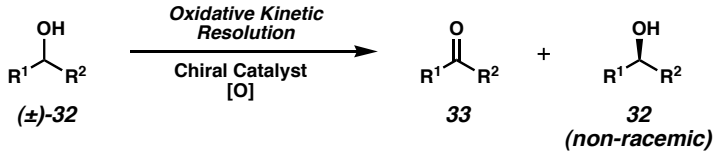
CHAPTER TWO

The Palladium-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols with Molecular Oxygen

2.1 Introduction

The oxidation of an alcohol to a carbonyl compound is one of the most ubiquitous reactions in organic chemistry.[1] Despite its prevalence, the enantioselective variant has been considerably less explored compared to other asymmetric oxidation processes (e.g., epoxidation, dihydroxylation, etc.). This relative neglect is somewhat understandable considering the nonintuitive nature of the problem—enantioselective alcohol oxidation involves the selective destruction of a stereocenter, in contrast to most asymmetric transformations, which involve the creation of stereogenicity. With the hope of developing a system that could be applicable to a broad range of dehydrogenative reactions, we first investigated the oxidative kinetic resolution of secondary alcohols using palladium(II) catalysis (Scheme 2.1.1).[2,3]

Scheme 2.1.1



2.2 Background

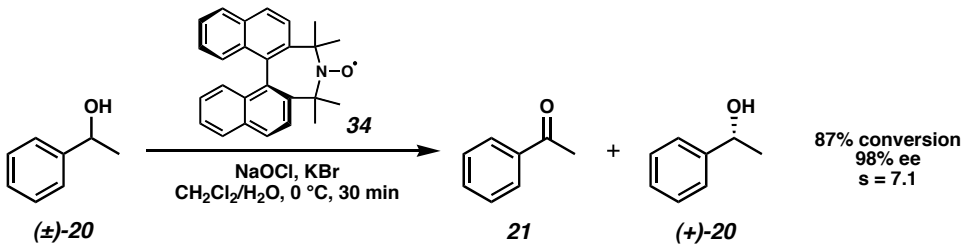
There have been numerous reports of nonenzymatic catalytic approaches to the kinetic resolution of secondary alcohols that do not involve alcohol oxidation.[4,5] The most extensively studied strategy toward kinetic resolution is via selective acylation,

pioneered by the works of Vedejs,[6] Fuji,[7] Fu,[8] Oriyama,[9] and Miller.[10] Other notable catalytic examples include resolutions via S_N2 displacements and allylic alcohol functionalizations (e.g., epoxidation, reduction).[11] One approach that has been relatively less explored is the resolution of secondary alcohols via enantioselective oxidation. At the onset of this project, there were only two general oxidative approaches to a resolution of this type.

2.2.1 Nitroxyl Radicals for the Oxidative Kinetic Resolution of Alcohols

The first approach toward a kinetic resolution via alcohol oxidation involves the use of nitroxyl radicals, which form the active *N*-oxoammonium species under oxidative conditions. Rychnovsky reported the oxidative kinetic resolution of secondary alcohols using chiral nitroxyl radical **34** (Scheme 2.2.1).[12] Sodium hypochlorite acts as the oxidizing agent for the nitroxyl radical. Modest selectivities were achieved across a range of substrates (s = 1.5-7.1).[13] This system represented the first example of a nonenzymatic catalytic enantioselective oxidation of secondary alcohols.

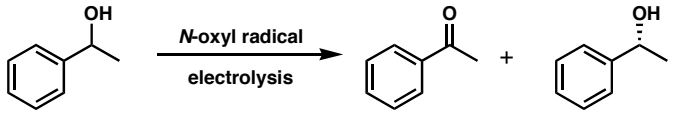
Scheme 2.2.1



Improvements to the nitroxyl radical approach were realized when electrolytic conditions were utilized. Some key examples of these systems are outlined in Table 2.2.1. Chiral nitroxyl radical **35** resolved *sec*-phenethyl alcohol (**20**) with some degree of selectivity,[14] while radical **34** (the same that was used by Rychnovsky) was significantly

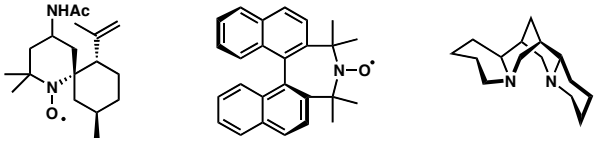
more selective.[15] The highly efficient TEMPO-(–)-sparteine system reported by Osa and Bobbitt is particularly noteworthy (entry 3).[16] In this system, (–)-sparteine is postulated to act as a chiral base in an enantioselective deprotonation step, conceptually different from the chiral nitroxyl radical examples (entries 1 and 2). Although high enantiomeric excesses can be obtained, this chemistry has yet to be utilized in any synthetic context.

Table 2.2.1 *N*-Oxyl radicals in oxidative kinetic resolutions of secondary alcohols.



(±)-20 ***21*** ***(+)-20***

entry	radical	% conversion	% ee *20*	s	ref
1	*35*	63.9	70.0	4.6	14
2	*34*	57.0	91.0	16	15
3	TEMPO (*+36*)	52.9	99.6	102	16

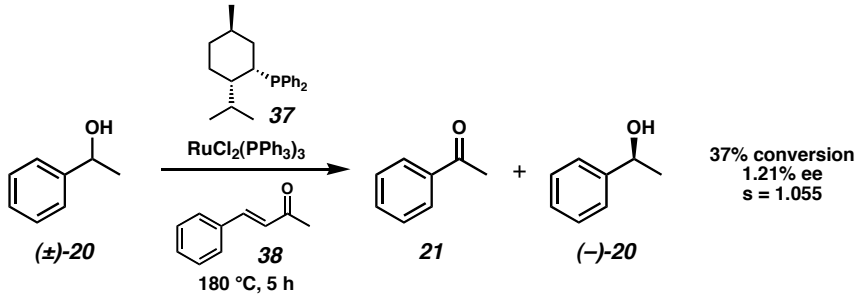


35 ***34*** ***36***

2.2.2 Transition Metal Approaches for the Oxidative Kinetic Resolutions of Alcohols

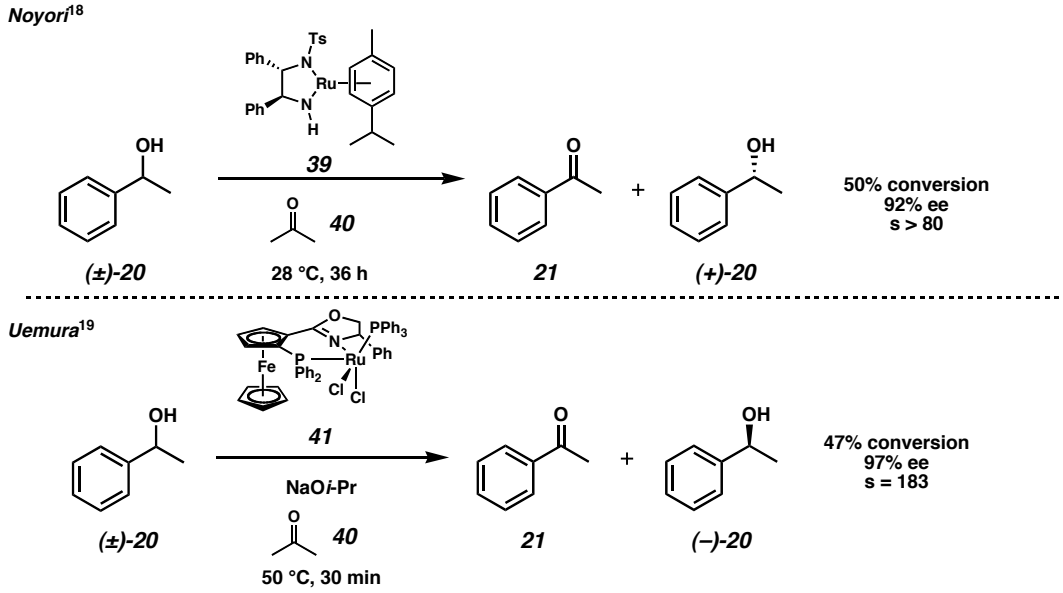
The other general approach to oxidative kinetic resolutions that has been investigated is transition metal catalysis. The first report of a metal-catalyzed enantioselective dehydrogenation was in 1976 by Ohkubo et al.[17] *sec*-Phenethyl alcohol (**20**) was oxidatively resolved via transfer hydrogenation in the presence of a ruthenium-phosphine catalyst with modest selectivity. Although the results were not synthetically useful (s = 1.055), this study demonstrated the viability of kinetic resolution through a transfer hydrogenation process.

Scheme 2.2.2



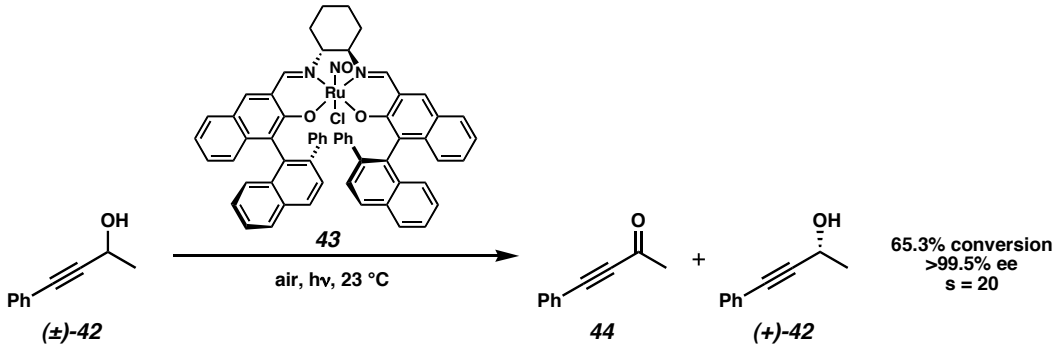
Noyori and Uemura have since developed highly enantioselective variants of the ruthenium-catalyzed kinetic resolution of secondary alcohols. Noyori demonstrated the use of ruthenium-diamine catalyst **39** to resolve secondary alcohols with acetone as the hydrogen acceptor (Scheme 2.2.3).[18] Uemura later reported a similar system using a ruthenium-ferrocenyloxazoline complex (**41**).[19] In both cases, an array of secondary alcohols were resolved to high enantiopurity with remarkable levels of selectivity (s > 100 for both).

