CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200902172

The Palladium-Catalyzed Aerobic Kinetic Resolution of Secondary Alcohols: Reaction Development, Scope, and Applications

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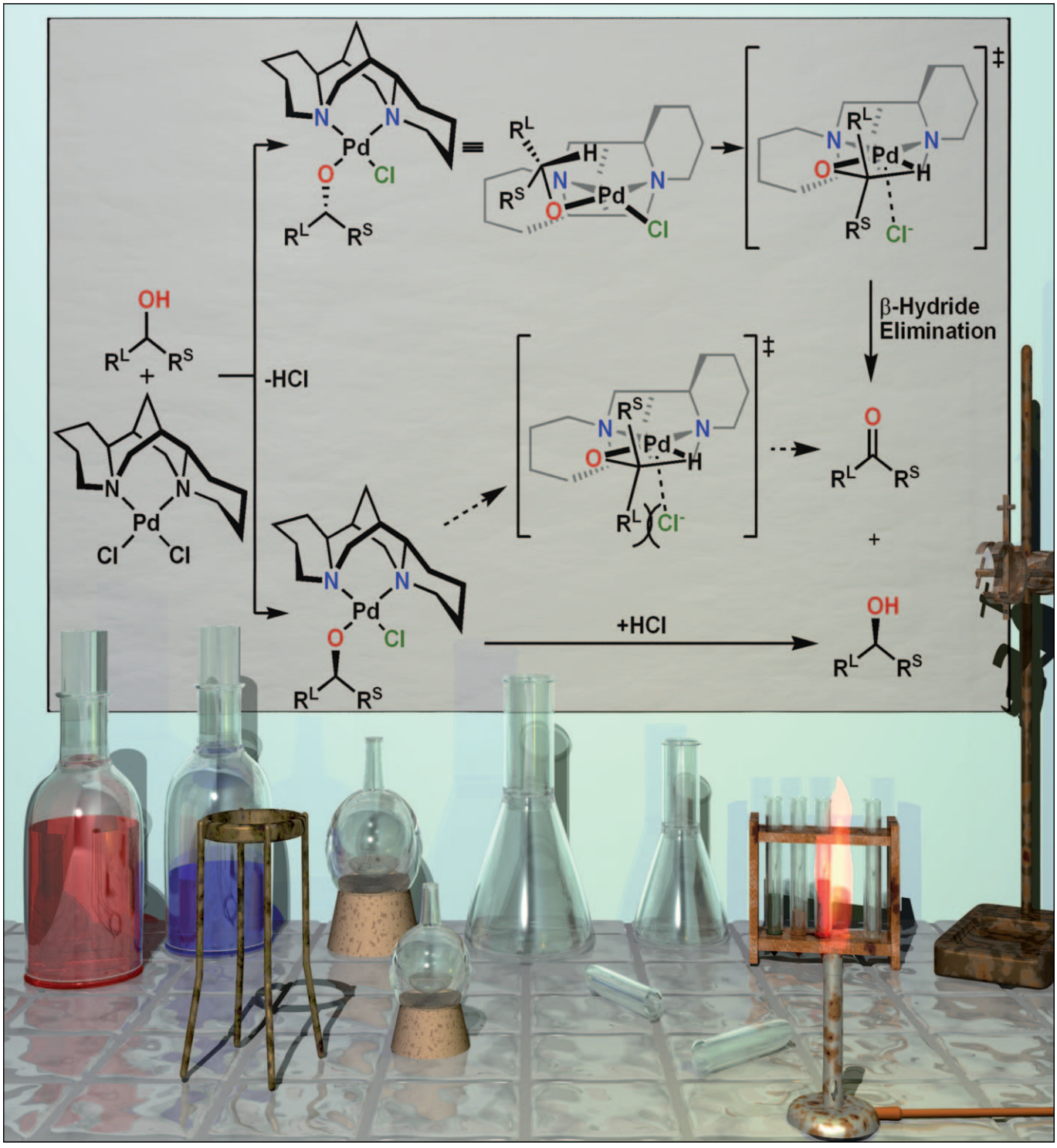


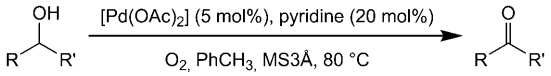
Abstract: The first palladium-catalyzed enantioselective oxidation of secondary alcohols has been developed, utilizing the readily available diamine (−)-sparteine as a chiral ligand and molecular oxygen as the stoichiometric oxidant. Mechanistic insights regarding the role of the base and hydrogen-bond donors have resulted in several improvements to the original system. Namely, addition of cesium carbonate and *tert*-butyl alcohol greatly enhances reaction rates, promoting rapid resolutions. The use of chloroform as solvent allows the use of ambient air as the terminal oxidant at 23 °C, resulting in enhanced catalyst selectivity. These improved reaction conditions have permitted the successful kinetic resolution of benzylic, allylic, and cyclopropyl secondary alcohols to high enantiomeric excess with good-to-excellent selectivity factors. This catalyst system has also been applied to the desymmetrization of *meso*-diols, providing high yields of enantioenriched hydroxyketones.

Keywords: alcohols · asymmetric catalysis · oxidation · palladium · synthetic methods

Introduction

The oxidation of alcohols to carbonyl compounds is one of the most fundamental reactions in organic chemistry.[1] Many different systems have been developed using a wide variety of oxidants.[2] Until recently, however, catalytic enantioselective variants have been largely unexplored.[3,4] The limited number of these alcohol oxidations is somewhat understandable, since this process is inherently complexity-minimizing.[5] While many enantioselective oxidative transformations involve the selective creation of stereogenicity from prochiral starting materials by transfer of a heteroatom to the organic substrate (e.g., epoxidation, dihydroxylation, sulfide oxidation),[6] enantioselective alcohol oxidation requires the selective destruction of a stereocenter in a stereoablative kinetic resolution process.[7,8] Kinetic resolutions have the ability to provide compounds of high enantiomeric excess for even modestly selective processes at higher levels of conversion. Furthermore, the ready availability of a wide range of racemic alcohols, the prevalence of chiral alcohols in organic synthesis, and the potential for product recycling by a simple reduction could make an oxidative kinetic resolution of alcohols a synthetically useful process for the production of enantioenriched materials.

As part of a general program directed toward enantioselective oxidation, we chose to pursue palladium(II) as a catalytic metal for this process. Not only is palladium catalysis prevalent in a variety of enantioselective transformations,[9] but a number of systems involving palladium have been applied to the aerobic oxidation of alcohols.[10,11] Particularly intriguing was a report by Uemura of racemic alcohol oxidation utilizing a palladium(II) catalyst and pyridine in toluene (Scheme 1).[12] Employing molecular oxygen as the sole stoichiometric oxidant, high yields of aldehydes and ketones were obtained for a variety of alcohols. These conditions



Scheme 1. Uemura's oxidation of alcohols.

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 simplified reaction complexity, producing water as the sole byproduct. Also, pyridine was found to be critical to the reaction both as 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 could lead to significant enantiodiscrimination in the oxidation, while the ligand acceleration could minimize racemic background oxidation by other palladium(II) species that could be present in the reaction. Finally, the non-coordinating nature of toluene could limit solvent displacement of a chiral ligand from the palladium center.

The proposed mechanism for the oxidation involves alcohol substitution and deprotonation of a palladium(II) complex to generate intermediate palladium alkoxide **1** (Scheme 2). Subsequent β-hydride elimination from this complex forms the product ketone and palladium hydride **2**, which then reacts with oxygen and another equivalent of alcohol to reform **1**. Efforts by a number of researchers have further clarified this mechanism.[13–15]

Based on this previous report of alcohol oxidation, we recently developed a palladium-catalyzed oxidative kinetic resolution of secondary alcohols.[16,17] Utilizing $[Pd(nbd)Cl_2]$ (nbd = norbornadiene) and the commercially available diamine (−)-sparteine, a variety of alcohols were resolved to high enantiomeric excesses, often with good corresponding catalyst selectivity. In this article, we describe in detail the development of this catalytic enantioselective oxidation,

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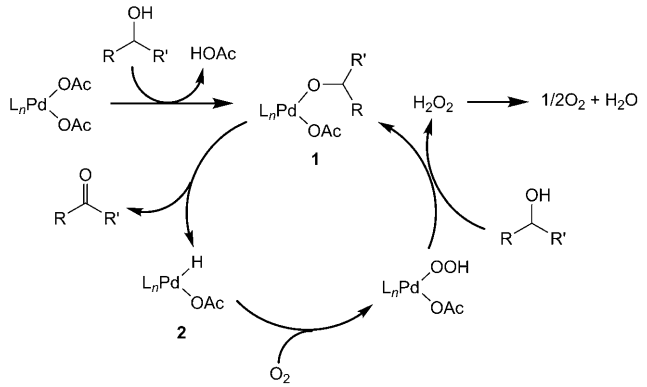
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902172.



