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Palladium-Catalyzed Enantioselective Oxidation of Alcohols: A Dramatic Rate Acceleration by Cs_2CO_3/*t*-BuOH

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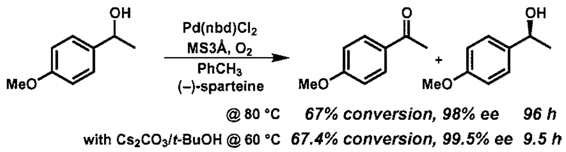
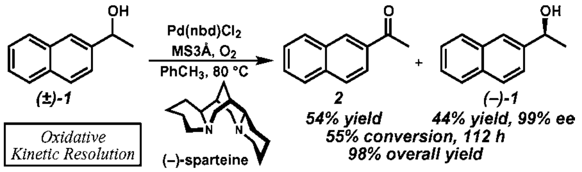
ABSTRACT



The addition of Cs_2CO_3 and *t*-BuOH provides a dramatic rate acceleration in the palladium-catalyzed aerobic oxidative kinetic resolution of secondary alcohols while maintaining the selectivity of the process.

We recently reported the oxidative kinetic resolution of secondary alcohols using a simple protocol involving a commercially available palladium complex, sparteine, and molecular oxygen (Scheme 1).[1−3] Although our previously described system was applied to a range of benzylic and allylic alcohols, the reaction times required to advance the resolutions to high conversion were often prohibitively long. For example, a typical reaction time was on the order of 4 days. In an effort to develop more active catalyst systems for the oxidative kinetic resolution of nonactivated alcohols and other asymmetric dehydrogenation reactions, we have discovered a modified set of conditions that accomplishes similar resolutions in a fraction of the time.[4,5]

Scheme 1



During the course of our investigations into the enantioselective oxidation of secondary alcohols, we prepared a number of Pd(II)·sparteine complexes and studied their reactivity.[6] In general, we found that the reactivity of these complexes toward the asymmetric oxidation of alcohols was poor when compared to the optimized method we developed, wherein a 4-fold excess of sparteine relative to the palladium source was used to form the complex in situ. Interestingly,

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[1] Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.

[2] Simultaneous to our publication a related system was reported; see: Jensen., D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475.

[3] The kinetic resolutions in refs 1 and 2 were based on a non-asymmetric alcohol oxidation employing $Pd(OAc)_2$, pyridine, and O_2; see: Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750.

[4] Recently, Stahl has been studying the mechanistic details of related, non-asymmetric systems; see: (a) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (c) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188.

[5] For 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.

[6] Bagdanoff, J. T.; Ferreira, E. M.; Trend, R. M.; Stoltz, B. M. Unpublished results.

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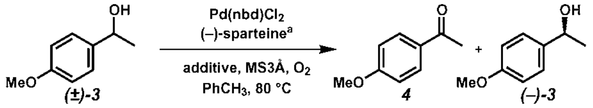
the reactivity of the system could be restored upon introduction of an additional 3 equiv of sparteine relative to the complex (particularly the chloride derivatives).[7] Intrigued by this finding, we hypothesized that the excess sparteine was serving as a general base for the ultimate neutralization of HCl liberated from the system, and thus investigated the effect of other bases on the reaction. Indeed, Sigman's kinetic work has confirmed this hypothesis.

As shown in Table 1, we surveyed the effect of a variety of external bases and additives on the oxidative kinetic resolution and compared the results to those previously reported (entry 1).[1,2] For all trials depicted in Table 1, a 1:1 ratio of $Pd(nbd)Cl_2$/sparteine was employed. Although addition of amine bases provided high levels of selectivity, resolutions performed under these conditions failed to proceed beyond low conversion (entries 2−4). The most dramatic effect was observed upon addition of carbonate salts. Specifically, inclusion of 1.0 equiv of powdered anhydrous Cs_2CO_3 resolved benzylic alcohol **3** in just 13 h, with comparable selectivity to our previously reported conditions.

