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Palladium-Catalyzed Aerobic Oxidative Kinetic Resolution of Alcohols with an Achiral Exogenous Base

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Abstract: Substitution of exogenous (−)-sparteine for a more practical achiral base in the aerobic oxidative kinetic resolution of secondary alcohols is described. Carbonate bases are the most effective of those screened and allow for effective kinetic resolution of benzylic, allylic, and aliphatic substrates. The procedure was also successfully extended to the oxidative desymmetrization of meso diols.

We have recently reported the development of Pd catalysts for the aerobic oxidative kinetic resolution of alcohols.[1−3] The most successful of these catalysts utilizes (−)-sparteine as the chiral agent. In the optimal system, 5 mol % of Pd[(−)-sparteine]Cl_2, **1**, is used along with a 20 mol % excess of (−)-sparteine in *tert*-butyl alcohol.[4] A wide range of alcohols are effectively resolved with use of these conditions. While (−)-sparteine is a relatively inexpensive chiral agent, the need for 25 mol % loading overall is impractical and certainly would become prohibitive if a less abundant chiral agent was utilized. Therefore, we sought to identify more practical conditions that limit the usage of exogenous (−)-sparteine.

Mechanistic work from our laboratory provides a framework for the elimination of exogenous sparteine.[5] In these studies, exogenous (−)-sparteine was observed to act as a Brønsted base to deprotonate Pd-bound alcohol. High concentrations of (−)-sparteine provided faster rates and higher k_{rel} values. Under these conditions, kinetic experiments are consistent with rate-limiting β-hydride elimination. Asymmetric induction is proposed to arise from a combination of two factors: a thermodynamic difference in diastereomeric alkoxides formed, and a kinetic difference in the reaction of these alkoxides (Figure 1). In this scenario, exogenous (−)-sparteine is acting purely as a Brønsted base and not directly influencing the asymmetric induction of the process.[6] Therefore, identification of an achiral base that allows for equilibration of the alkoxides and rate-limiting β-hydride elimination should give similar k_{rel} values as above and the need for exogenous (−)-sparteine should be avoided. Herein, we describe a new system for the aerobic oxidative kinetic resolution of secondary alcohols, utilizing a simple, achiral carbonate base as a replacement for exogenous (−)-sparteine.

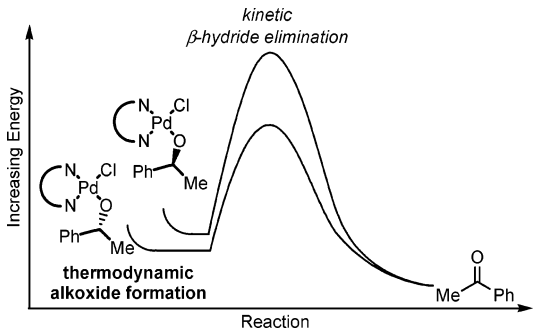

FIGURE 1. Origin of asymmetric induction.

An obvious choice of an achiral base would be a tertiary amine whose conjugate acid has a similar pK_a to protonated (−)-sparteine. However, tertiary amines have been observed to slow oxidations via competitive binding of the Pd.[7] Additionally, two other key pieces of information influenced the selection of bases: (1) chloride is an incompetent base for alcohol oxidation, and (2) acetate has been shown to be a viable base for this oxidation without any added (−)-sparteine.[8] Therefore, we choose to evaluate weakly coordinating bases in a bascity range similar to that of acetate and tertiary amines (pK_a of conjugate acids from 3 to 11 in H_2O). Screening was accomplished by using 5 mol % of isolated **1**, the base of interest, a balloon of O_2, and activated 3 Å molecular sieves in *tert*-butyl alcohol solvent for the aerobic oxidative kinetic resolution of *sec*-phenethyl alcohol (Table 1). At 20 mol % loading, a variety of bases permit aerobic oxidation, albeit with low conversions.[9] The nature of the counterion does play a role in the oxidation with bicarbonate and acetate derived bases giving lower k_{rel} values to that obtained with (−)-sparteine. In contrast, several carbonate and fluoride sources produce comparable k_{rel} values (k_{rel}: 17−25). The carbonate bases are especially interesting due to their convenience and low cost. Therefore, higher loadings of carbonate bases (50 mol %) were

(1) (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475. (b) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63.

