

The renaissance of palladium(II)-catalyzed oxidation chemistry

Matthew S. Sigman* and Mitchell J. Schultz

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, UT 84112-0850, USA. E-mail: sigman@chem.utah.edu; Fax: +801 581 8433; Tel: +801 585 0774

Received 15th June 2004, Accepted 21st July 2004

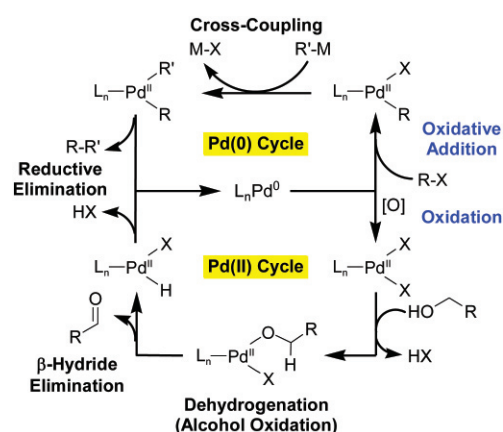
First published as an Advance Article on the web 23rd August 2004

Palladium(II)-catalyzed oxidations constitute a paramount reaction class but have remained immature over the past few decades. Recently, this field has reappeared at the forefront of organometallic catalysis. This emerging area article outlines recent developments in palladium(II)-catalyzed oxidation chemistry with discussion of potential future growth.

Introduction

Palladium(0) catalysis has dominated the landscape of catalyst development for the past several decades. Specifically, Pd-catalyzed cross-coupling, in a broad sense, has allowed synthetic chemists to consider bond constructions in a non-classical manner and chemists interested in organometallic catalysis to have a creative and practical outlet. Growth in this area continues to inspire new and innovative chemistry. In contrast, Pd(II)-catalyzed oxidation reactions have developed at a much slower pace in this same time period. This begs the question: why? Pd(II)-catalyzed reactions certainly can lead to synthetically useful products and provide organometallic chemists with a platform to investigate fundamental processes. The initial answer stems from the inherent mechanistic differences in Pd(0)- and Pd(II)-catalyzed methods (Scheme 1). In Pd(0) chemistry, the catalytic cycle is generally initiated by oxidative addition of an organic electrophile, often organic halides, followed by a Pd(II)-mediated process such as transmetalation (*i.e.* Stille and Suzuki), migratory insertion (Heck), or β -hydride elimination (Heck). The cycle is completed by reductive elimination to form the desired organic product and regenerate the Pd(0)Y catalyst.

In contrast, Pd(II) oxidation catalysis is initiated by Lewis acid activation of a substrate which allows for nucleophilic addition, often followed by β -hydride elimination. This process is referred to as dehydrogenation. Dehydrogenation can also occur directly after substrate binding as in Scheme 1. Either way, the resulting Pd-hydride can undergo reductive elimination to form a Pd(0) species. The fundamental issue arises here: how can the original Pd(II) catalyst be regenerated? Since a Pd(0)-catalyzed process is not desired, the use of an organic electrophile is generally not acceptable except in a few select cases. Instead, Pd(0) needs an alternative oxidant to reform Pd(II). This has classically been accomplished with the use of stoichiometric Cu(II) salts or benzoquinone, but more recently the use of molecular oxygen, the most practical oxidant, has received considerable attention.



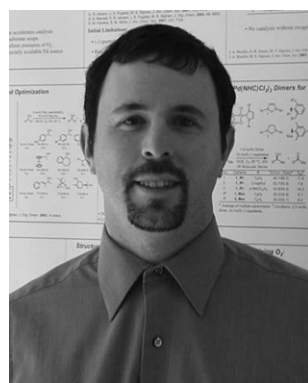
Scheme 1 Mechanistic differences in Pd(0)- and Pd(II)-catalyzed processes.

The use of the former generally utilizes 'ligandless' conditions making it difficult to develop chemo- or stereoselective processes. In contrast, the use of O₂ generally requires a ligand for efficient catalysis. This paper will outline the re-emergence of Pd(II) oxidation chemistry with a focus on both aerobic oxidative methodology,¹ where ligands have played a vital role, and newly developed bond activation chemistry.

Considering the brief nature of this paper, we will be unable to present a comprehensive review of this topic. Instead, we will discuss selected recent reports and original seminal work which highlight the re-emergence of this exciting field.

