CHAPTER 2

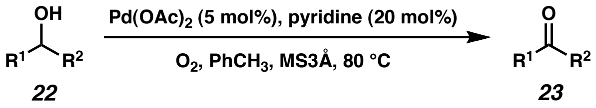
The Development of the Palladium-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols

2.1 Background and Introduction

Chiral alcohols are present in many natural products, pharmaceutical agents, and useful synthetic materials, and are highly versatile as synthetic intermediates in the construction of other functional groups. The ready availability of a wide range of racemic alcohols and the potential for recycling the product ketone by a simple reduction makes oxidative kinetic resolution a practical process for the preparation of enantioenriched alcohols. Thus, a general catalytic system for enantioselective alcohol oxidation would be of great benefit to the synthetic organic community.[1-6]

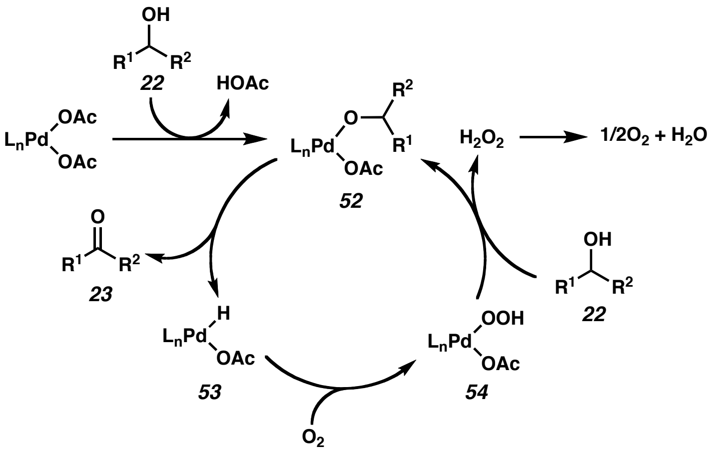
Because of its prevalence in a variety of enantioselective transformations[7] and known utility in the aerobic oxidation of alcohols, we chose to pursue palladium(II) as a catalytic metal for the oxidative kinetic resolution of secondary alcohols.[8,9] Particularly intriguing was a report by Uemura of racemic alcohol oxidation utilizing a palladium(II) catalyst and pyridine in toluene (Scheme 2.1.1).[10] Employing molecular oxygen as the sole stoichiometric oxidant, high yields of aldehydes and ketones were obtained for a variety of alcohols. These conditions were attractive for a number of reasons. Molecular oxygen, essential for cellular respiration in all aerobic organisms, is an inexpensive, abundant, and environmentally benign oxidant. The lack of additional co-oxidants reduces reaction complexity. Hydrogen peroxide, the sole byproduct of the oxidation, decomposes to water and molecular oxygen under the reaction conditions. Also, pyridine was found to be critical to the reaction as both ligand and base. Uemura reported no catalytic activity in the absence of pyridine, indicating a strong ligand acceleration effect. We anticipated that the use of chiral ligands in the place of pyridine would lead to significant enantiodiscrimination in the oxidation, while the ligand acceleration could minimize racemic background oxidation by other Pd(II) species that might be present in the reaction. Finally, the non-coordinating nature of toluene should limit solvent displacement of a chiral ligand from the palladium center.

Scheme 2.1.1 Uemura oxidation conditions.



The proposed mechanism for the oxidation involves ligand substitution by the alcohol (**22**) and deprotonation of a palladium(II) complex to generate intermediate palladium alkoxide **52** (Scheme 2.1.2). Subsequent β-hydride elimination from this complex forms the product ketone (**23**) and palladium hydride **53**, which then reacts with oxygen and another equivalent of alcohol **22** to reform **52**. Efforts by a number of researchers have further clarified this mechanism.[11-13]

Scheme 2.1.2 Uemura oxidation proposed mechanism.

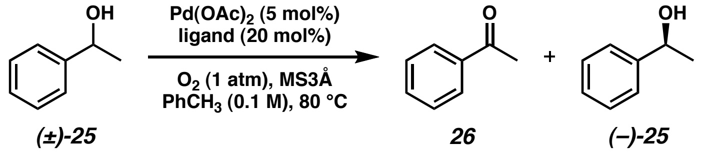


2.2 Reaction Development[†]

2.2.1 Original Conditions[14,15]

We initially focused on substituting an appropriate chiral ligand for pyridine in the oxidation. While many of the compounds evaluated as ligands led to little or no alcohol oxidation, some provided moderately reactive palladium complexes. (–)-Sparteine (**28**) rapidly emerged as a uniquely effective ligand for this transformation, providing modest levels of selectivity[16] in the oxidation of (±)-1-phenylethanol ((±)-**25**, Table 2.2.1).[17]

Table 2.2.1 Initial ligand screen for the oxidative kinetic resolution.

