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# Discovery of a Practical Direct $O_2$-Coupled Wacker Oxidation with Pd[(–)-sparteine]$Cl_2$

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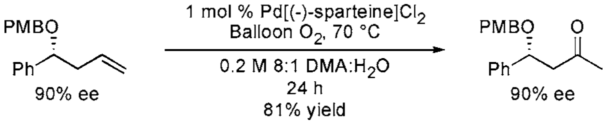
## ABSTRACT



**The discovery of a direct $O_2$-coupled Wacker oxidation with use of balloon pressure of $O_2$ and low catalyst loading is described. Use of (–)-sparteine as a ligand on Pd prevents olefin isomerization and leads to selective formation of methyl ketones from terminal olefins in good yields. Oxidation of enantiomerically enriched substrates is reported with no observed racemization.**

The Wacker oxidation, wherein a terminal olefin is converted to a methyl ketone, is an industrially and synthetically important transformation that has been extensively studied.[1,2] However, even with numerous methods available, the need for an improved and versatile Wacker oxidation is demonstrated in recent syntheses which required the use of 0.25 equiv to stoichiometric amounts of Pd and Cu.[3,4] As a specific example, Leighton and co-workers used two Wacker oxidations in their synthesis of Dolabelide D (Figure 1). While they were able to perform these oxidations with catalytic Pd, 25 mol % loading was required.

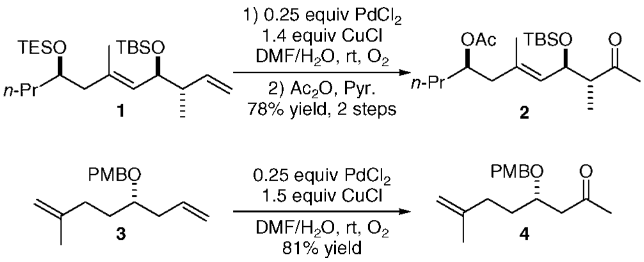


**Figure 1.** Recently reported Wacker oxidations in Leighton's synthesis of Dolabelide D.

Due to the complex nature of standard Wacker reactions (i.e., excess Cu salts and/or other cocatalysts), it is difficult to improve the reaction conditions systematically and rationally. Therefore, our goal was to eliminate the need for co-oxidants by using a ligand on Pd, thus simplifying the method while also providing an adjustable reaction parameter. Herein we report the discovery and application of a direct $O_2$-coupled Wacker oxidation catalyzed by Pd[(–)-sparteine]$Cl_2$ wherein the choice of solvent has a profound effect on olefin isomerization and selection of terminal oxidant.

Our initial forays into developing Wacker catalysts led to the use of *tert*-butyl hydroperoxide (TBHP) as the terminal

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[1] (a) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem.* **1962**, *74*, 93–102. For reviews on Wacker oxidations see: (b) Takacs, J. M.; Jiang, X.-t. *Curr. Org. Chem.* **2003**, *7*, 369–396. (c) Tsuji, J. *Synthesis* **1984**, 369–384.

[2] For recent book chapters on Wacker oxidations see: (a) Monflier, E.; Mortreux, A. In *Aqueous-Phase Organometallic Catalysis*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VHC: Weinheim, Germany, 2004; pp 481–487. (b) Hintermann, L. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VHC: Weinheim, Germany, 2004; Vol. 2, pp 379–388. (c) Jira, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VHC: Weinheim, Germany, 2002; Vol. 1, pp 386-405.

[3] Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264–10266.

[4] Schmidt, D. R.; Park. P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535–3537. For the total synthesis of Dolabelide D, see: Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796–2797.

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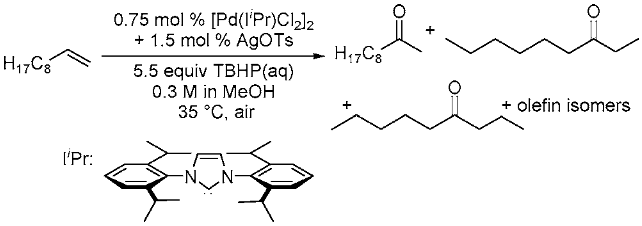
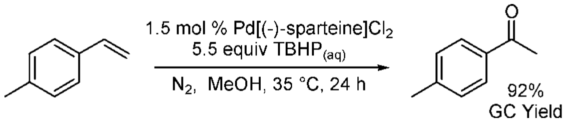
oxidant and catalyst **5** ($Pd(I^iPr)(OTs)_2$) employing an *N*-heterocyclic carbene ligand in the conversion of styrenes to acetophenone derivatives.[5] When evaluating decene as a substrate under these reaction conditions, oxidation is observed but a mixture of regiomeric ketones is formed due to rapid olefin isomerization (Scheme 1). Substrate isomerization is common with general Wacker conditions. For example, oxidation of terminal straight chain aliphatic alkenes with 10 mol % $PdCl_2$, 2 equiv of CuCl in 7 to 1 DMF to $H_2O$ under an $O_2$ atmosphere leads to 3−10% formation of isomeric carbonyl compounds.[1c,6] The relative selectivity for methyl ketone formation is not neccessarily reflective of the high rate of olefin isomerization. Tang and co-workers have shown the rate of olefin isomerization is over 30-fold greater than the rate of olefin oxidation, but the terminal olefin reacts significantly faster than internal olefins, leading mainly to methyl ketone formation.[6b] Under our current reaction conditions, the catalytic system promotes oxidation of all olefin isomers, leading to the production of 2-, 3-, and 4-decanone.

