

# *“Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments”*

Edited by Árpád Molnár (University of Szeged, Hungary), Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, Germany, 2013, 692 pages, ISBN: 978-3-527-33254-0, £125.00, €150.00, US\$190.00

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“Palladium-Catalyzed Coupling Reactions”, published by Wiley in 2013, is a comprehensive handbook and guide to modern aspects of this reaction type. The book focuses on state of the art techniques. The use of different reaction media, catalyst recycling, supported catalysts, microwave assisted synthesis and continuous flow reaction systems are all examined, making this book an excellent resource. The book avoids delving into the specifics of each type of coupling reaction and instead presents a variety of topics, discussing recent progress and potential future work in each given area. It was edited by Árpád Molnár, a Professor of Chemistry in the University of Szeged, Hungary, who has no less than 200 publications to his name. Numerous research papers in the field of catalyst development, coupled with review papers on many of the subjects covered in this book, qualify Professor Molnár for his position of editor.

The content of this book covers five general topics: an introduction and background to Pd-catalysed coupling reactions, Pd catalysts on various support materials, coupling reactions in different reaction media, reaction conditions for coupling reactions and industrial applications of Pd catalysed coupling reactions.

## **Introduction**

The area of Pd-catalysed coupling reactions has experienced a huge growth in popularity and has swiftly increased in maturity in its relatively short lifetime, having moved from using stoichiometric amounts of Pd-based reagents to achieving impressively high turnover numbers (TONs) in just a few decades. Since the initial Pd-catalysed coupling reactions described by Heck (1), Negishi (2) and Suzuki (3) during the 1970s a wide range of coupling reactions, using different organic halides and organometallic compounds have been discovered (**Figure 1**).

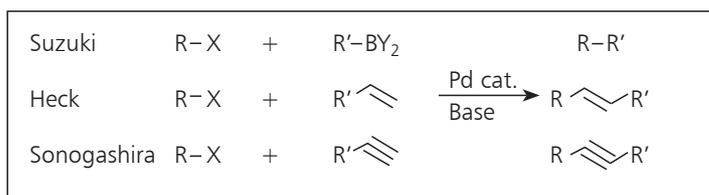


Fig. 1. Schematic of the Suzuki, Heck and Sonogashira coupling reactions

The first chapter of this book gives a comprehensive introduction to the area of Pd-catalysed coupling reactions, covering the history and characteristics of the reactions and classification of the various reaction types, which numbered 72 in a recent review (4). A mechanistic overview is given along with considerations to be taken with regards to the effect of the halides and nucleophiles employed, the nature of the Pd species, ligands employed and other related topics. The introduction is concluded with a section on future challenges for Pd-catalysed coupling reactions. Here aspects relating to practical, real world applications are discussed along with developments that will enable these reactions to be brought into common usage. Even though this introduction is relatively brief it gives an excellent and comprehensive overview of Pd-catalysed coupling reactions, explains why Pd is the catalytic metal of choice and provides a basis for the following chapters.

### Support Materials

There are four chapters that discuss the effects of the support material on the performance of Pd-catalysed coupling reactions. These are dealuminated ultrastable Y (USY) zeolites, magnetically separable nanocatalysts, ordered porous solids and polymers. In the first chapter, written by Kazu Okumura (Tottori University, Japan) the high TONs achievable by the use of USY zeolites is discussed. These materials are widely available due to their use in alkane cracking and make a suitable support for Pd due to nanometre sized pores within the zeolite structure. The preparation of USY zeolites, the dealumination process of the zeolite framework and the preparation of Pd/USY zeolite catalysts are discussed briefly followed by a number of examples of coupling reactions performed using these catalysts. As an introduction to this support type the author describes a typical Suzuki-Miyaura coupling of bromobenzene and phenylboronic acid in *o*-xylene with potassium carbonate as a base, used by Durgun *et al.* (5) to screen activity of Pd salts loaded on USY zeolites. [Pd(NH<sub>3</sub>)<sub>4</sub>]Cl<sub>2</sub>/USY exhibited high activity and using 0.7 × 10<sup>-4</sup> mol% of catalyst for the coupling reaction a

TON of 1.3 × 10<sup>6</sup> and a 99% yield were obtained. Work by the same group proved this catalyst type suitable for Suzuki-Miyaura coupling of heterocyclic compounds. High TONs and good yields were achieved in the coupling of 2-bromothiophene and thiophene-2-boronic acid indicating the possible use of Pd/USY catalyst in the synthesis of organic semiconductors.

