, copper-free Sonogashira, discovered by Heck, C–S coupling,  $\alpha$ -arylation). For informed chemists, conspicuously absent so far in the literature are also the C–O coupling and the asymmetric Suzuki-Miyaura reactions.

In Chapter 5, Mark Stradiotto (Dalhousie University, Canada) summarises the impact of sterically demanding phosphine ancillary ligands on achievement of monoarylation in Pd-catalysed Buchwald-Hartwig amination and  $\alpha$ -arylation reactions. The long-sought  $\text{NH}_2^+$  equivalent in anionic aromatic chemistry is overcome by the amination reaction which also supercedes the classical electrophilic aromatic substitution ( $\text{S}_{\text{E}}\text{Ar}$ ) nitration–reduction route to arylamines. Thus monoarylation of ammonia is especially useful in the synthesis of bioactive heterocycles and that of hydrazine gives a new twist to the Fischer indole reaction. The completely chemoselective synthesis of anilines, bearing primary and secondary amines, through use of Stradiotto's heterobidentate ligands cannot be easily achieved by classical methods. A useful feature of this chapter is the brief outlines for each topic discussed.

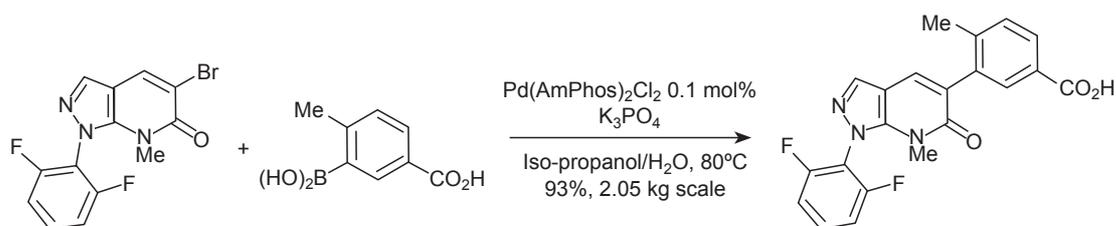


Fig. 1. Kilogram-scale Suzuki-Miyaura reaction using  $\text{Pd}(\text{AmPhos})_2\text{Cl}_2$  (Reproduced by permission of The Royal Society of Chemistry)

## C–O and C–S, Suzuki-Miyaura Cross-Coupling and Carbohalogenation

In Chapter 6, James Stambuli (Ohio State University, USA) discusses C–O and C–S bond formation reactions, areas that have progressed less than the corresponding C–C and C–N coupling processes. As gleaned also from other chapters, copper catalysis is making an impact on the C–O and C–S coupling reactions. Best choices of ligands are defined, including those that prevent thiolate attack on the Pd centre and most recent replacements for Pd (manganese, cobalt, nickel and rhodium) are noted. From this chapter, we appreciate that a long road has been travelled to give improvements and alternatives to the nucleophilic aromatic substitution ( $S_NAr$ ) and ancient Ullmann procedures.

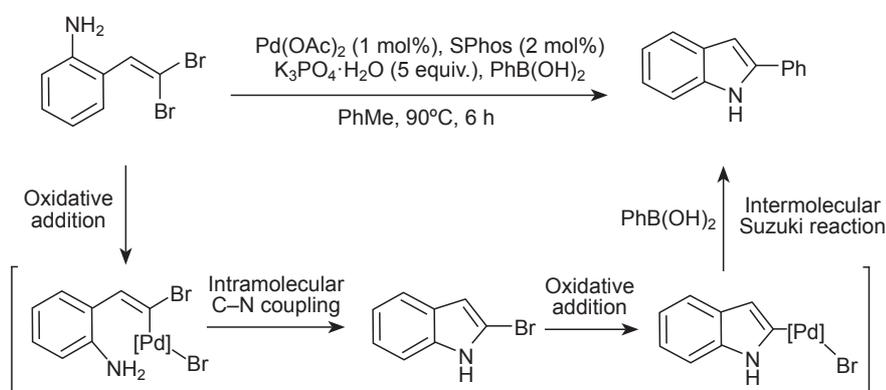
Chapter 7 by David Petrone, Christine Le, Stephen Newman and Mark Lautens (University of Toronto, Canada) provides a detailed view of the C-halogen reductive elimination process from transition metal complexes and then delves deeply into the carbohalogenation reaction. Surprisingly, the reductive elimination to form new or reform existing C-halogen bonds is a poor cousin to the equivalent oxidative addition in terms of synthetic use and its mechanism is incompletely understood and controversial. The review focuses on the Pd(0/II) species in these transformations as a background for the carbohalogenation reaction to which Lautens' group has made substantial contributions. Provided is a scheme displaying commendably the mechanistic divergences between the Heck and the new carbohalogenation process,