Scheme 2. Proposed mechanism for the palladium-catalyzed alcohol oxidation.

modification of these conditions leading to dramatic improvements in reaction rate and selectivity, our extensive substrate scope investigation, and applications, including the desymmetrization of *meso*-diols.

Results and Discussion

Reaction development: Our initial exploration of the aerobic kinetic resolution of secondary alcohols with catalytic Pd focused on substituting an appropriate chiral ligand for pyridine in the oxidation.[16] While many of the compounds evaluated as ligands led to little or no alcohol oxidation, some provided moderately reactive Pd complexes (Figure 1). However, (−)-sparteine rapidly emerged as a uniquely effective ligand for this transformation, providing modest levels of selectivity[18] in the oxidation of (±)-1-phenylethanol ((±)-**3**, Table 1).[19]

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 palladium(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 3).

Although useful in principle, a major limitation of this resolution is the sluggish reaction rates. Usually, over four days are 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 our studies to improve the reaction rate, we prepared the discrete complex $[Pd(sparteine)Cl_2]$ (**5**). The reactivity of this complex was substantially decreased relative to the complex generated in situ with a 4:1 sparteine/Pd loading (Table 2).[17a] Interestingly, reactivity could be restored by adding three equivalents of sparteine relative to complex **5**.

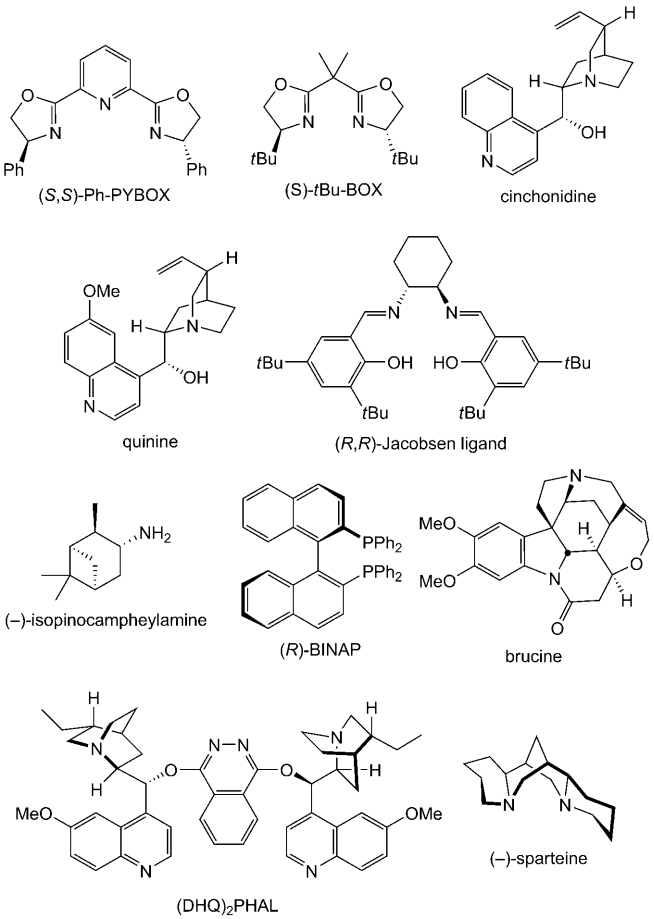
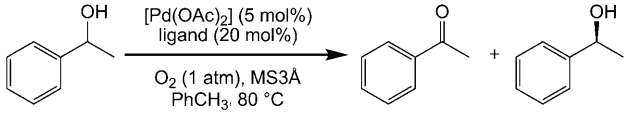


Figure 1. Ligands evaluated in Table 1.

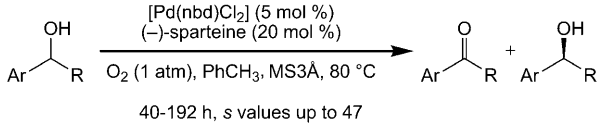
Table 1. Initial ligand screen.



	Ligand[a]	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1	(*S*,*S*)-Ph-PYBOX	72	2	–	–
2	(*S*)-*t*Bu-BOX	24	3	–	–
3	cinchonidine	72	2	–	–
4	quinine	24	0	–	–
5	(*R*,*R*)-Jacobsen ligand	24	3	–	–
6	(−)-isopinocampheylamine	24	0	–	–
7	(*R*)-BINAP	24	29.0	0	1.0
8	brucine	24	77.0	0	1.0
9	$(DHQ)_2PHAL$	24	31.6	8.7	1.6
10	(−)-sparteine	24	15.1	13.7	8.8

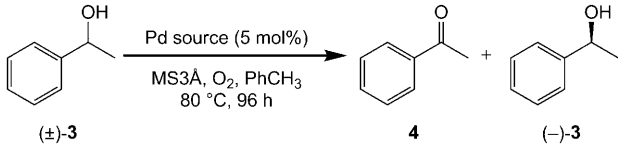
[a] See Figure 1. [b] Measured by GC. [c] Measured by chiral HPLC; see Supporting Information for details. [d] Selectivity factor.[18]

We hypothesized that the excess sparteine acts as a general base for the hydrogen chloride byproduct, generated as a result of palladium alkoxide formation. Indeed, kinetic studies have confirmed the role of sparteine as base.[15a] Without



Scheme 3. Initial conditions for the Pd-catalyzed enantioselective oxidation of alcohols.

Table 2. Effect of excess sparteine on the resolution for in situ and preformed catalysts.



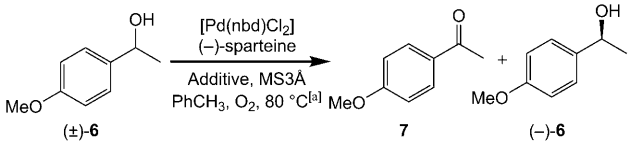
	Catalyst[a]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1	[Pd(nbd)Cl$_2$] (–)-sparteine (20 mol %)	59.9	98.7	23.1
2	[Pd(sparteine)Cl$_2$] (**5**)	4.6	3.4	6.0
3	[Pd(sparteine)Cl$_2$] (**5**) (–)-sparteine (15 mol %)	60.6	99.2	23.8

[a] 1 atm O_2, 500 mg MS3Å per mmol substrate, 0.1 M substrate in $PhCH_3$. [b] Measured by GC. [c] Measured by chiral HPLC; see Supporting Information for details. [d] Selectivity factor.[18]

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.

Early studies to supplant sparteine as a base centered on the addition of amines (Table 3).[20] Initially, triethylamine seemed promising (entry 3), but rapid catalyst deactivation

Table 3. Added base in the kinetic resolution.