The second chapter in this section, written by Kifah S. M. Salih and Werner R. Thiel (TU Kaiserslautern, Germany), concerned magnetically separable nanocatalysts. Using magnetically separable supports offers an easy solution to what can be a difficult problem – removing the catalyst from the reaction mixture. In the introduction the authors describe the solid state properties required of the paramagnetic particles, factors affecting the lifetime of the supported catalyst, some of the characterisation techniques employed and the types of catalyst attached to the magnetic particles. For example, Manorama *et al.* reported nickel ferrite particles with a dopamine functionalised surface on which they grafted Pd nanoparticles (6). This Pd catalyst was employed in high yielding Suzuki coupling reactions between aryl chlorides and phenylboronic acid and also Heck reactions between aryl chlorides and styrene. Once the reaction was complete the catalyst was magnetically removed from the reaction mixture and successive reactions were performed with similar yields (Figure 2).

Ease of separation of this catalyst type is key to its functionality. Pd leaching was looked at in several of the examples described. There was low or negligible leaching of metal from the nanoparticles after several uses of the catalyst. In one case, leaching of Pd was observed during the reaction with reabsorption of the metal back onto the support occurring after the reaction mixture had cooled to room temperature. A number of other magnetically separable catalysts are described, including catalysts based on Pd nanoparticles and also Pd complexes supported on magnetic particles.

The third chapter in this section discussed the use of ordered porous solids as a support for Pd

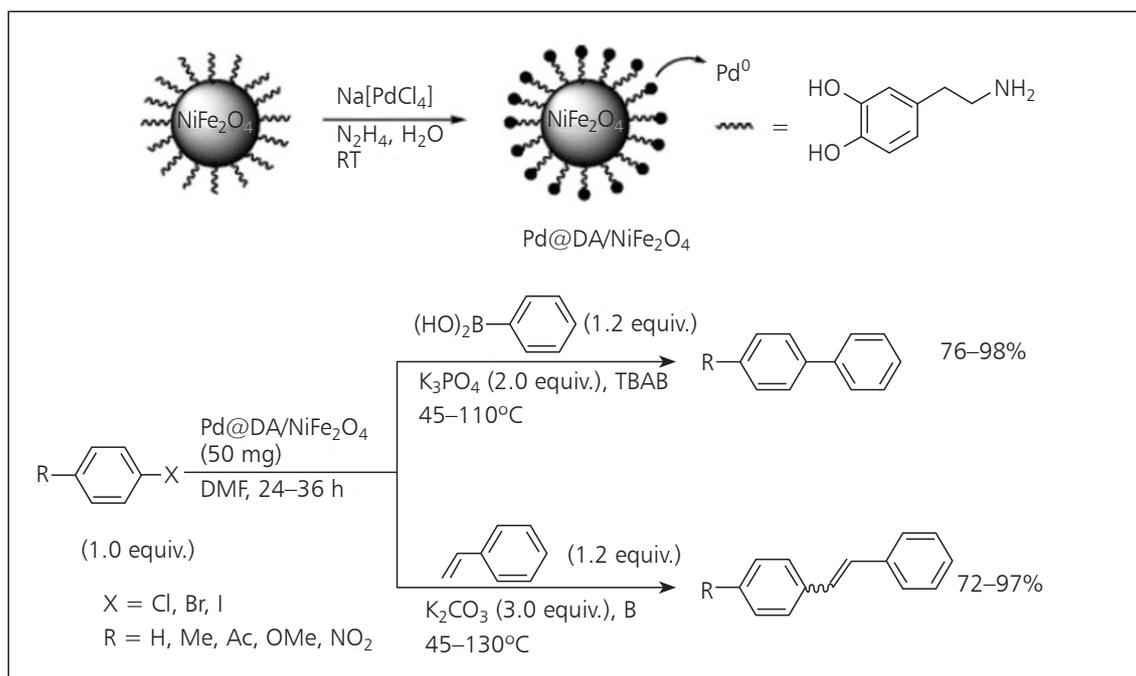


Fig. 2. Magnetically separable palladium catalyst used for Suzuki and Heck reactions (6) (Image courtesy of Wiley and Sons, Copyright 2013)