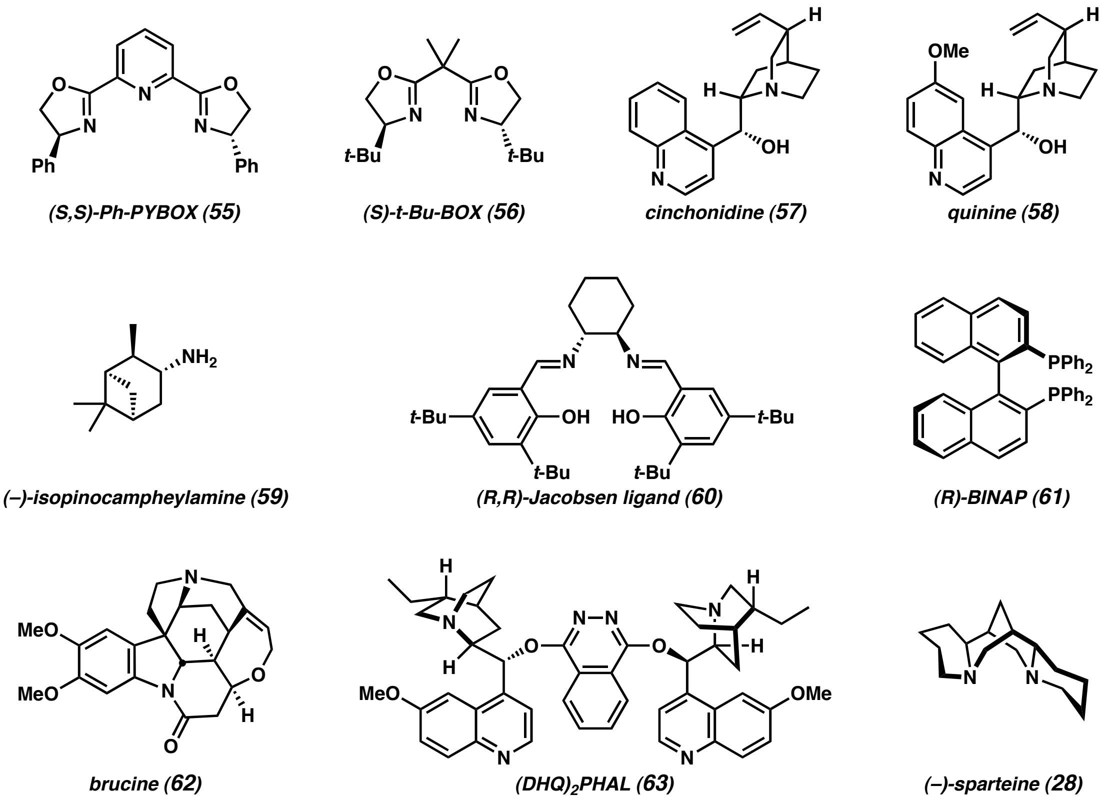


entry	ligand[a]	time	conversion[b]	alcohol ee[c]	*s*
1	(*S*,*S*)-Ph-PYBOX (***55***)	72 h	2%	–	–
2	(*S*)-*t*-Bu-BOX (***56***)	24 h	3%	–	–
3	cinchonidine (***57***)	72 h	2%	–	–
4	quinine (***58***)	24 h	0%	–	–
5	(*R*,*R*)-Jacobsen ligand (***59***)	24 h	3%	–	–
6	(–)-isopinocampheylamine (***60***)	24 h	0%	–	–
7	(*R*)-BINAP (***61***)	24 h	29.0%	0%	1.0
8	brucine (***62***)	24 h	77.0%	0%	1.0
9	(DHQ)$_2$PHAL (***63***)	24 h	31.6%	8.7%	1.6
10	(–)-sparteine (***28***)	24 h	15.1%	13.7%	8.8

[a] For structures, see Figure 2.2.1. [b] Measured by GC. [c] Measured by chiral HPLC.

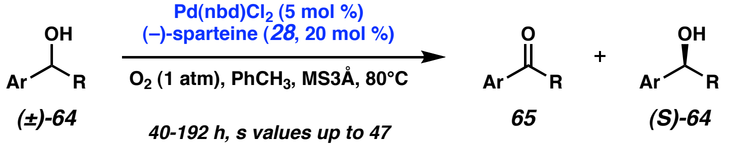
[†] This work was primarily performed by Eric M. Ferreira (Ph.D. 2005) and Jeffrey T. Bagdanoff (Ph.D. 2005), graduate students in the Stoltz group at California Institute of Technology.

Figure 2.2.1 Stuctures of ligands in Table 2.2.1.



Reexamination of the general mechanism proposed by Uemura was critical for optimization of the reaction. Notably, an acetate is coordinated to the palladium center throughout the catalytic cycle, indicating the possible importance of the Pd(II) counterion in the resolution. Investigation of a number of palladium sources permitted counterion modification, resulting in greatly improved reactivity and selectivity in the oxidation employing palladium chloride complexes. Pd(nbd)Cl_2 proved to be the most effective precatalyst, providing good selectivity in the oxidation of a number of benzylic alcohols (Scheme 2.2.1).

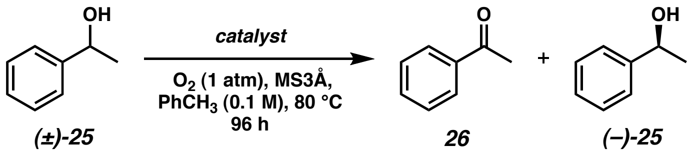
Scheme 2.2.1 Original resolution conditions.



2.2.2 Rate Acceleration with Exogenous Base and a Non-Oxidizing Alcohol[18]

Although useful in principle, a major limitation of this resolution was the sluggish reaction rates. Usually, 4 days or more were required to provide alcohols in high enantiomeric excess. The high operating temperature (80 °C) further demonstrates the low activity of the system. During the course of studies to improve the reaction rate, the discrete complex Pd(sparteine)Cl$_2$ (**66**) was prepared. The reactivity of this complex was substantially decreased relative to the complex generated in situ with a 4:1 sparteine:Pd loading (Table 2.2.2).[15a]

Table 2.2.2 Catalyst activity versus (–)-sparteine loading.



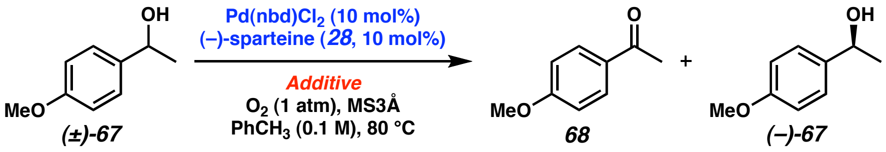
entry	catalyst	conversion[a]	alcohol ee[b]	*s*
1	Pd(nbd)Cl$_2$ (5 mol%) (–)-sparteine (***28***, 20 mol%)	59.9%	98.7%	23
2	Pd(sparteine)Cl$_2$ (***66***, 5 mol%)	4.6%	3.4%	6.0
3	Pd(sparteine)Cl$_2$ (***66***, 5 mol%) (–)-sparteine (***28***, 15 mol%)	60.6%	99.2%	24

[a] Measured by GC. [b] Measured by chiral HPLC.