Table 1. Additive Effects on the Oxidative Kinetic Resolution

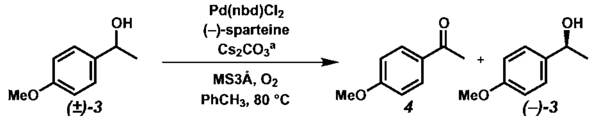


entry	additive	time (h)	conversion[b] (%)	ROH[c] ee (%)	s[d]
1	none[e]	96	67	98	12
2	Et_3N (0.4 equiv)	20	26	31	22
3	Et_3N (2.0 equiv)	13	19	19	11
4	DABCO (0.4 equiv)	13	7	8	20
5	Na_2CO_3 (1.0 equiv)	13	27	31	15
6	K_2CO_3 (1.0 equiv)	13	56	84	13
7	Cs_2CO_3 (1.0 equiv)	13	68	99	13

[a] 10 mol % $Pd(nbd)Cl_2$, 10 mol % (−)-sparteine, 1 atm of O_2, 0.1 M substrate concentration in $PhCH_3$. [b] Measured by ^1H NMR. [c] Measured by chiral HPLC. [d] See footnote 8. [e] 5 mol % $Pd(nbd)Cl_2$, 20 mol % (−)-sparteine.

Having observed a marked additive effect, we attempted to further improve the system by optimizing the catalyst loading, Pd/sparteine ratio, and by continuing to study the effects of additives. As shown in Table 2, increased amounts of sparteine still have a positive effect on the selectivity and the overall rate of the reaction (entries 1−3). In fact, by simply increasing the total amount of (−)-sparteine to that previously employed (4:1 sparteine/Pd), we could achieve alcohol resolution to high enantiopurity in only 5 h (entry 3).

Table 2. Catalyst and External Alcohol Effects



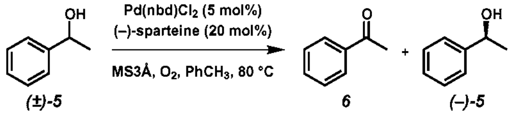
entry	additive	time (h)	conversion[b] (%)	ROH[c] ee (%)	s[d]
1	sparteine (5 mol %)	5	45	60	12
2	sparteine (10 mol %)	5	56	83	12
3	sparteine (30 mol %)	5	61	96	15
4	*n*-BuOH (1.0 equiv)	5.5	66	98	12
5	*n*-BuOH (2.0 equiv)	5.5	67	95	10
6	*n*-BuOH (10 equiv)	19	48	56	7
7	*t*-BuOH (1.0 equiv)	22.5[d]	57	90	16
8	*t*-BuOH (4.0 equiv)	11.5[d]	57	94	20
9	*t*-BuOH (10 equiv)	19[e]	57	90	16

[a] 10 mol % $Pd(nbd)Cl_2$, 10 mol % (−)-sparteine, 1 equiv of Cs_2CO_3, 1 atm of O_2, 0.1 M substrate concentration in $PhCH_3$. [b] Measured by ^1H NMR. [c] Measured by chiral HPLC. [d] Conducted at 50 °C. [e] Conducted at 45 °C.

Interestingly, it was found that alcohols that are not readily oxidized (i.e., nonactivated primary and tertiary alcohols), provide a beneficial effect on reactivity as well. In particular, the addition of *t*-BuOH increased the selectivity of the reaction at little expense to the overall rate. At slightly decreased temperatures (i.e., 50 °C), a selectivity factor (*s*) of 20 was observed over 11.5 h, with resolution of alcohol **3** to 57% conversion and 94% ee.[8]

To directly compare the effect of additives on the overall rate to that of our previous conditions, we carried out a parallel analysis at 80 °C. As shown in Scheme 2, there is a clear overall rate acceleration using Cs_2CO_3 and *t*-BuOH as additives. Specifically, under these conditions resolution of alcohol **5** to 94% ee is observed after only 3 h. Unfortunately, there is also a noticeable erosion in selectivity as compared to our original conditions. Most of this selectivity diminution can be overcome by simply performing the reaction at a slightly lower temperature and at somewhat increased substrate concentration in $PhCH_3$ (see Table 3, entry 1).