Scheme 2.2.3



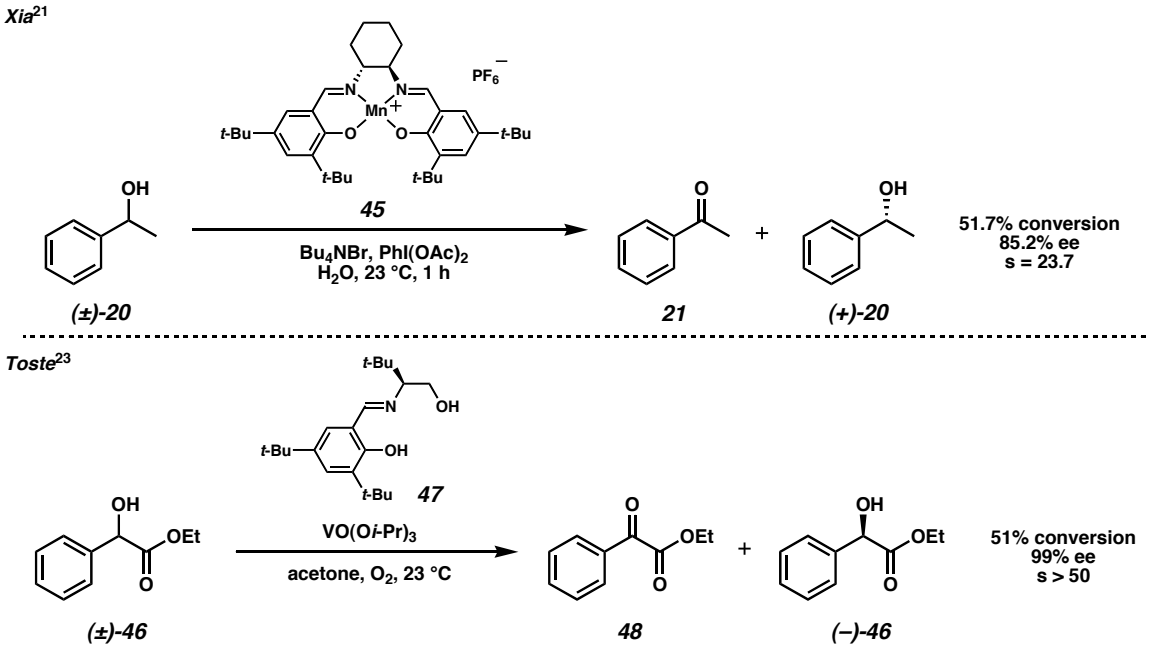
There have also been a few isolated reports of transition metal-catalyzed kinetic resolutions not involving direct transfer hydrogenation processes. Katsuki reported the oxidative kinetic resolution of secondary alcohols under air and irradiation using ruthenium-salen-derived catalyst **43**.[20] Only four alcohols (though structurally distinct from one another) were reported to be resolved by this system, and the reaction mechanism is presently unclear.

Scheme 2.2.4



Subsequent to our initial report on the kinetic resolution of secondary alcohols, more examples have surfaced. In 2003, Xia reported an oxidative kinetic resolution using a manganese-salen catalyst and iodobenzene diacetate as the stoichiometric oxidant (Scheme 2.2.5).[21] Selectivities up to 23.7 could be obtained by this system.[22] Toste recently described a vanadium-salicylaldimine catalyst system for the asymmetric oxidation of α-hydroxy esters.[23] High selectivities for a number of α-hydroxy esters were realized, though less activated alcohols (e.g., *sec*-phenethyl alcohol) were unreactive to this unique system.

Scheme 2.2.5



Despite these significant contributions, there still remained a need for a general catalytic enantioselective oxidation system. Importantly, we sought to develop a system that would be applicable to a variety of enantioselective oxidative transformations. Taking into consideration the ubiquitous nature of palladium catalysis in enantioselective reactions (e.g., Heck reactions,[24] π-allyl chemistry,[25] etc.), we decided to employ a palladium(II) system as our approach to this goal. Palladium(II) has been shown to catalyze the oxidation of alcohols to carbonyl compounds in the presence of a variety of stoichiometric cooxidants, including allyl carbonates, aryl halides, CCl_4, and molecular oxygen.[26] It was anticipated that a similar oxidative system consisting of a ligated palladium catalyst would be readily adaptable to asymmetric variants. Not only would this system serve as the basis for the development of an oxidative kinetic resolution of

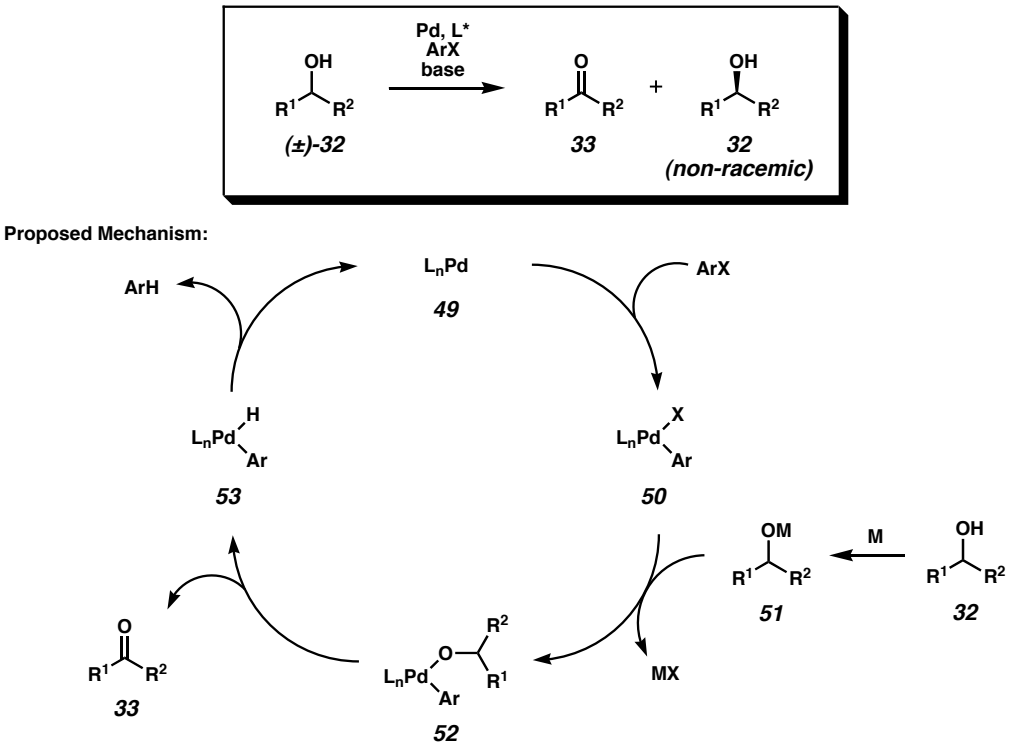
alcohols but also as a platform toward the development of several enantioselective dehydrogenation reactions.[27]

2.3 Reaction Development

2.3.1 Investigations of a Palladium/Aryl Halide System

Our initial strategy was to utilize an aryl halide as the stoichiometric oxidant with a ligated palladium catalyst. The mechanism envisioned for this reaction is outlined in Scheme 2.3.1. Starting with a palladium(0)-ligand complex (**49**), oxidative addition of the aryl halide affords Pd(II) intermediate **50**. Transmetallation with metal alkoxide **51** (generated from the alcohol and a metal base) produces a palladium alkoxide, which can undergo β-hydride elimination to afford palladium hydride **53**. Reductive elimination regenerates the Pd(0) catalytic species, with reduced arene as a byproduct. This system appeared especially attractive based on the number of variables that could potentially influence the asymmetric transformation (i.e., palladium source, chiral ligand, base, aryl halide, solvent, temperature, etc.).

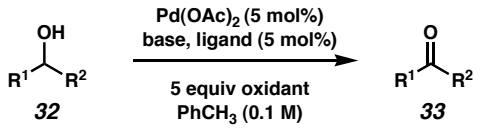
Scheme 2.3.1

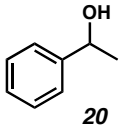
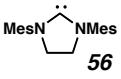
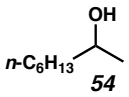
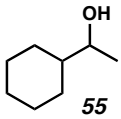


Most reports of palladium(II) oxidations of alcohols involved the use of highly coordinating solvents (e.g., DMSO, methanol). It was presumed that more mild conditions would be readily amenable to asymmetric catalysis—that is, in nonpolar solvents that would not disrupt any palladium-ligand intermediates, and preferably at reasonable temperatures for asymmetric reactions. Using *sec*-phenethyl alcohol (**20**) as our test substrate, a number of conditions were evaluated (Table 2.3.1). Starting with K_2CO_3 as the metal base, bromobenzene as the stoichiometric oxidant, and toluene as the solvent at 80 °C, oxidation to acetophenone was sluggish (entry 1). Switching to iodobenzene, which can undergo oxidative addition at lower temperatures, and from K_2CO_3 to the stronger NaO*t*-Bu as the metal base, the complete oxidation to acetophenone occurred in approximately 3 h at 30 °C (entry 3). Importantly, these

oxidative conditions were generally effective for a number of ligand types (monodentate, bidentate, carbene, pyridyl) and substrates, providing several options for asymmetric variants.

Table 2.3.1 Palladium-catalyzed alcohol oxidations with aryl halides as the stoichiometric oxidant.