Interestingly, we found that reactivity could be restored by adding 3 equivalents of (–)-sparteine (**28**) relative to complex **66**. The excess (–)-sparteine was suspected to act as a general base, neutralizing the hydrogen chloride byproduct generated during palladium alkoxide formation. Indeed, kinetic studies have confirmed the role of sparteine as base.[13a] Without this added (–)-sparteine, palladium alkoxide formation is much less favorable. Thus, it was anticipated that the addition of a stoichiometric base would promote palladium alkoxide formation, facilitating alcohol oxidation.

We initiated studies to supplant (–)-sparteine (**28**) as a base in the oxidative kinetic resolution. Early experiments centered on the addition of achiral amines (Table 2.2.3). After 13 h, triethylamine seemed promising (entry 3), but rapid catalyst deactivation led to little further conversion (entry 4). Use of additional equivalents proved more detrimental (entries 5 and 6). The more nucleophilic base DABCO was even poorer. However, carbonate bases were effective at accelerating the oxidations. Cesium carbonate was found to be optimal, leading to the greatest reactivity enhancement.[19]

Table 2.2.3 Base screening studies with amines and carbonates.

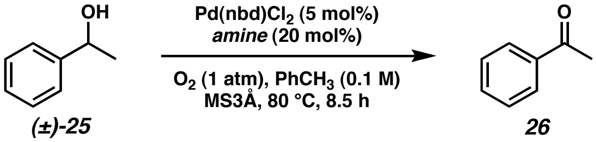


entry	additive	time	conversion[a]	alcohol ee[b]	*s*
1	(–)-sparteine (***28***, 30 mol%)	13 h	29%	34%	15
2	none	13 h	2%	<2%	–
3	Et_3N (0.4 equiv)	13 h	26%	31%	22
4	Et_3N (0.4 equiv)	26 h	29%	33%	13
5	Et_3N (2.0 equiv)	13 h	19%	19%	11
6	Et_3N (4.0 equiv)	13 h	14%	11%	6
7	DABCO (0.4 equiv)	13 h	7%	8%	20
8	Na_2CO_3 (1.0 equiv)	13 h	27%	31%	15
9	K_2CO_3 (1.0 equiv)	13 h	56%	84%	13
10	Cs_2CO_3 (1.0 equiv)	13 h	68%	99%	13

[a] Measured by ^1H NMR. [b] Measured by chiral HPLC.

The loss of reactivity with excess achiral amine bases is presumably due to competition between the amine and sparteine for coordination to the palladium center. We have demonstrated that monodentate amines do not generate catalytically active systems for alcohol oxidation with Pd(nbd)Cl_2 (Table 2.2.4).[10b] While (–)-sparteine (**28**) promotes rapid alcohol oxidation (entry 3), little oxidation occurs with either pyridine (entry 1) or quinuclidine (entry 2).

Table 2.2.4 Catalyst activity with (–)-sparteine and other amines.



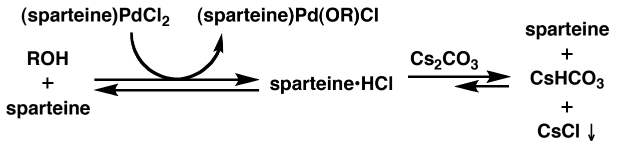
(±)-25 **26**

entry	amine	conversion[a]
1	pyridine	1.2%
2	quinuclidine	3.8%
3	(–)-sparteine (**28**)	36.6%

[a] Measured by GC. Conversion is the average of two experiments.

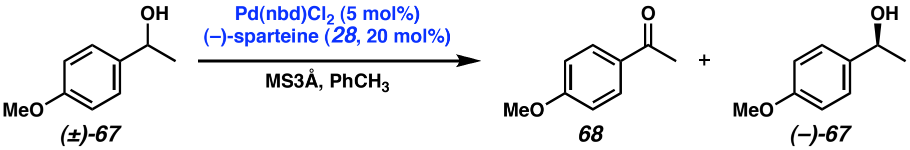
Even with added cesium carbonate, excess (–)-sparteine (**28**) relative to the palladium precursor is still beneficial. The solubility of cesium carbonate in toluene is minimal, even at elevated temperatures. Also, finely milled cesium carbonate performs much better than the granular base of lower surface area.[20] These observations suggest cesium carbonate is acting as a heterogeneous base. (–)-Sparteine (**28**), which is much more soluble in toluene, may act as a better kinetic base than the heterogeneous cesium carbonate for neutralizing hydrogen chloride generated in the formation of the palladium alkoxide (Scheme 2.2.2). While the pK_a values of sparteine•HCl[21] and cesium bicarbonate[22] are similar, the excess carbonate base could minimize sparteine•HCl concentration,[23] reducing the extent of protonation of the palladium alkoxide and accelerating the reaction.[24]

Scheme 2.2.2 Potential role of excess (–)-sparteine.



Another key development arose fortuitously from early investigations of the substrate scope. The inclusion of *tert*-butyl alcohol proved to be an excellent exogenous alcohol additive, providing more active catalytic systems for alcohol oxidation.[25] We optimized the process to maintain high selectivity across a range of secondary alcohols, while dramatically decreasing reaction times (Table 2.2.5, cf. entries 1 and 2). Furthermore, we found ambient air to be a competent replacement for molecular oxygen as the stoichiometric oxidant in these resolutions, providing a comparable reaction rate and selectivity (entry 3).

Table 2.2.5 Comparison of various conditions in toluene.

