Inorg. Chem. **2007**, *46*, 1903−1909

Inorganic Chemistry
Article

Forum

Recent Progress in Wacker Oxidations: Moving toward Molecular Oxygen as the Sole Oxidant

Candace N. Cornell and Matthew S. Sigman*

Department of Chemistry, University of Utah, 315 South 1400 East,
Salt Lake City, Utah 84112-8500

Received September 27, 2006

Wacker oxidations, the conversion of terminal olefins to methyl ketones with Pd(II) catalysts, have seen widespread use in synthetic applications. Standard synthetic Wacker conditions use catalytic $PdCl_2$ with stoichiometric CuCl under an aerobic atmosphere in a mixed-solvent system of *N*,*N*-dimethylformamide and H_2O. Though much attention has been directed toward elucidating the rate-determining step and the mechanism of nucleopalladation, the assumption that Cu does not participate in this portion of the catalytic cycle has recently been called into question based on an isolated Pd/Cu bimetallic species and the influence of Cu on product selectivity. Fortunately, recent advancements have been made toward the elimination of Cu additives, thereby alleviating these issues. Success in this area has come from the application of information gained in studying other direct-O_2-coupled Pd(II) oxidation systems, including ligand modulation, something which could not be achieved in the presence of Cu. The developments in peroxide-mediated and direct-O_2-coupled Wacker oxidations are highlighted herein.

Introduction

The Wacker oxidation, an aerobic $PdCl_2$-catalyzed, Cu-mediated aqueous oxidation of an olefin to a carbonyl, was initially reported in 1962 and utilized for the industrial production of acetaldehyde from ethylene.[1] To efficiently oxidize more complex substrates, mixed-solvent systems have been developed and are commonly used in targeted molecule synthesis.[1−4] The advantage of using Wacker oxidations to generate carbonyl compounds in synthesis arises from the obvious greater stability of a terminal olefin to acidic, basic, or nucleophilic conditions and can be illustrated by several recent applications (Figure 1).[5−8] Highlighted in these examples is the continued use of classical conditions developed by Tsuji using *N*,*N*-dimethylformamide (DMF)/H_2O mixtures and stoichiometric CuCl.[9] These conditions are more commonly used as compared to the many modified Wacker oxidation systems reported, most likely due to convenience and simplicity.[4]

A common issue in the Wacker oxidation as well as other Pd(II)-catalyzed oxidation reactions is efficient regeneration of the active Pd(II) catalyst by the terminal oxidant, which is why Cu is generally utilized.[10] Unfortunately, Cu is not always an innocent bystander, as is the case in Kobayashi and co-workers' total synthesis of macrosphelide H.[8] Under Tsuji's standard conditions with 10 mol % $PdCl_2$ and 1 equiv of CuCl at room temperature, only a 53% yield of oxidized terminal olefin products is observed with a 5:1 ratio of methyl ketone **1** to aldehyde **2**. Studies conducted on a model substrate showed that less acidic $Cu(OAc)_2$ did not improve the ratio of products, even with decreased concentrations of Cu (20 mol %).[11] A 72% isolated yield of **1** was only

---

* To whom correspondence should be addressed. E-mail: sigman@chemistry.utah.edu.

[1] Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem.* **1962**, *74*, 93−102.
[2] Clement, W. H.; Selwitz, C. M. *J. Org. Chem.* **1964**, *29*, 241−243.
[3] Tsuji, J. *Synthesis* **1984**, 369−384.
[4] Takacs, J. M.; Jiang, X.-T. *Curr. Org. Chem.* **2003**, *7*, 369−396.
[5] Shu, C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 2878−2879.
[6] Laventine, D. M.; Davies, M.; Evinson, E. L.; Jenkins, P. R.; Cullis, P. M.; Fawcett, J. *Tetrahedron Lett.* **2005**, *46*, 307−310.
[7] Jeannotte, G.; Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 4656−4662.
[8] Kobayashi, Y.; Wang, Y.-G.; Acharya, H. P. *Lett. Org. Chem.* **2004**, *1*, 297−307.
[9] Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9−13.
[10] Stahl Shannon, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420.
[11] Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.