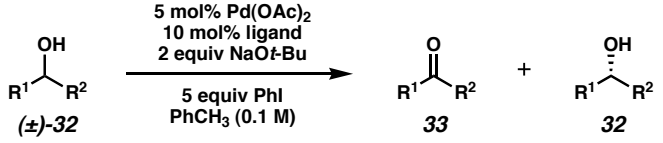


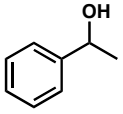
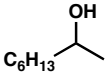
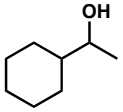
alcohol	entry	base	ligand	oxidant	temp./time	% conversion[a]
 20	1	K_2CO_3 (5 equiv)	dppe	PhBr	80 °C / 7.5 h	16
	2	Cs_2CO_3 (5 equiv)	dppe	PhI	80 °C / 5 h	75
	3	NaO*t*-Bu (2 equiv)	dppe	PhI	30 °C / 3 h	96
	4[b]	NaO*t*-Bu (2 equiv)	PPh_3	PhI	30 °C / 5 h	94
	5[b]	NaO*t*-Bu (2 equiv)	 56	PhI	30 °C / 2 h	97
	6	NaO*t*-Bu (2 equiv)	2,2'-dipyridyl	PhI	30 °C / 30 h	72
 54	7	NaO*t*-Bu (2 equiv)	dppe	PhI	30 °C / 1.5 h	65
 55	8	NaO*t*-Bu (2 equiv)	dppe	PhI	30 °C / 2 h	>99

[a] % conversion measured by ^{1}H NMR. [b] 10 mol% ligand added.

Having developed this mild oxidation system, an initial screen of chiral ligands was conducted, providing some promising results (Table 2.3.2). Although *sec*-phenethyl alcohol (**20**) was not resolved by any of the palladium-ligand complexes, aliphatic alcohols displayed modest levels of enantiodifferentiation. For example, 1-cyclohexylethanol was resolved to 65% ee at 58% conversion (s = 5.3) by treatment with (–)-Me-DUPHOS (**57**), $Pd(OAc)_2$, NaO*t*-Bu, and iodobenzene in CH_2Cl_2 at 30 °C (entry 10).

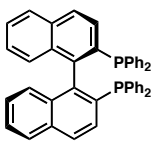
Table 2.3.2 Palladium-catalyzed enantioselective oxidations of secondary alcohols with iodobenzene.

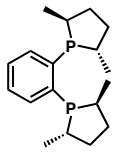


alcohol	entry	ligand	temp./time	% conversion[a]	% ee[b]	s
 (±)-20	1	(*R*)-BINAP	30 °C / 6 h	63	0	1.0
	2	(+)-Me-DUPHOS	30 °C / 96 h	66	0	1.0
	3	(*S,S*)-CHIRAPHOS	20 °C / 48 h	72	0	1.0
	4	(*R,R*)-DIOP	30 °C / 41 h	30	0	1.0
	5	(*R,R*)-Trost Ligand	30 °C / 65 h	17	0	1.0
 (±)-54	6	(+)-Me-DUPHOS	30 °C / 36 h	43	16	1.5
 (±)-55	7	(*R*)-BINAP	20 °C / 24 h	57	0	1.0
	8	(+)-Me-DUPHOS	30 °C / 65 h	51	20	1.8
	9	(*R,R*)-Trost Ligand	30 °C / 65 h	6	0	1.0
	10[c]	(+)-Me-DUPHOS	30 °C / 15 h	58[c]	65	5.3

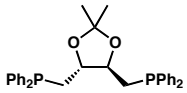
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by GC or HPLC. [c] CH_2Cl_2 as solvent.

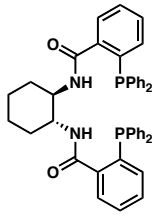
Figure 2.3.1 Ligands evaluated in Table 2.3.2.


(R)-BINAP (56)


(+)-Me-DUPHOS (57)


(S,S)-CHIRAPHOS (58)

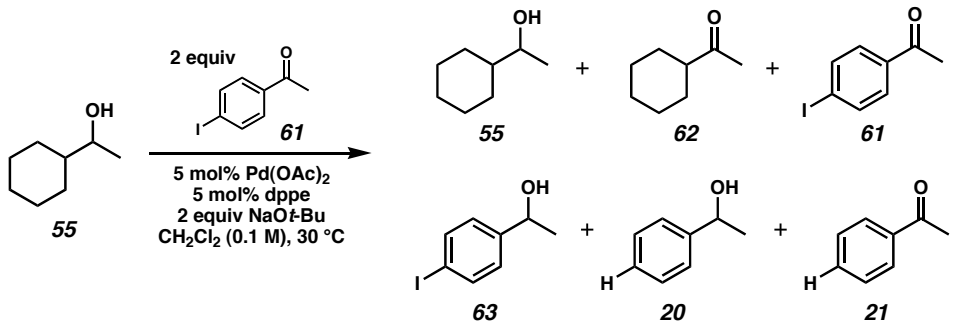

(R,R)-DIOP (59)


(R,R)-Trost Ligand (60)

Although the initial results were encouraging, it was soon found that these reactions were plagued by side reactions and inconsistencies. Specifically, during an investigation of the substituent effects on the aryl halide, an experiment with 4'-iodoacetophenone revealed a complicating side reaction (Scheme 2.3.2). In the oxidation

of alcohol **55**, three alcohols and their corresponding ketones were observed in the reaction mixture. Alcohols **63** and **20** could only arise from some reductive pathway. It was later found through control experiments that the presence of a metal base was promoting a background Meerwein-Ponndorf-Verley reduction/Oppenauer oxidation cycle between an alcohol and a ketone.[28] This nonselective process was likely racemizing the resolved alcohol in our systems to some extent, prohibiting high levels of enantiopurity. Moreover, the oxidation system showed a clear oxygen dependency; when these reactions were conducted under the rigorous exclusion of oxygen, alcohol oxidation barely proceeded. Recognizant of these difficulties and desirous of a simpler system, we decided to turn elsewhere.

Scheme 2.3.2

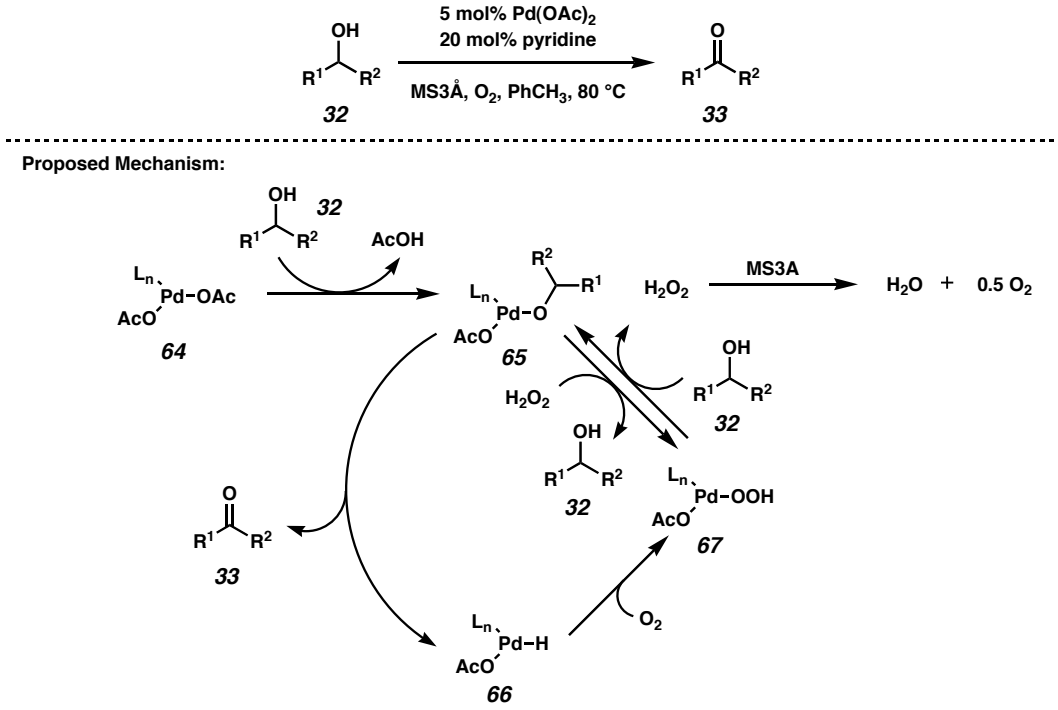


2.3.2 Oxidative Kinetic Resolution of Alcohols with a Palladium/Oxygen System

An alternative oxidative system that was considered was initially reported by Uemura in 1999 (Scheme 2.3.3).[26f] He described the oxidation of a number of alcohols to aldehydes and ketones using a palladium-pyridine (1:4 molar ratio) catalyst system in toluene at 80 °C. Molecular oxygen was used as the sole stoichiometric oxidant, and high yields were realized for an array of alcohol substrates. The mechanism proposed by Uemura (Scheme 2.3.3) begins with acetate exchange with an alcohol to provide

palladium alkoxide **65**. This intermediate can undergo β-hydride elimination to the resulting palladium hydride (**66**). Reoxidation of the palladium hydride by oxygen affords palladium peroxide **67**, which subsequently exchanges ligands with another alcohol to regenerate the palladium alkoxide. The byproduct, hydrogen peroxide, is proposed to disproportionate to H_2O and O_2 by the 3Å molecular sieves in the reaction mixture.