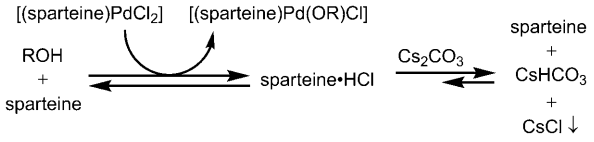


	Additive	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1	(–)-sparteine (0.3 equiv)	13	29	34	15
2	none	13	2	<2	–
3	Et_3N (0.4 equiv)	13	26	31	22
4	Et_3N (0.4 equiv)	26	29	33	13
5	Et_3N (2.0 equiv)	13	19	19	11
6	Et_3N (4.0 equiv)	13	14	11	6
7	DABCO (0.4 equiv)	13	7	8	20
8	Na_2CO_3 (1.0 equiv)	13	27	31	15
9	K_2CO_3 (1.0 equiv)	13	56	84	13
10	Cs_2CO_3 (1.0 equiv)	13	68	99	13

[a] 10 mol % [Pd(nbd)Cl$_2$], 10 mol % (–)-sparteine, 1 atm O_2, 500 mg MS3Å per mmol substrate, 0.1 M substrate in $PhCH_3$. [b] Measured by ^{1}H NMR spectroscopy. [c] Measured by chiral HPLC; see Supporting Information for details. [d] Selectivity factor.[18]

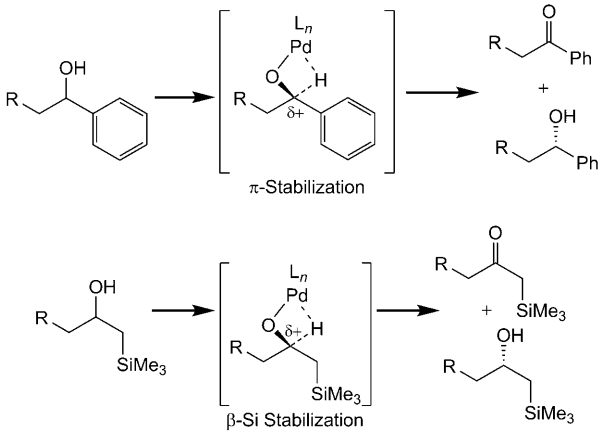
was ultimately observed. Additional equivalents proved more detrimental (entries 5 and 6). The more nucleophilic base 1,4-diazobicyclo[2.2.2]octane (DABCO) was even poorer. The loss of reactivity with these bases is presumably due to competition between the amine and sparteine for coordination to the palladium center.[21] However, carbonate bases were effective at accelerating the oxidations. Cesium carbonate was found to be optimal, leading to the greatest reactivity enhancement.[22] Surprisingly, excess sparteine relative to palladium was still required.

Several observations suggest cesium carbonate is acting as a heterogeneous base. 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.[23] Thus, sparteine, 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. While the pK_a values of sparteine·HCl[24] and cesium bicarbonate[25] are similar, the excess carbonate base could minimize sparteine·HCl concentration,[26] inhibiting protonation of the palladium alkoxide and accelerating the reaction (Scheme 4).[27]



Scheme 4. Potential role of excess sparteine and base.

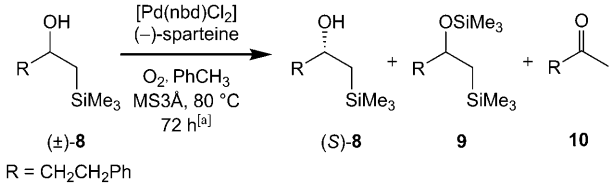
Another key development arose from our early investigations of the substrate scope. Generally, viable resolution substrates featured a π system that has the capacity to overlap with a cation at the alcohol carbon atom (Scheme 5).[15b] Because the transition state for β-hydride elimination involves some cationic character at this carbon atom, we speculated that methods of cation stabilization other than



Scheme 5. Stabilization of the β-hydride elimination transition state by resonance and a β-silicon.

adjacent aromatic rings could lower the energy barrier for alcohol oxidation, increasing reaction rate. Based on this hypothesis, β-silyl alcohol (±)-**8** was prepared and exposed to our palladium-catalyzed oxidation conditions. This alcohol could potentially benefit from β-silicon stabilization by hyperconjugation in the transition state.[28] Indeed, (±)-**8** proved to be a moderately active substrate for oxidative kinetic resolution, providing partially resolved alcohol in 16% *ee* (Table 4, entry 1). However, a problematic side reaction complicated analysis of this resolution. The partially enantioenriched alcohol underwent silyl transfer from the α-silyl ketone to provide oxidation-resistant silyl ether **9** and desilylated ketone **10**. To suppress formation of side product **9**, a primary alcohol was added to the reaction. This unactivated alcohol would not be readily oxidized under our resolution conditions, but could act as a sacrificial alcohol to react with the silyl ketone. As seen in entries 2–4, increasing amounts of *n*-butanol led to decreased formation of silyl ether **9**. Fortuitously, reaction rates also increased with up to 2.1 equivalents of *n*-butanol. Rate enhancement was not limited to the oxidation of silyl alcohol (±)-**8**, as increased rates were also observed in the resolution of other activated alcohols.

Table 4. *n*-Butanol as additive in the kinetic resolution.



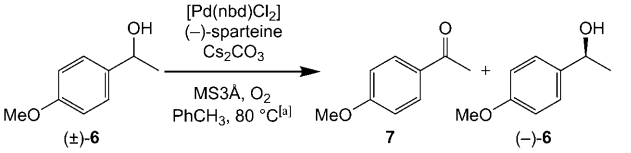
	*n*BuOH equiv	(*S*)-**8** [%][b] (*ee* [%])[c]	**9** [%][b]	**10** [%][b]
1	0.0	75 (16)	15	10
2	0.7	60 (34)	10	30
3	2.1	35 (81)	5	60
4	4.2	45 (61)	<5	50

[a] 5 mol% [Pd(nbd)Cl_2], 20 mol% (−)-sparteine, 1 atm O_2, 500 mg MS3Å per mmol substrate, 0.25 M substrate in $PhCH_3$. [b] Measured by ^{1}H NMR spectroscopy. [c] Measured by chiral HPLC; see Supporting Information for details.

Having observed a significant dependence on the rate of oxidative kinetic resolution with the inclusion of *n*-butanol, a variety of alcohol additives were evaluated for their ability to enhance the reaction rate when coupled with cesium carbonate in the resolution of alcohol (±)-**6** (Table 5). Addition of one equivalent of either *n*-butanol or trifluoroethanol led to enhanced reactivity (entries 2 and 5). Increasing equivalents led to decreased selectivity (entries 3 and 6). Large excess of either alcohol impeded the reaction (entries 4 and 7). This trend of initial rate acceleration followed by rate inhibition and selectivity erosion at high concentrations was observed across a wide variety of primary alcohol additives.

Interestingly, inclusion of *tert*-butyl alcohol proved to be an excellent exogenous alcohol additive, providing the highest and most reliable levels of selectivity across a wide range of concentrations (entries 8–10).[29] After optimizing exogenous base and *tert*-butyl alcohol equivalents, the dramatic effect of these additives on the resolution of (±)-1-phenyl-1-propanol ((±)-**11**) was realized (Table 6). This resolution provided highly enantioenriched (−)-**11** in only 4.5 h instead of 192 h without cesium carbonate and *tert*-butyl alcohol. Importantly, selectivity is maintained in these dramatically rate accelerated conditions. Further selectivity improvements could be obtained by decreasing the temperature to 60 °C.[30]

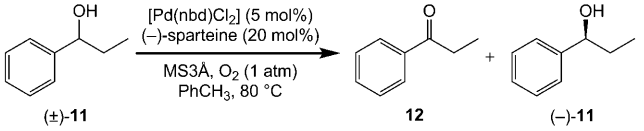
Table 5. Various non-oxidizing alcohols as additives.



	Additive	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[f]
1	none	5.5	31	35	12
2	*n*BuOH (1.0 equiv)	5.5	66	98	12
3	*n*BuOH (2.0 equiv)	5.5	67	95	10
4	*n*BuOH (8.0 equiv)	19	48	56	7
5	CF_3CH_2OH (1.0 equiv)	5.5	60	89	11
6	CF_3CH_2OH (2.0 equiv)	5.5	42	48	8
7	CF_3CH_2OH (8.0 equiv)	19	19	16	6
8[d]	*t*BuOH (1.0 equiv)	22.5	57	90	16
9[d]	*t*BuOH (4.0 equiv)	11.5	57	94	20
10[e]	*t*BuOH (8.0 equiv)	19	57	90	16

[a] 10 mol% [Pd(nbd)Cl_2], 10 mol% (−)-sparteine, 10 mol% Cs_2CO_3, 1 atm O_2, 500 mg MS3Å per mmol substrate, 0.1 M substrate in $PhCH_3$. [b] Measured by ^{1}H NMR spectroscopy. [c] Measured by chiral HPLC; see Supporting Information for details. [d] Conducted at 50 °C. [e] Conducted at 45 °C. [f] Selectivity factor.[18]

Table 6. Direct comparison of original and rate accelerated oxidative kinetic resolution conditions.