10.1021/ic061858d CCC: $37.00

Figure 1. Recent reports of the Wacker oxidation in directed synthetic applications.

achieved through the use of 5 equiv of $PdCl_2$, with no Cu present. As can be seen in this example, optimization of Wacker reactions is not apparent, and when standard methods fail, extreme conditions including stoichiometric amounts of Pd(II) can be required.

An approach to this problem, as demonstrated in Pd(II)-catalyzed aerobic alcohol oxidations, is to use ligands on Pd to stabilize the catalyst, to enhance reaction rates, and to tune the reaction parameters.[10,12] An additional benefit of developing a ligand-modulated system is the ability to directly use terminal oxidants such as O_2 or simple peroxides. Unfortunately, added Cu prevents the effective use of ligands under standard Wacker conditions due to the possibility of ligand exchange onto Cu during catalysis. Though progress has been reported in various Pd(II)-catalyzed direct-O_2-coupled oxidation reactions, ligand modulation in Wacker oxidations has been relatively limited until quite recently.[13] In this Forum Article, we will give a brief overview of proposed Wacker oxidation mechanisms to illustrate the complexity of removing Cu and its counterions, and we will highlight the recent advances toward and successes in the development of direct-O_2-coupled Wacker oxidations.

Mechanistic Overview. An extraordinary amount of research has been directed at elucidating the mechanistic details of the Wacker oxidation with contrasting results.[4,14−22] Central to the controversy surrounding the mechanism is whether the reaction proceeds via a rate-limiting intramolecular cis attack of a Pd-bound olefin (Scheme 1A)[14−19,23] or via an equilibrium trans (intermolecular) attack by H_2O, followed by rate-limiting chloride ion dissociation (Scheme 1B).[20−22] Bäckvall and co-workers contend that nucleopalladation occurs via trans attack based on kinetic analysis, though their system uses high [Cl^-], which critics believe skews the observed results. Stille and co-workers base their assertion of intermolecular nucleopalladation on kinetic studies and on the stereochemical outcome of CO insertion

---

(12) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221−229.

(13) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453−3516.

(14) Henry, P. M. *J. Org. Chem.* **1973**, *38*, 2415−2416.

(15) Zaw, K.; Henry, P. M. *J. Org. Chem.* **1990**, *55*, 1842−1847.

(16) Dumlao, C. M.; Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 1400−1405.

(17) Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498−3503.

(18) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082−7083.

(19) Henry, P. M. *Handb. Organopalladium Chem. Org. Synth.* **2002**, *2*, 2119−2139.

(20) Stille, J. K.; Divakaruni, R. *J. Organomet. Chem.* **1979**, *169*, 239−248.

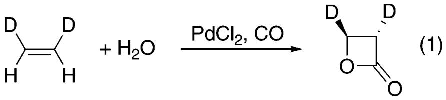
(21) Bäckvall, J. E.; Heumann, A. *J. Am. Chem. Soc.* **1986**, *108*, 7107−7108.

(22) Bäckvall, J. E.; Bjoerkman, E. E.; Pettersson, L.; Siegbahn, P. *J. Am. Chem. Soc.* **1984**, *106*, 4369−4373.

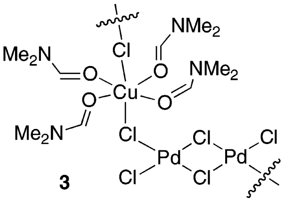
(23) Nelson, D. J.; Li, R.; Brammer, C. *J. Am. Chem. Soc.* **2001**, *123*, 1564−1568.