catalysts and was written by the editor of the book, Árpád Molnár. The physical properties of ordered porous solids make them ideal for use in catalysis: high surface area, uniform pore size and a defined, tunable structure. Materials that fall under the category of ordered porous solids include zeolites, ordered porous silica-based materials and metal organic frameworks amongst others. The chapter opens with an in-depth look at the synthesis and characterisation of these materials, focusing on two examples: the mesoporous silicas MCM and SBA. A background to the materials, techniques employed to control pore size and distribution, methods to tailor properties and functionalisation are all covered extensively. An Ullmann coupling of iodobenzene using a range of mesoporous silica-based materials performed by Li *et al.* highlighted the catalytic performance and ability to tailor a catalyst to a reaction (7). Under the selected reaction conditions a conversion of 27% and a yield of just 7% were obtained using Pd supported on SiO<sub>2</sub>. By altering the ordered porous silica materials to suit the reaction, with large pores of SBA-15 to accommodate the biaryl product and aluminium doped MCM-41 to increase the Lewis acidity, promoting adsorption of the iodobenzene, much improved conversion and reaction yields were obtained. The chapter concludes

with a summary of the current state of these materials together with a discussion of future prospects and challenges.

### Reaction Media

Chapters six and seven discuss reaction media employed for coupling reactions, namely ionic liquids (ILs) and aqueous media. The solvent employed as reaction medium has a considerable effect on the performance, outcome, cost and environmental impact of a chemical transformation, so it is appropriate that some consideration is given to the solvent selection. Traditional solvents used for Pd-catalysed couplings include dimethylformamide, *N*-methylpyrrolidinone and other polar solvents, many of which have undesirable health implications, and as with most volatile organic solvents, are flammable and environmentally unfriendly.

Chapter six, written by Michael T. Keßler, Frank Galbrecht and Martin H.G. Precht (Universität zu Köln, Germany) and Jackson D. Scholten (Universidade Federal do Rio Grande do Sul, Brazil), is dedicated to the use of ILs as a reaction medium for Pd-catalysed coupling reactions. ILs are organic salts with low melting points, generally below 100°C. The author cites a number of reasons for their use: tunable combination

of anions and cations to suit a particular reaction, stabilising effect of ILs on ligands and Pd complexes, solubility of organometallic compounds and ease of separation of reaction products once the reaction is complete. Again here, the authors detail a number of coupling reactions performed in ILs, discussing the use of both Pd complex-catalysed and Pd nanoparticle-catalysed reactions. The emphasis is on the advantages of ILs over more traditional solvents and the authors use a number of examples to highlight this, often with very high conversion rates, mild reaction conditions and excellent catalyst reuse and recycling potential.

In chapter seven, written by Kevin H. Shaughnessy (The University of Alabama, USA), cross-coupling reactions in aqueous media is the topic. Water being a cheap, non-toxic, non-flammable, renewable solvent makes it a sensible solvent choice. However, with organic compounds, problems of solubility along with often water labile reaction systems mean that the use of aqueous media is frequently avoided. The author discusses the resurgence of aqueous based organic chemistry, aspects of Pd that lend it to aqueous reaction systems and developments in water soluble ligands. The actual need for solubility is also discussed with efficient organic reactions being performed 'on water', that is, where solubility in the solvent is not required to achieve chemical transformations. A range of examples are given: firstly in aqueous media, then in biphasic systems of water and organic solvent mixtures. An example of a water-only mediated Suzuki reaction was performed by Basu *et al.* (8). A ligand free coupling of tropolone with an aryl trihydroxyborate allowed Pd(OAc)<sub>2</sub> and tetrabutylammonium bromide to catalyse the reaction at low temperatures and short reaction times in water (Figure 3).