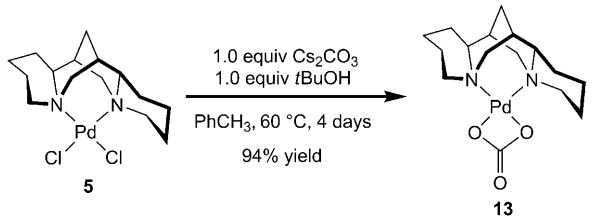


Additives	*t* [h]	Conv [%][a]	Alcohol *ee* [%][b]	*s*[c]
none	192	59	93	15
Cs_2CO_3 (1.2 equiv) *t*BuOH (4.0 equiv)	4.5	63	98	16

[a] Measured by ^{1}H NMR spectroscopy. [b] Measured by chiral HPLC; see Supporting Information for details. [c] Selectivity factor.[18]

While the purpose of the carbonate base fit well with our mechanistic model for the oxidative kinetic resolution, the role of *tert*-butyl alcohol remained more subtle. One possibility was that the modified reaction conditions were transforming [Pd(sparteine)Cl_2] into a more reactive complex.[31] To verify this theory, **5** was exposed to one equivalent each

of *tert*-butyl alcohol and cesium carbonate. After four days at 60 °C, carbonate **13** was isolated in nearly quantitative yield (Scheme 6). Surprisingly, **13** displayed neither catalytic nor even stoichiometric activity under kinetic resolution conditions. This finding suggests carbonate **13** is a catalyst deactivation product. While these additives provide dramatic rate enhancement, they could also detrimentally affect catalyst longevity.[32]



Scheme 6. Formation of inactive Pd complex **13**.

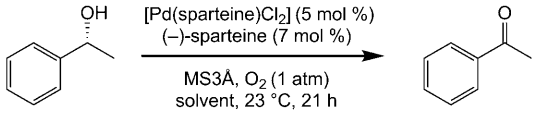
Alternatively, the observed rate enhancement could be due to the hydrogen bonding potential of *tert*-butyl alcohol. While hydrogen bonding plays an essential and well-documented role in the catalysis of a number of biological[33] and synthetic processes,[34] less is known about its role in organometallic 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.[15b,d]

Based on this hypothesis, a more rigorous solvent screen was performed with an emphasis on solvents capable of hydrogen-bond donation and solubilization of polar or charged intermediates (Table 7).[35] Surprisingly, while common polar 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. Oxidations conducted in the hydrogen-bond-donating solvent CH_2Cl_2 were the fastest (entry 1), but catalyst selectivity in kinetic resolutions suffered.[36] Chloroform, on the other hand, emerged 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) were less effective. Some other factors do not appear to explain the observed trends. Oxygen solubility is fairly similar in many of the solvents.[37] Also, there is no clear trend between reaction rate and dielectric constant, a measure of solvent polarity.[38]

Spectroscopic evidence for hydrogen-bond formation between chloroform and catalytic species is found in IR spectra of $CDCl_3$ (Table 8).[39] A significant shift in the C–D stretching frequency of $CDCl_3$ occurred in the presence of either (−)-sparteine (entry 2) or [Pd(sparteine)Cl_2] (**5**) (entry 3).[40,41] 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 **13**, suggesting little or no hydrogen bonding occurs.

The change in solvent allows decreased amounts of (−)-sparteine and cesium carbonate to be used with little effect on rate. Performing the reactions at 23 °C also provides a

Table 7. Impact of solvent on reaction rate.

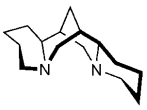
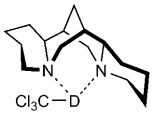
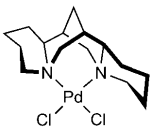
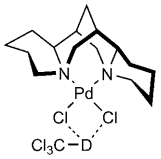
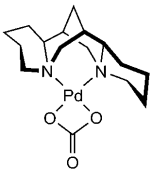


(+)-**3** **4**

	Solvent	Dielectric constant	Conv [%][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	37.3	3
20	CH_3NO_2	37.3	2
21	CCl_4	2.2	2

[a] Measured by GC relative to internal standard (tridecane); see Supporting Information for details.

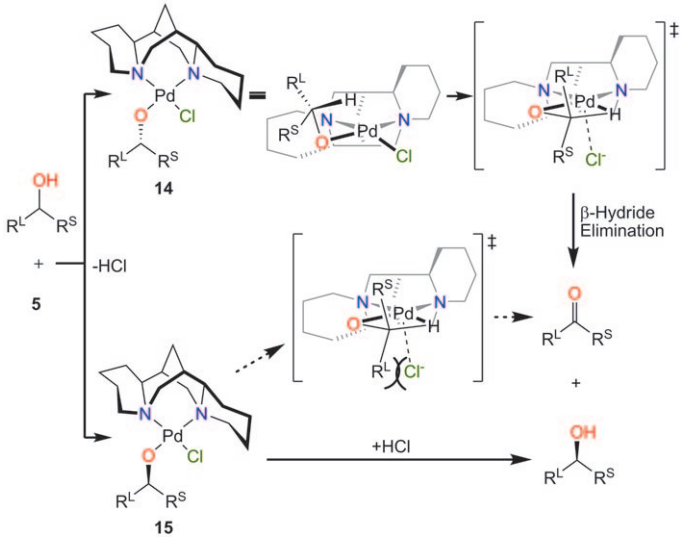
Table 8. C–D stretch of $CDCl_3$ in the presence of potential hydrogen-bond acceptors.

	Concentration [M]	Hydrogen bond acceptor	$\tilde{\nu}_{max}$ [cm^{-1}]	Predicted D–X bond
1	–	none	2258	–
2	0.25		2175	
3	0.25		2230	
4	0.10[a]		2258	–

[a] Near saturation concentration at 23 °C.

dramatic increase in the catalyst selectivity. Furthermore, as little as 5% O_2 atmosphere is sufficient for oxidation, permitting the use of ambient air as the terminal oxidant. These developments greatly improve the safety of the oxidative kinetic resolution, avoiding the use of flammable solvents at elevated temperatures under an oxygen atmosphere.[42]

Concurrent with studies centered on the development of improved conditions for oxidation, efforts were undertaken to understand the mechanism of the reaction. We were especially interested in elucidating the steric and electronic influences of the sparteine ligand on the outcome of the kinetic resolution. To this end, a number of palladium complexes with sparteine were prepared.[15c,i] Subsequent X-ray analysis of these crystalline complexes, coupled with theoretical calculations,[15d] allowed us to develop a model for selectivity in the oxidation (Scheme 7). Coordination of alcohol to com-

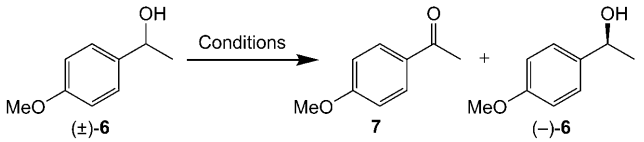


Scheme 7. Model for kinetic resolution selectivity.

plex **5** leads to one of two diastereomeric alkoxides, **14** or **15**. Alkoxide **14**, formed from the fast reacting enantiomer of alcohol, proceeds through a four-membered β-hydride elimination transition state to afford product ketone. Complex **15**, on the other hand, has a higher energy barrier to β-hydride elimination due to developing unfavorable steric interactions with the departing chloride counterion. Confronted with this high-energy transition state, protonation regenerates the observed enantiomer of alcohol.

As a result of our exploration of the oxidative kinetic resolution of secondary alcohols, four distinct sets of conditions have been developed (Table 9): the original conditions (A) in toluene with no exogenous base, the rate-enhanced conditions (B) that take advantage of cesium carbonate and *tert*-butyl alcohol additives, and the chloroform conditions at 23 °C under an atmosphere of either molecular oxygen (C) or ambient air (D). In general, resolutions performed without added carbonate base have slower rates but greater catalyst longevity. The rate-enhanced (B) conditions are the fastest, often achieving highly enantioenriched alcohol in a small fraction of the time required for the original (A) conditions. Reactions performed in chloroform at 23 °C (C and D) are the most selective, nearly doubling the selectivity factor (*s*) for the resolution of some alcohols. Typically, both molecular oxygen and ambient air can be used in oxidations in chloroform with similar rates and selectivities. The development of four distinct sets of conditions provides the opportunity to resolve the widest range of alcohol substrates in order to maximize the selectivity of the process, while maintaining reactivity and minimizing side reactions. The benefit of this flexibility is evident in the broad scope of this system.

