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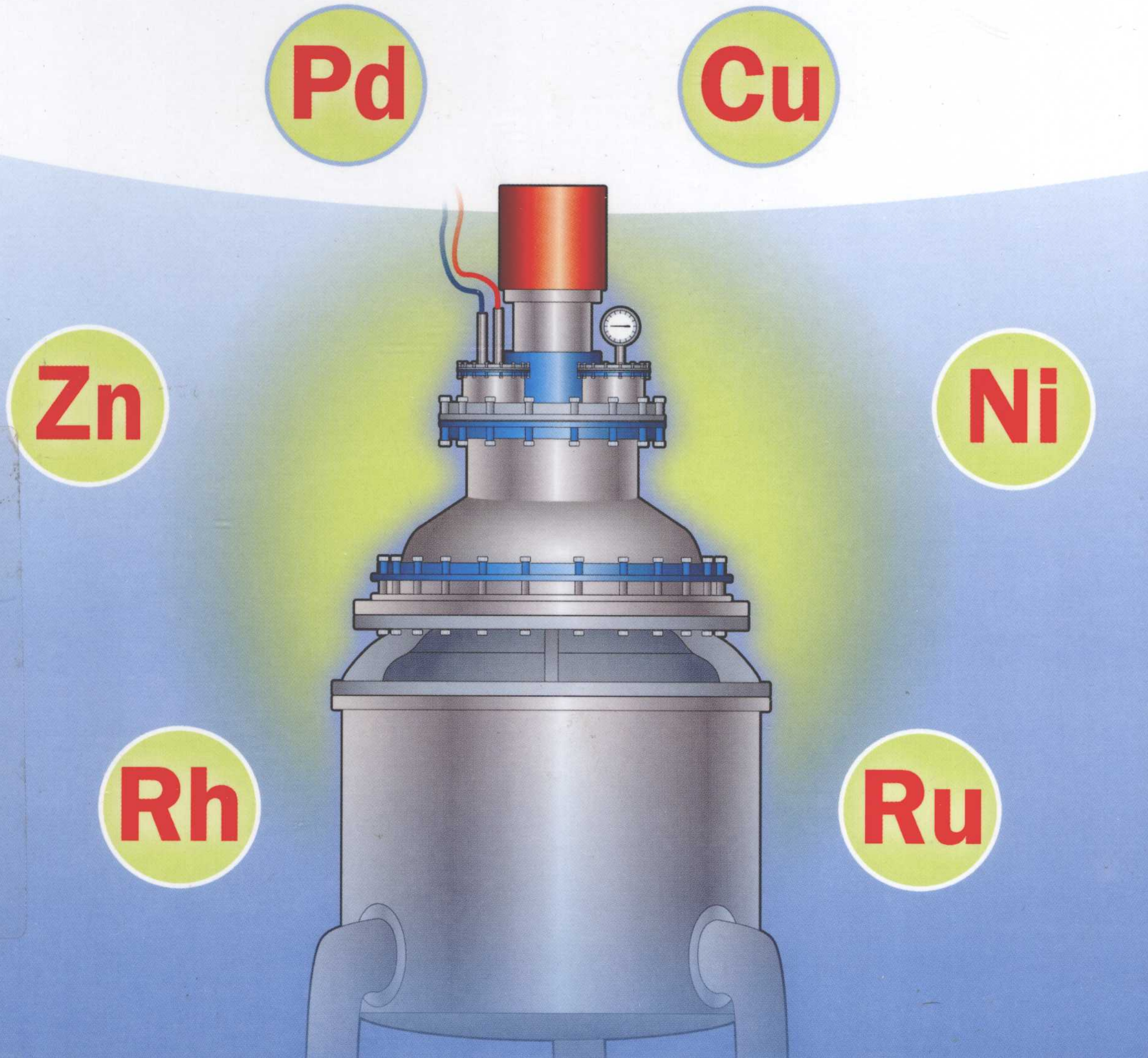
Transition Metal-Catalyzed Couplings in Process Chemistry

Case Studies from the Pharmaceutical Industry



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To Kari, Ana, and Sonia, for their love and support. And to my parents, for their gift of a good education.