Scheme 1. Wacker Oxidation Proposed Mechanisms

using *cis*-D_2-ethylene under Wacker-type oxidation conditions (eq 1).[20]



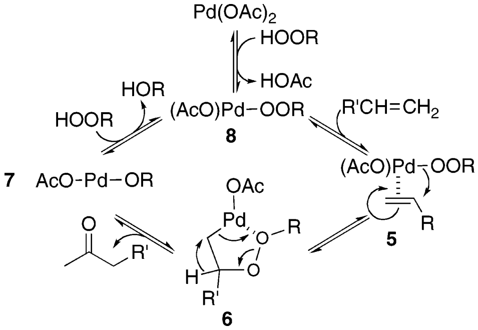
Support of intramolecular nucleopalladation has been reported by Henry and co-workers wherein a concerted four-centered transition state as shown in Scheme 1A is proposed.[15−18,24] Under the conditions employed by Henry and co-workers using lower [Cl^-], a second-order inhibition of rate on [Cl^-] is observed. Dissociation of two chloride ions is proposed, followed by binding of 1 equiv of H_2O and olefin, leading to an intramolecular attack. Their assertion has recently been further corroborated by Nelson and co-workers, who correlate relative rates of oxidation to ionization potentials, highest occupied molecular orbitals, and lowest unoccupied molecular orbitals.[23] Using this technique, significant similarities between the Wacker oxidation and hydroboration of olefins are observed, supporting rate-determining nucleophilic hydroxypalladation at low [Cl^-].



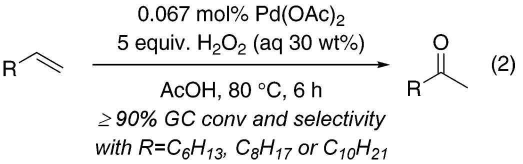
Unfortunately, one factor that is not considered in these mechanistic studies is the role of Cu. A central assumption is that the main role of Cu is to facilitate oxidation of Pd(0). The validity of this assumption has been called into question based on the isolation of a Pd/Cu bimetallic species **3**, which was found to be a competent catalyst in the oxidation of decene under aqueous aerobic conditions.[25] Therefore, the assumed active catalyst species in these kinetic and mechanistic studies of Wacker oxidations using a combination of DMF, CuCl, and $PdCl_2$ may not be accurate.

Figure 2. Relative rate of hexene oxidation with palladium peroxo catalyst **4** (isolated as $[(RCO_2)Pd(OOtBu)]_4$) illustrating decreased electron density of the carboxylate, which increases the reaction rate (ratio of Pd/olefin = 1).

Scheme 2. Mimoun et al.'s Proposed Mechanism for Peroxide-Mediated Wacker Oxidation Reactions



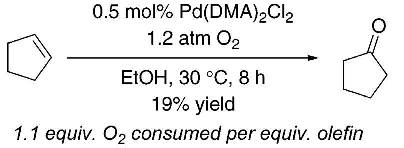
Use of Peroxides in Wacker Oxidations. While most of the reported Wacker oxidations utilize Cu/O_2, advances using peroxides as the terminal oxidant in the absence of Cu have been made. One such example was reported by Mimoun and co-workers.[26−31] Initial stoichiometric studies using $[Pd(OOtBu)(OOCR)]_4$ complexes **4** illustrated that decreased electron density on Pd increases the reactivity and selectivity for methyl ketone formation (with R = CH_3 at 4 h, a 1:1 ratio of methyl ketone to vinyl acetate is observed; Figure 2).[31] On the basis of these findings, Mimoun and co-workers were able to develop a system catalytic in Pd, wherein high conversion and selectivity were observed with terminal straight-chain olefins using 0.067 mol % $Pd(OAc)_2$ with 5 equiv of H_2O_2(aq) in acetic acid (eq 2). Isotopic labeling studies using $^{18}OH_2$ supported the hypothesis that the O atom incorporated into the ketone originated from the peroxide. On the basis of this finding, a mechanism was proposed wherein a palladacyclic intermediate (**6**) is formed from peroxide insertion into the olefin, followed by an α-hydride shift facilitated by O−O bond cleavage (Scheme 2).[30] An exciting aspect of the proposed catalytic cycle is that Pd does not necessarily proceed through Pd(0) because catalyst