Scheme 2.3.3

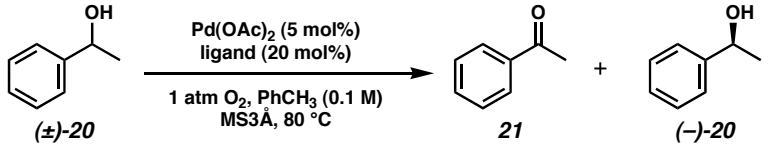


There were some important features to this system that made it particularly attractive for developing an oxidative kinetic resolution. No strong base was required, which would hopefully prevent the background reduction/oxidation cycle that had complicated the aryl halide system. Molecular oxygen is inexpensive and abundant, and the byproduct of the oxidation is water, both advantageous from an environmental and an

economical standpoint. Lastly, the system demonstrated a clear ligand dependence—when the reaction was performed in the absence of pyridine, the oxidation did not proceed efficiently. Because of this dependence on the ligand, it was anticipated that chiral ligands would have a significant enantioinducing effect on the alcohol oxidation.

Alcohol **(±)-20** was subjected to oxidative conditions analogous to Uemura's system, but substituting various chiral ligands for pyridine (Table 2.3.3). Each of these systems led to one of three results: (a) catalyst activity was completely suppressed (entries 1-6), (b) oxidation was observed but nonselective (entries 7 and 8), or (c) partial resolution via oxidation was achieved (entries 9 and 10). During this evaluation, (–)-sparteine (**36**) immediately emerged as a promising ligand for this transformation. After 24 h at 80 °C, *sec*-phenethyl alcohol was oxidized to acetophenone in 15.1% conversion, and alcohol **20** was recovered in 13.7% ee. Although those particular values are not synthetically useful, the selectivity factor of 8.8 was the highest observed in any of the systems studied up to this point.

Table 2.3.3 Initial ligand screen for the aerobic oxidative kinetic resolution of **20**.

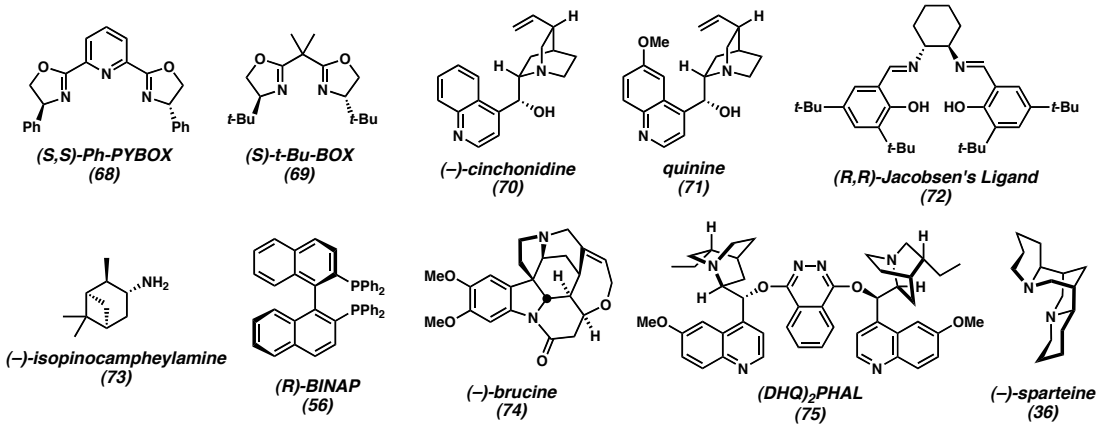


(±)-20 *21* *(–)-20*

entry	ligand	time	conversion (%)[a]	% ee *20*[b]	s
1	(*S,S*)-Ph-PYBOX	72 h	2	-	1
2	(S)-*t*-Bu-BOX	24 h	3	-	1
3	(–)-cinchonidine	72 h	2	-	1
4	quinine	24 h	0	-	1
5	(–)-isopinocampheylamine	24 h	0	-	1
6	(*R,R*)-Jacobsen's Ligand	24 h	3	-	1
7	(*R*)-BINAP	24 h	29.0	0	1
8	(–)-brucine	24 h	77.0	0	1
9	$(DHQ)_2PHAL$	24 h	31.6	8.7	1.6
10	(–)-sparteine	24 h	15 .1	13.7	8.8

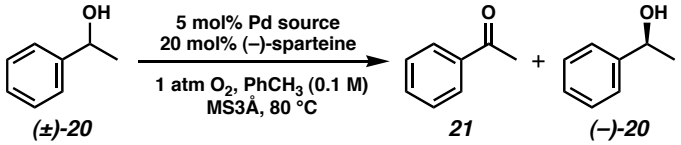
[a] % conversion measured by GC. [b] % ee measured by HPLC.

Figure 2.3.2 Ligands evaluated in Table 2.3.3.



Reexamination of the mechanism proposed by Uemura (Scheme 2.3.3) proved to be critical for the optimization of this reaction. In the mechanism, an acetoxy moiety is bound to the palladium center throughout the catalytic cycle. This moiety originates from the $Pd(OAc)_2$ used as a precatalyst. It was hypothesized that changing counterions by varying the palladium precursors would have marked effects on both the reactivity and selectivity of the oxidation. A variety of palladium sources were surveyed to test this hypothesis (Table 2.3.4). Indeed, palladium precatalysts with chloride counterions were found to be more reactive and selective than ones with acetate counterions. Eventually we found $Pd(nbd)Cl_2$ to be the most effective palladium precursor for this reaction, resulting in a selectivity of 23.1 for the oxidative kinetic resolution of *sec*-phenethyl alcohol (entry 7).[29]

Table 2.3.4 Palladium source examination for the oxidative kinetic resolution.



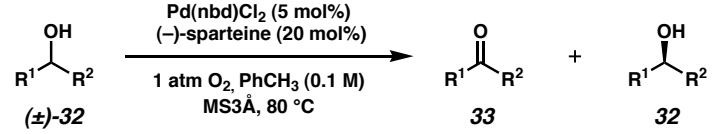
(±)-20 *21* *(–)-20*

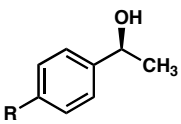
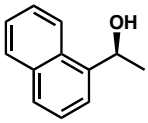
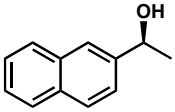
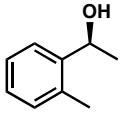
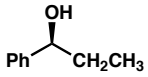
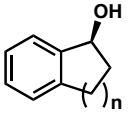
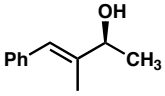
entry	Pd source	time	conversion (%)[a]	% ee *20*[b]	s
1	$Pd(OAc)_2$	24 h	15.1	13.7	8.8
2[c]	$Pd_2(dba)_3$	55 h	66.2	81.5	5.7
3	$PdCl_2$	96 h	62.6	98.0	16.3
4	$Pd(CH_3CN)_2Cl_2$	36 h	51.7	79.8	16.5
5	$Pd(PhCN)_2Cl_2$	36 h	57.4	92.1	16.9
6[c]	$[(allyl)PdCl]_2$	96 h	60.2	96.9	18.0
7	*$Pd(nbd)Cl_2$*[d]	*96 h*	*59.9*	*98.7*	*23.1*

[a] % conversion measured by GC. [b] % ee measured by HPLC. [c] 2.5 mol% Pd source (5 mol% Pd). [d] nbd: norbornadiene.

With the optimized resolution conditions in hand, investigations into the scope of the reaction were conducted. As shown in Table 2.3.5, a variety of activated alcohols (i.e., benzylic and allylic) can be resolved to high enantiomeric excess with good to excellent selectivities. 1-Phenylethanol derivatives are particularly good substrates for the kinetic resolution (entries 1-3). A number of different arenes can be substituted for the phenyl group, although steric hindrance from ortho substituents can significantly impact reactivity (entries 4-6). Endocyclic alcohols can be resolved to high levels of enantiopurity (entries 8 and 9). The resolution is not limited to benzylic alcohols, as demonstrated by the resolution of allylic alcohol **84** (entry 10).[30]

Table 2.3.5 The oxidative kinetic resolution of secondary alcohols with a palladium-sparteine system.



entry	unreacted alcohol, major enantiomer		time	conversion (%)[a]	isolated yield (%)[b]	% ee ROH[c]	s[d,e]
1		R = H *20*	96 h	59.9	37 (93)	98.7	23.1
2		R = OMe *76*	96 h	66.6	32 (96)	98.1	12.3
3		R = F *77*	54 h	63.3	32 (88)	97.4	14.4
4		*78*	192 h	55.9	43 (97)	78.4	9.8
5		*79*	112 h	55.2	44 (99)	99.0	47.1
6		*80*	144 h	48.4	49 (95)	68.7	13.1
7		*81*	192 h	59.3	40 (98)	93.1	14.8
8[f]		n = 1 *82*	54 h	67.5	30 (93)	93.4	8.3
9		n = 2 *83*	40 h	68.6	31 (99)	99.8	15.8
10		*84*	120 h	70.4	29 (99)	91.8	6.6

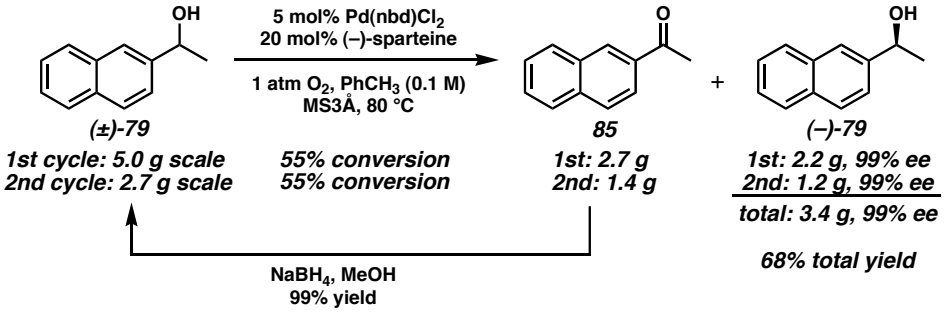
[a] % conversion measured by GC. [b] Isolated yield of enantioenriched alcohol is presented first. Number in parentheses refers to the total combined yield of alcohol and ketone. [c] % ee was measured by HPLC or GC. [d] Selectivity values represent an average of at least two experiments. [e] For each entry, comparable selectivities are observed through the course of the reaction. [f] Performed at 60 °C.