– Javier Magano

For Cynthia, for Caitlin.

– Joshua R. Dunetz

Foreword 1

The ever-increasing impact of transition metal catalysis on organic synthesis can be seen in our day-to-day reading of the top chemistry journals. The Nobel Prizes to Sharpless, Noyori, and Knowles (2001), Schrock, Grubbs, and Chauvin (2005), and Heck, Suzuki, and Negishi (2010) further highlighted the importance of catalytic processes in everyday synthetic chemistry. As the methodology matures, its application on larger scale in the pharmaceutical industry is investigated at an increasing rate. Key to success in this endeavor is the development of reliable and cost-effective protocols. Each example of the use of a given technique demonstrated on a large scale gives industrial chemists increased confidence about employing it in their own work in pharmaceutical process chemistry and manufacturing settings.

Catalytic chemistry as practiced today offers synthetic chemists a wide array of different approaches to effect the same bond disconnection. As can be seen in many of the examples described in this book, the synthetic route is something that evolves over time. Beginning with the medicinal chemistry route, process chemists look for improvements in terms of safety, yield, robustness, and, ultimately, cost. Even when the identities of the basic steps that will be utilized become clear, a significant amount of work remains. This is a result of the tremendous number of different catalysts, ligands, and reaction conditions that have been developed to accomplish almost any important transformation. Thus, a standard aspect of the synthetic chemists approach has been to screen a series of different reaction parameters in order to arrive at the optimal reaction conditions. The calculus of deciding, for example, which catalyst to utilize in a carbon–carbon cross-coupling reaction can be quite complex. In addition to the efficiency of the catalyst (in terms of both yield and volumetric productivity), the cost and availability of the ligand need to be considered. Moreover, the use of less expensive metals such as nickel, iron, or copper, rather than palladium, is often explored. In addition, there may be a benefit to using a simpler ligand and an aryl bromide (typically more expensive), rather than a more complex one that allows one to use an aryl chloride coupling partner. Superimposed on this is whether patent considerations limit the use of any given technology and, if so, how onerous are the licensing terms.

From the perspective of one who develops new catalysts and synthetic methods, an examination of case studies, such as the ones in this book, is most enlightening. Issues that are often not considered in depth in academic circles (e.g., the need to employ cryogenic conditions, the concentration of reagents, particularly avoiding high dilution reactions, and problems with reaction workup on scale) may hold the key to whether a given process might be applicable in the final manufacturing route.

It is clear that catalytic methods will have an ever more important role in the manufacturing of fine chemicals. Both societal and economic pressures will place an increasing emphasis on greener processes. In order to achieve success, the advent of new and more efficient catalysts and synthetic methods will be required. The lessons presented in this book will be invaluable to synthetic chemists working to develop more efficient processes. Specifically, chemists should make an effort to test their new reactions on increasingly complex substrates, particularly on heterocycle-containing ones. For it is here where their methods will have the greatest impact on the "real-world" practice of synthetic chemistry.

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Foreword 2

Industrial process chemists often rely on academic discoveries of new chemical reactions, catalysts, or ligands when designing novel synthetic routes to complex target molecules such as pharmaceuticals. The best chemistry is quickly taken up by industry and used in manufacturing processes, none more so than transition metal-catalyzed coupling reactions, which have proved so versatile in synthetic chemistry over the past 20 years. Many of these reactions have been named after their inventors, some of whom have been awarded the Nobel Prize for their discoveries and for their outstanding work.

A negative aspect of transition metal-catalyzed couplings for the process chemist is that the catalysts and ligands can be expensive and have the potential to increase process costs. So, for efficient manufacture of pharmaceuticals, the process chemist not only has to focus on obtaining a high yield but also has to study the reaction conditions in detail and examine catalyst turnover number and frequency, and in some cases catalyst/ligand recycling and reuse. Understanding the complex mechanism of these reactions leads to better process control and batch-to-batch consistency as well as process robustness for large-scale operation.