**Scheme 1.** Decene Oxidation with in Situ Formed $Pd(I^iPr)(OTs)_2$ (**5**) and $TBHP_{(aq)}$ in MeOH

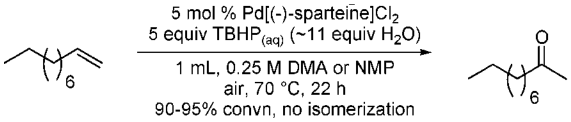


To improve the selectivity for methyl ketone formation, dative ligands, counterions, and solvents were probed. Initial evaluation of pyridine and $Et_3N$ as ligands on Pd, commonly used in Pd-catalyzed aerobic alcohol oxidations,[7] did not promote the Wacker oxidation and initially led us away from investigating other dative amine ligands. However, our recent report profiling the propensity for Pd[(−)-sparteine]$Cl_2$ to form stable monocationic species in solution,[8] and the observed olefin activation with Pd[(−)-sparteine]$Cl_2$ in hydroalkoxylation reactions[9] and oxidative acetal formation,[10] led us to evaluate this bidentate amine ligand under our Wacker-type oxidation conditions with TBHP. Thus, 4-methylstyrene was submitted to the reaction conditions with Pd[(−)-sparteine]$Cl_2$ as the catalyst. The formation of 4′-methylacetophenone is observed in high selectivity and GC yield (eq 1).



(1)

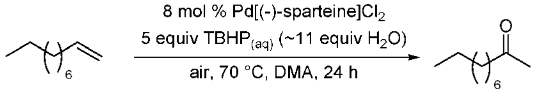
On the basis of this success, Pd[(−)-sparteine]$Cl_2$ was then evaluated as a catalyst for decene oxidation with $TBHP_{(aq)}$ in MeOH. Unfortunately, low chemo- and regioselectivity was again observed. Therefore, we decided to evaluate DMF as a solvent which, classically, has been shown to increase olefin miscibility and enhance selective methyl ketone formation.[1b,c,6a] Surprisingly, no conversion of decene was observed in DMF with catalytic Pd[(−)-sparteine]$Cl_2$ and $TBHP_{(aq)}$, but decene isomerization had been eliminated, even upon heating to 70 °C for 24 h. On the basis of this observation, *N*-methyl-2-pyrrolidinone (NMP) and *N*,*N*-dimethylacetamide (DMA) were evaluated as solvents. To our delight, conversion of decene to 2-decanone was observed with no detectable olefin isomerization over the course of the reaction with use of 5 mol % Pd[(−)-sparteine]$Cl_2$ at 70 °C (eq 2).



(2)

Upon scaling, catalyst decomposition was observed based on a black precipitate and diminished conversions, prompting several control experiments with unanticipated results. TBHP is not necessary for oxidation of the olefin, but enhances the reaction rate and selectivity (Table 1, entries 1 vs 4). An

**Table 1.** Discovery of a Direct $O_2$-Coupled Pd[(−)-sparteine]$Cl_2$-Catalyzed Wacker Oxidation of Decene



| entry | Δ conditions | % convn | % GC yield |
|---|---|---|---|
| 1 | std | 99 | 94 |
| 2 | no Pd | 0 | 0 |
| 3 | $N_2$ | 63 | 17 |
| 4 | no TBHP[a] | 46 | 33 |
| 5 | no TBHP[a]/$N_2$ | 21 | 8 |
| 6 | $Pd(CH_3CN)_2$/[a]/$O_2$ | 99(9 h) | 89[b] |
| 7 | $O_2$ | 98(9 h) | 89 |
| 8 | $Pd(CH_3CN)_2$/no TBHP[a]/$O_2$ | 95(6.5 h) | 55 |
| 9 | no TBHP[a]/$O_2$ | 74(6.5 h) | 59 |

[a] $H_2O$ added. [b] At 4 h, 80% convn >60% of remaining SM was internal olefin isomers, but only product was 2-decanone.