Table 9. Variety of conditions for the resolution of secondary alcohols.



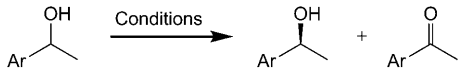
	Conditions	*t* [h]	Conv [%][a]	Alcohol *ee* [%][b]	*s*[c]
A	[Pd(nbd)Cl_2] (5 mol%), (−)-sparteine (20 mol%), O_2, $PhCH_3$ (0.1 M), MS3Å, 80 °C	96	67	96	12
B	[Pd(nbd)Cl_2] (5 mol%), (−)-sparteine (20 mol%), O_2, Cs_2CO_3 (1.2 equiv) *t*BuOH (4.0 equiv), $PhCH_3$ (0.25 M), MS3Å, 60 °C	9.5	67	99	15
C	[Pd(nbd)Cl_2] (5 mol%), (−)-sparteine (12 mol%), O_2, Cs_2CO_3 (0.4 equiv), $CHCl_3$ (0.25 M), MS3Å, 23 °C	48	63	99	27
D	[Pd(nbd)Cl_2] (5 mol%), (−)-sparteine (12 mol%), air, Cs_2CO_3 (0.4 equiv), $CHCl_3$ (0.25 M), MS3Å, 23 °C	24	62	99	25

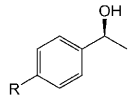
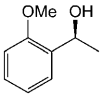
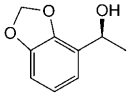
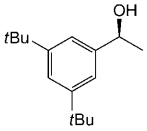
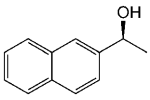
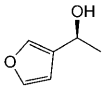
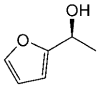
[a] Measured by GC relative to internal standard (tridecane). [b] Measured by chiral HPLC; see Supporting Information for details. [c] Selectivity factor.[18]

Substrate scope:[43] Our early studies focused on benzylic alcohols, as the racemates are commercially available or easily prepared. The resolution is quite general for this class of substrates, providing a wide range of 1-arylethanols in excellent enantiomeric excess (Table 10). Substitution on the aryl ring at the 3- and 4-positions (entries 1–8 and 12–14) is well tolerated. Substitution at the *ortho*-position leads to much slower rates of oxidation (entry 9), although reactivity improves if the substituent is constrained in a ring (entries 10 and 11). Some heteroaromatic substrates (entries 18 and 19) can also be resolved to high enantiomeric excesses.

Other structural variations are also tolerated by the catalyst system (Table 11). Cyclic benzylic alcohols are able to be resolved successfully. 1-Indanol (entries 1 and 2) is oxidized rapidly, albeit with decreased selectivity, compared to

Table 10. Resolution of 1-arylethanols.



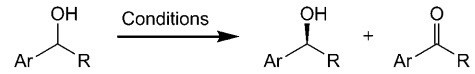
	Alcohol major enantiomer	Cond[a]	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1[e]		B	12.5	64	99	20
2[e]		C	48	60	99	31
3[f]		B	9.5	67	99	15
4[f]		C	45	63	99	27
5[f]		D	24	62	99	25
6[g]		A	54	63	97	14
7[g]		C	48	59	98	23
8[g]		D	24	57	93	20
9		C	164	60	89	12
10		B	15	57	99	47
11		C[h]	12	55	95	29
12		A	28	52	93	44
13		C	24	54	98	47
14		D	22	54	98	54
15		A	112	55	99	47
16		C	48	60	99	31
17		D	24	56	98	37
18		A	120	67	94	8.3
19		A	120	67	94	8.8

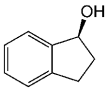
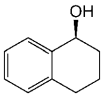
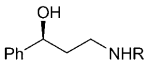
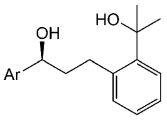
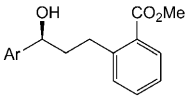
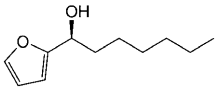
[a] Conditions A: [Pd(nbd)Cl_2] (5 mol%), (−)-sparteine (20 mol%), O_2 (1 atm), MS3Å (500 mg per mmol substrate), $PhCH_3$ (0.1 M substrate), 80 °C; Conditions B: [Pd(nbd)Cl_2] (5 mol%), (−)-sparteine (20 mol%), O_2 (1 atm), Cs_2CO_3 (0.5 equiv), *t*BuOH (1.5 equiv), MS3Å (500 mg per mmol substrate), $PhCH_3$ (0.25 M substrate), 60 °C; Conditions C: [Pd(nbd)Cl_2] (5 mol%), (−)-sparteine (12 mol%), O_2 (1 atm), Cs_2CO_3 (0.4 equiv), MS3Å (500 mg per mmol substrate), $CHCl_3$ (0.25 M substrate), 23 °C; Conditions D: [Pd(nbd)Cl_2] (5 mol%), (−)-sparteine (12 mol%), Cs_2CO_3 (0.4 equiv), MS3Å (500 mg per $mmol^{-1}$ substrate), $CHCl_3$ (0.25 M substrate), 23 °C, open to ambient air under a short tube of Drierite. [b] Conversion measured by GC or NMR spectroscopy. [c] Measured by chiral HPLC or chiral GC; see Supporting Information for details. [d] Selectivity factor.[18] [e] R = H. [f] R = OMe. [g] R = F. [h] Conducted at 40 °C.

1-tetralol (entries 3–5). Other functional groups on the alcohol substrate, including protected amines (entries 9 and 10), a tertiary alcohol (entry 11), and even aryl bromides (entries 11 and 12), are tolerated under the reaction conditions.[44]

The broad utility of chiral allylic alcohols in organic synthesis led us to investigate this important class of molecules

Table 11. Resolution of other benzylic alcohols.



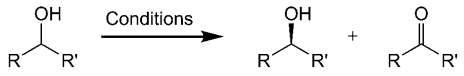
	Alcohol major enantiomer	Cond[a]	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1		B[e]	12	74	99	10
2		C	23	70	98	10
3		B[e]	12	62	99	21
4		C	24	58	98	28
5		D	16	60	99	28
6		B[f]	4.5	63	98	16
7		C	72	63	98	24
8		D	48	57	95	22
9[g]		A	14.5	70	97	9.0
10[h]		A	24	58	93	18
11[i]		B	4.5	71	99	15
12[i]		B	4.5	63	93	11
13		C	122	55	75	9.0

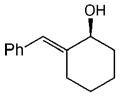
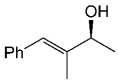
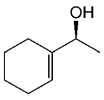
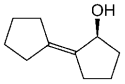
[a–d] See footnotes [a–d] in Table 10. [e] Conducted at 40 °C. [f] Conducted at 80 °C. [g] R = Ac. [h] R = Boc. [i] Ar = 3-bromophenyl.

next. Conditions in chloroform are particularly effective for these substrates, providing enhanced selectivity over the other methods (Table 12, cf. entries 11 and 12). While acyclic allylic alcohols are challenging, often leading to oxidation with low selectivity, many cyclic allylic alcohols are resolved successfully. Of particular note are vinyl bromides (entries 1, 2, and 5), which rapidly decompose with darkening of the reaction mixture at elevated temperatures, indicating the formation of aggregated palladium(0). While 2-bromocyclopent-2-enol (entry 5) oxidizes fast enough to allow moderate resolution at 60 °C with cesium carbonate and *tert*-butyl alcohol, 2-bromocyclohex-2-enol (entries 1 and 2) is cleanly resolved with no decomposition only at lower temperatures. Alkyl enol ethers are stable in the reactions and are resolved to high enantiomeric excess (entries 4, 7, and 8), providing access to enantioenriched α-hydroxyketone derivatives. The catalyst is also tolerant of a variety of alkene substitution patterns. Cyclopentenols are usually oxidized more quickly, though less selectively, than cyclohexenols (cf. entries 4 and 7).

Our success with benzylic alcohols led us to explore aryl substituents on cyclic allylic alcohols. These substrates are readily prepared through Suzuki coupling of arylboronate

Table 12. Resolution of allylic alcohols.



