"Solid-Phase Organic Syntheses: Solid-Phase Palladium Chemistry"

Edited by Peter J. H. Scott (University of Michigan, USA), Wiley Series on Solid-Phase Organic Syntheses, Vol. 2, John Wiley & Sons, Inc, Hoboken, New Jersey, USA, 2012, 184 pages, ISBN: 978-0-470-56665-7, £100.00, €120.00, US$150.00

http://dx.doi.org/10.1595/147106713X667470 http://www.platinummetalsreview.com/

Reviewed by David W. Knight

Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Main College, Park Place, Cardiff CF10 3AT, UK

Email: knightdw@cardiff.ac.uk

The purpose of this relatively small volume is to provide methods for carrying out representative examples of palladium-catalysed couplings on a solid support, essentially in the style of *Organic Syntheses* (1). There are contributions from both academic and industrial groups. This is a somewhat specialised area of synthesis, requiring techniques additional to those employed in 'normal' organic synthesis. Solid-phase synthesis has a number of pros and cons. The idea of immobilising part of, say, a drug candidate to a solid support on quite a large scale and then coupling a series of 'second' parts of the drug target to samples of the initial species can be a very convenient and attractive approach to library synthesis and one which is potentially very efficient and rapid. Alternatively, a diverse series of precursors can be built up on a solid support then cyclised using palladium catalysis. On the downside, it is often rather time-consuming to follow the progress of such syntheses and to manage the inevitable differences in reaction rates between a diverse range of reactants.

Hence, the purpose of this book is to provide experimental guidance across a range of palladium-catalysed coupling reactions of the types which have made such an important impact on organic synthesis in general. These reactions represent a true paradigm shift in the way that organic synthesis is currently viewed and executed.

Palladium-Catalysed Solid-Phase Organic Synthesis

A clear introduction by Carmen Gil (Instituto de Química Médica, Madrid, Spain) delineates the scope of the book. Following a generalised introduction to solid-phase organic synthesis (SPOS), individual representative examples are given to define the Heck, Suzuki, Stille and Sonogashira reactions. Illustrative of this and the style of diagrams in the book are the three diverse routes to indoles developed by Kazuo Yamazaki, Yosuke Nakamura and Yoshinori Kondo

(Tohoku University, Japan) (**Figure 1**) (2). This is followed by a brief but useful discussion of polymer-bound reagents and catalysts and the cleavage of polymer-bound products using palladium catalysis which, very significantly, can be completely orthogonal to typical acid- or base-catalysed methods.

There follows a collection of five chapters, each giving examples of palladium-catalysed SPOS. The first of these is by Vaibhav Mehta and Erik Van der Eycken (University of Leuven, Belgium) and describes the synthesis of halo-pyrazinones bound to Wang amide resin (**Figure 2**) and the subsequent homologation of these using Stille and Sonogashira couplings, and finally cleavage from the resin. An alternative strategy combines these steps: pyrazinone derivatives linked to the resin by a sulfur atom undergo coupling with phenylboronic acid at this site with concomitant cleavage from the resin.

A second chapter, by Zheming Ruan *et al.* (Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, USA), outlines how to carry out the amidation of polymer-bound allyl esters. Kwangyong Park and Chul-Hee Cho (Chung-Ang University, Seoul, South Korea) then illustrate the coupling of polymer-supported arylsulfonates with aryl Grignard reagents and Wei Zhang (University of Massachusetts, Boston, USA) and Yimin Lu (Fluorous Technologies, Inc, Pittsburgh, USA) show how the methodology can be used to synthesise a series of aminoimidazo[1,2-*a*] pyridines and pyrazines using fluorous sulfonates as leaving groups. A final chapter in this section describes the application of the Sonogashira reaction for resin-to-resin transfer reactions and was written by Judit Tulla-Puche (University of Minnesota, USA; and Institute for Research in Biomedicine, Barcelona, Spain), Rita Majerle and George Barany (University of Minnesota, USA) and Fernando Albericio (Institute for Research in Biomedicine, Barcelona; CIBER-BBN, Networking Centre on Bioengineering, Biomaterials and Nanomedicine, Barcelona; and University of Barcelona, Spain).