### Reaction Conditions

The next section of the book, consisting of three chapters, covers reaction conditions of coupling

reactions. The topics covered here are microwave assisted synthesis, catalyst recycling and continuous flow reactions. Despite microwave assisted reactions and catalyst recycling appearing in numerous described reactions in previous chapters the editor considered the exceptional results possible when employing these techniques worthy of separate chapters. In the chapters on microwave synthesis and catalyst recycling the 'green' aspects of the subject are highlighted. In the case of microwave synthesis, reduced reaction times, minimised side products and improved yields are cited as reasons for its consideration.

As in other chapters the authors, Ke-Hu Wang and Jun-Xian Wang (Northwest Normal University, China), discuss a range of microwave assisted coupling reactions, most of which were reported within the previous decade. In most cases the short reaction times (with some reactions completing in a matter of minutes) are emphasised as a unique feature of microwave assisted synthesis, often coupled with excellent yields.

In the chapter on catalyst recycling Árpád Molnár places the focus on some of the shortcomings in reported recyclable catalysts. In the lengthy introduction, some common misconceptions with regards to what is a stable, recyclable catalyst are addressed. Where at times, efficacy is maintained while catalytic metal is being lost, the true recyclable nature of the catalyst is brought into question. This topic is covered in detail along with some techniques that can be utilised to monitor low levels of Pd loss. Nanoparticle, complex-based and polymer immobilised catalysts are covered along with a number of other reusable catalyst types. Here, numerous impressive examples of robust catalysts are discussed, with some performing twenty runs of a Heck coupling reaction without loss of performance (9). The design of reactions is also brought into question here. Low numbers of repeat runs using

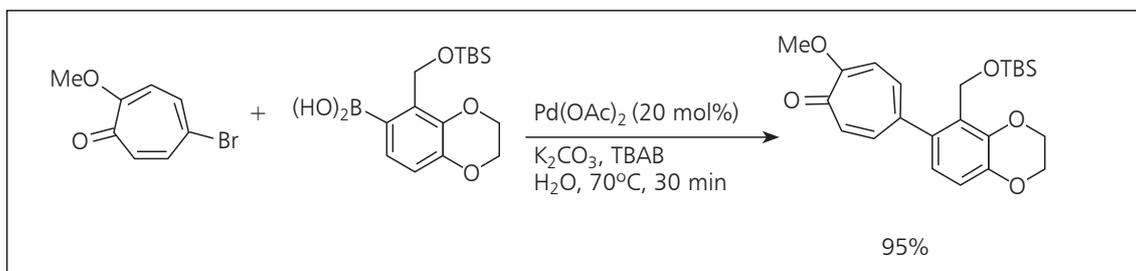


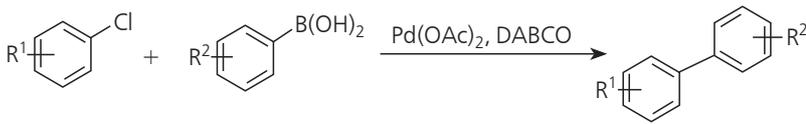
Fig. 3. A ligand free coupling of tropolone with an aryl trihydroxyborate catalysed by Pd(OAc)<sub>2</sub> and tetrabutylammonium bromide using water as reaction solvent (8) (Image courtesy of Wiley and Sons, Copyright 2013)

the more reactive halides give impressive results, whereas for transformations performed with less reactive compounds, high numbers of test reactions and adequate characterisation to ensure no loss of catalyst are required to truly call a catalyst recyclable.

