

The Palladium-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols with Molecular Oxygen

Eric M. Ferreira and Brian M. Stoltz*

The Arnold and Mabel Beckman Laboratories of
Chemical Synthesis, Division of Chemistry and
Chemical Engineering, California Institute of Technology
Pasadena, California 91125

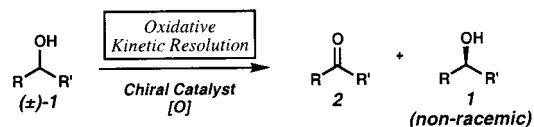
Received March 9, 2001

Revised Manuscript Received June 19, 2001

The oxidation of secondary alcohols is one of the most common and well-studied reactions in chemistry.¹ Although excellent catalytic enantioselective methods exist for a variety of oxidation processes, such as epoxidation,² dihydroxylation,³ and aziridination,⁴ it is surprising that there are relatively few catalytic enantioselective examples of the ubiquitous alcohol oxidation.⁵ In connection with a general program dealing with the discovery of new catalytic oxidation systems, we present herein the development of a catalytic oxidative kinetic resolution of secondary alcohols that uses molecular oxygen as the terminal oxidant (see Scheme 1).^{6–8}

Among the many hundred known processes for alcohol oxidation,⁹ comparatively few metal-catalyzed examples have been developed.¹⁰ One notable exception has been the use of catalytic palladium(II) systems, which often provide efficient oxidation of *sec*-alcohols to ketones in high yield.¹¹ Interestingly, palladium(II) oxidations have been successfully implemented

Scheme 1



using a wide variety of co-oxidants, including allyl carbonates, aryl halides, CCl_4 , and molecular oxygen. We have investigated a number of these general systems in the presence of chiral ligands and studied the kinetic resolution of *sec*-alcohols. Although the nonenzymatic kinetic resolution of *sec*-alcohols via acylation has been extensively studied by the groups of Vedejs, Fu, Miller, and others,⁷ oxidative methods for alcohol resolution remain rare.¹² Furthermore, to our knowledge there are no reported examples of palladium-catalyzed oxidative kinetic resolutions of *sec*-alcohols.

From exploratory studies that focused on chiral phosphine ligands, it was rapidly established that modest levels of asymmetric induction were attainable in the presence of organic oxidants.¹³ Although initially promising, reactions carried out under these conditions were plagued by a variety of side reactions and inconsistencies.¹⁴ In an effort to minimize the complexity of the reaction conditions, we turned our attention toward catalytic systems that employ oxygen as the stoichiometric oxidant. Using 1-phenylethanol as a test case, we surveyed a number of variations of the catalytic reaction and found that the conditions developed by Uemura^{11f} were particularly suited to the rapid screening of a variety of chiral ligands. From the structurally diverse set of ligands explored for the oxidation reaction (see Table 1), (–)-sparteine quickly emerged as the most selective. Upon further optimization, the nature of the palladium source was found to be critical (see Table 2). Thus, substituting PdCl_2 for $\text{Pd}(\text{OAc})_2$ induced a marked increase in the selectivity factor (*s*).^{13b} For example, oxidative kinetic resolution of 1-phenylethanol using $\text{Pd}(\text{OAc})_2$ proceeded with a selectivity factor of 8.8, whereas the analogous resolution using PdCl_2 was found to have a selectivity factor of 16.3, thereby providing acetophenone in 62.6% conversion and unreacted alcohol of 98.0% ee. Further evaluation of the palladium source revealed that $\text{Pd}(\text{nbd})\text{Cl}_2$ provided the most selective catalytic system tested to date (Table 2, entry 7, *s* = 23.1).^{15,16}

(1) (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, England, 1991. (b) Luzzio, F. A. *Org. React.* **1998**, *53*, 1. (c) Tidwell, T. T. *Org. React.* **1990**, *39*, 297. (d) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph Series; American Chemical Society: Washington, DC, 1990.