numerous examples of synthetic utility (indoles *via* gem-dihalo olefin coupling stand out, **Scheme I**), including aspects of selective coupling of polyhalogenated systems, containing Handy's predictive guide, and density functional theory (DFT) corroboration of the experimental results. The chapter shows a flourish of considerable new synthetic potential.

The brief but instructive Chapter 8 by Alastair Lennox and Guy Lloyd-Jones (University of Edinburgh, UK) is the present best source for the mechanistic understanding of the Suzuki-Miyaura cross-coupling, named the 'gold standard' for biaryl construction, which can be appreciated by the given examples of 'blockbuster' drugs whose synthesis critically incorporates this reaction. A survey of 40,000 reactions in the preparation of this review is a sound basis for discussion of mechanistic aspects for which evidence is currently weak or not available, for example, for the transmetalation step. The requirement for boron preactivation and the practical aspects of various boron coupling reagents, including the recently introduced and promising triisopropylborate and cyclic triol salts are features also to be appreciated. The categorisation of Suzuki-Miyaura couplings into three groups is tentative but practically useful.

## Mizoroki-Heck and Beyond

Chapter 9 (>100 pp) by Irina Beletskaya and Andrei Cheprakov (Moscow State University, Russia) is a masterful, well organised and definitive review of the Heck reaction that the authors use in a generic sense to cover the family of reactions, the main one of which is



Scheme I. Synthesis of 2-substituted indoles *via* Pd-catalysed tandem C–N/C–C coupling of gem-dibromoolefins (Reproduced by permission of The Royal Society of Chemistry)

of course the Mizoroki-Heck reaction (~50 pp). (For an opinion of the value of the Heck reaction see Fuhrhop and Li:

“Synthesis: the preparation of large molecules from smaller ones by the formation of C-C bonds. The Wittig, Heck, and Diels-Alder reactions are all the methods a beginner needs to know. Most compounds can be made by these reactions if they are followed by intelligent functional group interconversions (FGIs)” (2)).

After a historical account, rightfully acknowledging chemists along the path to Heck’s discovery, the diversity of this dominant C–C bond forming reaction is unfolded, always by reference to mechanism which the authors are eminently qualified to analyse. The differences between the Heck, general cross-coupling, and C–H activation reactions is such an area of mechanistic ambiguity that it demands further studies. Carbonylative and decarbonylative (‘masked carbanion’, discovered by Blaser and Spencer (3)) reactions are demystified. The Mizoroki-Heck reaction is given a deserved comprehensive presentation and includes many elements of theoretical and practical value, some perhaps unappreciated, for example: mechanistic pathways using mono- and bidentate ancillary ligands, the functioning of Pd nanoparticles as precatalysts, the qualitative rules for ligand acceleration, the status of the Pd(II)/Pd(IV) mechanism and the new developments in copper-catalysed reactions. The increasingly used oxidative Heck and Fujiwara-Moritani reactions are given merited coverage. The most intriguing deborylative (Heck discovery, 1975), desilylative and destannylative Heck reactions are remarkably evolving methods of new synthetic opportunities. In spite of the authors’ modest concluding comment, this chapter provides the depth and the breadth of the Heck reaction that will be read with great benefit for some time (for a personal account, see (4); for obituaries see (5, 6)). 456 References are listed and a SciFinder search for 2010–2015 reveals 3371 hits; therefore, this chapter is perceptively discriminating no doubt due to the authors’ command of the area.