2.3.3 Scale up and Recycling

One of the major criticisms leveled on kinetic resolutions is that the theoretical maximum yield of the reaction is only 50%. The scale up experiment depicted in Scheme 2.3.4 demonstrates the simplicity with which this potential drawback is overcome. On a multigram kinetic resolution of **(±)-79**, we were able to recover alcohol **79** in 44% yield

and 99% ee after one resolution. The recovered ketone (**85**) was quantitatively reduced by sodium borohydride to regenerate the racemic alcohol, which was then subjected to a second resolution. After the two cycles, alcohol **79** was isolated in 68% total yield and 99% ee. A trivial ketone reduction and recycling sequence provides an opportunity to access >50% yield of a starting racemic alcohol from the oxidative resolution process.

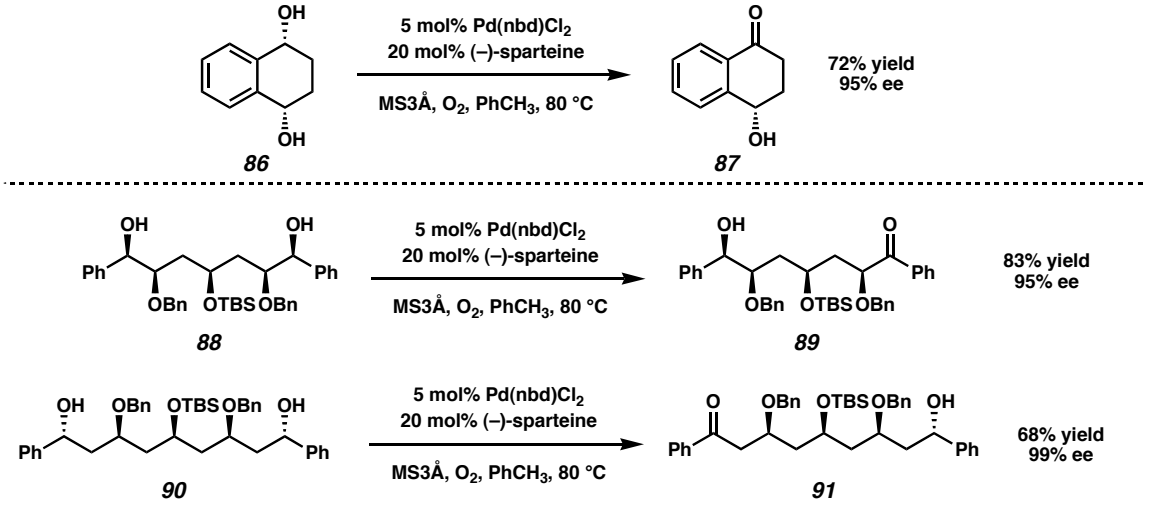
Scheme 2.3.4



2.3.4 Desymmetrization of Meso Diols

The palladium-catalyzed oxidative kinetic resolution can also be applied to the desymmetrization of meso diols by the same selective process. Meso diol **86** was subjected to the standard kinetic resolution to afford the hydroxyketone (**87**) in 72% yield and 95% ee. Jeffrey Bagdanoff, a graduate student in the Stoltz laboratory, later applied this desymmetrization concept toward the enantioselective synthesis of complex acyclic polyols.[31] In both of these transformations (**88** → **89**, **90** → **91**), four stereocenters are set enantioselectively in a single step. The desymmetrized ketone products were isolated in high yields and enantiopurities.

Scheme 2.3.5



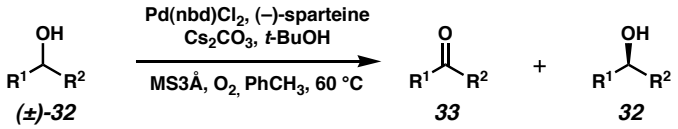
2.4 Further Developments

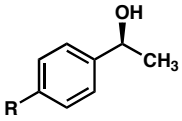
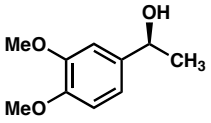
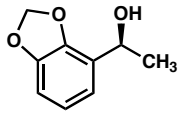
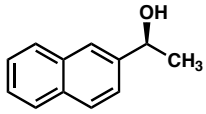
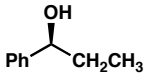
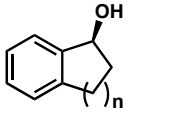
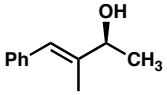
2.4.1 Improved Reaction Conditions

At this point, the palladium-catalyzed oxidative kinetic resolution could be utilized to access an array of enantiopure secondary alcohols. The conditions developed, however, were noticeably sluggish (approximately 2-8 days, see Table 2.3.5). During the course of these investigations, a palladium•sparteine complex was prepared to test its reactivity in the resolution. In general, we found that the reactivity of this complex was significantly lower than our optimized system, wherein a fourfold excess of (–)-sparteine relative to the palladium precursor is added, forming the complex in situ. Interestingly, the reactivity of the resolution with the palladium•sparteine complex could be restored to the optimal levels if 3 equivalents of (–)-sparteine relative to the complex were added. It could also be restored to near optimal levels by adding an achiral base (e.g., 4-methyl-2,6-di-*tert*-butylpyridine) instead of (–)-sparteine.

Based on these results, it was anticipated that the oxidative kinetic resolution could be affected by the presence of a stoichiometric base. Jeffrey Bagdanoff therefore sought to improve the reaction rates of the established system by probing the effects of bases and other additives. Eventually, it was found that the addition of both Cs_2CO_3 and *t*-BuOH to the standard conditions resulted in a dramatic rate acceleration.[32] As shown in Table 2.4.1, all of the resolutions are complete in less than 24 h, and the alcohols can be accessed in high enantiopurity.

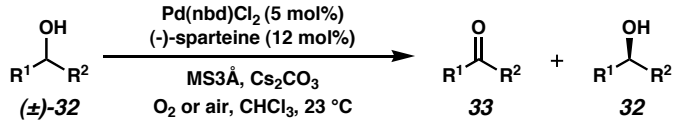
Table 2.4.1 The rate-accelerated palladium-catalyzed oxidative kinetic resolution.

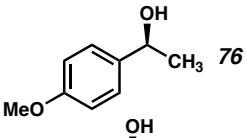
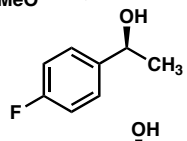
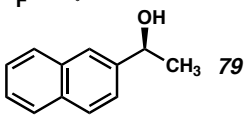
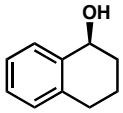
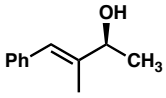
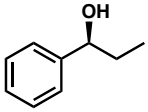


entry	unreacted alcohol, major enantiomer		time	conversion (%)	% ee ROH	s
1		R = H *20*	12.5 h	63.9	99.6	20.0
2		R = OMe *76*	9.5 h	67.4	99.5	14.9
3		R = F *77*	12.5 h	65.7	97.4	12.1
4		*92*	18 h	63.8	98.3	15.4
5		*93*	15 h	56.5	99.7	47.4
6		*79*	12 h	66.1	99.4	15.8
7		*81*	4.5 h	62.8	98.0	16.1
8		n = 1 *82*	12 h	74.0	99.5	10.1
9		n = 2 *83*	12 h	61.5	99.0	20.9
10		*84*	12 h	65.1	87.9	7.5

In hopes of further understanding the effects of the individual reaction parameters, Jeffrey Bagdanoff conducted a more thorough screening of various conditions for the oxidative kinetic resolution. Ultimately, it was found that chloroform was uniquely effective as a solvent for the reaction.[33,34] This modification allowed the resolution to be conducted at room temperature, resulting in a uniform increase in selectivity factors (Table 2.4.2). Moreover, the reactions could be performed in the presence of ambient air without an appreciable loss of selectivity. Curiously, the resolutions proceeded with faster reaction rates in ambient air; the reasons behind this observation are presently unclear.

Table 2.4.2 The palladium-catalyzed oxidative kinetic resolution at room temperature.

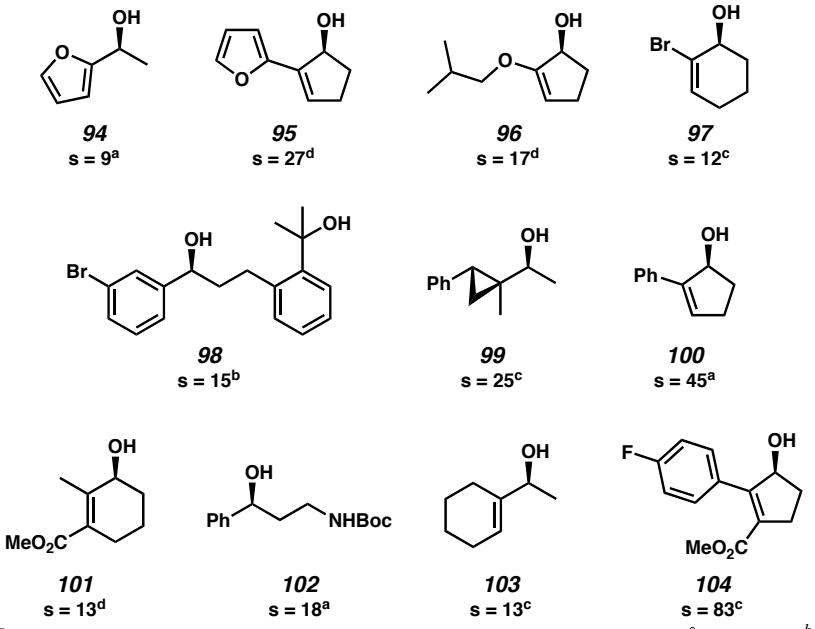


entry	unreacted alcohol, major enantiomer		atm	time	conversion (%)	% ee ROH	s
1		*76*	O_2	48 h	62.6	99.9	27.1
			air	24 h	62.3	99.8	25.4
2		*77*	O_2	48 h	59.3	98.0	23.0
			air	24 h	56.7	93.0	19.5
3		*79*	O_2	48 h	59.3	99.6	31.1
			air	24 h	55.5	98.0	37.3
4		*83*	O_2	24 h	57.5	98.0	27.6
			air	16 h	60.2	99.6	28.0
5		*84*	O_2	48 h	62.6	98.7	17.9
			air	44 h	64.7	98.9	15.7
6		*81*	O_2	72 h	62.6	98.2	24.4
			air	48 h	56.8	94.9	21.7