(2) (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley & Sons: New York, 2000; pp 231–280. (b) Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley & Sons: New York, 2000; pp 287–325.

(3) Bolm, C.; Hildebrand, J. P.; Muniz, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley & Sons: New York, 2000; pp 399–428.

(4) Müller, P. In *Advances in Catalytic Processes*; JAI Press Inc.: Greenwich, CT, 1997; Vol. 2, pp 113–151.

(5) (a) Ohkubo, K.; Hirata, K.; Yoshinaga, K.; Okada, M. *Chem. Lett.* **1976**, 183. (b) Berti, C.; Perkins, M. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 864. (c) Ishii, Y.; Suzuki, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2822. (d) Ma, Z.; Huang, Q.; Bobbitt, J. M. *J. Org. Chem.* **1993**, *58*, 4837. (e) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194. (f) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288. (g) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (h) Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.; Osa, T.; Bobbitt, J. M. *Tetrahedron Lett.* **1999**, *40*, 6469. (i) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 5119. (j) Kuroboshi, M.; Yoshihisa, H.; Cortona, M. N.; Kawakami, Y.; Gao, Z.; Tanaka, H. *Tetrahedron Lett.* **2000**, *41*, 8131.

(6) For excellent discussions on kinetic resolution, see: (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (b) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294. (c) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley & Sons: New York, 1988; Vol. 18, pp 249–330.

(7) For leading references describing outstanding nonenzymatic catalytic acylation approaches to the kinetic resolution of *sec*-alcohols, see: (a) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (b) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (c) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813.

(8) For a recent monograph describing enzymatic approaches to kinetic resolution, see: Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, U.K., 1994.

(9) Larock, R. C. *Comprehensive Organic Transformations*; Wiley & Sons: New York, 1999; pp 1234–1248.

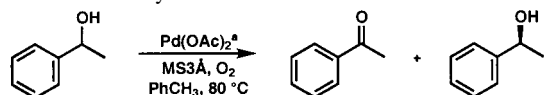
(10) For example, of the 297 examples listed in ref 9, only 67 are metal-catalyzed. Some notable examples include the use of catalytic Ru, Co, Cr, W, Mo, Fe, Os, Ir, Yb, Zr, V, Ce, and Pd.

(11) For leading references, see: (a) Blackburn, T. F.; Schwartz, J. J. *Chem. Soc., Chem. Commun.* **1977**, 157. (b) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1979**, *20*, 1401. (c) Nagashima, H.; Tsuji, J. *Chem. Lett.* **1981**, 1171. (d) Ait-Mohand, S.; Hémin, F.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 2473. (e) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (f) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750. (g) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science*, **2000**, *287*, 1636.

(12) Three noteworthy examples include the ruthenium system of Noyori (ref 5f), Rychnovsky's nitroxyl radical system (ref 5e), and the use of baker's yeast, see: Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Poli, S.; Sinigaglia, M. *Tetrahedron Lett.* **1993**, *34*, 883.

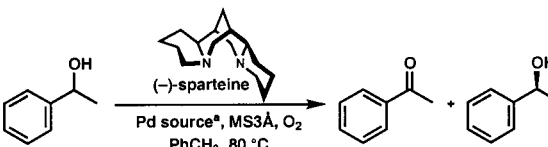
(13) (a) For example, racemic 1-cyclohexylethanol could be resolved to 65.5% ee at 58.0% conversion (selectivity = *s* = 5.3) by exposure to (–)-Me-DUPHOS, $\text{Pd}(\text{OAc})_2$, NaOr-Bu, and iodobenzene in CH_2Cl_2 at 30 °C. (b) The selectivity factor (*s*) was determined using the equation: $s = \frac{k_{\text{rel}}(\text{fast/slow})}{\ln[(1 - C)(1 - ee)]/\ln[1 - C]}$, where *C* = conversion.^{6c} Kagan has defined *s* as the chemical stereoselectivity factor, while the biochemical stereoselectivity factor (solved by an equivalent equation) is defined as *E*. Additionally, this distinction in terminology was recently adopted by Eliel and Wilen, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; pp 395–415. For a full account of the nomenclature used in this communication, see ref 6c.