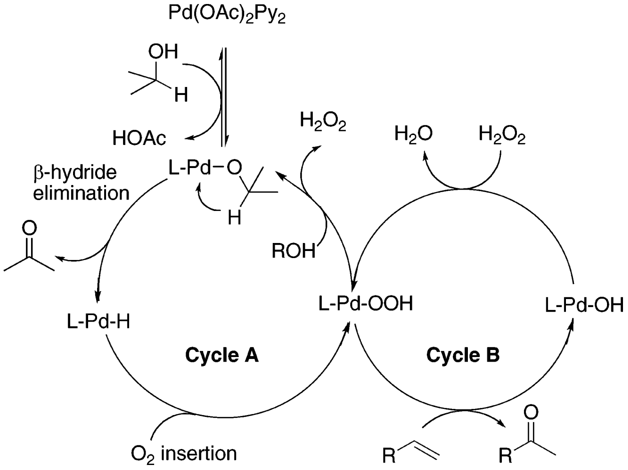
---

[24] Henry, P. M. *J. Org. Chem.* **1973**, *38*, 1681−1684.
[25] Hosokawa, T.; Nomura, T.; Murahashi, S.-I. *J. Organomet. Chem.* **1998**, *551*, 387−389.
[26] Mimoun, H. *Angew. Chem.* **1982**, *94*, 750−766.
[27] Mimoun, H. *Pure Appl. Chem.* **1981**, *53*, 2389−2399.
[28] Mimoun, H. *J. Mol. Catal.* **1980**, *7*, 1−29.
[29] Igersheim, F.; Mimoun, H. *Nouv. J. Chim.* **1980**, *4*, 711−713.
[30] Roussel, M.; Mimoun, H. *J. Org. Chem.* **1980**, *45*, 5387−5390.
[31] Mimoun, H.; Charpentier, R.; Mitschler, A.; Fischer, J.; Weiss, R. *J. Am. Chem. Soc.* **1980**, *102*, 1047−1054.

Scheme 3. Takehira's Wacker Coupled Alcohol Oxidation



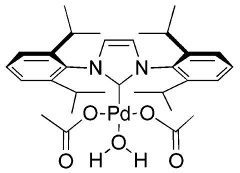
Scheme 4. Uemura and Co-workers Proposed Catalytic Cycles for Coupled Aerobic Alcohol Oxidation and Palladium Peroxo Wacker Oxidation



regeneration can occur via a proton transfer from a peroxide to **7**, regenerating active catalyst **8.** This potentially alleviates the probability of Pd(0) aggregation and catalyst deactivation, which is a common problem in these oxidations.

Hydrogen peroxide can also be formed in situ via other Pd(II)-catalyzed processes, including aerobic alcohol oxidation, in which O_2 is initially reduced to H_2O_2. Serendipitously, Takehira and co-workers discovered that this is indeed the case in their Pd(II)-catalyzed Wacker oxidation of cyclopentene to cyclopentanone in an ethanol solvent (Scheme 3).[32] It was Uemura and co-workers who expanded the scope of alcohol-oxidation-coupled Wacker reactions via their application of expertise gained through the study of ligand-modulated direct-O_2-coupled Pd-catalyzed alcohol oxidation.[33,34] Uemura and co-workers proposed the formation of a palladium hydroperoxo species formed via O_2 insertion into the Pd−H bond. The hydride is generated from β-hydride elimination of the palladium alkoxide during alcohol oxidation (Scheme 4, catalytic cycle A). They envisioned that this peroxide species could then be coupled to a Wacker-type oxidation (catalytic cycle B) similar to that proposed by Mimoun and co-workers. Use of 5 mol % Pd$(OAc)_2$ and 20 mol % pyridine, in a 1:1 mixed-solvent system of PhMe and isopropyl alcohol under an O_2 atmosphere at 60 °C, was successful for the oxidation of straight-chain terminal olefins.

In a similar attempt to use the knowledge gained studying the mechanism of Pd(II)-catalyzed aerobic alcohol oxidation systems with (−)-sparteine, N-heterocyclic carbenes (NHC), and Et_3N as ligands,[35−46] we wanted to probe whether Pd$(I^iPr)(OAc)_2$ (**9**) would convert styrene to acetophenone via a direct-O_2-coupled Wacker oxidation. However, through our studies, we found that simple peroxides are much more effective in the oxidation of styrene derivatives.[47] This finding was based on the observation that Wacker oxidations with cationic NHC/Pd(II) complexes only proceeded in tetrahydrofuran (THF) under aerobic conditions. We hypothesized that this was due to the production of a peroxide via oxidation of the ethereal solvent. The hypothesis was substantiated by the observation of γ-butyrolactone formation when THF was used as the solvent in the oxidation. On the basis of this information, a new mild oxidation system has been developed that utilizes 1.5 mol % Pd$(I^iPr)(OTf)_2$ and TBHP(aq) in methanol at 35 °C and converts styrenes to methyl ketones in high selectivity (Table 1). This selectivity is especially noteworthy because styrenes are a notoriously difficult substrate class due to facile polymerization and oxidative cleavage to benzaldehyde.