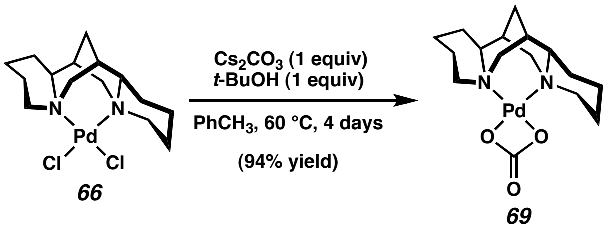


entry	conditions	time	conversion[a]	alcohol ee[b]	*s*
1	O_2 (1 atm) $PhCH_3$ (0.1 M) 80 °C	96 h	66.6%	98.1%	12
2	*O_2 (1 atm)* Cs_2CO_3 (50 mol%) *t*-BuOH (1.5 equiv) $PhCH_3$ (0.25 M), 60 °C	9.5 h	67.4%	99.5%	15
3[c]	*ambient air (1 atm)* Cs_2CO_3 (40 mol%) *t*-BuOH (1.5 equiv) $PhCH_3$ (0.25 M), 60 °C	7 h	64.0%	99.1%	17

[a] Measured by GC. [b] Measured by chiral HPLC. [c] Pd(sparteine)Cl_2 (**66**, 5 mol%) and (–)-sparteine (**28**, 15 mol%) were used.

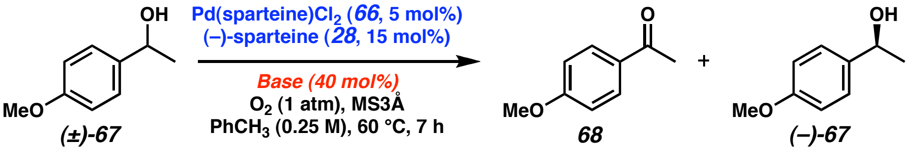
While the purpose of the carbonate base fit well with our mechanistic model for the oxidative kinetic resolution, the role of *tert*-butyl alcohol was less clear. One possibility was that the modified reaction conditions were transforming Pd(sparteine)Cl_2 into a more reactive complex. In order to test this theory, we exposed dichloride complex **66** to *tert*-butyl alcohol and cesium carbonate. After 4 days at 60 °C, carbonate **69** was isolated in 94% yield (Scheme 2.2.3). Carbonate complex **69** displayed neither catalytic nor even stoichiometric activity under kinetic resolution conditions. This finding suggests carbonate **69** is a catalyst deactivation product. While these additives provide dramatic rate enhancement, they could also detrimentally affect catalyst longevity.[26]

Scheme 2.2.3 Synthesis of palladium carbonate **69**.



An alternative explanation for the beneficial effect of *tert*-butyl alcohol involves the formation of trace amounts of CsO*t*-Bu in situ. We have examined the addition of several *tert*-butoxide salts to these resolutions (Table 2.2.6, entries 2-4). These oxidations maintain the high reactivity observed with the *tert*-butyl alcohol conditions (entry 1). However, the recovered alcohol is nearly racemic with any of these bases. Thus, it is unlikely that CsO*t*-Bu is forming in oxidative kinetic resolution conditions with *tert*-butyl alcohol and cesium carbonate.

Table 2.2.6 Evaluation of tert-butoxide additives.

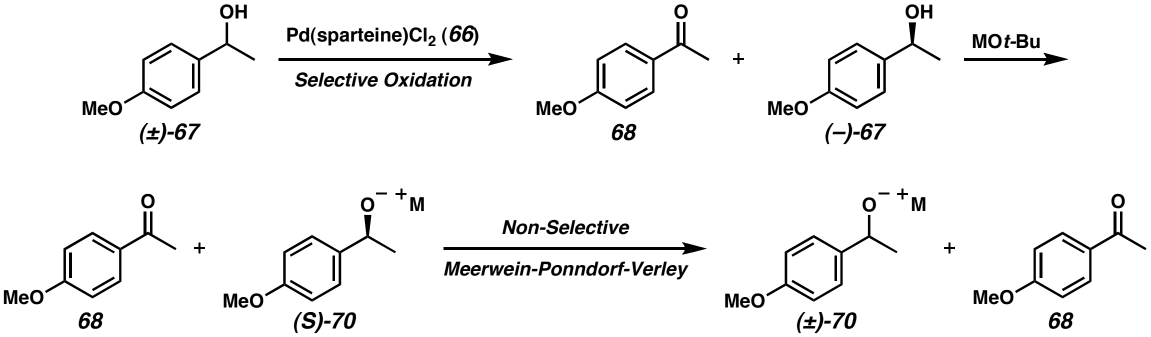


entry	base	conversion[a]	alcohol ee[b]	*s*
1	Cs_2CO_3 *t*-BuOH (1.5 equiv)	62.1%	98.6%	18
2	CsO*t*-Bu	48.1%	0.6%	1.0
3	KO*t*-Bu	61.3%	0.6%	1.0
4	NaO*t*-Bu	65.7%	2.3%	1.0

[a] Measured by GC. [b] Measured by chiral HPLC.

It is possible that these alkoxides modify the catalyst such that all selectivity is lost in the oxidation. Alternatively, a competing Meerwein-Ponndorf-Verley reduction[27] could be occurring (Scheme 2.2.4). Selective, Pd(sparteine)Cl_2-catalyzed alcohol oxidation and deprotonation of secondary alcohol (–)-**67** could provide ketone **68** and alkoxide (*S*)-**70**. Non-selective, metal-promoted Meerwein-Ponndorf-Verley reduction of the ketone could then afford product ketone **68** and racemized alkoxide (±)-**70**.

Scheme 2.2.4 Possible racemization mechanism with *tert*-butoxide.