Chapter 10 by Xiao-Feng Wu (Leibniz Institute for Catalysis, Germany) and Christopher Barnard (Johnson Matthey, UK) concentrates on the Heck, Sonogashira, Suzuki and C–H activated carbonylation reactions. With respect to the Heck carbonylation, there is no overlap with Chapter 9; in fact, Chapter 10 presents

useful intramolecular, including heterocyclic, versions. In spite of a partial mechanistic understanding, all of these methods provide different retrosynthetic thinking, especially for the construction of alkynones by the classical Grignard and Friedel-Crafts reactions. A litany of new reactions is schematically indicated with the following highlights: the use of aryldiazonium coupling partners, the preparation of <sup>11</sup>C and <sup>13</sup>C labelled ketones (although lacking examples of industrial reactions), and the advantages of NHC complexes. Perhaps most significant are the results from the rapidly evolving C–H activation-carbonylation process whose application to the synthesis of substituted and heteroannulated aromatics will certainly see further advances.

Chapter 11 by Ben Glasspoole (Sigma-Aldrich, USA), Eric Keske and Cathleen Crudden (Queen’s University, Canada) address work on the Suzuki-Miyaura cross-coupling reaction from perspectives of: (a) stereospecific coupling of chiral organoborons; (b) chiral electrophile partners for stereospecific couplings; and (c) racemic electrophiles in dynamic resolution tactics. All three topics are expertly tackled from which may be arguably underlined: the challenges ( $\beta$ -hydride elimination and their invisibility for symmetrical nucleophiles, steric effects) faced in reactions of secondary aliphatic boranes (overcome in Crudden’s group); the coupling of racemic and enantioenriched allylic boranes (provided in tabular data); the use of benzylic carbamates and esters to displace the need for enantiomerically pure alkyl halides in coupling with organoboron derivatives; the power of Ni-catalysed radical-mediated asymmetric arylation of racemic  $\alpha$ -,  $\gamma$ - and  $\delta$ -chloroamides; and the initial demonstration of arylation of tertiary halides. The chapter critically discusses the highs and the lows of current methods for stereo-selective and -specific  $sp^2$ - $sp^3$  and  $sp^3$ - $sp^3$  bond formation which are of growing significance in new synthetic method development.

## C–H Activation

In Chapter 12, Upendra Sharma, Atanu Modak, Soham Maity, Arun Maji and Debabrata Maity (Indian Institute of Technology Bombay, India) discuss a topic of high current activity – the direct arylation by C–H activation which, it should be noted, is formally not a cross-coupling reaction. With a very good historical preamble on today’s named coupling methods using two prefunctionalised substrates, presented critically is the moving frontier of the C–H activated arylation methods based on using one

prefunctionalised system. The chapter has a strong mechanistic orientation, for example **Figure 2**. The subdivision by metal (Pd, Rh, Ru, Ir, Cu) shows clearly that Pd is king of the catalytic highway. Examples of illustrative reactions are outlined, mechanistic pictures are presented, and, notably, experimental needs, costs, catalysts and ligands are examined. A glossary of acronyms, for example chemical manganese dioxide (CMD) appears early in the book but is not defined until later. Also, a table of directing groups, giving an eye blink view of the section on directing scaffolds, would have been valuable. Sections on direct arylation of heterocycles and of  $sp^3$  bond C–H activation represent tips of the iceberg of current research, as are the initial results of remaining challenges, such as erasable and traceless directing groups, which are described in this well formulated chapter.

