

The Devil in The Details: The Influence of Trace Metal Contaminants in Modern Organometallic Catalysis

Joseph A. Macor

Literature Seminar

10/25/2011

Organometallic catalysis has had a tremendous impact on mankind over the past century. It contributes to approximately 20% of the gross domestic product in the USA, and is utilized in an estimated 80% of all chemical processes worldwide.¹ Advances in this field continue to provide synthetic transformations with greater selectivity and enhanced yields at lower catalyst loadings. Low effective concentrations (often < 1 mol%) contribute to the success of a particular catalyst, but subsequently create a unique problem: the possibility of trace contaminants playing an active role in the catalytic cycle. Although there are a few historical cases that show how such unanticipated participation can be serendipitous (Ni impurities lead to the discovery of the Ziegler-Natta polymerization catalyst),² as well as detrimental (Pb impurities in Zn metal hinder the Simmons-Smith cyclopropanation),³ this issue is becoming increasingly prevalent in contemporary catalytic systems.

The impact of active participation from trace contaminants is determined by the importance in understanding the exact mechanism behind a given chemical reaction. Often, there is little desire to understand how a process works so long as it effectively produces the intended result.⁴ Since many metals can be costly both to purchase and to remove, there is also a distinct financial incentive in harnessing their catalytic ability via trace impurities in cheaper reagents. However, if one were unaware of the possibility of trace contaminant participation in a catalytic cycle, the simple act of switching suppliers could possibly lead to catastrophic financial losses. The utility of any synthetic transformation lies in its reproducibility, and an innate mechanistic understanding is paramount to the success of new methodology.

A particular example of the influence of trace metal impurities is the Suzuki reaction (Figure 1). This palladium cross-coupling reaction provides an extremely versatile and facile way of selectively forming carbon-carbon bonds. In 2003, Leadbeater and coworkers proposed that typical Suzuki couplings could be performed with lower levels of palladium catalyst via the assistance of microwave irradiation.⁵ To their surprise, couplings proceeded even with no added palladium source whatsoever. The reaction gave comparable yields with only an aryl iodide, boronic acid, and a base in the reaction mixture. In an attempt to understand the mechanism behind this apparent “transition metal free” reaction, they discovered ~50 ppb levels of Pd in the commercial grade Na_2CO_3 employed as a base. The use of an ultrapure (0.21 ppb Pd) sample of Na_2CO_3 led to negligible yields and resulted in a reassessment of the original report. It was concluded that ppb levels of palladium impurities were the active catalyst.⁶

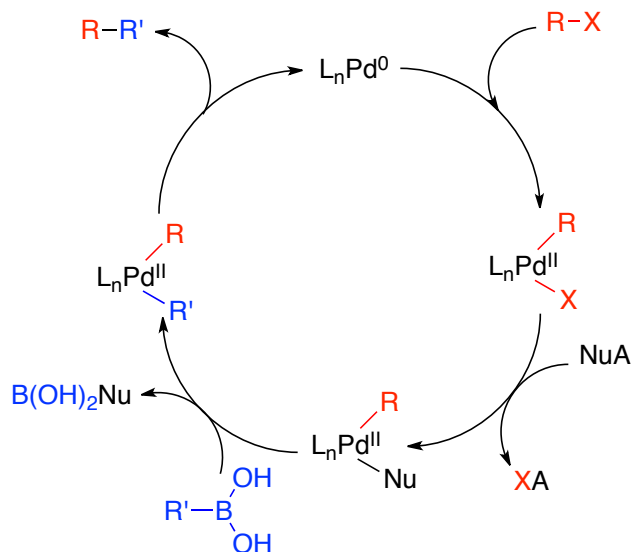


Figure 1. Generic Suzuki Coupling Cycle.

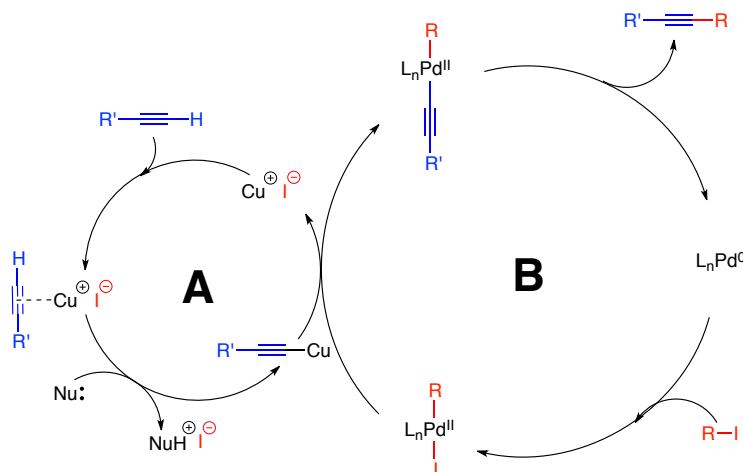


Figure 2. Generic Sonogashira Coupling With Cu (A) and Pd (B) Cycles.