9

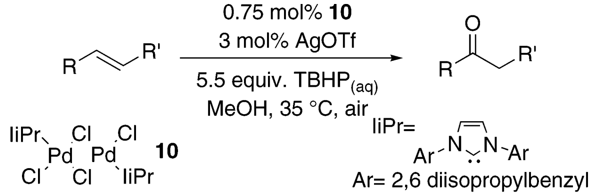
Pd(IiPr)(OAc)$_2$-(H$_2$O)

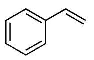
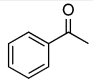
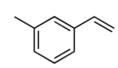
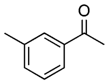
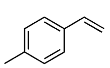
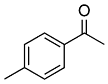
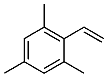
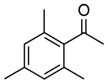
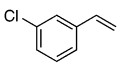
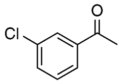
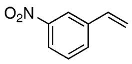
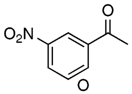
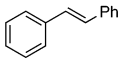
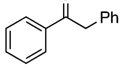
Several experiments were performed to gain greater insight into the mechanistic aspects of the transformation. Analysis of the empirical rate law yielded a first-order dependence on [Pd$(I^iPr)(OTf)_2$] (0.3−6.0 mol %) and an inverse first-order dependence on [H_2O] (0.5−12 M), but direct kinetic analysis of substrate nucleopalladation was not possible because the reaction was found to be zero-order, with no rate dependence on [olefin] or [TBHP]. The inverse first-order dependence on [H_2O] and first-order dependence on [catalyst] support a rate-limiting dissociation of H_2O from a Pd catalyst. The crystal structural analysis of isolated Pd$(I^iPr)(H_2O)_3^{2+}\cdot(H_2O)_2\cdot(OTf^-)_2$ shows three molecules of

---

(32) Takehira, K.; Hayakawa, T.; Orita, H. *Chem. Lett.* **1985**, 1835−1838.
(33) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201−216.
(34) Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *Perkin Trans. 1* **2000**, 1915−1918.
(35) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475−7476.
(36) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202−8203.
(37) Schultz, M. J.; Park, C. C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034−3035.
(38) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810−3813.
(39) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63−65.
(40) Mandal, S. K.; Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 4600−4603.
(41) Mandal, S. K.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 7535−7537.
(42) Mueller, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 7005−7013.
(43) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724−9734.
(44) Mueller, J. A.; Cowell, A.; Chandler, B. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 14817−14824.
(45) Schultz, M. J.; Adler, R. S.; Zierkiewicz, W.; Privalov, T.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 8499−8507.
(46) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343−3352.
(47) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796−2797.

Table 1. Pd(I^{i}Pr)OTf$_2$ Wacker Oxidation of Styrene Derivatives



Entry	Substrate	Product	Time (h)	% yield
1			24	75
2			32	83
3			16	86
4			24	71
5			48	80
6^a			24	79
7^b			48	42

^{a} 2.25 mol % **10** and 12 mol % AgOTf. ^{b} 35% of the starting material converts to benzaldehyde via oxidative cleavage.