## Flow and Green Cross-Coupling and APIs

The review (Chapter 13) on cross-coupling chemistry in continuous flow by Timothy Noël and Volker Hessel (Eindhoven University of Technology, The Netherlands) begins with an instructive table on the pros and cons of this new technology over batch processes. Presented by two experts in this rapidly emerging field that, of necessity, involves also chemical engineers, the reader receives step-by-step instruction on how to set up a flow experiment, be aware of technical difficulties and hazards and be concerned about safety issues on scale. The myth of reactions in water being ‘green’

is laid to rest by considering that it needs to be treated before release into the environment. Laudably, examples for Pd, Cu and Fe catalysed flow reactions are presented with comparison of cost and toxicity, as are comparisons of batch vs. flow procedures. The ‘metal-free’ reaction, as currently often carelessly stated in the literature, is given the proper caveat by need for fluorescence or inductively coupled plasma mass spectrometry (ICP-MS) metal detection that apparently may be carried out by a first year student (see also review of Chapter 16 below). As this chapter emphasises, the benefits of flow will occur with increased attention to gas-liquid coupling reactions, more efficient operation, increased engineering automation, and introduction of flow chemistry courses in curricula.

Chapter 14 by Kevin Shaughnessy (University of Alabama, USA), which takes up the ‘green’ theme in depth, will be valuable reading especially for academics. As stated in the introduction, the philosophy in industry has changed since passing of the Pollution Prevention Act by the US government in 1990 from ‘how to deal with hazardous substance’ to ‘how to design processes of minimum waste and hazard’. The chapter focuses on using various solvents with emphasis on water, even though its ‘green-ness’ is questioned (see also review on Chapter 13 above). Shaughnessy makes many important points, some of which are very familiar to both academic and industrial chemists (for example, atom economy, protecting group avoidance, toxicity) and some not to academics (for instance environmental (E) factor = mass of waste/mass of product, life-cycle assessment (LCA)

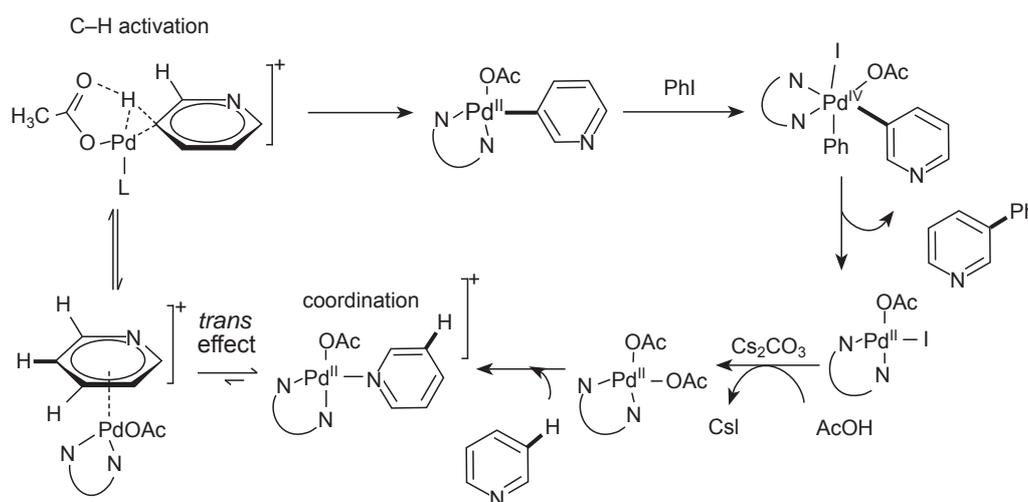


Fig. 2. C-2 Arylation of pyridine using a Pd(OAc)<sub>2</sub>/1,10-phenanthroline catalyst system (Reproduced by permission of The Royal Society of Chemistry)

= a cradle to grave evaluation from raw materials to materials returned back to Earth). Although examples of large scale reactions appear to be absent, aspects of cross-coupling in aqueous media are given thorough treatment in which choice of hydrophilic or hydrophobic metal-ligand combinations and surfactant-mediated reactions (original observation by Jefferey) are highlighted. Heterogeneous, recyclable catalysis such as nanoparticles, which are clearly of value in industry, and other green alternative solvents, such as polyethylene glycol (PEG) and ionic liquids, as well as novel conditions such as microwave and thermomorphic techniques receive coverage. Although all chemists are innately 'green', commandments such as solvent minimisation, E factor and LCA which are currently not given sufficient attention, especially by academics, are vital and appreciated points from reading this chapter.