(2) For a closely related system, see: (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725. (b) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett*, **2003**, *5*, 835.

(3) For examples of other oxidative kinetic resolutions, see: (a) Sun, W.; Wang, H.; Xia, C.; Li, J.; Zhao, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1042. (b) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 5119. (c) Nishibayashi, I.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (d) Gross, Z.; Ini, S. *Org. Lett.* **1999**, *1*, 2077. (e) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288. (f) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194.

(4) Mandal, S. K.; Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 4600.

(5) (a) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202. (b) Mueller, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 7005.

(6) At low (−)-sparteine concentrations where deprotonation is both rate determining and enantiodetermining, exogenous (−)-sparteine acts as a chiral Brønsted base. See ref 5b for details.

(7) (a) Schultz, M. J.; Park, C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *Org Lett.* **2002**, *4*, 4179.

(8) Acetate was introduced into the reaction as the counterion on Pd and the resulting kinetic resolution proved to be poor. See ref 5b for details.

(9) k_{rel} is calculated by using the following equation: $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion and ee = enantiomeric excess. See: Kagan, H. B.; Fiaud, J. C. Kinetic Resolution. *Top. Stereochem.* **1988**, *18*, 249.

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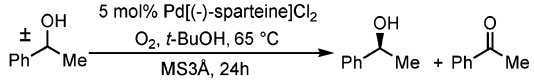
TABLE 1. Screen of Achiral Bases



entry	base	loading, mol %	% conv (% ee)[a]	k_{rel}[b]
1	(−)-sparteine	20	66.1 (94.2)	16
2	KF	20	35.0 (46.3)	21
3	CsF	20	38.3 (54.2)	25
4	Cs_2CO_3	20	38.1 (51.3)	18
5	K_2CO_3	20	26.7 (31.2)	18
6	Na_2CO_3	20	34.6 (44.0)	17
7	$CaCO_3$	20	34.3 (45.8)	24
8	$KHCO_3$	20	30.7 (38.8)	22
9	$NaHCO_3$	20	20.9 (21.7)	13
10	NH_4HCO_3	20	17.0 (15.3)	7.9
11	NaOAc	20	29.0 (31.4)	10
12	KOAc	20	17.8 (15.7)	7.3
13	AgOAc	20	<15	NA
14	K_2CO_3[c]	50	58.3 (95.3)	19
15	Na_2CO_3[c]	50	59.0 (96.6)	20
16	$CaCO_3$[c]	50	59.0 (96.0)	19
17	KF[d]	100	60.0 (97.0)	19

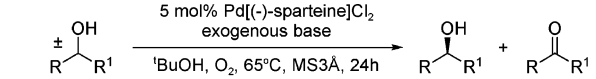
[a] Conversion determined by using the internal standard. [b] Data represent a single experiment. [c] Substrate concentration increased from 0.25 to 0.375 M. [d] 30 h.

evaluated and provided for an effective oxidative kinetic resolution (entries 14−16). While it is difficult to directly correlate the pK_a of the bases and the effectiveness of the kinetic resolution, it is interesting to note HCO_3^- has a very similar pK_a value (10.33) in H_2O to the protonated tertiary amine, Et_3N^+H (10.75).

The scope of the aerobic oxidative kinetic resolution of secondary alcohols was explored by using 50 mol % of Na_2CO_3 as exogenous base with 5 mol % of **1** (Table 2).[10] Aryl-substituted acyclic (entries 1−8 and 13−15) and cyclic (entries 9−12) alcohols are generally good substrates under the new conditions. Several aliphatic (entries 16−19) and allylic (entries 20−22) substrates are also resolved effectively. In almost all cases, the kinetic resolutions perform similarly to the previously reported (−)-sparteine system with the notable exceptions of one aromatic (entry 14) and one aliphatic (entry 16) alcohol.

To verify the feasibility of the reaction on a common laboratory scale, an oxidative kinetic resolution was performed on a 10-mmol (1.22 g) scale for *sec*-phenethyl alcohol (entry 2). Good overall mass recovery was observed for both the optically enriched alcohol (% yield, 31.4; % ee, 99.3) and the prochiral ketone byproduct (62% isolated yield, 64% conversion by GC). This larger scale reaction did require a slightly longer reaction time of 32 h, compared to 24 h for the smaller scale reaction, and showed a slight decrease in k_{rel} values (18 as compared to 20).