Scheme 2



additives	time	conversion	ee	s
none	96 h	59.9%	98.7%	23.1
Cs_2CO_3 (1.2 equiv) *t*-BuOH (4.0 equiv)	3 h	60.0%	94.0%	14.7

Having identified a number of highly reactive catalytic systems, we began to investigate the substrate scope using

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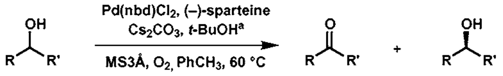
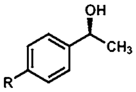
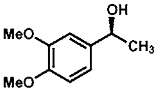
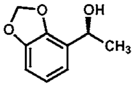
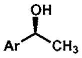
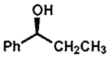
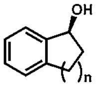
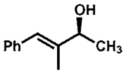
(7) Sigman observed a similar phenomenon[2] and has recently published a kinetic study of the effect; see: Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202.

(8) The selectivity factor (s) was determined using the equation $s = k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion.[5c]

Table 3. Cs_2CO_3/*t*-BuOH-Modified Oxidative Kinetic Resolution



entry	unreacted alcohol, major enantiomer	time	conversion[b]	ee ROH[c]	s
1.	 R = H	12.5 h	63.9%	99.6%	20.0
2.	R = OMe	9.5 h	67.4%	99.5%	14.9
3.	R = F	12.5 h	65.7%	97.4%	12.1
4.		18 h[d]	63.8%	98.3%	15.4
5.		15 h	56.5%	99.7%	47.4
6.	 Ar = 2-Naphthyl	12 h	66.1%	99.4%	15.8
7.		4.5 h[e]	62.8%	98.0%	16.1
8.	 n = 1	12 h[d]	74.0%	99.5%	10.1
9.	n = 2	12 h[d]	61.5%	99.0%	20.9
10.		12 h	65.1%	87.9%	7.5

[a] 5 mol % $Pd(nbd)Cl_2$, 20 mol % (−)-sparteine, 0.5 equiv of Cs_2CO_3, 1.5 equiv of *t*-BuOH, 1 atm of O_2, 0.25 M substrate concentration in $PhCH_3$. [b] Measured by GC relative to an internal standard (tridecane). The total GC yield (alcohol + ketone) was >95% in all cases. [c] Measured by chiral HPLC. [d] Conducted at 40 °C. [e] Conducted at 80 °C.

the combination of $Pd(nbd)Cl_2$, (−)-sparteine, Cs_2CO_3, and *t*-BuOH at 60 °C under an oxygen atmosphere,[9,10] with a substrate concentration of 0.25 M in $PhCH_3$ (see Table 3). As shown in Table 3, essentially all of the activated benzylic and allylic alcohols that were previously good substrates serve as excellent substrates under the new conditions. A range of electron rich and poor benzylic alcohols can be resolved to high enantiopurity by oxidative kinetic resolution in well under 24 h. A particularly striking example is the resolution of 1-phenylpropanol (entry 7). Previously, the reaction time for this resolution required 8 days to proceed to 59.3% conversion (93.1% ee) with a selectivity factor of 14.8.[1] *Using our Cs_2CO_3/t-BuOH-modified conditions, the oxidation proceeds in only 4.5 h to 62.8% conversion and 98.0% ee (s = 16.1).*

In summary, we have developed a highly reactive set of conditions for the oxidative kinetic resolution of activated secondary alcohols. Resolutions that previously required up to a week to proceed to high conversion and enantiopurity can now be achieved in less than 16 h, typically with comparable selectivity. Studies aimed at understanding the dramatic effect of the Cs_2CO_3/*t*-BuOH system, further improving the reactivity, and establishing conditions for the resolution of nonactivated alcohols are currently under investigation in our laboratory. Results toward these ends will be published in due course.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) 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.

(10) Unfortunately, reactions conducted under an atmosphere of air rather than O_2 were less effective in terms of both enantioselectivity and reactivity.