	Alcohol major enantiomer	Cond[a]	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1[e]		C	33	64	96	12
2[e]		D	25	55	86	16
3[f]		C	31	51	74	13
4[g]		C	74	52	86	23
5[e]		B	4	75	97	7.0
6[f]		B	7	66	93	9.2
7[g]		C	45	65	99	15
8[g]		D	24	61	97	17
9		C	27	61	96	16
10		D	24	63	98	17
11		B	12	65	88	7.5
12		C	48	63	99	18
13		D	44	65	99	16
14		C	43	64	97	13
15		D	43	61	91	12
16		C	75	57	94	19

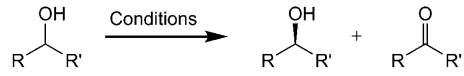
[a–d] See footnotes [a–d] in Table 10. [e] R = Br. [f] R = *i*Pr. [g] R = O*i*Bu.

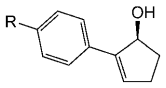
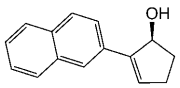
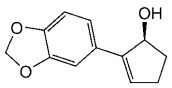
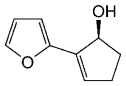
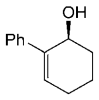
esters and iodoenones[45] followed by ketone reduction.[46] To our delight, subjection of these alcohols to any of our developed kinetic resolution conditions affords highly enantioenriched allylic alcohols with short reaction times (Table 13).[47] Both electron-rich (entries 7–9) and electron-poor (entries 13–15) 2-aryl substituents lead to excellent selectivity. The lack of an electronic influence on these resolutions suggests selectivity is primarily due to steric factors, as elucidated by our selectivity model (Scheme 7). Even heteroaromatic substitution (entries 22–24) and a larger ring size (entries 25–27) are tolerated, albeit with somewhat longer reaction times.

Substitution at the 3-position of cyclic allylic alcohols was also explored (Table 14). Again, allylic alcohols with 2-aryl substituents are oxidized rapidly, and with exceptionally high selectivity (entries 1–6). These resolutions have some of the highest selectivities seen with this catalyst system. 3-Substituted alcohols with 2-alkyl substituents are resolved to high enantiomeric excess as well (entries 7–13). Interestingly, analogous 2-alkyl allylic alcohols unsubstituted at the 3-position oxidize with poor selectivity.[48]

Other forms of activation of the racemic alcohols were also explored, such as α-cyclopropyl substituents. Several substrates were exposed to our oxidative kinetic resolution conditions (Table 15). Again, the chloroform conditions are

Table 13. Resolution of 2-aryl allylic alcohols.



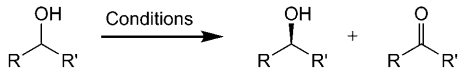
	Alcohol major enantiomer	Cond[a]	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1[e]		A	7	57	99	35
2[e]		B	1.5	53	99	89
3[e]		D	10	56	99	47
4[f]		B	3.5	58	99	31
5[f]		C	11	58	99	28
6[f]		D	10	56	99	39
7[g]		A	31	58	99	30
8[g]		B	1.5	54	97	46
9[g]		C	24	55	92	23
10[h]		A	10	57	99	33
11[h]		B	3.5	60	99	24
12[h]		C	11	58	99	30
13[i]		A	10	59	99	26
14[i]		C	10	57	94	21
15[i]		D	10	59	99	26
16		A	10	59	99	28
17		B	1.5	53	94	36
18		D	10	56	99	45
19		A	24	54	99	59
20		C	10	59	99	25
21		D	6	57	97	27
22		B	10	64	99	19
23		C	72	57	96	23
24		D	42.5	57	98	27
25		A	17	52	99	122
26		B	3	57	97	27
27		C	24	55	97	33

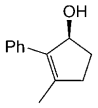
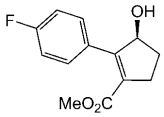
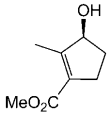
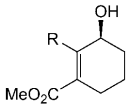
[a–d] See footnotes [a–d] in Table 10. [e] R = H. [f] R = Me. [g] R = OMe. [h] R = F. [i] R = CF_3.

especially effective in providing highly selective oxidation (cf. entries 1 and 2, entries 4 and 6). Even 1-cyclopropylethanol (entries 1–3), with relatively little steric differentiation between alcohol substituents, is able to be resolved to high enantiomeric excess. These resolutions also produce alcohols with three contiguous stereocenters (entries 4–11), including a quaternary stereocenter (entries 7 and 8). Furthermore, for entries 4–11, the product ketones are also enantioenriched (Figure 2). Importantly, these molecules have the opposite configuration at C(3) and C(4) relative to the resolved alcohol, opening the door to enantiodivergent opportunities in synthesis.

Though a broad range of secondary alcohols is successfully resolved with this system, limitations to the methodology exist. A number of alcohols display limited rates of oxidation, preventing their resolution (Figure 3). Benzylic alcohols with *ortho*-substituents (e.g. (±)-**18** and (±)-**19**) and sterically hindered alcohols such as (±)-**20** and (±)-**21** have dramatically decreased oxidation rates. The presence of vicinal heteroatoms (e.g. (±)-**22** and (±)-**23**) impedes the oxi-

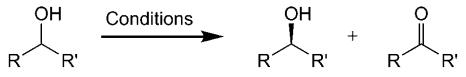
Table 14. Resolution of 3-substituted cyclic allylic alcohols.

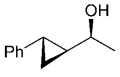
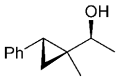
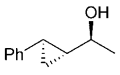


	Alcohol major enantiomer	Cond[a]	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1		A	4	53	99	83
2		B	1	53	98	63
3		D	6	55	94	26
4		A	4	56	99	50
5		B	1	56	99	51
6		C	9	51	95	83
7		A	8	73	98	8.6
8		B	1	61	85	9.0
9		C	10	78	99	7.5
10[e]		B	8	65	99	15
11[e]		C	27	58	94	19
12[e]		D	43	64	97	13
13[f]		C	72	61	91	11

[a–d] See footnotes [a–d] in Table 10. [e] R = Me. [f] R = Bn.

Table 15. Resolution of cyclopropylcarbinyl alcohols.



	Alcohol major enantiomer	Cond[a]	*t* [h]	Conv [%][b]	Alcohol *ee* [%][c]	*s*[d]
1		B	22	76	96	6.1
2		C	72	67	99	13
3		D	68	66	96	10
4		A	23	69	99	12
5		B	3	59	91	14
6		C	25	59	99	28
7		C	71	60	99	25
8		D	38	57	89	15
9		A	17	66	99	15
10		B	9	71	99	10
11		C	24	51	76	15

[a–d] See footnotes [a–d] in Table 10.

dation, presumably through catalyst coordination and deactivation.[49] Finally, unactivated alcohols (e.g. (±)-**24** and (±)-**25**), particularly primary alcohols, are slow to oxidize under any of our developed conditions.[50]

In addition to unreactive alcohols, certain classes of alcohols are resolved with poor selectivity (Figure 4). In some cases, the steric difference between the two alcohol substituents seems too small for the catalyst to adequately distinguish between enantiomers (e.g. (±)-**26**, (±)-**27**, and (±)-**28**). Substrates with electron-poor aromatic substituents are much less selectively resolved than their electron-rich counterparts (cf. (±)-**29** and (±)-**30** with Table 10 entries 4 and 12, respectively). At least in the case of benzylic alcohols, steric effects alone do not fully account for these selectivity differences. Saturated alcohols, such as (±)-**31** also tend to display lower selectivity factors in the resolution.

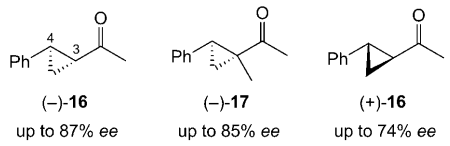


Figure 2. Enantioenriched ketones obtained from the kinetic resolution.