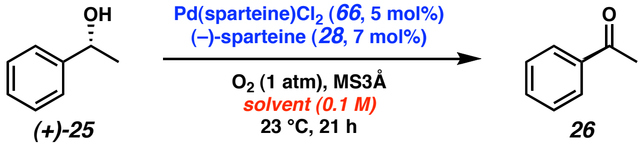


2.2.3 Chloroform as Solvent in the Resolution[28]

Having eliminated several potential roles for a non-oxidizing alcohol in the resolution, we hypothesized that the observed rate enhancement could be due to the hydrogen bonding potential of *tert*-butyl alcohol. While hydrogen bonding plays an essential and well-documented role in the catalysis of a number of biological[29] and synthetic processes,[30] less is known about its function in organometallic transformations. A hydrogen-bond donor may enhance reactivity by stabilizing and solubilizing polar or charged intermediates in the nonpolar solvent toluene. In particular, cationic palladium complexes generated as the immediate products of alcohol coordination and β-hydride elimination result in the formation of chloride anions, which could be solubilized by hydrogen-bond donors.[13b,d]

Based on this hypothesis, we performed a more rigorous solvent screen, with an emphasis on solvents capable of hydrogen-bond donation and solubilization of polar or charged intermediates (Table 2.2.7). Surprisingly, while common organic solvents led to little oxidation (entries 12, 15, 16, 19, and 20), halogenated solvents that could act as weak hydrogen-bond donors provided rapid reactions (entries 1-6). Oxidations conducted in the hydrogen-bond donating solvent dichloromethane are the fastest (entry 1), but catalyst selectivity in kinetic resolutions suffers.[31] Chloroform, on the other hand, emerges as an outstanding nonflammable solvent for rapid and selective oxidation, even at 23 °C (entry 2). Strikingly, chlorinated solvents lacking the ability to donate a hydrogen bond (entries 13, 14, 17, and 21) are less effective. Other factors do not appear to explain the observed trends. Oxygen solubility is fairly similar in many of the solvents.[32] Also, there is no clear trend between reaction rate and dielectric constant, a measure of solvent polarity.[33]

Table 2.2.7 Solvent screen with Pd(sparteine)Cl_2.

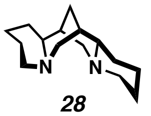
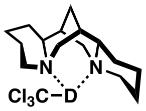
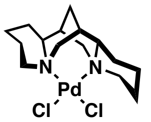
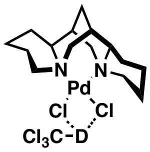
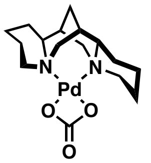


entry	solvent	dielectric constant	conversion[a]
1	CH_2Cl_2	8.9	83%
2	***$CHCl_3$***	***4.8***	***74%***
3	CH_2Br_2	7.8	73%
4	$CHCl_3$/1 equiv *t*-BuOH	4.8/12.5	72%
5	$CHBr_3$	4.4	68%
6	$ClCH_2CH_2Cl$	10.4	46%
7	$PhCH_3$/1 equiv *t*-BuOH	2.4/12.5	39%
8	$PhCH_3$/*t*-BuOH (1:1)	2.4/12.5	29%
9	$PhCH_3$	2.4	23%
10	pinacolone	12.7	21%
11	*tert*-amyl alcohol	5.8	21%
12	THF	7.5	14%
13	$Cl_2C{=}CHCl$	3.4	10%
14	Cl_3CCH_3	7.2	9%
15	EtOAc	6.1	8%
16	2-propanol	20.2	7%
17	$Cl_2C{=}CCl_2$	2.3	6%
18	H_2O/2-propanol	80.1/20.2	3%
19	CH_3CN	36.6	3%
20	CH_3NO_2	37.3	2%
21	CCl_4	2.2	2%

[a] Measured by GC.

Spectroscopic evidence for hydrogen-bond formation between chloroform and catalytic species was found in IR spectra of $CDCl_3$ solutions (Table 2.2.8).[34] A significant shift in the C–D stretching frequency of $CDCl_3$ occurred in the presence of either (–)-sparteine (**28**, entry 2) or Pd(sparteine)Cl_2 (**66**, entry 3).[35,36] The observed decrease in λ_{max} corresponds to a lower energy C–D stretching frequency due to a weaker C–D bond over free $CDCl_3$ when hydrogen-bond accepting species are present. Notably, no shift in the C–D stretch was observed with the catalytically inactive carbonate **69**, suggesting little or no hydrogen bonding occurs.

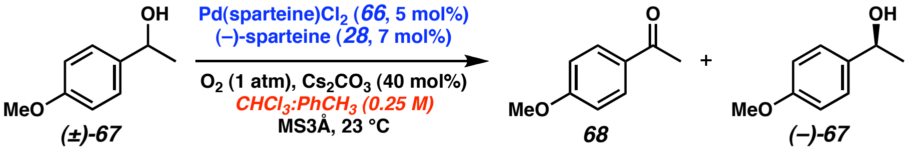
Table 2.2.8 IR data supporting hydrogen-bond donation.

entry	concentration	$CDCl_3$ solution	λ_{max} (cm^{-1})	predicted D-X bond
1	–	neat	2258	–
2	0.25 M	 **28**	2175	
3	0.25 M	 **66**	2230	
4	0.10 M^{a}	 **69**	2258	–

[a] Near saturation concentration at 23 °C.

Based on these findings of discrete interactions between chloroform and a catalytically active species, we anticipated that chloroform, like *tert*-butyl alcohol, could provide a beneficial role in the oxidative kinetic resolution as an additive. As shown in Table 2.2.9, a 1:1 ratio of chloroform and toluene (entry 2) performs as well as pure chloroform (entry 1) as solvent. There is a clear difference in rate between the stoichiometric (entry 3) and substoichiometric (entry 4) chloroform additions, indicating that the function of chloroform in these resolutions is not exclusively a bulk solvent polarity effect.

Table 2.2.9 Chloroform:toluene ratio variation.

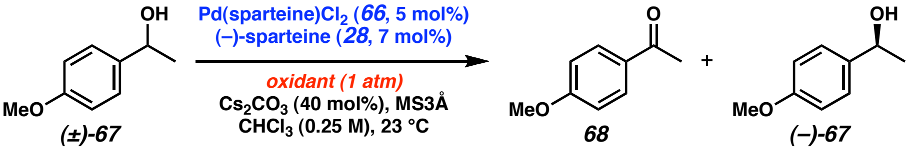


entry	$CHCl_3$:$PhCH_3$	time	conversion[a]	alcohol ee[b]	*s*
1	1:0	21 h	55.9%	92.0%	20
2	1:1	21 h	55.1%	91.0%	21
3	1:50 (1 equiv $CHCl_3$)	66 h	54.8%	91.3%	22
4	1:125 (40 mol% $CHCl_3$)	109 h	55.7%	87.5%	16

[a] Measured by GC. [b] Measured by chiral HPLC.