Many transition metal-catalyzed couplings can be adversely affected by impurities in raw materials or solvents and lack of reproducibility can sometimes ensue. The temptation to abandon this chemistry and find something more reproducible should be avoided since a detailed and painstaking study of the effect of small amounts of process impurities on catalyst performance usually results in an efficient and robust process – perseverance pays off! Understanding the detailed interactions, mechanisms, side reactions, and so on is part of the fascination of process chemistry.

Process chemists are expert at examining the effect of changing reaction parameters on yield and product quality; these days statistical methods of optimization such as design of experiments and principal component analysis (still surprisingly not taught in many university chemistry departments) are widely used to maximize yield, minimize impurity formation, and optimize space–time yield (a useful measure of process throughput) to produce an efficient, scalable, and robust process.

Transition metal-catalyzed couplings can also present unusual difficulties for the process chemist with regard to product workup and isolation, since the often toxic and usually homogeneous catalyst needs to be removed from the pharmaceutical product to ppm levels. Transition metals are notorious for liking to complex with the type of molecules used in the pharmaceutical industry, and special technologies and/or novel reagents need to be used in the workup and isolation strategies. Detailed crystallization studies may also be required to produce products within specification.

In the case studies presented in this unique book, the chapter authors provide fascinating stories of the innovative process research and development needed to convert a transition metal-catalyzed coupling reaction into an economic and robust manufacturing process for the manufacture of kilograms or even tons of complex products in high purity. The trials and tribulations are described for all to see. The editors and chapter authors are to be congratulated on producing an outstanding work that should be of value not only to process chemists but also to those teaching industrial applications of academic discoveries.

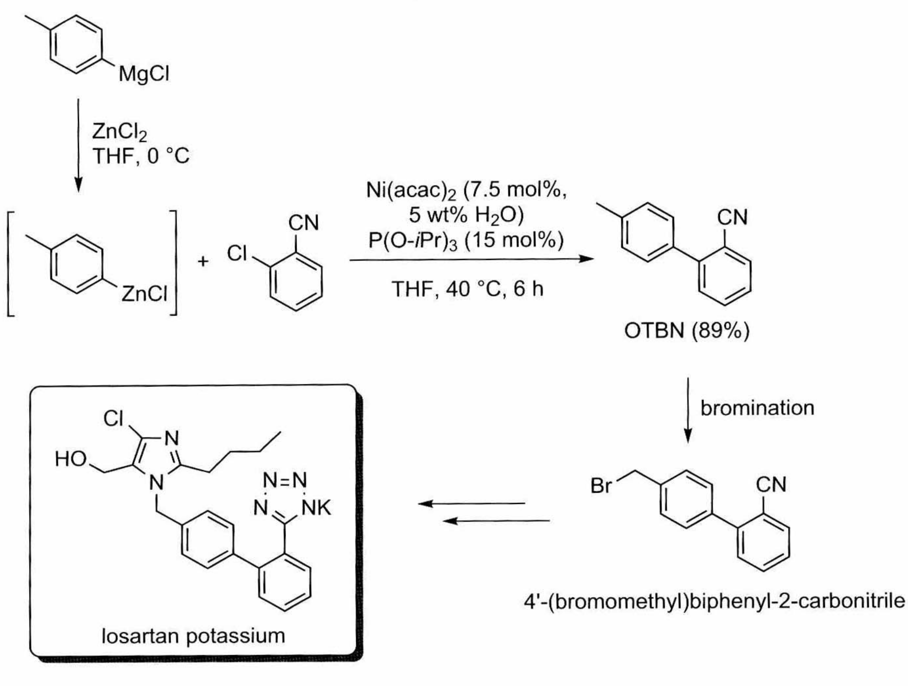
Scientific Update LLP
Editor, Organic Process Research and Development

Trevor Laird

Foreword 3

Selecting metals and designing ligands for transformations in organic chemistry, mostly hydrogenations and couplings, were largely academic pursuits for several decades. As these reactions became increasingly popular, chemists in industry applied them to the synthesis of many drug candidates. The value of transition metal-catalyzed cross-couplings was evident in the pharmaceutical industry since the 1990s with the manufacturing of the family of sartans, antihypertensive agents.[1)] The power of transition metal-catalyzed couplings was recognized with the Nobel Prize awarded in 2010 to Professors Heck, Negishi, and Suzuki.