TABLE 2. Scope of the Aerobic Oxidative Kinetic Resolution



Entry	Alcohol R	Alcohol R^1	%conv(%ee)[a,b]	k_{rel}[b,c] Na_2CO_3	k_{rel}[b,c] (-)-sparteine[d]
1	C_6H_5	Me	59.0(96.6)	20	16
2[e]	C_6H_5	Me	64.1(99.3)	18	--
3	C_6H_5	Et	55.0(78.0)	10	--
4	4-MeC_6H_4	Me	58.9(93.0)	15	19
5	4-FC_6H_4	Me	58.5(89.0)	13	13
6	2-naphthyl	Me	67.3(99.5)	15	18
7[f]	7-MeO-2-naphthyl	Me	62.0(94.0)	12	12
8	4-$MeOC_6H_4$	Me	65.8(99.0)	15	--
9	α-tetralol		57.3(93.0)	18	22
10	1-benzosuberol		58.0(95.0)	19	18
11[f]	4-chromanol		66.9(99.4)	15	14
12[f]	1-acenaphthol		68.0(99.2)	13	13
13	4-BrC_6H_4	Me	66.0(97.8)	13	--
14	2-furyl	Me	67.0(97.0)	11	16
15	ferrocenyl	Me	69.0(99.9)	17	18
16	^{t}Bu	Me	42.3(51.2)	9.3	17
17	cyclopropyl	Me	59.1(86.0)	10	9.1
18[f]	$(Ph)_2CH$	Me	54.4(88.2)	19	20
19	*endo*-borneol		73.5(98.5)	8.6	8.3
20	1-cyclohexenyl	Me	68.1(92.3)	7.6	9.0
21	*trans*-sobrerol		73.9(99.0)	9.1	10
22[f]		Me	70.4(99.6)	13	13

[a] Conversion determined by GC, using tetradecane as the internal standard. See the Supporting Information for chiral separations. [b] Data represent a single experiment. [c] 20 mol % of (−)-sparteine or 50 mol % of Na_2CO_3. [d] Conversion and ee data correspond to the system with Na_2CO_3. See ref 4 for values with (−)-sparteine. [e] Reaction performed on a 10-mmol scale (1.22 g). [f] Conversion determined by ^{1}H NMR.

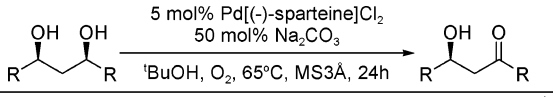
The methodology was further extended to the oxidative desymmetrization of meso 1,3-diols which yield enantiomerically enriched β-hydroxycarbonyl compounds.[11] Generally good yields (71−77%) and ee values (76−93.4%) of β-keto alcohols are obtained from various meso 1,3-diols (Table 3). These values are again very similar to that reported for the (−)-sparteine system.

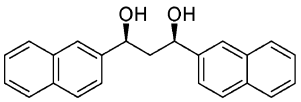
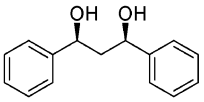
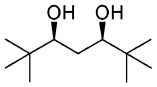
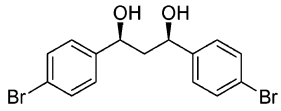
While the new system performs similarly to the previously reported system with exogenous (−)-sparteine and does provide a more practical kinetic resolution strategy, it is unclear if carbonate is solely acting as a Brønsted base in this chemistry and not modifying the catalyst. To investigate this issue, Pd[(−)-sparteine]Cl_2 was treated with 1.2 equiv of Na_2CO_3 in *tert*-butyl alcohol at 65 °C in the absence of alcohol. The excess Na_2CO_3 and the solvents were removed to yield a new complex, which was identified as Pd[(−)-sparteine](CO_3) via X-ray crystal-

