

Palladium-Catalyzed Coupling Reactions

The great importance of palladium-catalyzed cross-coupling reactions and C–C bond formation in modern organic chemistry was confirmed by the award of the 2010 Nobel Prize in Chemistry to Heck, Negishi, and Suzuki. The usefulness of related chemical named reactions, i.e., the Sonogashira, Stille, Kumada, and Hiyama couplings, should not be forgotten, as they form a useful synthetic toolbox in industrial processes (e.g., for pharmaceuticals, agrochemicals, molecular materials) and academic endeavors (in total synthesis, multicomponent reactions, fundamentals of catalysis, etc.).

Originally, such catalytic processes were developed and refined under classical homogeneous conditions, and the search for their improvement in practical terms has followed many different paths. The book *Palladium-Catalyzed Coupling Reactions—Practical Aspects and Future Developments*, edited by Árpád Molnár, is devoted to a comprehensive examination of these practical advances. Thus, it deals with the emergence of heterogeneous and bi(or poly)-phasic processes, and the use of unusual solvents (ionic liquids, water) and of microwave and microflow technology in palladium-catalyzed coupling reactions. A final chapter describes a selection of large-scale industrial applications of palladium-catalyzed coupling reactions, thus exemplifying some of the practical aspects discussed in the previous chapters. Taking into account the large number of books devoted either to palladium-catalyzed cross-coupling under classical homogeneous conditions, or to heterogeneous catalysis (including nanocatalysts and technical processes), the editor and the authors have been audacious enough to provide an interesting attempt to bridge the gap between these topics.

As a consequence of the multi-author nature of the book, each of the chapters can stand by itself—but the resulting impression is of unequal levels of merit and interest in the individual chapters. Thus, it is appropriate to examine the contents of the book chapter-by-chapter.

Chapter 1, “Palladium-Catalyzed Cross-Coupling Reactions—a General Introduction” (101 references), gives a textbook (undergraduate) level introduction to the topic. In a revised and augmented future version of the book, it would probably be necessary to correct some misleading or partial views. For instance, it is rather astonishing to find that leaving groups from electrophilic carbons are classified in a way that presents a C–OTf bond as being less reactive than C–F. A second

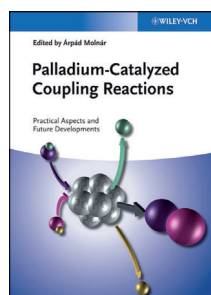
example is the weak section on ligands, in which the phosphane-ligand type is treated in the same way as exotic “macrocyclic palladium complexes”, whereas objectively their respective impacts on palladium-catalyzed coupling are simply orthogonal. Under ligand chemistry, the high turnover numbers (some greater than 10000) provided by mono-, di-, and polyphosphanes are simply ignored (despite the hundreds of publications), even though achieving high turnovers is repeatedly emphasized as a central topic of the book. Finally, a more “organic” approach in the general introduction would have been appropriate for newcomers to the field, at least to emphasize the wide variety of organic backbones that are accessible from such Pd-catalyzed cross-couplings.

Following that introduction, Chapter 2, “High-Turnover Heterogeneous Palladium Catalysts in Coupling Reactions: The Case of Pd Loaded on De-Aluminated Y Zeolites” (44 references), is an interesting but very specialized contribution on this topic. It could instead have been included in Chapter 4, which also treats this general theme on a broader basis. Overlapping between chapters, and repetition of material, has in general been poorly handled with regard to the self-consistency of the book. The introduction to structural characterization of zeolites is very interesting, and the organic species obtained are described in a nice diversity, demonstrating the potential of these catalysts.

The title of Chapter 3 is “Palladium-Catalyzed Coupling Reactions with Magnetically Separable Nanocatalysts” (32 references). This short chapter is one of several that are devoted to recovery and recycling of catalysts; again, it might instead have been part of a larger chapter. It is focused on describing various magnetic species (nanoparticles/molecular complexes) and their catalytic performance, mainly in Heck, Suzuki, and Sonogashira coupling reactions. It is a pertinent introduction to the field for graduate students. A detailed description of the magnetic separation processes would have been useful (apparatus/magnetic field, filtration process, percent recovery achieved).

Chapter 4, “The Use of Ordered Porous Solids as Support Materials in Palladium-Catalyzed Cross-Coupling Reactions” (179 references), is a very detailed and rather technical review of the various classes of ordered porous solids that have been used for this purpose. A very careful compilation of results is given, with an in-depth discussion that is addressed to experts. The summary and discussion of future prospects also includes a collection of examples, and shows that this field is not yet sufficiently mature for a full understanding.

Chapter 5, “Coupling Reactions Induced by Polymer-Supported Catalysts” (170 references), is a high-quality contribution from the research group led by Karimi. After a short but sound general



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introduction, for beginners it first describes work with the polymers on which there has been most development, and thus it is interesting for both undergraduate and graduate students. Other support systems include ionic polymers, organometallic polymers, and those based on either nanotubes or a porous ordered structure, the discussion of which is informative for scientists with more experience in the subject. The summary and outlook part of this chapter is well-organized, clear, and concise.