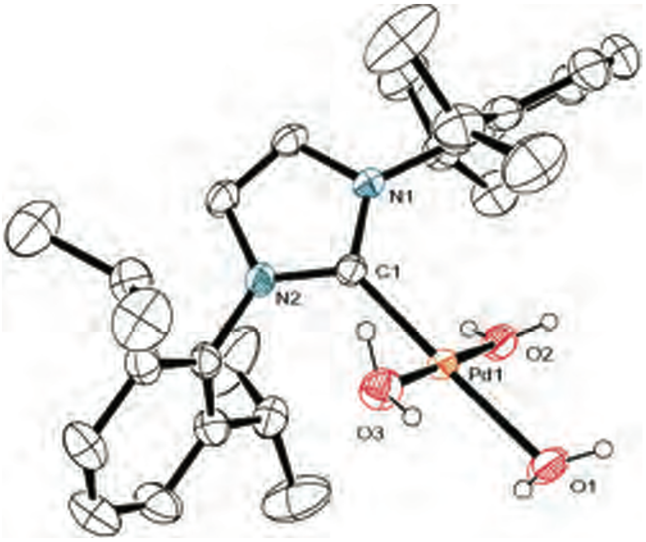


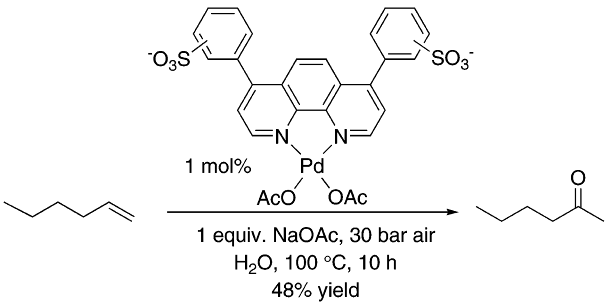
Figure 3. ORTEP plot of Pd(I^{i}Pr)•$(H_2O)_3^{2+}$•$(H_2O)_2$•$(OTf^-)_2$. Counterions and outersphere H_2O's are removed for clarity (R^2 = 0.06).

H_2O bound to the Pd center, wherein one H_2O would need to dissociate before substrate binding (Figure 3).

Isotopic labeling studies to establish the active nucleophile and mode of decomposition to acetophenone were also conducted (Scheme 5). Use of 1.1 equiv of $^{18}OH_2$ was used to determine the source of O incorporated into the carbonyl. At T = 15 min, <20% of ^{18}O incorporation (1.3% product) was observed, supporting that TBHP is the oxygen source. To ascertain whether an α-hydride shift mechanism was dominant, α-D-styrene was submitted to the oxidation conditions with >80% of the deuterium label incorporated into the product, establishing that the H atoms present in the starting material are conserved in the product. Overall, these results are consistent with the mechanism proposed by Mimoun and co-workers and provide a mechanistic reference for future peroxide-coupled Wacker oxidation development.

Scheme 5. Isotopic Labeling Studies of NHC-Modulated Pd(II)-Catalyzed Styrene Oxidation

Direct-O_2-Coupled Wacker Oxidations. Though both Takehira and Uemura's alcohol-coupled Wacker oxidations eliminate the need for metal co-oxidants and illustrate how mechanistic evidence can be applied to new methodology, these systems still involve a co-reductant. Up until 2006, Sheldon and co-workers had reported the only direct-O_2-coupled Wacker oxidation system (eq 3).[48,49] The water-soluble phenanthroline ligand is proposed to decrease Pd(0) aggregation and enhance the rate of catalyst reoxidation by decreasing the redox potential of Pd(II)/Pd(0), thereby reducing catalyst decomposition. Kinetic analysis on the system was conducted using a water-soluble substrate to eliminate difficulties of monitoring a biphasic system and shows a first-order dependence on [substrate]. The rate dependence was half-order in [Pd], supporting a dimeric catalyst resting state. No rate dependence on [NaOAc] was observed, but the additive was necessary for a reasonable catalyst lifetime. The data suggest a rate-limiting formation of the monomeric catalyst via substrate binding. Sheldon's system successfully implements ligand modulation for direct-O_2-coupled Wacker oxidation. Use of H_2O as a solvent, though it eases isolation of the products, limits the potential synthetic utility of this oxidation system in that most substrates are not miscible, resulting in diminished yields, and the system requires high pressures and temperatures.