The change in solvent to chloroform also allows decreased amounts of (–)-sparteine (**28**) to be used with little effect on rate. Performing the reactions at 23 °C provides a dramatic increase in the catalyst selectivity (cf. Table 2.2.10, entry 1 and Table 2.2.5). Furthermore, as little as 5% O_2 atmosphere is sufficient for oxidation, enabling the use of ambient air as the terminal oxidant (entry 2). These milder conditions greatly improve the operational simplicity and safety of the oxidation, avoiding the use of flammable solvents at elevated temperatures under an oxygen atmosphere.

Table 2.2.10 Chloroform conditions with O_2 or ambient air.



entry	oxidant	time	conversion[a]	alcohol ee[b]	*s*
1	O_2	48 h	62.6%	99.9%	27
2	ambient air	24 h	62.3%	99.8%	25

[a] Measured by GC. [b] Measured by chiral HPLC.

2.3 Conclusion

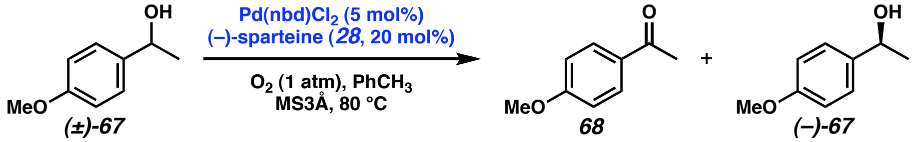
The first palladium-catalyzed enantioselective oxidation of secondary alcohols has been developed, utilizing the readily available diamine (–)-sparteine as chiral ligand and molecular oxygen as the sole stoichiometric oxidant. Mechanistic insights regarding the role of base and hydrogen bond donors have resulted in several improvements to the original system. Namely, addition of cesium carbonate and *tert*-butyl alcohol greatly enhances reaction rates, promoting accelerated resolutions. The use of chloroform as solvent allows resolutions to be conducted at 23 °C, resulting in enhanced catalyst selectivity. Finally, the use of ambient air as the terminal oxidant for reactions in either toluene or chloroform further increases the operational simplicity and safety of the process. These developments have led to a process with a broad substrate scope[37] and many practical applications, including the desymmetrization of *meso*-diols,[14] the preparation of synthetically useful molecules,[38] and the total synthesis of complex natural products.[39] Our efforts in these areas are reported in Chapters 3 and 5. Further studies in catalyst development are disclosed in Chapter 4.

2.4 Experimental Section

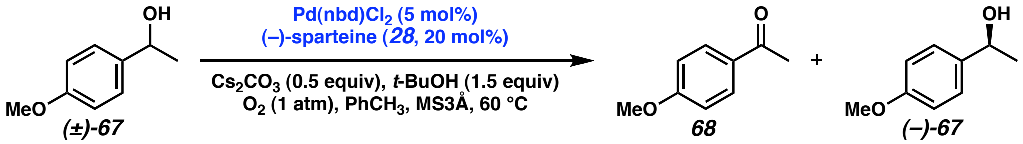
2.4.1 Materials and Methods

Pd(sparteine)Cl_2 (**66**) was prepared as previously reported.[13c] Cesium *tert*-butoxide was prepared by the method of Chisholm.[40] (+)-1-Phenylethanol ((+)-**25**) was purchased from Acros Organics. Pyridine was distilled over CaH_2. Solvents were dried by passage through an activated alumina column under argon. Powdered 3Å molecular sieves were stored in a 120 °C drying oven until immediately prior to use. Other chemicals were purchased from the Sigma-Aldrich Chemical Company and used as received. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV at 254 nm and *p*-anisaldehyde staining. Analytical achiral GC was performed on an Agilent 6850 GC with FID detector using an Agilent DB-WAX (30.0 m x 0.25 mm) column at 1.0 mL/min He carrier gas flow. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OD-H or Chiralcel OJ column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm at 1.0 mL/min mobile phase. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). The absolute configurations of resolved alcohols were assigned based on comparisons of optical rotations to literature values or by analogy.

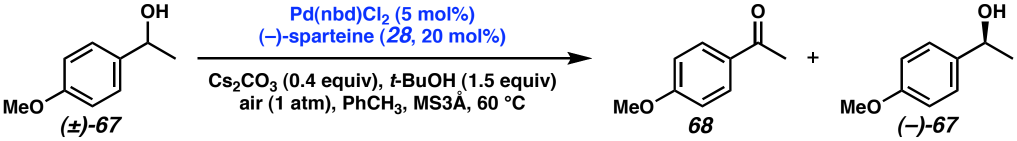
2.4.2 General Oxidative Kinetic Resolution Conditions



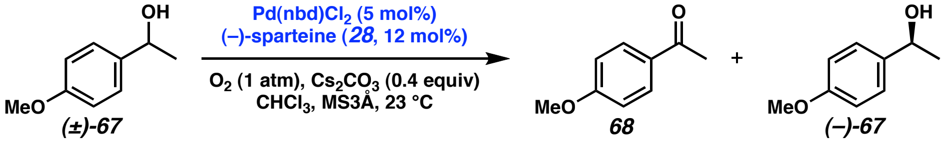
Original Resolution Conditions in PhCH$_3$ with No Achiral Base.[14] To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, Pd(nbd)Cl$_2$ (6.7 mg, 0.025 mmol, 0.05 equiv) followed by toluene (2.5 mL) and then (–)-sparteine (**28**, 23.0 μL, 0.10 mmol, 0.20 equiv) were added.[41] The reaction tube was then cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). Then, the tube was heated to 80 °C with vigorous stirring under O_2 atmosphere (1 atm, balloon) for 20 min. A solution of alcohol (±)-**67** (76.1 mg, 0.50 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in toluene (2.5 mL) was added, and the reaction was allowed to proceed under O_2 atmosphere at 80 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee.