(14) (a) In particular, control experiments indicated that treatment of a mixture of either acetophenone and 1-cyclohexylethanol or 1-phenylethanol and 1-cyclohexylethanolone with NaOr-Bu in CH_2Cl_2 resulted in a Meerwein–Ponndorf–Verley reduction/Oppeneuer oxidation cycle to yield a mixture of all four compounds in each case. For a review, see: Djerassi, C. *Org. React.* **1951**, *6*, 207. (b) Adding to the complexity of these conditions was an observed oxygen dependence; thus, experiments performed with rigorous exclusion of oxygen were found to result in low catalyst turnover and hence almost no conversion to the ketone.

Table 1. Ligand Screen for the Pd-catalyzed Oxidative Kinetic Resolution of 1-Phenylethanol.


entry	ligand ^b	time	conversion	ee ROH	s
1.	Ph-PYBOX	72 h	2%	-	1
2.	BINAP	24 h	29.0%	0%	1
3.	cinchonidine	72 h	2%	-	1
4.	brucine	24 h	77.0%	0%	1
5.	(DHQD) ₂ PHAL	24 h	31.6%	8.7%	1.6
6.	(-)-sparteine	24 h	15.1%	13.7%	8.8

^a 5 mol % Pd(OAc)₂, 20 mol % ligand, 1 atm O₂. ^b For ligand structures, see Supporting Information.

Table 2. Importance of the Palladium Source for the Oxidative Kinetic Resolution of 1-Phenylethanol


entry	Pd source	time	conversion	ee ROH	s
1.	Pd(OAc) ₂	24 h	15.1%	13.7%	8.8
2.	Pd ₂ (dba) ₃	55 h	66.2%	81.5%	5.7
3.	PdCl ₂	96 h	62.6%	98.0%	16.3
4.	Pd(CH ₃ CN) ₂ Cl ₂	36 h	51.7%	79.8%	16.5
5.	Pd(PhCN) ₂ Cl ₂	36 h	57.4%	92.1%	16.9
6.	[(allyl)PdCl] ₂	96 h	60.2%	96.9%	18.0
7.	Pd(nbd)Cl ₂ ^b	96 h	59.9%	98.7%	23.1

^a 5 mol % Pd, 20 mol % (-)-sparteine, 1 atm O₂. ^b nbd = norbornadiene.

With the optimized system in hand, we initiated investigations into the reaction's scope. As shown in Table 3, we have demonstrated that palladium-catalyzed kinetic resolutions with (-)-sparteine as a ligand provide uniformly excellent levels of asymmetric induction with a variety of activated alcohols (i.e., benzylic and allylic).¹⁷ Benzylic alcohols with functionalized aromatic rings serve particularly well as substrates for the resolution, with selectivity factors as high as 47.1 (entries 1–7). Additionally, the resolution is not limited to 1-substituted ethanol derivatives (entries 7–9). Substrates containing fused ring systems can also be accessed in high levels of enantiopurity (entries 8 and 9, ee > 93%). Importantly, the potential utility and versatility of the catalytic oxidative kinetic resolution is further established by the reaction of a substituted allylic alcohol (entry 10).¹⁸

Particularly noteworthy is the preparative reaction shown in Scheme 2. The oxidative kinetic resolution performs well on multigram scale with good recovery (44%) of optically enriched alcohol (-)-**3** in 99% ee. Quantitative reduction of ketone **4** provides an opportunity for the preparation of chiral alcohol (-)-**3** in >50% overall yield from a racemic mixture via multiple oxidative kinetic resolution cycles.