(3)

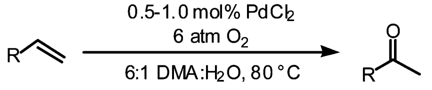
More recently, Kaneda and co-workers discovered a direct-O_2-coupled Wacker oxidation in a dimethylacetamide (DMA)/H_2O solvent system, at elevated temperatures, under high

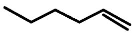
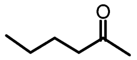
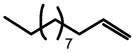
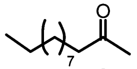
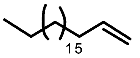
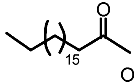
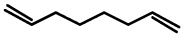
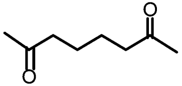
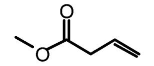
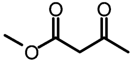
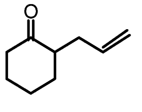
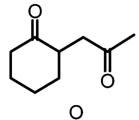
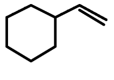
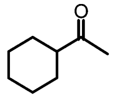
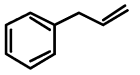
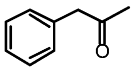
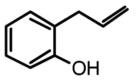
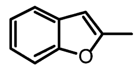
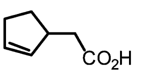
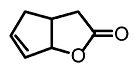
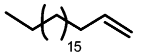
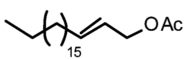
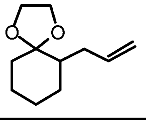
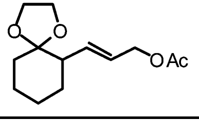
---

(48) ten Brink, G.-J.; Arends, I. W. C. E.; Papadogianakis, G.; Sheldon, R. A. *Appl. Catal. A* **2000**, *194−195*, 435−442.

(49) ten Brink, G.-J.; Arends, I. W. C. E.; Papadogianakis, G.; Sheldon, R. A. *Chem. Commun.* **1998**, 2359−2360.

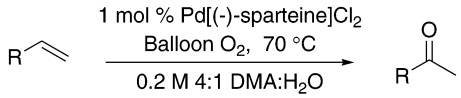
Table 2. Kaneda and Co-workers Direct-O_2-Coupled $PdCl_2$ Functionalization of Olefins

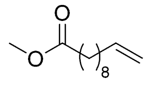
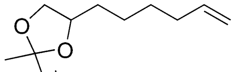
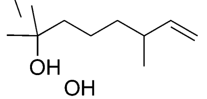
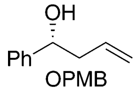
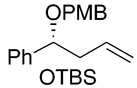
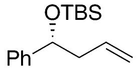


Entry	Substrate	Product	Time (h)	% Yield
1			3	78
2[a]			3	85
3[a]			3	76
4[b]			40	78
5[b]			40	92
6[b]			24	88
7[b]			3	66
8[b]			40	85
9[c]			4	95
10[c]			4	80
11[d,e]			40	82
12[d,f]			40	75

[a] 10:1 DMA/H_2O. [b] 1.0 mol % $PdCl_2$. [c] 10 mol % NaOAc and no H_2O. [d] 1 mol % $PdCl_2$ and 20 mol % NaOAc, 4-Å MS, 10:1 DMA/AcOH. [e] 10:1 linear/branched, 6:1 *E*/*Z*. [f] 2 mol % $PdCl_2$, 20:1 linear/branched, >99:1 *E*/*Z*.

Table 3. Pd[(−)-sparteine]Cl_2-Catalyzed Direct-O_2-Coupled Wacker Oxidation under Balloon Pressure of O_2



Entry	Substrate	Time (h)	% Yield
1	dodecene	18	85
2	dodecene (air balloon)	18	71[a]
3	10-undecen-1-ol	18	72
4	4-cis-decene	18	0[b]
5		24	73
6		24	62[c]
7		24	79[c]
8		48	56[b,d,e]
9		24	81[d,e]
10		24	85[b,e]

[a] 6:1 DMA/H_2O. [b] 2.0 mol % Pd[(−)-sparteine]Cl_2. [c] 2.5 mol % Pd[(−)-sparteine]Cl_2. [d] 8:1 DMA/H_2O. [e] No racemization observed.