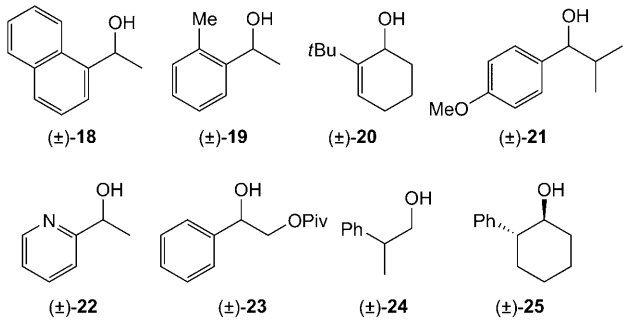


Figure 3. Examples of alcohols displaying poor reactivity.

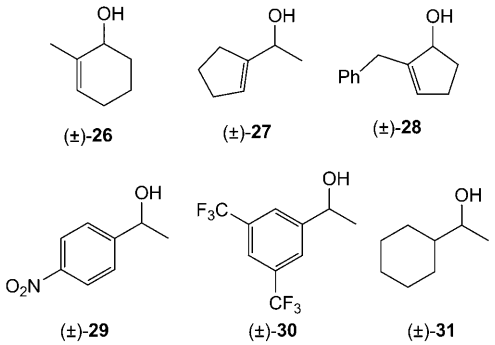
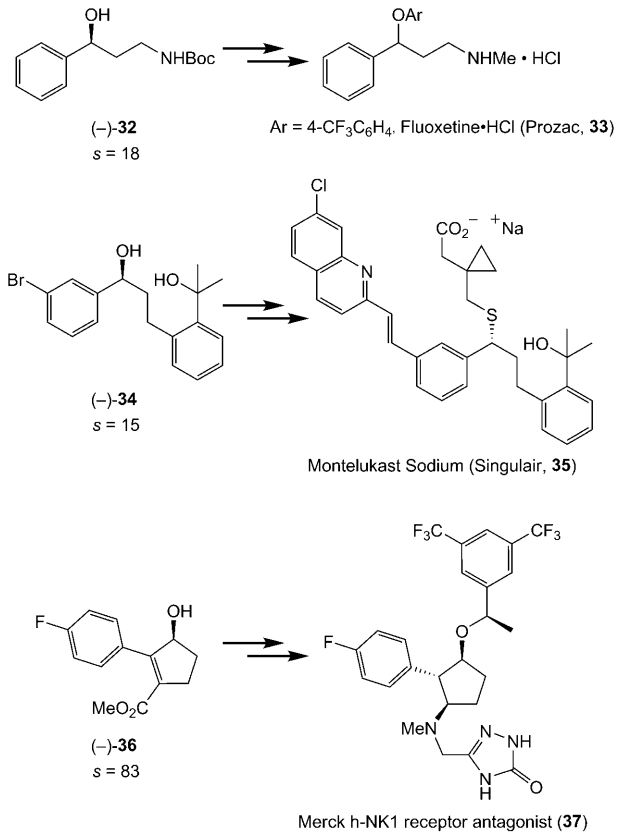


Figure 4. Examples of alcohols oxidized with poor selectivity.

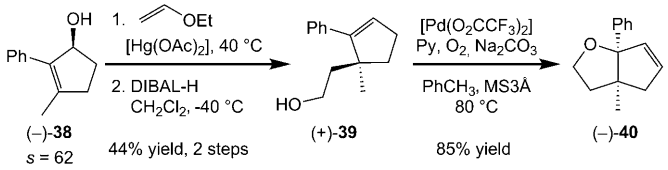
Applications: The wide use of alcohols in synthesis provides numerous applications for our kinetic resolution.[51] A number of alcohols successfully resolved are intermediates in the synthesis of a variety of pharmaceuticals (Scheme 8).[44,52] Boc-protected γ-aminoalcohol (−)-**32**, resolved with good selectivity, is an intermediate in the synthesis of a number of related antidepressants, including fluoxetine·HCl (**33**). Tertiary alcohol (−)-**34** and a related ester were transformed to a known intermediate in the synthesis of the leukotriene receptor antagonist montelukast sodium (**35**). Finally, allylic alcohol (−)-**36** is an intermediate



Scheme 8. Secondary alcohols as drug intermediates.

in the enantioselective synthesis of human neurokinin-1 (hNK-1) receptor antagonist **37**.

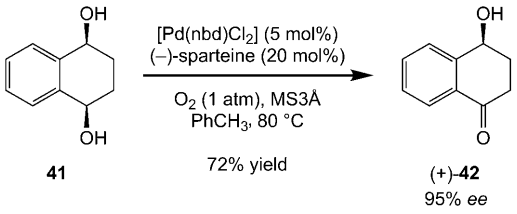
To further highlight the utility of the method, we have explored the Claisen rearrangement of resolved cyclic allylic alcohols such as (−)-**38** (Scheme 9).[47] Vinyl ether formation



Scheme 9. Conversion of a resolved alcohol to a functionalized tetrahydrofuran.

and treatment with DIBAL-H at low temperature induces Claisen rearrangement and subsequent reduction to form primary alcohol (+)-**39**. Importantly, because our kinetic resolution is able to produce alcohol (−)-**38** in high enantiomeric excess, the product alcohol is also highly enantioenriched. Furthermore, this alcohol can undergo a second palladium-catalyzed oxidative process developed in our laboratories[53] to form highly enantioenriched tetrahydrofuran (−)-**40** containing vicinal, fully substituted stereocenters.

In addition to kinetic resolution, our catalyst system is well suited for selective oxidation of *meso*-diols to hydroxyketones.[17a,c,d] These reactions have the potential to provide highly enantioenriched products in greater than 50% yield. One example of this process was demonstrated with our initially developed resolution conditions (Scheme 10).[16] Selective oxidation of diol **41** provides ketoalcohol (+)-**42** in 72% yield and 95% *ee*.



Scheme 10. Desymmetrization of diol **41**.

Further efforts in the area of *meso*-diol desymmetrization were inspired by the abundance of complex polyol- and polyether-containing natural products, such as polymethoxydienes **43a–e** (Figure 5).[54] We envisioned access to these molecules in enantioenriched form by late stage desymmetrization of a *meso*-diol stereochemical framework. This polyether array could be prepared through diastereoselective bi-

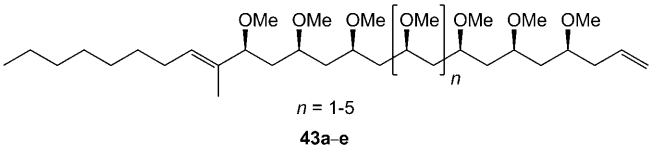
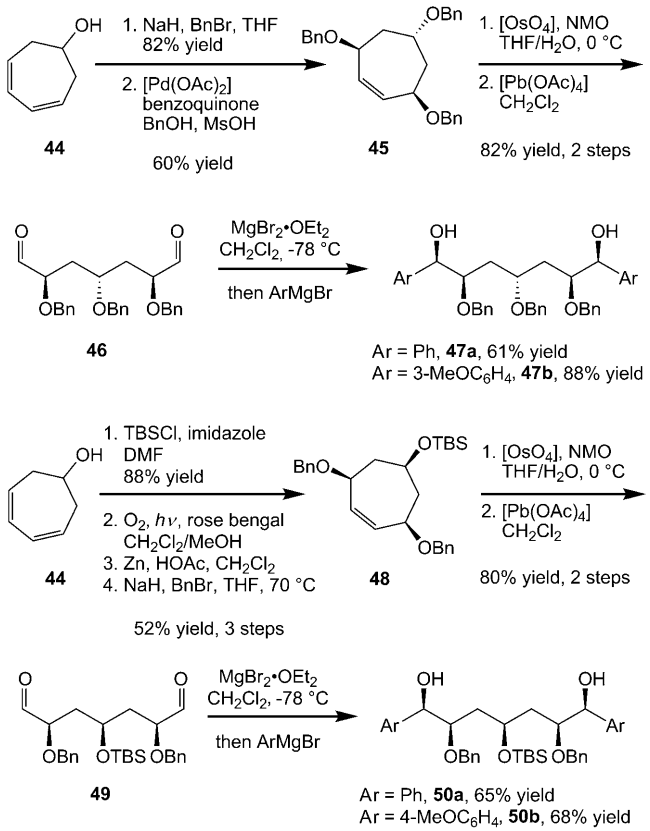


Figure 5. Polyether natural products potentially accessible by *meso*-diol desymmetrization.

directional chain synthesis from a simple symmetric precursor.[55,56]