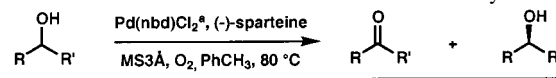
In conclusion, we have developed the first palladium-catalyzed oxidative kinetic resolution of secondary alcohols. The resolution employs molecular oxygen as the terminal oxidant in conjunction with the naturally occurring diamine ligand (-)-sparteine.¹⁹ Efforts











(15) We attribute the differences observed in Table 2 to subtle differences in solubility of the Pd sources in PhCH₃ at 80 °C and their ability to form diamine complexes. Further experiments are ongoing.

(16) Palladium–sparteine complexes have been used for catalytic allylic substitution reactions and olefin polymerization reactions. See Supporting Information for a complete list of references.

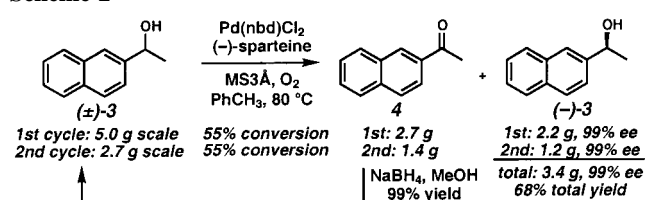
(17) To date the resolution of saturated *sec*-alcohols is sluggish and proceeds with modest selectivity (e.g., 1-cyclohexylethanol, *s* = 4).

(18) In all cases, the absolute stereoconfiguration of the enantioenriched alcohol was determined by comparison to data for known optically pure substances and was consistent with that shown in Table 3.

Table 3. the Oxidative Kinetic Resolution of Secondary Alcohols


entry	unreacted alcohol, major enantiomer	time	C	isolated yield ^b	ee ROH ^c	s ^{d,e}
1.	 R = H	96 h	59.9%	37% (93%)	98.7%	23.1
2.	 R = OMe	96 h	66.6%	32% (96%)	98.1%	12.3
3.	 R = F	54 h	63.3%	32% (88%)	97.4%	14.4
4.	 Ar = 1-Naphthyl	192 h	55.9%	43% (97%)	78.4%	9.8
5.	 Ar = 2-Naphthyl	112 h	55.2%	44% (99%)	99.0%	47.1
6.	 Ar = o-tolyl	144 h	48.4%	49% (95%)	68.7%	13.1
7.		192 h	59.3%	40% (98%)	93.1%	14.8
8.	 n = 1	54 h ^f	67.5%	30% (93%)	93.4%	8.3
9.	 n = 2	40 h	68.6%	31% (99%)	99.8%	15.8
10.		120 h	70.4%	29% (99%)	91.8%	6.6

^a 5 mol % Pd(nbd)Cl₂, 20 mol % (-)-sparteine, 1 atm O₂, 0.1 M substrate concentration in PhCH₃. ^b Isolated yield of enantioenriched alcohol is presented first. The number in parentheses is the total combined yield of alcohol and ketone. ^c The degree of enantioselectivity was measured directly by chiral HPLC or GC of the recovered alcohols. Conversion was measured by GC using a DB-WAX column. See Supporting Information. ^d Selectivity (*s*) values represent an average of at least two experiments, while conversion and ee values are for specific cases. ^e For each entry, comparable selectivities are observed throughout the course of the run. ^f Performed at 60 °C.

Scheme 2

to expand the scope of the resolution^{17,20} and to understand the observed selectivity of this reaction are ongoing.

Acknowledgment. We are grateful to the California Institute of Technology, the Camille and Henry Dreyfus Foundation, and the Merck Research Laboratories for generous financial support. B.M.S. thanks the Camille and Henry Dreyfus Foundation for a New Faculty Award. We thank the MacMillan group for generously sharing their HPLC and GC equipment. We acknowledge Professors John E. Bercaw, Robert H. Grubbs, and David W. C. MacMillan and their groups for chemicals and helpful discussions.

Supporting Information Available: Detailed experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA015791Z

(19) Although we have never experienced an accident, all reactions must be performed with appropriate caution in a fume hood due to the flammable nature of mixtures of oxygen and organic solvents.

(20) Recently, the scope of the reaction was extended to include the oxidative desymmetrization of meso diols. For example:

