Palladium-Catalyzed Enantioselective Oxidations of Alcohols Using Molecular Oxygen

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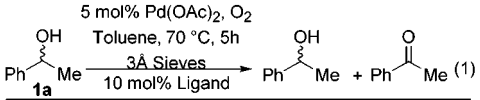
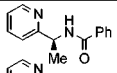
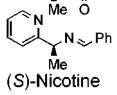
The use of molecular oxygen as a stoichiometric reoxidant in combination with a catalytic metal has exceptional practical advantages for applications in organic synthesis.[1] This is in part due to the favorable economics associated with molecular oxygen and the formation of environmentally benign byproducts in the oxidation manifold (water and hydrogen peroxide). An excellent example of the use of molecular oxygen in organic synthesis is the metal-catalyzed aerobic oxidation of alcohols to aldehydes and ketones.[2,3] We became interested in extending the scope of these oxidations to asymmetric catalysis.[4] To this end, we envisioned two potentially useful reactions: (1) the oxidative kinetic resolution of racemic secondary alcohols,[5] kinetic resolutions that have previously been accomplished using acylation[6] and oxidation,[7,8] and (2) the oxidative desymmetrization of *meso*-diols.[9] Herein we report a convenient, enantioselective aerobic oxidation of alcohols mediated by Pd(II) and a chiral diamine.

Aerobic oxidations of alcohols using catalytic Pd(II) salts have been reported.[3a−d] Of particular interest is the observation that amine additives[3a−c] both effect ligand-accelerated catalysis[10] and extend the substrate scope. Therefore, we initiated our investigation for an oxidative kinetic resolution catalyst by screening various chiral amine ligands in addition to common ligands for Pd-mediated asymmetric reactions (Table 1, eq 1). Bi- and tridentate ligands were generally poor templates for oxidation giving low conversions (entries b, f, g, and h). In contrast, Pd(II) complexes derived from pyridine ligands with 3-substitution gave high conversions, albeit with low k_{rel} values[11] (entries c and e). The most promising result from this initial screen was that (−)-sparteine, a chiral tertiary diamine, gave the best k_{rel} (2.6).

Table 1. Initial Screening



Entry	Ligand[a]	%Conv. (%ee)[b]	k_{rel}
a		5	<1.1
b		0	ND
c	(*S*)-Nicotine	70	<1.1
d	Quinine	8	<1.1
e	Quinine (OTBS)	72(21)	1.4
f	(*R*)-BINAP[c]	7	<1.1
g	(*S,S*)-Ph-BOX[c]	5	<1.1
h	(*S,S*)-Ph-PyBOX	1	ND
i	(+)-Troger's Base	84(11)	1.1
j	**(-)-Sparteine**	**14(7)**	**2.6**

[a] Ligand structures are available in the supporting info. [b] Conversion determined using internal standard. [c] 5 mol % Ligand.

To improve both the reaction rate and k_{rel}, the reaction parameters of the (−)-sparteine/Pd(II) catalyst system were optimized. Ten reaction parameters in a single apparatus were simultaneously examined under identical temperature and oxygen pressure (balloon pressure).[12,13] During each screen, aliquots were periodically analyzed using an autosampling GC equipped with a chiral column. The optimization procedure allowed us to efficiently examine the effect of solvent, component concentration, Pd(II) source, and molecular sieves[14] on k_{rel} and reaction rate. After screening these parameters, two sets of conditions were identified. Conditions A: 0.5 M **1a** in 1,2-dichloroethane,[15] 20 mol % (−)-sparteine, and 5 mol % of $Pd(OAc)_2$ and conditions B: 0.25 M **1a** in 1,2-dichloroethane, 20 mol % (−)-sparteine, and 5 mol % of a soluble $PdCl_2$ source ($Pd(MeCN)_2Cl_2$ and $Pd(COD)Cl_2$ gave similar results). Using both conditions the effect of temperature was evaluated. For $Pd(OAc)_2$, the temperature was found to have a significant influence on enantioselectivity wherein a temperature of 60 °C gave the highest k_{rel} value, while no significant temperature effect was observed for $PdCl_2$ sources. Overall for **1a**, the initial conditions were optimized from a k_{rel} of 2.6 to 17.5 using conditions B.