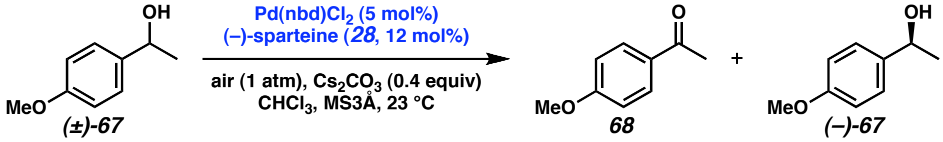
Rate Accelerated Resolution Conditions in PhCH$_3$ under O_2.[18] To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, Pd(nbd)Cl$_2$ (6.7 mg, 0.025 mmol, 0.05 equiv), followed by toluene (1 mL) and then (–)-sparteine (**28**, 23.0 μL, 0.10 mmol, 0.20 equiv) were added.[41] The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The tube was heated to 60 °C with vigorous stirring under O_2 atmosphere (1 atm, balloon) for 20 min. Finely powdered Cs_2CO_3 (81.5 mg, 0.25 mmol, 0.50 equiv) was added, followed by a solution of alcohol (±)-**67** (76.1 mg, 0.5 mmol, 1.0 equiv), anhydrous *t*-BuOH (71.5 μL, 0.75 mmol, 1.5 equiv), and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in toluene (1 mL). The reaction was allowed to proceed under O_2 atmosphere at 60 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee.



Rate Accelerated Resolution Conditions in $PhCH_3$ under Ambient Air. To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, $Pd(nbd)Cl_2$ (6.7 mg, 0.025 mmol, 0.05 equiv), followed by toluene (1 mL) and then (–)-sparteine (**28**, 23.0 μL, 0.10 mmol, 0.20 equiv) were added.[41] A short tube containing Drierite was attached to the reaction tube. The tube was heated to 60 °C with vigorous stirring under O_2 atmosphere (1 atm, balloon) for 20 min. Finely powdered Cs_2CO_3 (81.5 mg, 0.25 mmol, 0.50 equiv) was added, followed by a solution of alcohol (±)-**67** (76.1 mg, 0.5 mmol, 1.0 equiv), anhydrous *t*-BuOH (71.5 μL, 0.75 mmol, 1.5 equiv), and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in toluene (1 mL). The reaction was allowed to proceed under air atmosphere at 60 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee.



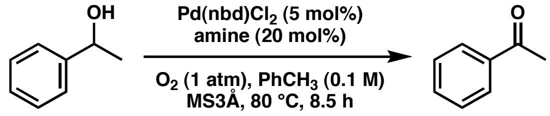
$CHCl_3$ Conditions with O_2.[28] To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, Pd(nbd)Cl_2 (6.7 mg, 0.025 mmol, 0.05 equiv), followed by $CHCl_3$ (1 mL)[42] and then (–)-sparteine (**28**, 13.8 μL, 0.06 mmol, 0.12 equiv) were added.[43] The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was allowed to warm to 23 °C and stirred vigorously under O_2 atmosphere (1 atm, balloon) for 15 min. Finely powdered Cs_2CO_3 (65.2 mg, 0.20 mmol, 0.40 equiv) was added, followed by a solution of alcohol (±)-**67** (76.1 mg, 0.5 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in $CHCl_3$ (1 mL). The reaction was allowed to proceed under O_2 atmosphere at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee.



$CHCl_3$ Conditions with Ambient Air.[28] To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, Pd(nbd)Cl_2 (6.7 mg, 0.025 mmol, 0.05 equiv), followed by $CHCl_3$ (1 mL)[42] and then (–)-sparteine (**28**, 13.8 μL, 0.06 mmol, 0.12 equiv) were added.[43] A short tube containing Drierite was attached to the reaction tube. The reaction was stirred vigorously at 23 °C for 15 min. Finely powdered Cs_2CO_3 (65.2 mg, 0.20 mmol, 0.40 equiv) was added, followed by a solution of alcohol

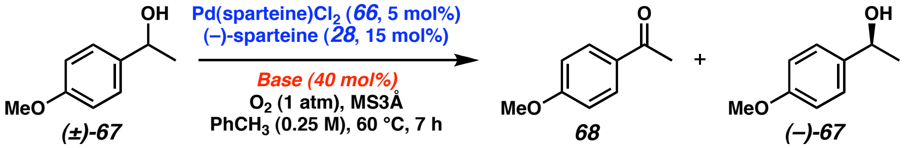
(±)-**67** (76.1 mg, 0.5 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in $CHCl_3$ (1 mL). The reaction was allowed to proceed under an ambient air atmosphere at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee.

2.4.3 Screening and Optimization Studies

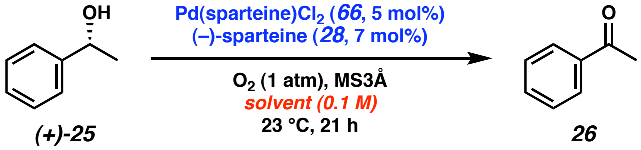


(±)-25 *26*

Amine Screening Procedure with Pd(nbd)Cl_2. To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, Pd(nbd)Cl_2 (6.7 mg, 0.025 mmol, 0.05 equiv) followed by toluene (2.5 mL) and the amine (0.10 mmol, 0.20 equiv) were added. The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The tube was heated to 80 °C with vigorous stirring under O_2 atmosphere (1 atm, balloon) for 20 min. A solution of (±)-1-phenylethanol ((±)-**25**, 60.3 μL, 0.50 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in toluene (2.5 mL) was added, and the reaction was allowed to proceed under O_2 atmosphere at 80 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion to acetophenone (**26**). Conversions given are the mean of two experiments.