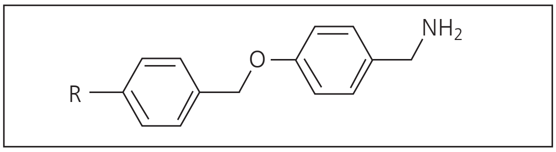


Fig. 2. The structure of Wang amide resin, which can be used as a support for palladium catalysts

Immobilised Catalysts and Ligands

The third part of the book is concerned with the elaboration of immobilised catalysts and ligands (see **Figure 3** for examples). Specific chapters feature detailed descriptions of the preparations of polymer-supported palladium for Suzuki and Heck reactions by Peter Styring (University of Sheffield, UK) and Maria Dell'Anna, Piero Mastrorilli and Cosimo Nobile (Acque e di Chimica del Politecnico di Bari, Italy). Moumita Roy, Pravin Likhar and M. Lakshmi Kantam (Indian Institute of Chemical Technology, Hyderabad, India)

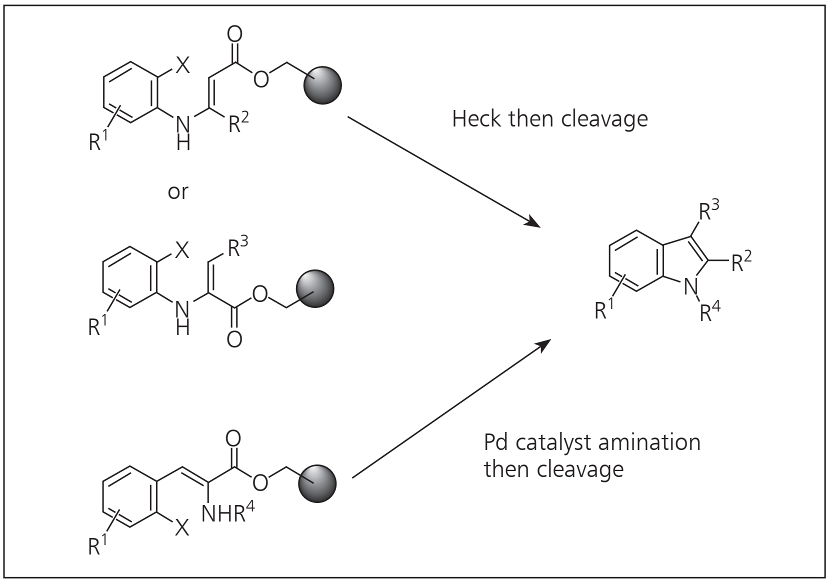


Fig. 1. Three diverse routes to indoles by palladium-catalysed solid-phase organic synthesis (2)