Next, the substrate scope of the oxidative kinetic resolution was evaluated (Table 2). Using both conditions, benzylic secondary alcohols are generally good substrates for oxidative kinetic resolution with k_{rel} values ranging from 8.7 to 23.6. Using Pd-

(1) Barton, D. H. R.; Martell, A. E.; Sawyer, D. T. *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*; Plenum Press: New York, 1993.

(2) For a recent review, see: Sheldon, R. A.; Arends, I. W. C. E.; Dijksman, A.*Catal. Today* **2000**, *57*, 157.

(3) Recent examples: (a) Ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750. (c) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **1998**, *39*, 6011. (d) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (e) Markó, I. E.; Giles, P. G.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044.

(4) Asymmetric dihydroxylation has been accomplished using O_2, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 334. (b) Döbler, C.; Mehltretter, G.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3026.

(5) For a review of practical issues in kinetic resolutions, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

(6) Catalytic acylation: (a) Vedejs, E.; MacKay, J. A. *Org. Lett.* **2001**, *3*, 535. (b) Bellemine-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009. (c) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (d) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (e) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265. (f) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (g) Ruble, J. C.; Tweddell, J. Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (h) Ruble, J. C.; Latham, H. A.; Fu. G. C. *J. Am. Chem. Soc.* 1997, *119*, 1492. (i) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169.

(7) Recent oxidative approaches: (a) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* 2000, *41*, 5119. (b) Nishibayashi, I.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (c) Gross, Z.; Ini, S. *Org. Lett.* **1999**, *1*, 2077 (d) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288. (e) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194.

(8) Epoxidation: Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(9) For examples of nonenzymatic desymmetrization of *meso*-diols via acylation see: (a) Yamada, S.; Katsumata, H. *J. Org. Chem.* **1999**, *64*, 9365. (b) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397. (c) Via acetal cleavage, see: Fujioka, H.; Nagatomi, Y.; Kotoku, N.; Kitagawa, H.; K. *Tetrahedron* **2000**, *56*, 10141. (d) Kinugasa, M.; Harada, T.; Oku, A. *J. Am. Chem. Soc.* **1997**, *119*, 9067.

(10) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed.. Engl.* **1995**, *34*, 1059.

(11) $k_{rel} = \ln[(1 - C)(1 - ee)]/ \ln[(1 - C)(1 + ee)]$ where C is the conversion and ee is the enantiomeric excess. For an excellent discussion of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. Kinetic Resolution. *Top. Stereochem.* **1988**, *18*, 249.

(12) CAUTION: Organic solvents are highly flammable under O_2.

(13) See Supporting Information for details.

(14) Molecular sieves have been used as a catalyst to disproportionate H_2O_2 formed in the reaction. See ref 3b.

(15) In the absence of O_2, catalytic oxidation is not observed. DCE has been used as a terminal oxidant in Pd(II)-catalyzed alcohol oxidations. For a leading reference, see: Aït-Mohand, S.; Hénin, F.; Muzart, J. *Tetrahedron. Lett.* **1995**, *36*, 2473.

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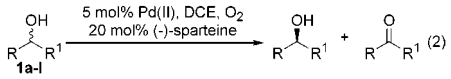
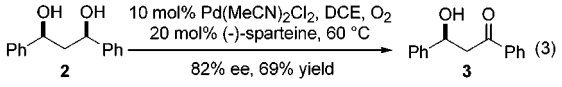
Table 2. Substrate Scope



entry		substituent R	substituent R^1	conditions[a]	% conv (% ee)[b,c]	average[d] k_{rel}
1	**1a**	C_6H_5	Me	A	65.9(98.2)	13.0
2				B	53.9(86.9)	17.5
3	**1b**	C_6H_5	Et	A	59.4(82.0)	8.7
4				B	57.5(88.5)	11.6
5	**1c**	*p*-$MeOC_6H_4$	Me	A	67.2(99.0)	15.1
6				B	72.1(99.0)	10.0
7	**1d**	*p*-MeC_6H_4	Me	A	60.8(96.6)	14.0
8				A	57.0(94.3)	17.1
9	**1e**	*p*-$CF_3C_6H_4$	Me	A	59.4(83.2)	9.1
10				B	48.6(70.3)	12.5
11	**1f**	*m*-$CF_3C_6H_4$	Me	A	63.6(92.7)	9.6
12				B	47.5(71.5)	15.9
13	**1g**	*m*-$MeOC_6H_4$	Me	A	66.7(98.4)	12.9
14	**1h**	*p*-FC_6H_4	Me	A	52.9(80.7)	12.2
15	**1i**	2-Naphthyl	Me	A	65.7(95.9)	10.1
16[e]	**1j**	*tert*-Bu	Me	A	58.5(77.8)	7.6
17	**1k**	*o*-$MeOC_6H_4$	Me	B	48.2(66.3)	14.0
18	**1l**	*p*-BrC_6H_4	Me	B	43.5(66.1)	23.6