2.4.2 Expanding the Substrate Scope toward Total Synthesis Applications

Up to this point, the substrates that had been investigated in the development of conditions for the oxidative kinetic resolution were primarily simple secondary alcohols. A significant effort has been put forth in expanding this substrate scope, especially in light of the development of new conditions. Work by David Ebner, Daniel Caspi, and Ryan McFadden, graduate students in the Stoltz laboratory, has demonstrated that a variety of secondary alcohols can be resolved with high selectivities (Figure 2.4.1).[35] Functional groups such as enol ethers, vinyl and aryl bromides, esters, and carbamates are all compatible with the reaction conditions. It was also found that no single set of conditions is superior for every substrate. Some of the substrates investigated are key building blocks for important pharmaceuticals, such as monteleukast sodium (Singulair®),[36] fluoxetine hydrochloride (Prozac®),[37] and Merck's promising human neurokinin-1 receptor antagonist[38] (from alcohols **98**, **102**, and **104**, respectively).

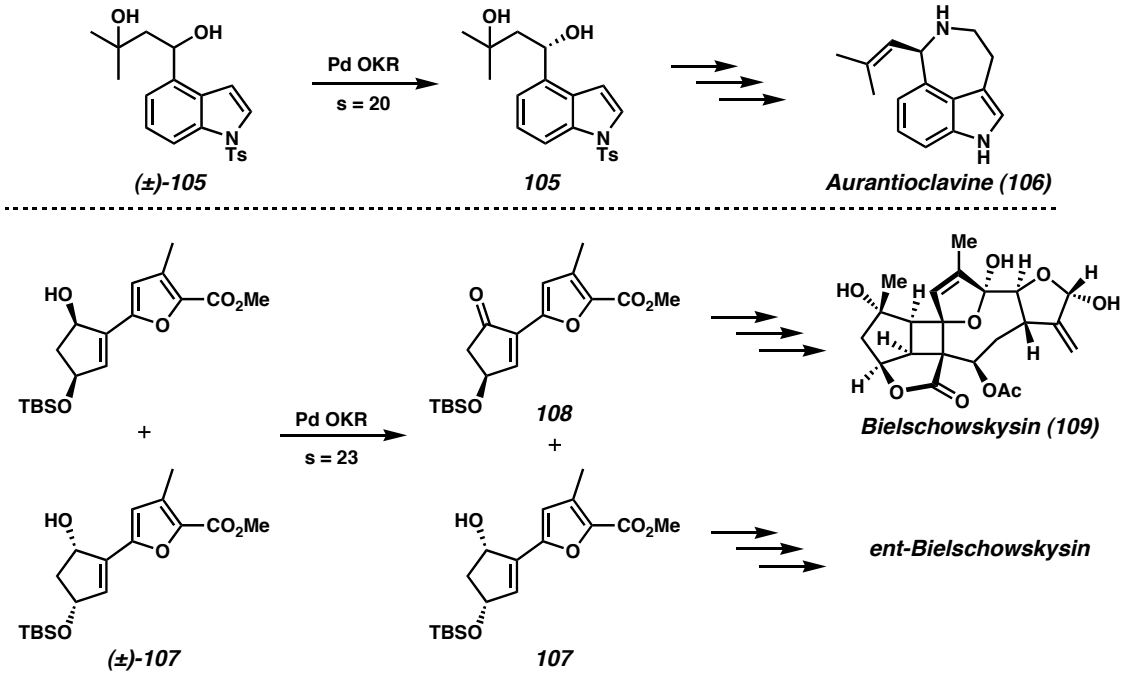
Figure 2.4.1 Enantioenriched substrates accessed by the oxidative kinetic resolution.



[a] 5 mol% $Pd(nbd)Cl_2$, 20 mol% (–)-sparteine, toluene, O_2, MS3Å, 80 °C. [b] 5 mol% $Pd(nbd)Cl_2$, 20 mol% (–)-sparteine, Cs_2CO_3, *t*-BuOH, toluene, O_2, MS3Å, 60 °C. [c] 5 mol% $Pd(nbd)Cl_2$, 12 mol% (–)-sparteine, Cs_2CO_3, $CHCl_3$, O_2, MS3Å, 23 °C. [d] 5 mol% $Pd(nbd)Cl_2$, 12 mol% (–)-sparteine, Cs_2CO_3, $CHCl_3$ air, MS3Å, 23 °C.

The palladium-catalyzed oxidative kinetic resolution has also been utilized in the context of total synthesis of bioactive natural products (Scheme 2.4.1). Yeeman Ramtohul, a former postdoctoral scholar in the Stoltz laboratory, has applied the resolution to secondary alcohol **105**, which we anticipated to be a viable intermediate in the enantioselective synthesis of aurantioclavine (**106**).[39] Michael Meyer, a graduate student in the Stoltz laboratory, has also performed a resolution of cyclopentenol **107** as a method of accessing both enantiomers of a key intermediate in work toward the total synthesis of bielschowskysin (**109**).[40]

Scheme 2.4.1



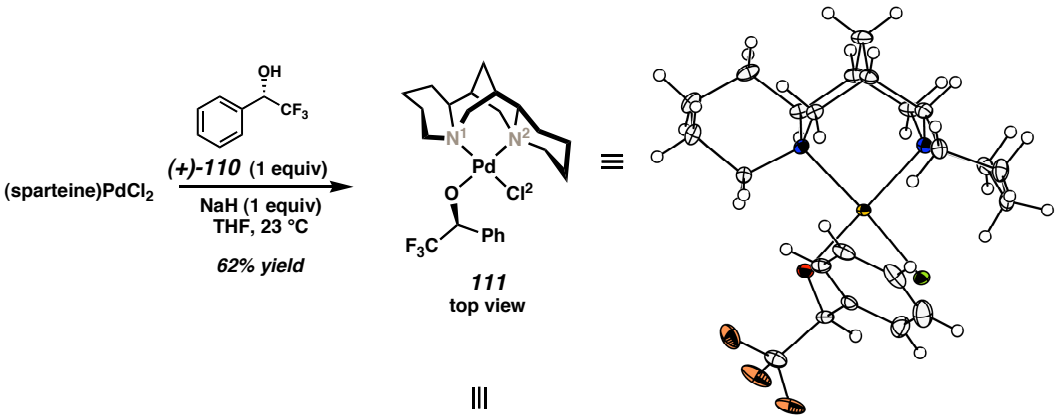
2.5 Mechanistic Studies

2.5.1 Coordination Studies on Palladium-Sparteine Systems

There have also been significant developments in understanding the mechanistic details and the origin of selectivity in the palladium-catalyzed oxidative kinetic resolution. Raissa Trend, a graduate student in the Stoltz laboratory, has studied a number of palladium•sparteine complexes to ascertain the mode of enantioinduction.[41] Specifically, (*S*)-(+)-α-(trifluoromethyl)benzyl alcohol (**(+)-110**) was reacted with sodium hydride and (sparteine)palladium dichloride to generate a single palladium species (Scheme 2.5.1). The alcohol chosen represents a steric model for the reactive enantiomer of *sec*-phenethyl alcohol (**20**) in the kinetic resolution. However, because of the low reactivity of alcohol **110** under the oxidative conditions, the palladium alkoxide could be isolated and characterized by X-ray crystallography. The crystal structure

vividly illustrates the orientation with which the alcohol binds to the palladium-sparteine catalyst. The phenyl (R_L) is positioned in the open region above the square plane of the metal complex (**111**, side view), and the benzylic C-H bond is pointed toward the metal plane parallel to the palladium-chloride bond. Importantly, the palladium-chloride bond is somewhat distorted out of the square plane, implicating how the chloride anion moves away from the metal center to reveal a site for β-hydride elimination.

Scheme 2.5.1

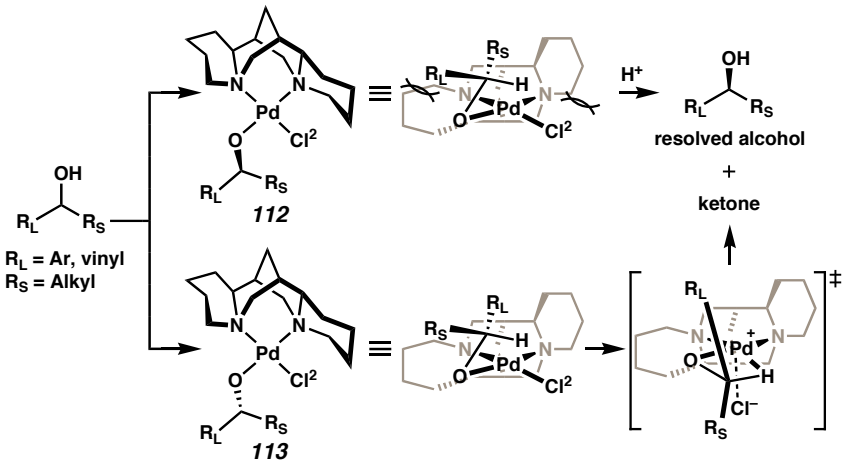


Atoms	Distance (Å)
Pd–N^1	2.1243(17)
Pd–N^2	2.0925(16)
Pd–O	2.0012(14)
Pd–Cl	2.3316(5)
N^1–Pd–Cl angle = 164.59(5)°	

Based on the above studies, a model for selectivity in the kinetic resolution was proposed (Scheme 2.5.2).[41] Both of the alcohols bind preferentially at the position indicated to form diastereomeric alkoxides **112** and **113**. Due to steric interactions with the sparteine ligand, alkoxide **112** cannot adopt the necessary orientation to undergo β-hydride elimination; it therefore protonates and dissociates from the complex.