Chapter eleven written by William R. Reynolds and Christopher G. Frost (University of Bath, UK) covers the use of continuous flow reactors as a reaction system for coupling reactions. In previous chapters reactions were performed in batch style flasks or vessels. Excellent reaction efficiencies, both in yield and cost reduction, have been seen in bulk chemical processes for years. In recent decades considerable time has been dedicated to continuous flow reactors for organic synthesis and good reaction efficiencies have been achieved as a result. Lower energy requirements, better temperature control, improved mass transfer, lowered reaction volume giving greater control over the chemical reactions and ease of scaling from lab to industrial scale are cited as some reasons for continuous flow being an attractive alternative to batch type reactions. An effective example of improved reaction efficiency was conducted by Li *et al.* (10). In this example efficiencies of flow reactors were compared to batch reactors in the Suzuki coupling of aryl chlorides with phenylboronic acids using Pd(OAc)<sub>2</sub> as catalyst and DABCO (1,4-diazabicyclo[2.2.2]octane) as a ligand. After a 4 h residence time continuous flow reactions of both electron-rich and electron-poor aryl chlorides had completed with almost quantitative yields. The

batch reacted counterparts had considerably lower conversions after 4 h and reaction times of 24 h were required to bring the reactions to completion (Figure 4). Reactor technology and design is also discussed, along with catalyst immobilisation techniques, continuous separation and the use of microreactors.

All of the chapters so far have presented impressive results but only in research scale coupling reactions. The final chapter in the book, by Andreas Dumrath, Christa Lübke, and Matthias Beller (Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Germany) concerns industrial applications, mainly focusing on examples from the recent past. The focus of the introduction differs from the other chapters in that it includes a discussion based on real life reaction scale-up along with economic considerations, metal prices, the cost of the base and reactants employed, intellectual property implications and toxicity of catalysts where pharmaceutical products are concerned. A slightly different approach to examples is taken in this chapter, often presenting a background to the desired product, along with different reaction options and routes taken to catalyst and reaction selection. A Heck-Mizoroki coupling of benzyl acrylate with a bromonaphthalene was used in the synthesis of an oral pharmaceutical by GlaxoSmithKline (11). By replacing a late stage reaction with this coupling, the downstream chemistry was simplified resulting in better scalability along with a large reduction



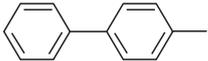
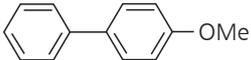
| Entry | Product   | Conversion, % |             |              |
|-------|---|---------------|-------------|--------------|
|       |   | Flow (4 h)    | Batch (4 h) | Batch (24 h) |
| 1     |  | 98            | 61          | 98           |
| 2     |  | 99            | 35          | 57           |

Fig. 4. Comparison of a flow vs. batch process for a Suzuki reaction (Image courtesy of Wiley and Sons, Copyright 2013)

in raw material cost. Other techniques covered in other chapters in this book are also used in industry including microwave assisted synthesis, continuous flow coupling reactions and reusable catalysts. This chapter exhibits a number of excellent examples of improvements to reaction rates and conditions achieved by incorporating Pd catalysed coupling reactions. Despite the complexity of a number of these compounds, equivalent or improved yields and stereocontrol was achieved by using these coupling reactions, often with an economic benefit due to fewer side products, the use of lower quantities of reagents and a reduced need for purification steps.

### Summary

This book is an excellent, modern summary of the state of Pd-catalysed coupling reactions. The focus on highly efficient reactions and recyclability of the catalysts is in tune with the ethos being adopted by many in the chemical industry. Atom efficiency and the application of cleaner, less wasteful chemistry is now very achievable. This book would be an excellent starting place for an organic chemist who is interested in reducing costs and increasing efficiencies of existing reaction processes or one who is designing new synthetic routes.

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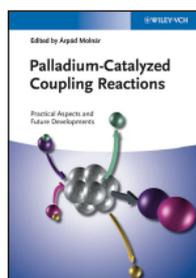
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### The Reviewer



Robert Hanley obtained a BSc in pharmaceutical science from Cork Institute of Technology, Ireland, and a Master's degree in green chemistry from Imperial College London, UK. He previously worked for Johnson Matthey Pharmaceutical Materials, Ireland, in the area of prostaglandin synthesis. Currently he is working as a development chemist for Johnson Matthey within the Emission Control Technologies division, his main area of research being diesel oxidation catalysts.



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