[a] Conditions A, $Pd(OAc)_2$ at 60 °C and 0.5 M in substrate, Condition B, $Pd(MeCN)_2Cl_2$ at 70 °C and 0.25 M in substrate. [b] Enantioselectivity and conversion were determined by GC using commercial chiral columns and tetradecane as an internal standard. [c] Data represents a single experiment. [d] The k_{rel} value is an average of multiple experiments and measured at 24 h. [e] At 80 °C.

$(OAc)_2$, it can be seen that substituents on the aromatic ring influence enantioselectivity with electron-rich alcohols giving higher k_{rel} values than electron-poor substrates. However, no such correlation is observed using $PdCl_2$ sources. By increasing the size of R^1 from methyl to ethyl, a decrease in the k_{rel} is observed. Using 1.0 g of the *p*-methyl substrate, **1d**, in an oxidative kinetic resolution, $Pd(COD)Cl_2$ was the most effective Pd(II) source giving the resolved alcohol in an isolated yield of 41.9% at 92.0% ee with a slightly retarded rate. Resolution of an aliphatic alcohol was also possible with a k_{rel} of 7.6 at 80 °C (entry 10). Overall, the $PdCl_2$-derived catalyst proved to be the most effective in terms of k_{rel} values.



An oxidative desymmetrization of a 1,3-*meso*-diol was also investigated (eq 3). Treating the 1,3-diol **2** to $Pd(MeCN)_2Cl_2$/(−)-sparteine conditions resulted in enantioselective oxidation providing **3** in 82% ee and 69% yield (93% ee, 59% yield recrystallized). Further oxidation of **3** to the diketone proved exceedingly slow.

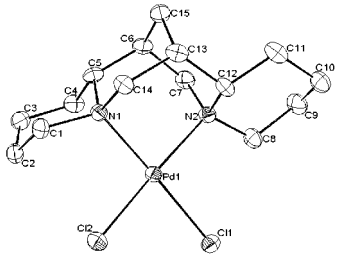
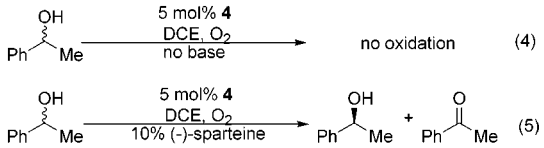


Figure 1. X-ray analysis of $Pd(Cl)_2$/(−)-sparteine complex **4**.

To investigate the nature of the catalyst structure, an orange single-crystal of the (−)-sparteine/$PdCl_2$ complex, was obtained. X-ray analysis of **4** showed the (−)-sparteine bound bidentate to one side of a slightly distorted square plane of Pd (Figure 1).[16] Additionally, the Pd−N bonds are slightly asymmetric with a difference of 0.05 Å. Complex **4** was evaluated as a catalyst in the oxidative kinetic resolution of **1a** at 5 mol % and found to be catalytically incompetent (eq 4). However, addition of (−)-sparteine (10 mol %) reestablished normal catalytic activity and enantioselectivity (eq 5), suggesting an exogenous base is necessary for oxidation.



In conclusion, a convenient method for enantioselective aerobic alcohol oxidation has been discovered using a (−)-sparteine/Pd(II) catalyst. All reagents are commercially available and are used without extensive purification. Benzylic alcohols give moderate to good k_{rel} values in an oxidative kinetic resolution, and a *meso*-1,3-diol is a good substrate for oxidative desymmetrization. The application of enantioselective oxidations to other substrate types, the identification of second-generation catalysts with antipodal selectivity, and understanding of the origin of enantioselectivity are currently being investigated.

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Supporting Information Available: Experimental procedures and characterization data are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA015827N

(16) For Pd(II)/(−)-sparteine π-allyl complexes, see: (a) Trost, B. M.; Dietsche, T. *J. Am. Chem. Soc.* **1973**, *95*, 8200. (b) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683.