Meanwhile, alkoxide **113** can undergo partial chloride dissociation and β-hydride elimination from a four-coordinate metal center with an axially disposed chloride.[42] Since alkoxide **113** leads to ketone production and alkoxide **112** leads to alcohol dissociation, an overall resolution results.

Scheme 2.5.2

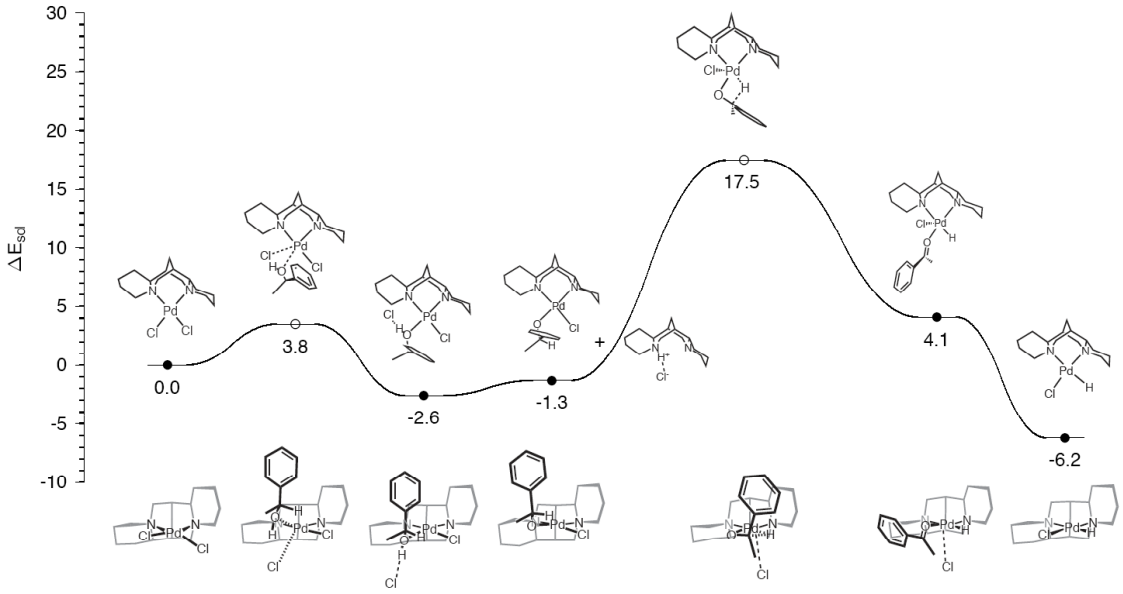


2.5.2 Computational Studies

The counterion effect seen in the initial studies (*vide supra*), with chloride being a much more effective anion than acetate, can be rationalized by these studies and those of Robert Nielsen, a graduate student in the Goddard research group at Caltech.[43] The chloride ion of the palladium alkoxide partially dissociates prior to β-hydride elimination. The anion is still associated to the metal center, however, via electrostatic interactions. This partially associated anion serves as another steric interaction to enhance the degree of selectivity. Calculations have shown that an acetate group presents a somewhat different, less selective steric environment, while the absence of an anion results in almost no selectivity. The observed association of the chloride ion to the metal center helps to explain the counterion effects in the kinetic resolution. The full mechanistic

profile up to ketone dissociation, with calculated energies of the intermediates, is depicted in Scheme 2.5.3.[43]

Scheme 2.5.3



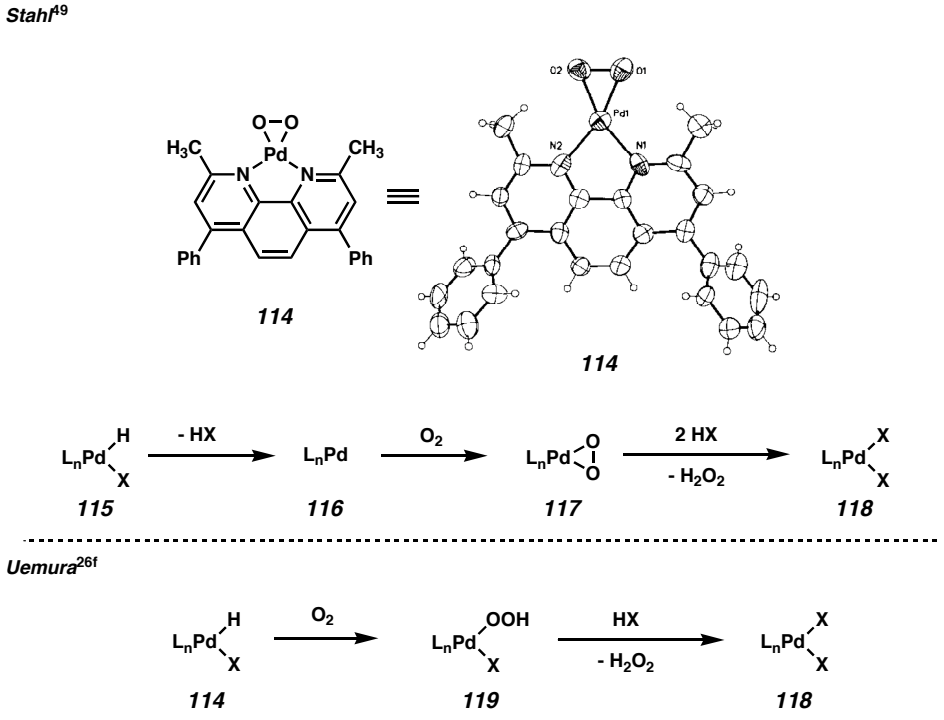
2.5.3 Kinetic Studies of Palladium(II) Oxidative Systems

Sigman and Stahl have recently reported detailed kinetic analyses on the palladium-catalyzed oxidation of alcohols. Stahl studied the palladium-pyridine oxidation system of Uemura, where he found that β-hydride elimination from a (py)Pd(OAc)(alkoxide) intermediate was rate-determining.[44] Sigman focused on the palladium-sparteine resolution system, where he observed that the rate-determining step was dependent on the sparteine stoichiometry.[45,46] At low sparteine levels, deprotonation of the intermediate alcohol complex is rate-limiting; on the other hand, at high sparteine concentrations, β-hydride elimination becomes rate-determining.[47] The origin of selectivity in reactions at high sparteine concentrations, relevant to our studies, was

believed to arise from a combination of the kinetic difference in the β-hydride elimination step and the thermodynamic difference in the diastereomeric alkoxides.[48]

Stahl has also investigated the catalyst turnover steps that follow β-hydride elimination.[49] By using a bathocuproine ligand, Stahl was able to oxidize a palladium(0) center to palladium(II) with molecular oxygen. He isolated and characterized palladium-peroxo species **114** (Scheme 2.5.4). **114** was converted to the diacetate in the presence of acetic acid, demonstrating how an intermediate diamine-palladium(0) species can regenerate the catalytically active diamine-palladium(II) species with molecular oxygen.[50] Uemura has proposed an alternative pathway, where dioxygen simply inserts into the palladium-hydride bond generated from the β-hydride elimination step, thereby avoiding a palladium(0) intermediate altogether.[26f]

Scheme 2.5.4



2.6 Conclusion

We have developed the first example of a palladium-catalyzed oxidative kinetic resolution of secondary alcohols. The reaction uses a simple system of $Pd(nbd)Cl_2$, (–)-sparteine, molecular sieves, and dioxygen to access a variety of secondary alcohols in high enantiopurity. The reaction performs remarkably well upon scale up and can be used to desymmetrize simple and complex meso diols. Further developments have led to improvements on the original system, and the substrate scope has been expanded to compounds relevant to both pharmaceuticals and natural product syntheses. The development of this reaction has also prompted intriguing mechanistic studies that have shed light on palladium(II) oxidative transformations. While developments are still ongoing, we began to explore new directions with this interesting catalytic system, the results of which will be discussed in later chapters of this thesis.

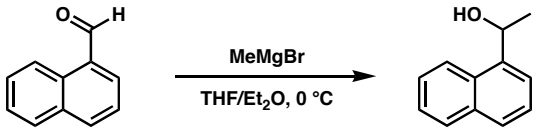
2.7 Experimental Section

2.7.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen or an argon atmosphere, using freshly distilled solvents. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed on a Chiralcel OJ, AS, or OD-H column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical achiral GC was performed using an Agilent DB-WAX (30.0 m x 0.25 mm) column. Analytical chiral GC was carried out using either a Chiraldex B-DM column (30.0 m x 0.25 mm) or a Chiraldex G-TA column (30.0 m x 0.25 mm) purchased from Bodman Industries. Preparatory reversed-phase HPLC was performed on a Beckman HPLC with a Waters DeltaPak 25 x 100 mm, 100 μm C18 column equipped with a guard, 0.1% (w/v) TFA with CH_3CN/H_2O as the eluent. Bisphosphines in Figure 2.3.1 as well as **72** (Jacobsen's ligand) were purchased from Strem Chemicals, Inc., Newburyport, MA. All other organic compounds were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. $Pd(nbd)Cl_2$ was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI; all other palladium salts were purchased from Strem Chemicals, Inc., Newburyport, MA. Commercially available racemic alcohols in Table 2.3.5 (entries 1, 2, 3, 5, 7, 8, and 9), 1-cyclohexylethanol, and 2-octanol were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Commercially available samples of enantiopure alcohols for

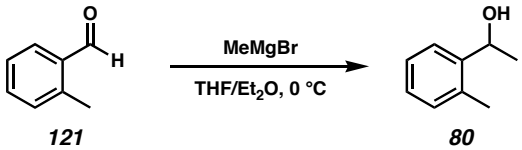
analytical comparison purposes (entries 1, 4, 7, 8, and 9) were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Non-commercially available enantiopure alcohols prepared by palladium-catalyzed oxidative kinetic resolution (Table 2.3.5, entries 2[51], 3[52], 5[53], 6[54], and 10[55]) were compared by optical rotation to known values.