1) The "sartan" family of drugs is widely prescribed to treat hypertension. Losartan potassium was marketed in 1995, and at least five other antihypertensive agents with *ortho*-substituted, unsymmetrical biaryl moieties have been marketed since [1]. Many of these APIs could be manufactured by reaction of amines with the commercially available 4′-(bromomethyl)biphenyl-2-carbonitrile, which can be derived by bromination of *o*-tolylbenzonitrile (**OTBN**). A group from Catalytica described Ni- and Pd-catalyzed preparations of OTBN using inexpensive components [2].



Transition metal-catalyzed couplings are more complicated to optimize than many organic reactions, especially for researchers in industrial process R&D. On scale, the charges of expensive transition metals and ligands are minimized, as the benefits of any increased selectivity from the catalyst must be balanced with the overall contribution to the cost of goods and with any difficulties encountered during workup and isolation. On scale, the transition metals charged may be recovered and reused. The amount of water in a process often must be controlled, as water can activate or deactivate reactions and produce impurities such as those from protodeboronation in Suzuki couplings. Starting materials, for example, halides or sulfonates, may be chosen to promote reactivity and decrease excess charges needed; starting materials may also be selected to mitigate reactivity or minimize the formation of by-products, such as those from olefin migration. Processes must be well understood both to avoid the introduction of inhibitors and to control the generation of inhibitors, thus minimizing the charges of metal and ligands and making operations more rugged. Some transition metal-catalyzed reactions are driven by equilibrium, necessitating the development of practical workups to quench reactive conditions; simply pouring a reaction mixture onto a column of silica gel as is often done in the laboratory may be ineffective on scale. Last but not least, removing the metals to control the quality of the product can influence the workup and isolation of the product. These considerations are discussed in this book.

Many of the investigations in these chapters were oriented toward preparing tens to hundreds of kilograms of products from transition metal-catalyzed couplings. In the case studies, critical considerations ranged from selection of routes and starting materials to reducing cycle times on scale. Details of some manufacturing processes are also divulged. Routinely conducting processes on scale is the culmination of many efforts and demonstrates the thorough understanding of the process chemist and engineer.

In addition to the case studies in these chapters, two valuable chapters from academia are included. The chapter from Professor Leadbeater describes conditions using both microwave heating and continuous operations, which can be useful for making larger amounts of material with minimal process development. The chapter from Professor Lipshutz, recipient of a US Presidential Green Chemistry Award in 2011, describes the use of emulsions for running moisture-sensitive reactions in largely aqueous media. This area will also be fruitful for future transition metal-catalyzed scale-ups.

Cost considerations will become even more crucial to process development in industry. Environmental and toxicity considerations may make the selection of some solvents and transition metals less attractive, and these will affect the cost of goods and influence process development. The availability of some transition metals may be affected by international politics, resulting in increased costs. We will probably see the increased use of catalysts containing less expensive transition metals, perhaps doped with small amounts of other metals; examples might be iron catalysts containing palladium or copper [3,4]. With the use of different transition metals, different ligands will likely be designed. Extremely small charges of transition metals and ligands can be effective [5], making the recovery of metals no longer economical [6]. Thorough understanding will continue to be critical for developing rugged catalytic processes.

Javier Magano and Joshua Dunetz put a huge amount of work into their 2011 review "Large-scale applications of transition metal-catalyzed couplings for the synthesis of pharmaceuticals" [7]. Therein, they described details of the reaction sequences, workup conditions used to control the levels of residual metals, and critical analyses of the advantages and disadvantages of such processes run on scale. These considerations are evident in this book too, as Javier and Josh have extended the analyses for developing practical processes to scale up transition metal-catalyzed reactions. This book will also be important in the continuing evolution of chemical processes. I am sure that this valuable book will stimulate many thoughts for those involved in process R&D of transition metal-catalyzed processes.

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Author of "Practical Process Research & Development – A Guide for Organic Chemists"

Neal G. Anderson

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