Aerobic alcohol oxidations

Over the past decade, significant progress has been made in the development and mechanistic understanding of Pd(II) catalysts for



Matthew S. Sigman

Matt Sigman received a B.S. in chemistry from Sonoma State University in 1992 before obtaining his Ph.D. in organometallic chemistry at Washington State University with Professor Bruce Eaton in 1996. He then moved to Harvard University to complete an NIH postdoctoral stint with Professor Eric Jacobsen. In 1999, he joined the faculty of the University of Utah where his research group has focused on the development of aerobic oxidative catalytic processes. He has recently received the Camille Dreyfus Teacher-Scholar Award and the Pfizer Award for Creativity in Organic Chemistry.

Mitchell Schultz received his B.S. in chemistry from Southwest Minnesota State University in 2001. He is currently pursuing his Ph.D. at the University of Utah working in the Sigman group. His research focuses on developing new catalyst systems for Pd-catalyzed aerobic alcohol oxidations.



Mitchell J. Schultz

the aerobic oxidation of alcohols. Muzart has recently reported a comprehensive review of this topic including enantioselective variants.² In this reaction, Pd(II) initially acts as a Lewis acid by activating the alcohol for deprotonation. Subsequent β -hydride elimination completes the alcohol oxidation. Through the use of nitrogenous ligands, enhancement of this catalytic reaction has been realized.¹ However, this simple transformation still suffers from the use of relatively high catalyst loadings and/or oxygen pressures. We,³ as well as Tsuji and co-workers,⁴ have recently reported catalysts capable of high turnovers using relatively low pressures of oxygen in the form of ambient air. These catalysts both use bulky ligands which presumably inhibit Pd black formation (Fig. 1). The use of diverse ligands could provide significant improvements including chemo-, regio-, and stereo-selective reactions. The growth potential in this area is great; ultimately the use of low catalyst loadings and low levels of O₂ could create an industrially friendly oxidation system.

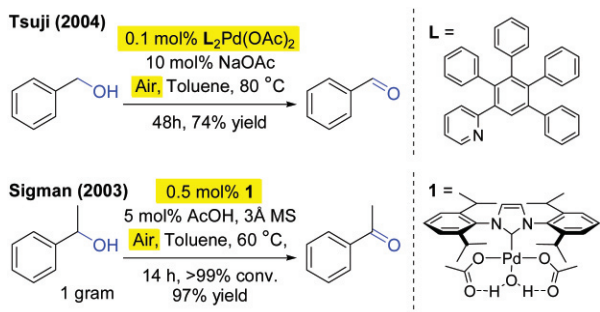


Fig. 1 Recent use of low catalyst loadings and ambient air pressure in Pd-catalyzed alcohol oxidations.

Olefin functionalization

When thinking about oxidation chemistry, olefins are usually considered as nucleophiles where they attack an activated oxygen species such as in an epoxidation reaction. In Pd(II) chemistry, an Umpolung-type reaction occurs, where Pd(II) acts as a Lewis acid activating the olefin for subsequent nucleophilic attack resulting in nucleo-palladation. This reaction motif is most commonly represented by the Wacker oxidation where water attacks the olefin followed by β -hydride elimination to yield the methyl ketone product. While the Wacker oxidation is a fundamental process and has significant value in synthetic chemistry, we are going to focus on the reactions of more complex nucleophiles in this paper.

Oxygen nucleophiles

One area that has seen a revitalization is Wacker-type cyclizations of alcohols and olefins. Hosokawa *et al.* reported in 1973 that (CH₃CN)₂PdCl₂ mediated the cyclization of allyl phenols with pendant olefins to form benzofuran compounds.⁵ Uozumi and Hayashi reported the first highly enantioselective variant of this Wacker-type cyclization using chiral bis(oxazoline)ligands based on a 1,1'-binaphthyl backbone and 10 mol% of a cationic Pd source (Fig. 2).⁶ In this chemistry, enantiomeric excesses of up to 97% were achieved. Re-oxidation of the Pd species was accomplished with benzoquinone. More recently, Stoltz and co-workers reported a Pd(II)/(-)-sparteine catalyst for this reaction with up to 90% ee obtained using O₂ as the terminal oxidant.⁷ Even though high enantiomeric excess is achieved in these systems, both require high catalyst loadings with enantioselective variants seen only for allyl phenol derivatives. Additionally, Stoltz's group reported in this paper the cyclization of a broad scope of oxygen nucleophiles using an alternative system of 5 mol% Pd(TFA)₂/20 mol% pyridine. Future work in this area will most likely extend the scope of both the cyclizations and nucleophile used in enantioselective variants.