Another widely used palladium cross-coupling reaction is the Sonogashira reaction (Figure 2), which is one of the most powerful synthetic methods of introducing an alkyne into an aromatic system.⁷ In 2006, reports began to surface on a palladium-free method using only a Cu(I) salt as the active catalyst.⁸ Systematic studies followed in order to elucidate the mechanism behind the transformation. It was observed that the purity of the base, alkyne, and the equipment were all significant factors and that the addition of as little as 10 ppb palladium drastically enhanced the rate of the reaction. This led to the conclusion that the copper itself was not acting as the catalytic species, but rather delivering the alkyne to trace palladium impurities via transmetalation in a typical Sonogashira fashion.⁹

Similarly, it was also reported in 2008 that a standard Sonogashira coupling could be effectively accomplished with the use of a AuI(PPh₃)₂ catalyst.¹⁰ Interest had been given to the possibility of using gold in conventional palladium chemistry, as the Au(III)/Au(I) cycle is isoelectronic with Pd(0)/Pd(II) and both d⁸ metal centers are square planar. It has been experimentally determined however, that aryl halides cannot be added to a Au(I) center in an oxidative addition fashion as with Pd(0). It is likely that the observed outcome was therefore the result of a usual Sonogashira reaction with extremely low concentrations of palladium as the active catalyst, mediated by the gold taking on the traditional role of copper.¹¹

Another particularly important example of active contamination can be found in the use of iron-catalyzed cross-couplings using FeCl₃.¹² Original reports claimed this to be an effective route to a variety of arylated amides, phenols, thiols, and alkynes. Further insight determined that the yields of such were highly dependent on the source of the iron salt, and that optimum reaction conditions had stark parallels with known copper systems. It was soon deduced that iron was not responsible for the observed transformations, but instead ppm levels of copper contaminants.

In light of such instances, meticulous methodology is beginning to become commonplace when the presence of metal impurities is questionable. This includes purchasing new glassware, extensive purification and elemental analysis of reagents, physical quarantine of researchers, and verification of results by other research groups.^{4,13} The total impact that widespread awareness of trace metal contaminants will have on the field of organometallic catalysis is currently unknown, although an increasing trend has been seen where researchers are less inclined to adopt newer methodology.⁴ Regardless, the active participation of *any* impurities should always be considered a potentially viable pathway in any chemical reaction.

References:

1. Howard, P.; Morris, G.; Sunley, G. Introduction: Catalysis in the Chemical Industry, in "Metal-catalysis in Industrial Organic Processes", Chiusoli, G.; Maitlis, P. Royal Society of Chemistry, Cambridge, UK, **2006**, Chapter 1, 1-22.
2. Jacobsen, E.; Breinbauer, R. Nickel Comes Full Cycle. *Science* **2000**, *287*, 437-438.
3. Takai, K.; Kakiuchi, T.; Utimoto, K. A Dramatic Effect of a Catalytic Amount of Lead on the Simmons-Smith Reaction and Formation of Alkylzinc Compounds from Iodoalkanes. Reactivity of Zinc Metal: Activation and Deactivation. *J. Org. Chem.* **1994**, *59*, 2671-2673.
4. Leadbeater, N. Cross Coupling: When is Free Really Free? *Nature Chem.* **2010**, *2*, 1007-1009.
5. Leadbeater, N.; Marco, M. Transition-Metal-Free Suzuki-Type Coupling Reactions: Scope and Limitations of the Methodology. *J. Org. Chem.* **2003**, *68*, 5660-5667.
6. Arvela, R.; Leadbeater, N.; Sangi, M.; Williams, V.; Granados, P.; Singer, R. A Reassessment of the Transition-Metal Free Suzuki-Type Coupling Methodology. *J. Org. Chem.* **2005**, *70*, 161-168.
7. Chinchilla, R.; Nájera, C. The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **2007**, *107*, 874.
8. Saejueng, P.; Bates, C.; Venkataraman, D. Copper(I)-Catalyzed Coupling of Terminal Acetylenes with Aryl or Vinyl Halides. *Synthesis* **2005**, *10*, 1706-1712.
9. Gonda, Z.; Tolnai, G.; Novak, Z. Dramatic Impact ppb levels of Palladium on the "Copper-Catalyzed" Sonogashira Coupling. *Chem. Eur. J.* **2010**, *16*, 11822-11826.
10. González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. Catalysis by Gold(I) and Gold(III): A Parallelism between Homo- and Heterogeneous Catalysts for Copper-Free Sonogashira Cross-Coupling Reactions. *Angew. Chem. Int. Ed.* **2007**, *46*, 1536-1538.
11. Lauterbach, T.; Livendahl, M.; Rosellon, A.; Espinet, P.; Echavarren, A. Unlikelihood of Pd-Free Gold(I)-Catalyzed Sonogashira Coupling Reactions. *Org. Lett.* **2010**, *12*, 3006-3009.
12. Buchwald, S.; Bolm, C. On the Role of Metal Contaminants in Catalyses with FeCl₃. *Angew. Chem. Int. Ed.* **2009**, *48*, 5586-5587.
13. Sun, C.; Li, H.; Yu, D.; Yu, M.; Zhou, X.; Lu, X.; Huang, K.; Zheng, S.; Li, B.; Shi, Z. An Efficient Organocatalytic Method for Constructing Biaryls Through Aromatic C-H Activation. *Nature Chem.* **2010**, *2*, 1044-1049.