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(5) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796−2797.

(6) (a) Clement, W. H.; Selwitz, C. M. *J. Org. Chem.* **1964**, *29*, 241−243. (b) Tang, H. G.; Sherrington, D. C. *J. Mol. Catal.* **1994**, *94*, 7−17. (c) Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.

(7) For reviews on Pd-catalyzed aerobic alcohol oxidations see: (a) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221−229. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (c) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362−367. (d) Muzart, J. *Tetrahedron* **2003**, *59*, 5789−5816.

(8) Mueller, J. A.; Cowell, A.; Chandler, B. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 14817−14824.

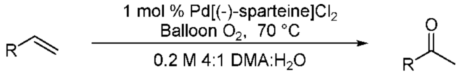
(9) Gligorich, K. M.; Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2794−2795.

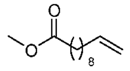
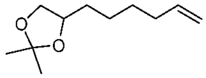
(10) Balija, A. M.; Stowers, K. J.; Schultz, M. J.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 1121−1124.

anaerobic atmosphere ($N_2$) leads to significantly decreased methyl ketone formation (entry 3). In contrast, a pure $O_2$ atmosphere leads to an increase in reaction rate and does not compromise selectivity (entry 7). Complete removal of TBHP and use of a balloon atmosphere of $O_2$ resulted in the discovery of a direct $O_2$-coupled Wacker oxidation with no observable olefin isomerization by GC (entry 9). (−)-Sparteine as a ligand also plays a significant role, as $Pd(CH_3CN)_2Cl_2$ promotes significant isomerization of the substrate during the reaction and Pd metal precipitates from the mixture, but unlike our previous system, methyl ketone is the only product observed (entries 6 and 8). It should be noted that Kaneda and co-workers have recently reported a similar system using catalytic $Pd(CH_3CN)_2Cl_2$ in DMA/$H_2O$ mixtures that requires 6 atm of $O_2$.[11]

Optimization of the reaction conditions for a direct $O_2$-coupled Pd[(−)-sparteine]$Cl_2$-catalyzed Wacker oxidation led to the use of 1 mol % Pd[(−)-sparteine]$Cl_2$ with 0.2 M substrate in a 4:1 DMA:$H_2O$ mixed solvent system under balloon pressure $O_2$ with vigorous stirring at 70 °C (Table 2). Increasing the concentration of $H_2O$ enhances the reaction rate, but must also be balanced with substrate miscibility and catalyst stability. Balloon pressure air is tolerated with a decreased concentration of $H_2O$ to avoid catalyst decomposition (6:1 DMA:$H_2O$) (entry 2). The chemoselectivity is highlighted by evaluating a substrate containing an olefin and a primary alcohol where olefin oxidation occurs in preference to alcohol oxidation, even though Pd[(−)-sparteine]$Cl_2$ is known to oxidize alcohols at elevated temperatures (entry 4).[7,8] By evaluating *cis*-4-decene (entry 5), the chemoselectivity of this method is further showcased in that both olefin isomerization and internal olefin oxidation are eliminated. Additionally, both a methyl ester and acetal functional group were tolerated (entries 6 and 7).

**Table 2.** Initial Scope of the Pd[(−)-sparteine]$Cl_2$-Catalyzed Direct $O_2$-Coupled Wacker Oxidation

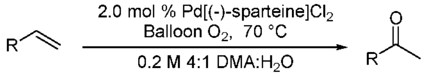


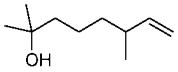
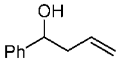
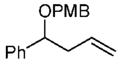
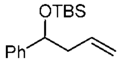
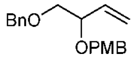
| entry | substrate | time (h) | % yield[a] |
|---|---|---|---|
| 1 | dodecene | 18 | 85[b] |
| 2 | dodecene (air balloon) | 18 | 71[c] |
| 3 | tridecene | 18 | 83[b] |
| 4 | 10-undecen-1-ol | 18 | 72 |
| 5 | *cis*-4-decene | 18 | 0[d] |
| 6 |  | 24 | 73 |
| 7 |  | 24 | 62[e] |

[a] Average isolated yield of multiple experiments. [b] Isolated yield reflects purity of SM (internal olefins). [c] 6:1 DMA:$H_2O$. [d] 2.0 mol % Pd[(-)-sparteine]$Cl_2$. [e] 2.5 mol % Pd-[(-)sparteine]$Cl_2$.