Amine nucleophiles

Using stoichiometric and catalytic Pd(II) chemistry developed by Hegedus *et al.*⁸ and catalytic work by Larock's^{9b} and Andersson's^{9a}

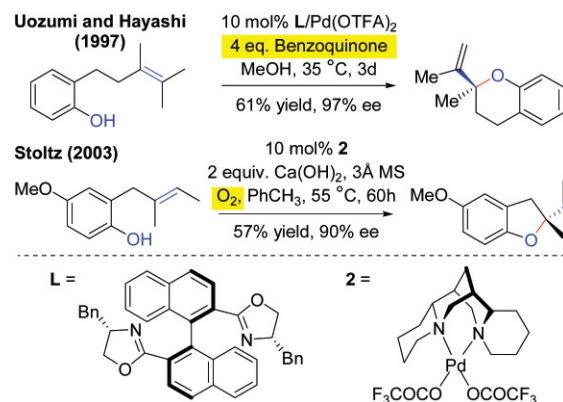


Fig. 2 Pd(II)-catalyzed Wacker-type enantioselective cyclizations.

groups using Pd(OAc)₂/DMSO/O₂ as a template, Stahl and co-workers reported the intramolecular oxidative amination of olefins¹⁰ and, more recently, reported intermolecular amination of styrene derivatives (Fig. 3).^{11,12} The key finding in both of these latter studies is that the use of nitrogenous ligands has a significant effect on both catalytic efficiency and regioselectivity of the amine addition. Of particular note, changing of the nitrogenous ligand from pyridine in the intramolecular chemistry to triethylamine in the intermolecular chemistry is necessary for a competent system. Stoltz's group also reports an example of an intramolecular variant of this transformation using 5 mol% Pd(TFA)₂/20 mol% pyridine.⁷ Another interesting aspect of these recent studies is that it seems necessary to reduce the pK_a of the amine nucleophile by using carbamates or sulfonamides. This implies that deprotonation of the nucleophile, potentially Pd(II)-catalyzed, is necessary in the catalytic cycle. Future work in this area will most likely focus on more efficient catalysis as well as the development of enantioselective variants in the case of intramolecular oxidative amination.

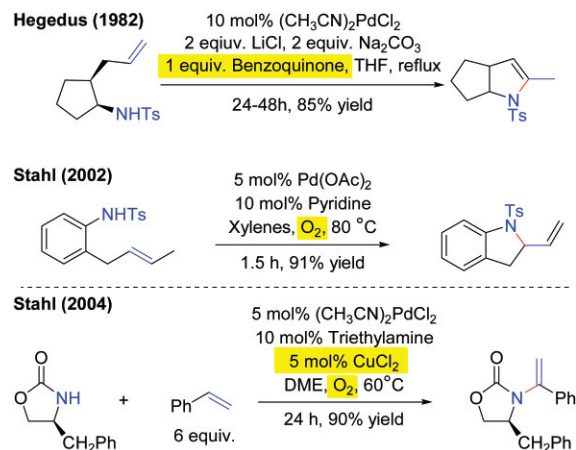


Fig. 3 Inter- and intra-molecular aerobic oxidative amination catalyzed by Pd(II).

Carbon nucleophiles

A variety of carbon nucleophiles could be very attractive to add to olefins in a synthetic sense. In 1979, Saegusa and co-workers published a Pd(II)-mediated intramolecular addition of silyl enol ethers to olefins.¹³ In 1980, Hegedus *et al.* published back to back papers on intermolecular Pd-mediated alkylation and acylation of olefins.¹⁴ Recently, Widenhoefer and co-workers published a report on Pd-catalyzed oxidative alkylation of γ -alkenyl- β -diketones (Fig. 4).¹⁵ Ligandless, aerobic conditions can be employed using 10 mol% CuCl₂ as a co-catalyst. Several features are noteworthy in that the length of the chain between the nucleophile and olefin has a significant effect on the outcome of the reaction. ϵ -Alkenyl- β -diketones lead to hydroalkylation products, presumably through protonation of the resultant Pd-C bond.¹⁶ Additionally, a nucleo-

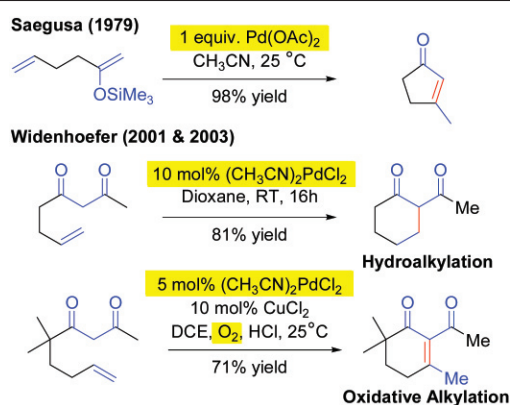


Fig. 4 Addition of carbon nucleophiles to olefins.

phile with a low pK_a , such as a β -diketone, is necessary for catalysis. Considerable opportunities lie in the area of carbon nucleophiles where little is known about the effect of ligands, and the nature of the nucleophile.