pressures of O_2 (6 atm, 80 °C) with significantly enhanced substrate scope (Table 2).[50] Of particular note, DMF, the solvent used in Tsuji's Wacker oxidations, yields only trace amounts of the product. The excellent catalyst stability observed in DMA may be a result of a more negative redox potential of Pd(0) in DMA compared to other solvents. The basic, coordinating nature of the solvent may also provide direct ligation to the Pd catalyst.[25,51] Their kinetic analysis of the system showed first-order dependence on both pO_2 and [Pd], supporting rate-limiting catalyst regeneration. This system is also unique in that not only can it be applied to selective methyl ketone formation (entries 1−8) but also it is successful for intramolecular Wacker-type cyclizations (entries 9 and 10) and allylic ester formation with acetic acid acting as the nucleophile rather than H_2O (entries 11 and 12).

A further improvement in the practicality of direct-O_2-coupled Wacker oxidations came with our recent disclosure that 1−2 mol % Pd[(−)-sparteine]Cl_2 in a DMA/H_2O solvent under balloon pressure of O_2 is a highly effective catalyst system (Table 3).[52] A key aspect of this finding is that olefin isomerization, a common side reaction in Wacker oxidation, is suppressed by use of the ligand. A lower concentration of O_2 is tolerated (air balloon) with a slight decrease in the isolated yield (entry 2). Development of the system was directed toward the use in targeted molecule synthesis; therefore, a range of functional groups was probed. High selectivity for terminal olefin oxidation was established because no oxidation of primary or benzylic alcohols or olefin isomerization is observed (entries 3, 4, and 8). Enantiomerically enriched protected alcohols oxidize with no observed racemization, further showcasing the potential synthetic utility of this method (entries 8−10).

Conclusions

Though the Wacker oxidation has been studied for about half a century, a detailed mechanistic understanding of the process continues to be elusive because of the utilization of added ions and co-oxidants. This lack of understanding may explain the difficulties in developing variants that do not require additives where the interplay of oxidant, solvent, and ligand is clearly complex. As has been observed within the

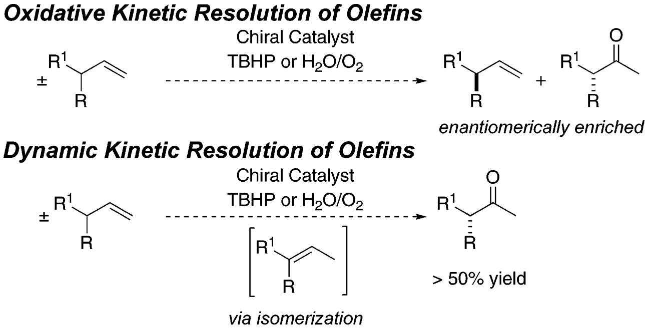
---

(50) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481−485.

(51) Hosokawa, T.; Takano, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1996**, *118*, 3990−3991.

(52) Cornell, C. N.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 4117−4120.

Scheme 6. Potential Applications of Wacker Oxidations to Asymmetric Catalysis



developments in our laboratory, the change from peroxide-mediated to direct-O_2-coupled Wacker oxidations required a change in both the ligand and the solvent. This nonobvious modification in the reaction conditions may also be associated with a different mechanistic scenario, highlighting the challenges in developing truly practical and applicable methods for the Wacker oxidation. The recent developments in this field should allow the community to begin probing the mechanism in detail without the encumbrance of co-oxidants and potentially apply these findings to the development of new Pd(II)-catalyzed oxidative olefin functionalization reactions, including asymmetric variants. To date, an asymmetric intermolecular Wacker oxidation has not been reported. Two possible asymmetric Wacker oxidation reactions include an oxidative kinetic resolution to yield both enantioenriched substrate and methyl ketone and a dynamic kinetic resolution where isomerization of the olefin would racemize the adjacent chiral center while selectively oxidizing one enantiomer of the substrate (Scheme 6). The elimination of Cu and the use of chiral ligands on Pd enhance the plausibility of such transformations being accomplished.

Acknowledgment. This work is supported by the National Institute of Health (Grant NIGMS RO1 GM3540). M.S.S. thanks the Dreyfus Foundation (Teacher−Scholar) and Pfizer for their support. We are grateful to Johnson Matthey for the gift of various Pd salts.

IC061858D