To demonstrate the utility of our palladium-catalyzed oxidation system in this area, we developed a unified synthetic approach to several *meso*-diol stereochemical arrays. Synthesis of these *meso*-diols commenced from readily available alcohol **44** (Scheme 11).[57] Alcohol protection as a benzyl ether and palladium-catalyzed diene oxidation provides *anti*-tris-benzyl ether **45**.[58] Alkene dihydroxylation and oxidative cleavage with $[Pb(OAc)_4]$ affords *meso*-dialdehyde **46**. No epimerization of the sensitive α-benzyloxy stereocenter is observed with this two-step procedure. Diastereoselective chelation-controlled addition of aryl Grignard reagents produces *meso*-diols **47a** and **47b**. The *syn*-ether array was generated by a similar sequence. Again starting from alcohol **44**, TBS ether formation followed by [4+2] cycloaddition with singlet oxygen, reductive opening, and benzylation of the resulting diol affords *syn*-bis-benzylether **48**.[59] Alkene



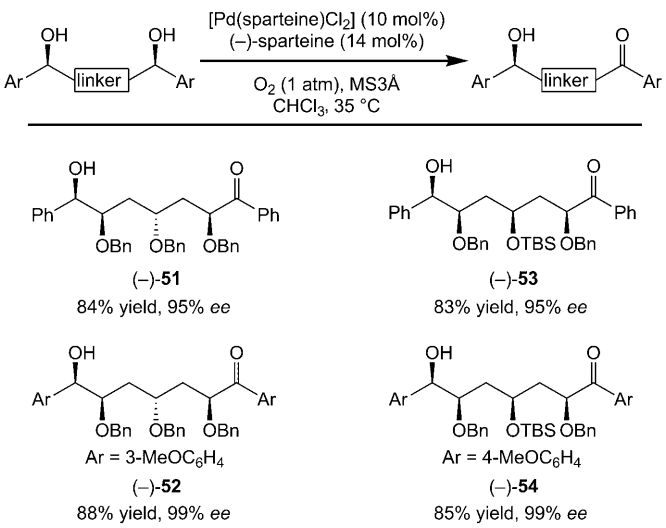
Scheme 11. Preparation of *meso*-diols from a common starting material.

cleavage and diastereoselective addition of aryl nucleophiles produces diols **50a** and **50b**.

Having generated the desired *meso*-diol substrates, we looked to apply our enantioselective oxidation conditions. Exposure of the *meso*-diols to catalytic quantities of [Pd(sparteine)Cl_2] (**5**) and excess (−)-sparteine under a balloon of oxygen in chloroform provides highly enantioenriched hydroxyketones in excellent yields (Scheme 12). These reactions establish the absolute configuration of four stereocenters in a single catalytic asymmetric operation. Based on these methods, we have begun to construct even more complex polyether structural motifs toward the synthesis of a variety of natural product frameworks.

Conclusions

Enantioselective oxidation with palladium(II) catalysts is a powerful method for the preparation of enantioenriched secondary alcohols. Research in this area has led to dramatic improvements in reaction rate, selectivity, and operational simplicity. The development of a number of distinct methods has allowed the kinetic resolution of a wide range of substrates. Benzylic, allylic, and α-cyclopropyl alcohols can be resolved to high enantiomeric excesses, in many cases with excellent selectivity. A variety of applications, including the desymmetrization of *meso*-diols, have demonstrated the utility of this oxidation in synthesis. Ongoing efforts to enhance reactivity, to use other chiral ligands in place of sparteine,[60] and to apply this kinetic resolution to natural product synthesis will be reported in due course.



Scheme 12. Oxidative desymmetrization of *meso*-diols.

Experimental Section

General oxidative kinetic resolution conditions

Kinetic resolution conditions A: Molecular sieves (3 Å, 250 mg) were added to an oven dried reaction tube with stir bar. After cooling, [Pd(nbd)Cl_2] (6.7 mg, 0.025 mmol, 0.05 equiv) followed by toluene (2.5 mL) and then (−)-sparteine (23.0 μL, 23.4 mg, 0.10 mmol, 0.20 equiv) were added. The reaction tube was then cooled to −78 °C, then vacuum evacuated and purged with O_2 (3×). Then, the tube was heated to 80 °C with vigorous stirring under O_2 atmosphere (1 atm, balloon) for 20 min. A solution of (±)-**6** (70.5 μL, 76.1 mg, 0.50 mmol, 1.0 equiv) and tridecane (36.6 μL, 27.7 mg, 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*. Purification of 4-methoxyacetophenone (**7**) and (−)-**6** was accomplished by direct chromatography of the crude reaction mixture.

Kinetic resolution conditions B: Molecular sieves (3 Å, 500 mg) were added to an oven dried reaction tube with stir bar. After cooling, [Pd(nbd)Cl_2] (13.5 mg, 0.050 mmol, 0.05 equiv), followed by toluene (2 mL) and then (−)-sparteine (46.0 μL, 46.9 mg, 0.20 mmol, 0.20 equiv) were added. The reaction tube was cooled to −78 °C, then vacuum evacuated and purged with O_2 (3×). 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 (163 mg, 0.50 mmol, 0.50 equiv) was added, followed by a solution of (±)-**6** (141 μL, 152 mg, 1.0 mmol, 1.0 equiv), anhydrous *t*BuOH (143 μL, 111 mg, 1.5 mmol, 1.5 equiv), and tridecane (73.2 μL, 55.3 mg, 0.30 mmol, 0.30 equiv) in toluene (2 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*. Purification of **7** and (−)-**6** was accomplished by direct chromatography of the crude reaction mixture.

Kinetic resolution conditions C: Molecular sieves (3 Å, 500 mg) were added to an oven dried reaction tube with stir bar. After cooling, [Pd(nbd)Cl_2] (13.5 mg, 0.050 mmol, 0.05 equiv), followed by chloroform

(2 mL, ACS reagent grade, stabilized with amylenes) and then (−)-sparteine (27.6 μL, 28.1 mg, 0.12 mmol, 0.12 equiv) were added. The reaction tube was cooled to −78 °C, then vacuum evacuated and purged with O_2 (3×). 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 (130 mg, 0.40 mmol, 0.40 equiv) was added, followed by a solution of (±)-**6** (141 μL, 152 mg, 1.0 mmol, 1.0 equiv) and tridecane (73.2 μL, 55.3 mg, 0.30 mmol, 0.30 equiv) in chloroform (2 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*. Purification of **7** and (−)-**6** was accomplished by direct chromatography of the crude reaction mixture.

Kinetic resolution conditions D: Molecular sieves (3 Å, 500 mg) were added to an oven dried reaction tube with stir bar. After cooling, [Pd(nbd)Cl_2] (13.5 mg, 0.050 mmol, 0.05 equiv), followed by chloroform (2 mL, ACS reagent grade, stabilized with amylenes) and then (−)-sparteine (27.6 μL, 28.1 mg, 0.12 mmol, 0.12 equiv) were added. 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 (130 mg, 0.40 mmol, 0.40 equiv) was added, followed by a solution of (±)-**6** (141 μL, 152 mg, 1.0 mmol, 1.0 equiv) and tridecane (73.2 μL, 55.3 mg, 0.30 mmol, 0.30 equiv) in chloroform (2 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*. Purification of **7** and (−)-**6** was accomplished by direct chromatography of the crude reaction mixture.

Acknowledgements

The authors are grateful to the NDSEG (predoctoral fellowship to D.C.E.), the NSF (predoctoral fellowships to D.C.E. and E.M.F.), the University of California TRDRP (predoctoral fellowship to J.T.B.), Bristol-Myers Squibb Company (predoctoral fellowship to E.M.F.), the American Chemical Society Division of Organic Chemistry and Bristol-Myers Squibb Foundation (predoctoral fellowship to R.M.T.), Eli Lilly (predoctoral fellowships to D.D.C. and R.M.M.), the NIH-NIGMS (R01 GM65961-01), King Abdullah University of Science and Technology (KAUST, Award No. KUS-I1-006–02), California Institute of Technology, A. P. Sloan Foundation, the Dreyfus Foundation, Research Corporation, Abbott, Amgen, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Johnson and Johnson, Eli Lilly, Merck, Novartis, Pfizer, and Roche for generous funding.

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Received: August 5, 2009
Published online: November 10, 2009