C–H bond functionalization

Clearly, the discovery and development of methods to selectively functionalize C–H bonds leads to applications in diverse fields. Pd has been a player in this field and recently several reports have highlighted the ability for Pd to catalyze chemo- and regio-selective C–H bond functionalization.

Indole functionalization

In 1978, Trost *et al.* reported an efficient total synthesis of Ibogamine using two Pd-catalyzed processes (Fig. 5).¹⁷ The key step was a cationic Pd-mediated intramolecular addition of an indole to an olefin. The mechanism of this process is not well understood but original isotopic labeling experiments indicate that palladation of the C–H bond on the indole followed by migratory insertion of the olefin leads to the product, much like a Heck-type arylation. In 2003, Stoltz and Ferreira reported a Pd-catalyzed variant of this reaction type using O_2 as the stoichiometric oxidant.¹⁸ An added feature of this transformation is that the nature of the pyridine derivative and Pd source had a considerable effect on the catalysis. The mechanism proposed by Stoltz and Ferreira is consistent with the one proposed by Trost *et al.* Several interesting questions are raised by this unique reactivity including the nature of the palladation step (what oxidation state is Pd in during this step?). Besides the interesting mechanistic questions, discovery of enantioselective variants, and applications to synthetic targets are certainly areas of future development.

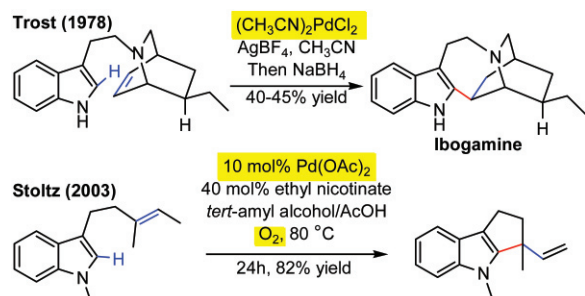


Fig. 5 Oxidative annulations of indoles.

Recent C–H bond functionalizations

Two reports highlight the recent activity in this area (Fig. 6). Sanford and co-workers reported that $Pd(OAc)_2$ in the presence of stoichiometric $PhI(OAc)_2$ can catalytically activate and functionalize an aryl or sp^3 C–H bond.¹⁹ The key aspect of this study

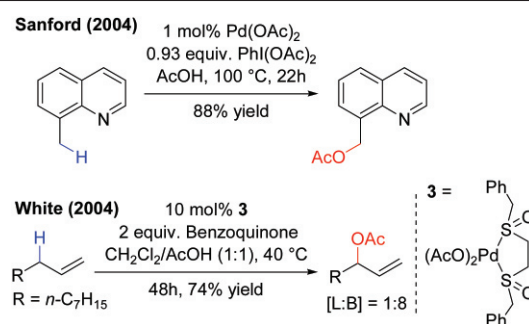


Fig. 6 Recent Pd-catalyzed C–H functionalizations.

was the use of an adjacent pyridine to direct this in a regioselective fashion. The oxidation chemistry is proposed to enter a $Pd(II)/Pd(IV)$ cycle. White and Chen also reported a $Pd(OAc)_2$ -catalyzed allylic oxidation of olefins using a novel bisulfonamide ligand to control the regio- and chemo-selectivity of the process.²⁰ The reoxidant in this chemistry is benzoquinone. Instead of realizing Wacker-type products, the new complex catalyzes a reaction that yields the branched allylic oxidation product. Additionally, by using a DMSO/AcOH solvent mixture the distribution of products is switched from mainly branched to linear. These two contributions are just the beginning of new reaction development in selective C–H bond functionalization catalyzed by $Pd(II)$.

An emerging area?