Having discovered a system with promising scope, we now wanted to challenge the system with substrates substituted at the allylic or homoallylic position. The substrates were chosen to not only model those employed by Leighton and co-workers (Figure 1), but to probe functional group tolerance of the system further. Dihydromyrcenol (**6**), which contains allylic substitution and a tertiary alcohol, was successfully oxidized to the corresponding methyl ketone (Table 3, entry 1). Upon scaling this transformation to 7.5 mmol from a standard 0.8 mmol scale, a slight enhancement in isolated yield was obtained (entry 2). Oxidation of the homoallylic alcohol **7** again showcases that olefin oxidation is preferred in this system even in the presence of an activated benzylic alcohol (entry 3). The predominant byproducts of the oxidation with **7** are Wacker cyclization isomers. Therefore, the homoallylic silyl and PMB protected alcohols were evaluated and led to good yields (entries 4 and 5). It should be noted that even though the catalyst is chiral, no kinetic resolution of the racemic substrates is observed. An allylic ether, known to be a problematic substrate in Wacker oxidations,[3,12] was also evaluated. Though only a 34% yield was achieved with substrate **10** (an intermediate in Crimmins' and co-workers' synthesis of Ophirin B),[3] the potential for significant improvement over current methods employing stoichiometric Hg, Pd, and Cu is still noteworthy.

**Table 3.** Wacker Oxidation of Allylic and Homoallylic Substituted Olefins



| entry | substrate | time (h) | % yield[a] |
|---|---|---|---|
| 1 |  **6** | 24 | 79[b] |
| 2 | | 24 | 83[b,c] |
| 3 |  **7** | 48 | 69[d] |
| 4 |  **8** | 24 | 80[d,e] |
| 5 |  **9** | 24 | 87 |
| 6 |  **10** | 48 | 34[f] |

[a] Average isolated yield of multiple experiments. [b] 2.5 mol % Pd-[(-)-sparteine]$Cl_2$. [c] 7.5 mmol scale. [d] 8:1 DMA:$H_2O$. [e] 1.0 mol % Pd[(-)-sparteine]$Cl_2$. [f] 5.0 mol % Pd-[(-)sparteine]$Cl_2$, 80 °C, 0.15 M.

Similar enantiomerically enriched substrates were evaluated to determine if racemization occurs under the current Wacker conditions.[13] Enantiomerically enriched substrate (*S*)-**7** was converted to the corresponding methyl ketone in a slightly diminished yield but no racemization is observed

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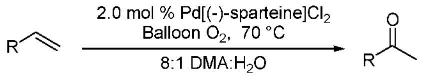
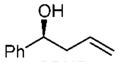
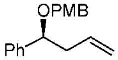
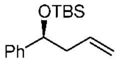
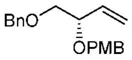
(11) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481−485.

(12) Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678−4679.

(13) Enantiomercially enriched 1-hydroxy-1-phenyl-3-butanone was synthesized by using the method reported in: Lee, J.-Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837−1839.

**Table 4.** Wacker Oxidation of Enantiomerically Enriched Substrates



| entry | substrate | time (h) | % ee (olefin) | % yield[a] | % ee (ketone) |
|---|---|---|---|---|---|
| 1 |  | 48 | 92 | 56 | 92 |
| 2[b] |  | 24 | 90 | 81 | 90 |
| 3[c] |  | 24 | 93 | 85 | 93 |
| 4[d] |  | 48 | >99 | 37 | >99 |

[a] Average isolated yield of multiple experiments. [b] 1.0 mol % Pd-[(-)-sparteine]$Cl_2$. [c] 4.1 mmol scale. [d] 5.0 mol % Pd-[(-)sparteine]$Cl_2$, 80 °C, 0.15 M.

(Table 4, entry 1). Both the PMB and TBS protected alcohols were excellent substrates for the Wacker oxidation with >80% isolated yields and no racemization (entries 2 and 3). The relatively low catalyst loadings (compared to 25%) and elimination of co-oxidants vastly improves the practicality of Wacker oxidations of protected homoallylic alcohols. Finally, no racemization is observed in the conversion of an allylic ether to the corresponding carbonyl (entry 4).

In summary we have discovered a ligand modulated direct $O_2$-coupled Wacker oxidation that operates at ambient pressures of $O_2$. The substrate scope and chemoselectivity of the system is highlighted by the functional group tolerance and ability to oxidize enantiomerically enriched substrates with no racemization. Discovery of a direct $O_2$-coupled Wacker oxidation will allow the first mechanistic studies on a Wacker oxidation that does not require additives to be performed. This and further evaluation of the potential utility of this direct $O_2$-coupled Wacker oxidation method are currently underway.

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**Supporting Information Available:** Experimental procedures and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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