(10) General procedure for the oxidative kinetic resolution of secondary alcohols and desymmetrization of meso diols: In a 5-mL round-bottom flask equipped with a sidearm and stirbar, 0.7 mL of *tert*-butyl alcohol, 5.6 mg (0.013 mmol, 0.05 equiv) of [(−)-sparteine]$PdCl_2$, 14 mg (0.13 mmol, 0.50 equiv) of Na_2CO_3, 0.25 mmol (1.0 equiv) of the alcohol or meso diol, and 25 mg of freshly activated crushed molecular sieves (3 Å) were combined. The flask was then attached to the bottom of a reflux condenser. A balloon filled with oxygen gas was then attached to the top of the condenser via a three-way joint. The apparatus was then evacuated (water aspirator) and refilled with oxygen from the balloon three times and heated in an oil bath at 65 °C. Aliquots (0.1 mL) of the reaction were then periodically taken via syringe. The aliquot was quenched with 2% TFA/methanol. The sample was analyzed with use of a GC or HPLC equipped with a chiral column.

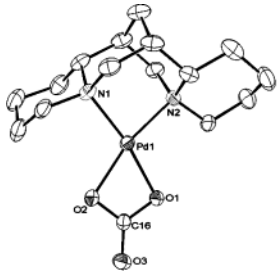
(11) For examples of nonenzymatic desymmetrization of meso diols, see: (a) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410. (b) Hodgson, R.; Majid, T.; Nelson, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, *14*, 1631. (c) Jiang, L.; Burke, S. D. *Org. Lett.* **2002**, *4*, 3411−3414. (d) Harada, T.; Sekiguchi, K.; Nakamura, T.; Suzuki, J.; Oku, A. *Org. Lett.* **2001**, *3*, 3309. (e) Harada, T.; Yamanaka, H.; Oku, A. *Synlett* **2001**, *1*, 61. (f) Yamada, S.; Katsumata, H. *J. Org. Chem.* **1999**, *64*, 9365. (g) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397. (h) Via acetal cleavage, see: Fujioka, H.; Nagatomi, Y.; Kotoku, N.; Kitagawa, H. *Tetrahedron* **2000**, *56*, 10141. (i) Kinugasa, M.; Harada, T.; Oku, A. *J. Am. Chem. Soc.* **1997**, *119*, 9067.

TABLE 3. Oxidative Desymmetrization of Meso 1,3-Diols



entry	diol	yield(%)[a]	ee(%)[a,b]
1		77	84.0
2		73	84.2
3		71	76.0
4		73	93.4

[a] Data represent a single experiment. [b] See the Supporting Information for chiral separations.



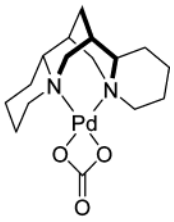


FIGURE 2. ORTEP diagram of Pd[(−)-sparteine](CO_3).

lography (Figure 2).[12] The structure clearly shows carbonate incorporated as a bidentate dianionic ligand on the square plane of palladium. To test whether the new complex is catalytically relevant, crystals of Pd[(−)-sparteine](CO_3) were submitted to the standard reaction conditions without exogenous Na_2CO_3. Very little catalysis is observed (12% conversion at 24 h). After adding exogenous Na_2CO_3 to the new complex, the oxidation was again very slow. Therefore, carbonate is presumably acting primarily as a Brønsted base and not involved in any ground state modifications to the catalyst structure. While the precise details of this new system are not defined, the mechanistic analysis outlined in the Introduction seems to provide a reasonable explanation for the observed outcome of this kinetic resolution in which an achiral Brønsted base at high concentration can effectively equilibrate diastereomeric alkoxides followed by rate-limiting β-hydride elimination.

In summary, we have disclosed a simple and effective method for the oxidative kinetic resolution of secondary alcohols using catalytic Pd[(−)-sparteine]Cl_2 and an achiral carbonate as an exogenous base. These conditions offer a more practical method for oxidative kinetic resolution by replacing a valuable chiral agent with an inexpensive achiral base. Future work will focus on identifying a new ligand for aerobic oxidative kinetic resolution with antipodal selectivity and allowing modular structural modifications for improved asymmetric catalysis.

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Supporting Information Available: Experimental procedures, characterization data, chiral chromatographic separation details, and NMR spectra and X-ray analysis of Pd[(−)-sparteine](CO_3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information for the isolation, characterization, and X-ray structural data.