It is definitely funny to refer to $Pd(II)$ oxidation catalysis as an ‘emerging area’ in chemistry considering the rich history and beautiful work reported in the 1970s and 1980s. However, after about a 15 year hiatus, significant effort has refocused on this vital, fundamental, and potentially powerful set of reactions with an eye towards the practical aspects inherent to oxidation chemistry; the development of catalytic, stereoselective, and aerobic variants. One key component of the re-emergence of $Pd(II)$ oxidation catalysis is the introduction of ligands to afford efficient re-oxidation, especially when using aerobic conditions, and to facilitate selective chemistry. An interesting feature of this field is the significant number of young principal investigators attracted to it, bringing a broad set of interests including organometallic, inorganic, and organic synthetic chemistry. This diversity makes for contributions which are both highly insightful and applicable. As this renaissance of $Pd(II)$ -catalyzed oxidation chemistry continues, we would not be surprised if long-standing unsolved problems in catalysis are undertaken and conquered.

References

- 1 For a very recent comprehensive review of this area, see: S. S. Stahl, *Angew. Chem., Int. Ed.*, 2004, **43**, 3400–3420.
- 2 J. Muzart, *Tetrahedron*, 2003, **59**, 5789–5816.
- 3 D. R. Jensen, M. J. Schultz, J. A. Mueller and M. S. Sigman, *Angew. Chem., Int. Ed.*, 2003, **42**, 3810–3813.
- 4 T. Iwasawa, M. Tokunaga, Y. Obora and Y. Tsuji, *J. Am. Chem. Soc.*, 2004, **126**, 6554–6555.
- 5 T. Hosokawa, K. Maeda, K. Koga and I. Moritani, *Tetrahedron Lett.*, 1973, **10**, 739–740; for the formation of non-aromatic products, see: T. Hosokawa, H. Ohkata and I. Moritani, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1533–1536.
- 6 Y. Uozumi, K. Kato and T. Hayashi, *J. Am. Chem. Soc.*, 1997, **119**, 5063–5064.
- 7 R. M. Trend, Y. K. Ramtohl, E. M. Ferreira and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2003, **42**, 2892–2895.
- 8 L. S. Hegeudus, G. F. Allen, J. J. Bozell and E. L. Waterman, *J. Am. Chem. Soc.*, 1978, **100**, 5800–5807; L. S. Hegeudus, G. F. Allen and E. L. Waterman, *J. Am. Chem. Soc.*, 1976, **98**, 2674–2676; L. S. Hegeudus and J. M. McKearin, *J. Am. Chem. Soc.*, 1982, **104**, 2444–2451.
- 9 (a) M. Rönn, J.-E. Bäckvall and P. G. Andersson, *Tetrahedron Lett.*, 1995, **36**, 7749–7752; (b) R. C. Larock, T. R. Hightower, L. A. Hasvold and K. P. Peterson, *J. Org. Chem.*, 1996, **61**, 3584–3585.
- 10 S. R. Fix, J. L. Brice and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2002, **41**, 164–166.

-
- 11 V. I. Timokhin, N. R. Anastasi and S. S. Stahl, *J. Am. Chem. Soc.*, 2003, **125**, 12996–12997.
 - 12 For Pd-catalyzed intermolecular oxidative amination of non-styrene derivatives, see: T. Hosokawa, M. Takano, Y. Kuroki and S. Murahashi, *Tetrahedron Lett.*, 1992, **33**, 6643–6646.
 - 13 Y. Ito, H. Aoyama, T. Hirao, A. Machizuki and T. Saegusa, *J. Am. Chem. Soc.*, 1979, **101**, 494–496; Saegusa does report a catalytic example but 50% Pd(OAc)₂ is utilized.
 - 14 L. S. Hegedus, R. E. Williams, M. A. McGuire and T. Hayashi, *J. Am. Chem. Soc.*, 1980, **102**, 4973–4979; L. S. Hegedus and W. H. Darlington, *J. Am. Chem. Soc.*, 1980, **102**, 4980–4983.
 - 15 T. Pei, X. Wang and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2003, **125**, 648–649.
 - 16 R. A. Widenhoefer and T. Pei, *J. Am. Chem. Soc.*, 2001, **123**, 11290–11291.
 - 17 B. M. Trost, S. A. Godleski and J. P. Genêt, *J. Am. Chem. Soc.*, 1978, **100**, 3930–3931.
 - 18 E. M. Ferreira and B. M. Stoltz, *J. Am. Chem. Soc.*, 2003, **125**, 9578–9579.
 - 19 A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300–2301.
 - 20 M. S. Chen and M. C. White, *J. Am. Chem. Soc.*, 2004, **126**, 1346–1347.