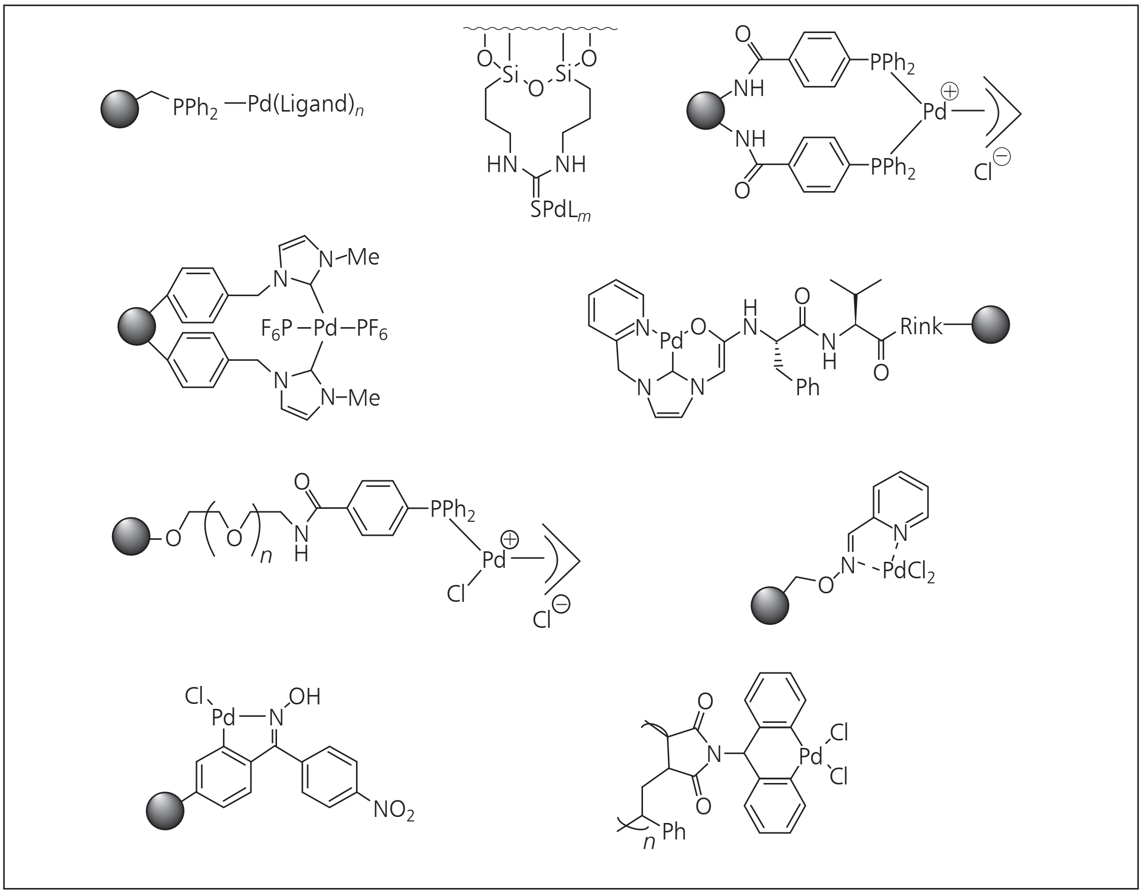


Fig. 3. A selection of polymer-bound palladium catalysts

highlight the synthesis of palladium immobilised on polyaniline for use in Suzuki couplings in water, while Katarzyna Glegola and Eric Framery (Université Claude Bernard Lyon 1, France) detail the preparation of a supported aryldicyclohexylphosphine ligand for use in the same reactions. This section is rounded off by a method for the formation of diaminobutane (DAB) dendrimers as supports for palladium catalysts by Karine Heuzé, Agnés Fougeret, Julietta Lemo and Daniel Rosario-Amorin (Université de Bordeaux, France).

Palladium-Mediated Multifunctional Cleavage

The fourth part of the book details methods for the palladium-mediated multifunctional cleavage of products from supporting resins. This is illustrated by the work of François Carreaux (Université de Rennes 1, France), Herve Deleuze (Université de Bordeaux, Talence, France) and Christelle Pourbaix-L'Ebraly (Galapagos SASU, Romainville, France) who provide methods for reacting polymer-bound boronic acids with aryl halides, the boronic acids being present as esters formed with a polymer-based diol. Phenol-based resins are the basis of a method for making bound immobilised enol phosphates which undergo smooth Suzuki couplings to provide a range of cyclic aryl enamides as described by Tom Woods (University of Auckland, New Zealand). Sylvia Vanderheiden, Nicole Jung and Stefan Bräse (Karlsruhe Institute of Technology, Germany) show how resin-bound triazines can be cleaved using Heck methodology while Andrew Cammidge and Zainab Ngaini (University of East Anglia, Norwich, UK) describe the palladium-mediated cleavage of tetrafluoroaryl sulfonate linkers.

Richard Brown and Martin Fisher (University of Southampton, UK) next show how allylic amines can be synthesised by palladium-catalysed displacement of aryl-substituted allylic alcohols from hydroxypolystyrene by primary or secondary amines. A final section from the same group (Lynda Brown, Richard Brown and Martin Fisher) show how similar methodology, when carried out intramolecularly, can be used to obtain 4-methylene pyrrolidines.

Conclusions

The general style of the narrative throughout the book includes the use of many useful footnotes and, while the methods have not been checked by an independent group, they appear to be thorough, complete and clear. A substantial amount of characterisation data is often, but not always, included, usually along with a sensible discussion and relevant literature references.

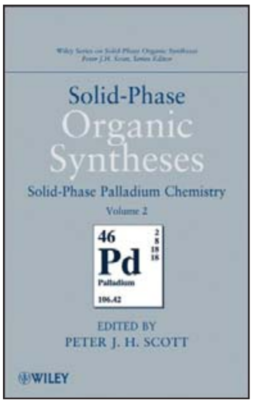
Once a few of these methods have been read and understood, a pattern emerges of how to carry out this type of synthesis. I do think the book is perhaps a little short on breadth, although this may be justified by the repetitive nature of the methods. I would have liked to see a little more discussion on how to follow such reactions and also, in some cases, more justification of why one should use solid state methods in preference to more conventional chemistry. Although many of the methods have obvious applications in library synthesis, a few seem to lack practical usefulness – this could perhaps have been discussed further.

Overall, though, the adoption of an *Organic Syntheses* style is an excellent idea and works very well. Along with other related volumes, this collection serves to demystify polymer-supported methods for palladium-catalysed reactions and provides a very useful collection of clear methods. It will certainly be of interest and use to those new to the field. It should be available to anyone contemplating using such methodology, including research students, academics and industrial chemists.

References

1 *Organic Syntheses*: A Publication of Reliable Methods for the Preparation of Organic Compounds: http://www.orgsyn.org/ (Accessed on 22nd April 2013)

2 K. Yamazaki, Y. Nakamura and Y. Kondo, *J. Org. Chem*., 2003, **68**, (15), 6011



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The Reviewer

David W. Knight is a Professor of Synthetic Organic Chemistry at Cardiff University, UK. His research interests include the development of novel synthetic methodologies, especially in the area of heterocyclic ring formation and subsequent applications of these in natural product and other target syntheses. He regularly makes use of palladium-catalysed coupling methods, even to the extent of recently optimising a version of the Suzuki-Miyaura method for styrene synthesis. He has published over 300 original research papers.