Chapter 6, “Coupling Reactions in Ionic Liquids” (132 references), and the following chapter are concerned with the use of unusual solvents in Pd-catalyzed cross-couplings. Ionic liquids have some advantages over organic solvents, which are explained here; however, their disadvantages (toxicity, final treatment, limitations in reactivity, characterization, HF issues, water content, etc.) are scarcely mentioned. The treatment of the literature is not complete, for example with regard to reactions such as Sonogashira couplings with metal complexes, and consequently the chapter provides only a general introduction for non-experts.

In Chapter 7, “Cross-Coupling Reactions in Aqueous Media” (172 references), the approach is very different. The difficulties encountered in the use of water as a solvent for C–C coupling reactions (limited solubility of some substrates, sensitivity of some functional groups) are not avoided. With more than 80 schemes, Shaughnessy nicely describes studies of many different systems in water, not only for C–C coupling reactions (including Hiyama, Stille, cyanation, and other couplings that are not systematically covered in other chapters), but also for C–Heteroatom couplings (C–N, C–S). Even a highly topical recent area such as C–H direct functionalization is addressed. This is a chapter of high quality and is of interest for the wide community of chemists.

Chapter 8 is devoted to “Microwave-Assisted Synthesis in C–C and Carbon–Heteroatom Coupling Reactions” (110 references). A major advantage of microwave-assisted synthesis is access to reactions with a short time-scale. This is nicely detailed in this chapter, which not only covers the most studied couplings, but—like the previous chapter—addresses most of the useful “toolbox” palladium couplings (including the use of exotic organotellurium coupling reagents, decarbonylative couplings, and carbonylation and cyanation reactions). In this chapter, a section devoted to technical aspects (instrumentation, principles) of microwave-assisted coupling reactions, analogous to that in Chapter 11 on flow techniques, would have been more informative than the historical paragraph on microwave “market evolution”. Note

also that sonochemistry could have been introduced here to enrich the discussion.

Chapter 9, “Catalyst Recycling in Palladium-Catalyzed Carbon–Carbon Coupling Reactions” (130 references), is a high-quality contribution in which Molnár collates key information about catalyst recycling, and discusses a selection of examples in which consistent yields of recycling have been obtained. The proposed approach is useful (with comparative tables collecting the most convincing studies), and a critical in-depth discussion is given, with particular emphasis on cumulative high turnover numbers. This chapter is a major contribution for the advances in heterogeneous catalytic systems that have been inspired by homogeneous catalysis. One might criticize that it appears too late in the sequence of chapters. I recommend careful reading of this contribution at any level of personal experience.

The title of Chapter 10, “Nature of the True Catalytic Species in Carbon–Carbon Coupling Reactions with Heterogeneous Palladium Precatalysts” (69 references), seems at first sight to be a little bit “ambitious”, but it provides a concise and very informative view about the nature of the catalyst (whether as nanoparticles or molecular Pd^0 , and whether as heterogeneous or soluble species). The analysis of the state of the art is focused on Heck, Suzuki, and Sonogashira reactions. Essential background knowledge with pertinent references is provided. In particular, the relationships existing between molecular Pd^0 leaching and the activation of (only) facile substrates are appropriately emphasized.

In Chapter 11, “Reactions in Continuous-Flow Systems” (86 references), Frost and Reynolds give a comprehensive and informative overview of the advantages associated with the emerging method of continuous-flow systems in comparison with batch processes. The discussion is well-organized, and covers different and complementary perspectives; in particular it considers the coupling reactions in continuous flow, the catalytic systems, and the technical processes. The chapter is detailed with schemes, tables, and even pictures of processes. This is one of the best contributions in the book, and is of interest for a large audience of students and researchers. This is also a perfect source for building an advanced teaching course on this topic.

The volume concludes with Chapter 12, “Palladium-Catalyzed Cross-Coupling Reactions—Industrial Applications” (142 references). This contribution from the Beller group is probably the chapter that best fits the book’s subtitle “Practical Aspects and Future Developments”, and indeed it is full of very relevant practical information. It cites dozens of references extracted from the ACS journal *Organic Process Research & Development*, and thus covers the industrial imple-

mentation of specific processes. Consistently with the other chapters, it describes examples of several relevant developments, such as the scale-up of microwave-assisted processes, continuous-flow and microfluidic systems, automated synthesis, pressurized gaseous reactions, and so forth. In addition, mention is made of purification tricks and processes that are of practical importance and are not often addressed in the other chapters. Finally, future developments are indicated, such as the coupling of heteroaromatic or functionalized substrates that demand special treatment, as well as domino-coupling processes. This chapter is well-written and richly illustrated with schemes that demonstrate the impressive potential of Pd-catalyzed coupling for targeting intermediates and valuable molecules that are “genuinely” in the applied category.

In conclusion, from this relevant book we learn that catalyst optimization in the area of heterogeneous catalysis has a tendency to focus on more simple substrates, and for synthetic chemists to embrace this technology it may be necessary for further collaborations to emerge and take on more structurally challenging examples. The high quality of several important chapters “informs, educates, and inspires”, and makes this book a pertinent source on practical aspects of palladium-catalyzed coupling reactions.

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