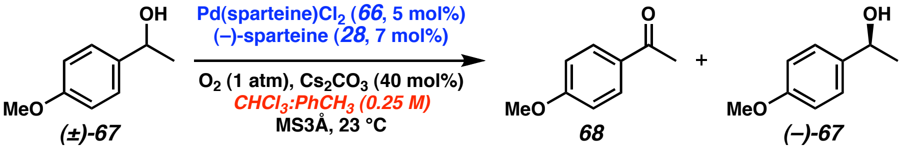


Alkoxide Base Screen in PhCH$_3$. To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, Pd(sparteine)Cl$_2$ (**66**, 10.3 mg, 0.025 mmol, 0.05 equiv), followed by toluene (1 mL) and then (–)-sparteine (**28**, 17.2 μL, 0.075 mmol, 0.15 equiv) were added. The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O$_2$ (3x). The tube was heated to 60 °C with vigorous stirring under O$_2$ atmosphere (1 atm, balloon) for 20 min. The alkoxide base (0.20 mmol, 0.40 equiv) was added, followed by a solution of (±)-**67** (76.1 mg, 0.5 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in toluene (1 mL). The reaction was allowed to proceed under O$_2$ atmosphere at 60 °C. Aliquots were filtered through a small plug of silica gel (Et$_2$O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee. Conversions and enantiomeric excesses given are the mean of two experiments.



Single Enantiomer Solvent Screens with Pd(sparteine)Cl$_2$ (66). To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After allowing the tube to cool, Pd(sparteine)Cl$_2$ (**66**, 10.3 mg, 0.025 mmol, 0.05 equiv) was added, followed by the solvent (1 mL) and then **28** (8.0 μL, 0.035 mmol, 0.07 equiv). The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O$_2$ (3x).

The reaction was allowed to warm to 23 °C and stirred vigorously under a balloon of O_2 (1 atm) for 15 min. A solution of (+)-**25** (60.4 μL, 0.50 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in the solvent (1 mL) was added. The reaction was allowed to proceed under O_2 atmosphere at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion to acetophenone (**26**).

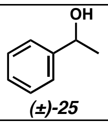
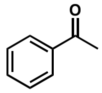
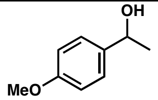
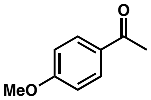


$CHCl_3$:$PhCH_3$ Ratio Screens with Pd(sparteine)Cl_2 (66). To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After allowing the tube to cool, Pd(sparteine)Cl_2 (**66**, 10.3 mg, 0.025 mmol, 0.05 equiv) was added, followed by the solvent mixture (1 mL) and then **28** (8.0 μL, 0.035 mmol, 0.07 equiv). The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was allowed to warm to 23 °C and stirred vigorously under a balloon of O_2 (1 atm) for 15 min. Finely powdered Cs_2CO_3 (65.2 mg, 0.20 mmol, 0.40 equiv) was added, followed by a solution of alcohol (±)-**67** (76.1 mg, 0.5 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in the solvent mixture (1 mL). The reaction was allowed to proceed under O_2 atmosphere at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee.

2.4.4 Methods for Determination of Conversion

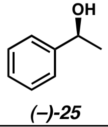
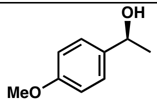
All conversions were determined by GC (Table 2.4.1) relative to internal standard (tridecane), unless otherwise noted in the text.

Table 2.4.1 Methods for determination of conversion.

entry	alcohol	ketone	GC conditions	alcohol retention time (min)	ketone retention time (min)
1	 ***(±)-25***	 ***26***	100 °C, 5 min; Ramp 13 °C/min	10.6	8.9
2	 ***(±)-67***	 ***68***	100 °C, 5 min; Ramp 13 °C/min	14.4	13.9

2.4.5 Methods for Determination of Enantiomeric Excess

Table 2.4.2 Methods for determination of enantiomeric excess.

entry	compound (major enantiomer)	ee assay and column	assay conditions	(*S*) enantiomer retention time (min)	(*R*) enantiomer retention time (min)
1	 ***(–)-25***	HPLC OJ	4% *i*PrOH/hexanes	17.8	20.8
2	 ***(–)-67***	HPLC OD-H	3% EtOH/hexanes	15.7	16.7

2.5 Notes and References

(1) For a discussion of previous methods for catalytic asymmetric alcohol oxidation, see Chapter 1.

(2) For a general discussion of nonenzymatic kinetic resolutions, including resolutions of alcohols, see: (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5-26. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974-4001.

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Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638-11643.

(4) For alcohol kinetic resolutions involving S_N2 displacement, see: (a) Chandrasekhar, S.; Kulkarni, G. *Tetrahedron: Asymmetry* **2002**, *13*, 615-619. (b) Sekar, G.; Nishiyama, H. *J. Am. Chem. Soc.* **2001**, *123*, 3603-3604.

(5) For alcohol kinetic resolutions involving allylic epoxidation, see: (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240. (b) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978-2979.

(6) For alcohol kinetic resolution involving allylic hydrogenation, see: Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708-710.

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(23) Addition of sparteine•HCl inhibits alcohol oxidation, see ref 13a.

(24) Sigman has proposed that excess chloride ion in solution may inhibit displacement of chloride by alcohol in Pd(sparteine)Cl_2. Thus, formation of insoluble CsCl may sequester excess chloride and promote alcohol coordination. For details, see ref 13f.

(25) *tert*-Butyl alcohol was found to be a competent solvent for this oxidation, see ref 15b.

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(31) Goddard has proposed that the solubilization of charged intermediates by dichloromethane may be so great as to nearly completely separate the chloride anion from the palladium complex in the β-hydride elimination transition state,

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(34) The IR spectrum of $CHCl_3$ was also investigated. However, the C-H stretch was not well resolved. $CDCl_3$ performs identically to $CHCl_3$ as reaction solvent.

(35) For a discussion of the hydrogen bonding of chloroform and its effect on IR vibrational frequencies, see: Green, R. D. *Hydrogen Bonding by C–H Groups*; John Wiley & Sons: New York, 1974.

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(41) Alternatively, 5 mol% Pd(sparteine)Cl_2 (**66**) and 15 mol% (–)-sparteine (**28**) can be used.

(42) $CHCl_3$ stabilized with amylenes. $CHCl_3$ stabilized with EtOH must be distilled prior to use.

(43) Alternatively, 5 mol% Pd(sparteine)Cl_2 (**66**) and 7 mol% (–)-sparteine (**28**) can be used.