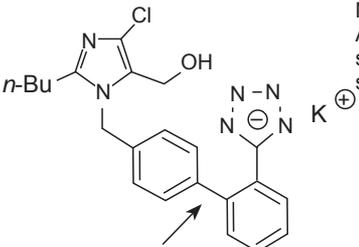
Chapter 15 by Javier Magano (Pfizer Global Research & Development, USA) and Joshua Dunetz (Gilead Sciences, Inc, USA) is a well-placed wide-ranging review, with 171 references, of recent large-scale cross-coupling reactions in service of the synthesis of pharmaceuticals. With a forceful table of statistics regarding numbers of >100 mmol reactions carried out in the 2000–2013 period, the impact of the 2010 Nobel Prize in Chemistry is truly respected and is undeniably shown by a table of commercial drugs which are synthesised by C–C (mainly), C–N and C–S coupling methods, for example **Scheme II**. There follow sections on some of these household name reactions that offer instructive details in schemes and commentary. The value of organic synthesis is alive in this chapter for sharing with students and laypersons alike. A brief section on C–H activation processes (only four to date of the review) is evidence of rapid application of

this evolving methodology. A discussion of preferred metals (currently Pd > Cu > Ni > Fe) and a glossary of abbreviations terminate this welcome chapter.

In the significant and fittingly last chapter (Chapter 16), Kazunori Koide (University of Pittsburgh, USA) defines the necessary standards for metal removal for APIs (for Pd = 10 ppm, for example, 2 µg of Pd in a 200 mg ibuprofen tablet) and the trials and tribulations in this achievement which are a process chemist's nightmare since scrupulous metal removal can delay scale up campaigns. This major problem has led to the development of new fluorimetric and colorimetric analytical methods, many in the Koide laboratories, for the detection of trace amounts of Pd. These are delineated by required criteria and are illustrated. The synthesis of Pd sensors and chemodosimeters are exemplified which, rather appropriately, illustrates cases involving Suzuki-Miyaura and Sonogashira couplings as the key steps. An informed synthetic organic chemist surveying this chapter may be tempted to devise new 'ideal metal detection' molecules.

## Conclusion

To conclude, the volume under review amassed by Colacot is a *magnum opus* of contemporary organic chemistry. The studious chemist of this volume, should receive a 95% grade (as with yields, there is no 100%) on the quiz posed at the beginning of this review. Dipping into sections of interest will provide the practicing chemist with knowledge and insight from scientists in the trenches of the areas discussed. Whether in a university or industrial lab, the chemist will take information from this compendium into the lab (if allowed) and immediately profit.

Active ingredient name	Commercial name	Structure	Type of coupling	Applicant	Indication	FDA approval date	Exclusivity expiration date (USA)
Losartan potassium	Cozaar		Suzuki-Miyaura. Also used for structurally similar drugs	Merck	Angiotensin II receptor antagonist for the treatment of high blood pressure	28th April 1995	Generic (August 2009)

Scheme II. Losartan drug synthesised by Suzuki-Miyaura cross-coupling reaction (Reproduced by permission of The Royal Society of Chemistry)

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"New Trends in Cross-Coupling: Theory and Applications"

## The Reviewer



Victor Snieckus was born in Lithuania and fled with his parents to Germany during World War II. He obtained the BSc at the University of Alberta, Canada; graduate degrees at the University of California, USA, under the supervision of D. S. Noyce, and University of Oregon, USA, with Virgil Boekelheide and carried out postdoctoral studies at National Research Centre, Canada with O. E. Edwards. He taught at the University of Waterloo, USA, until 1998 and then moved to Queen's University, Canada, as the inaugural Bader Chair of Organic Chemistry. He continues fundamental research as Bader Chair Emeritus as well as Director of Snieckus Innovations, an institute for the synthesis of small molecules for the pharmaceutical and agrochemical industries. He is a recipient of the American Chemical Society Cope Scholar Award, Arfvedson-Schlenk Preis of the Gesellschaft Deutscher Chemiker (GDCh), Canadian Society for Chemistry Bernard Belleau and Alfred Bader Awards, is a Lithuanian Academy of Sciences Laureate, and is a Royal Society of Canada Fellow.