2.7.2 Preparative Procedures



120 *78*

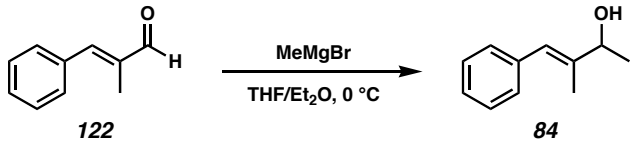
Alcohol 78. To a solution of 1-naphthaldehyde (2.72 mL, 20.0 mmol) in 20 mL THF at 0 °C was added MeMgBr (10.0 mL, 3.0 M in Et_2O, 30.0 mmol) dropwise over 10 min. The reaction mixture was maintained at 0 °C for 30 min, then poured into saturated NH_4Cl (100 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford alcohol **78** (R_F = 0.17 in 4:1 hexanes/EtOAc) as a yellow oil, which solidified upon refrigeration.



121 *80*

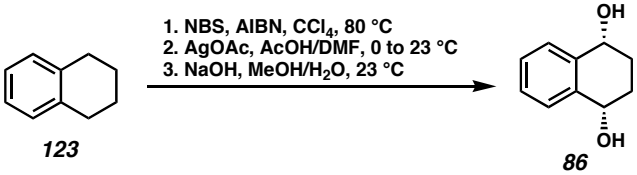
Alcohol 80. To a solution of *o*-tolualdehyde (3.16 mL, 27.3 mmol) in 27 mL THF at 0 °C was added MeMgBr (10.0 mL, 3.0 M in Et_2O, 30.0 mmol) dropwise over 10 min. The reaction mixture was maintained at 0 °C for 30 min, then poured into saturated

NH_4Cl (100 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to afford alcohol **80** (R_F = 0.19 in 4:1 hexanes/EtOAc) as a yellow oil.



122 *84*

Alcohol 84. To a solution of α-methyl-*trans*-cinnamaldehyde (3.81 mL, 27.3 mmol) in 27 mL THF at 0 °C was added MeMgBr (10.0 mL, 3.0 M in Et_2O, 30.0 mmol) dropwise over 10 min. The reaction mixture was maintained at 0 °C for 10 min, then poured into saturated NH_4Cl and ice (200 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to afford alcohol **84** (R_F = 0.31 in 4:1 hexanes/EtOAc) as a yellow oil.



123 *86*

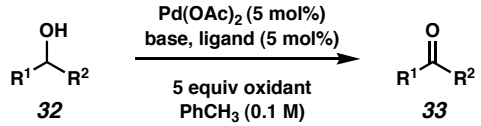
Meso Diol 86. Meso diol **86** was synthesized according to the procedure of Yamada.[56] A 200 mL round-bottom flask holding a solution of tetralin (4.08 mL, 30.0 mmol) in CCl_4 (40 mL) at 23 °C was wrapped in foil. NBS (10.7 g, 60.0 mmol) and AIBN (148 mg, 0.900 mmol) were added sequentially, and the mixture was heated to 80 °C. After

20 min, the reaction mixture turned from yellow to white. The mixture was cooled to room temperature, suction-filtered, and the filtrate was concentrated in vacuo. The crude dibromide was carried to the subsequent step without further purification.

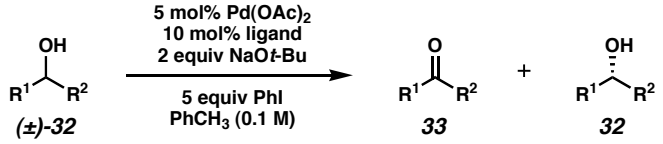
The crude dibromide (assume 30.0 mmol) was dissolved in DMF (10 mL) and AcOH (30 mL) at 23 °C. The mixture was cooled to 0 °C, and AgOAc (10.0 g, 60.0 mmol) was added. The yellow slurry was allowed to warm to 23 °C and stirred for 2.5 h. AgBr was removed by suction-filtration, and the filtrate was concentrated in vacuo. The residue was neutralized with saturated $NaHCO_3$ (30 mL), diluted with water (100 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 5% $Na_2S_2O_3$ (2 x 100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 → 2:1 hexanes/EtOAc eluent) to provide the diacetate (2.86 g, 38% yield over 2 steps, R_F = 0.71 in 1:1 hexanes/EtOAc) as a mixture of dl and meso forms.

To a solution of the diacetate (3.53 g, 14.2 mmol) in 71 mL MeOH at 23 °C was added 2.0 M aq. NaOH (17.8 mL, 35.5 mmol). The mixture was stirred at 23 °C for 2.5 h, then acidified with 2.0 M HCl (~20 mL). The mixture was concentrated in vacuo, and the residue was dissolved in $CHCl_3$/EtOH (1:1, 60 mL). The solids were removed by filtration, and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (1:1 → 3:1 EtOAc/hexanes eluent) afforded the diol (R_F = 0.19 in 1:1 hexanes/EtOAc) as a mixture of dl and meso forms. The meso diol (**86**) was isolated by reversed-phase preparative HPLC (100% H_2O → 3:7 CH_3CN/H_2O eluent). The spectroscopic information for **86** was identical to the reported data.[56]

2.7.3 Palladium(II) Oxidation Procedures

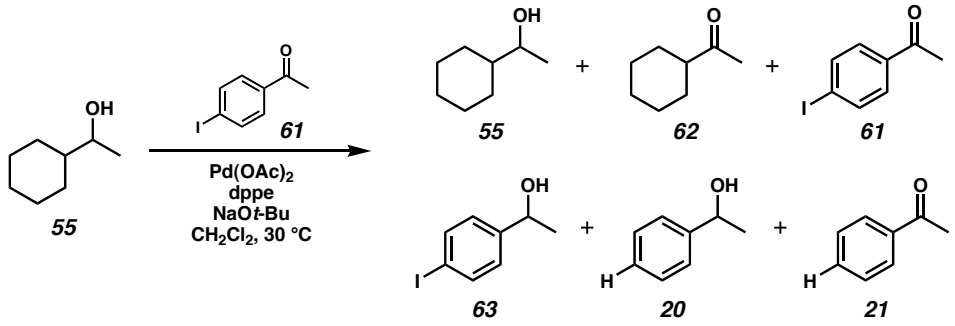


General Procedure for the Racemic Oxidation of Alcohols Using Aryl Halides (Table 2.3.1). To a solution of $Pd(OAc)_2$ (11.2 mg, 0.0500 mmol), ligand (0.0500 mmol), and base (2.00 mmol) in 10 mL toluene at 23 °C was added the alcohol (1.00 mmol), then the aryl halide (5.00 mmol). The solution was heated to the specified temperature and stirred. After the listed time, the solution was cooled to room temperature and quenched with H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude material was analyzed by ^1H NMR to determine conversion values.

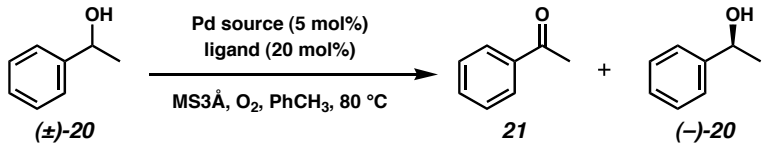


General Procedure for the Enantioselective Oxidation of Alcohols Using Aryl Halides (Table 2.3.2). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.0250 mmol), ligand (0.0500 mmol), and NaO*t*-Bu (1.00 mmol) in 5.0 mL toluene at 23 °C was added the alcohol (0.500 mmol), then the aryl halide (2.50 mmol). The solution was maintained at the specified temperature for the listed time. The solution was then cooled to room temperature and quenched with H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$,

and concentrated in vacuo. The crude material was analyzed by ^{1}H NMR to determine conversion values. Enantiomeric excess was determined by GC or HPLC analysis (see Table 2.7.2 for details).

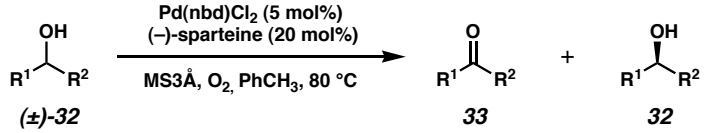


Observation of Background Oxidation/Reduction Pathways (Scheme 2.3.2). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.0250 mmol), dppe (10.0 mg, 0.0250 mmol), and NaO*t*-Bu (96.1 mg, 1.00 mmol) in 5.0 mL CH_2Cl_2 at 23 °C was added 1-cyclohexylethanol (69.0 μl, 0.500 mmol), then 4'-iodoacetophenone (246 mg, 1.00 mmol). The solution was heated to 30 °C and stirred. After 11 h, the solution was cooled to room temperature and quenched with H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Alcohols **55**, **63**, and **20**, and ketones **62**, **61**, and **21** were all detected by ^{1}H NMR.



General Procedure for the Oxidative Kinetic Resolution of Secondary Alcohols. Ligand and Palladium Source Screening Trials (Tables 2.3.4 and 2.3.5). A 25 mL

Schlenk flask equipped with a magnetic stir bar was charged with powdered molecular sieves (MS3Å, 0.25 g) and flame-dried under vacuum. After cooling under dry N_2, Pd complex (0.025 mmol, 0.05 equiv) was added followed by toluene (5.0 mL), and then an appropriate ligand (0.10 mmol, 0.20 equiv). The flask was vacuum-evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. The alcohol (0.50 mmol, 1.0 equiv) was introduced and the reaction monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values. Aliquots of the reaction mixture (0.2 mL) were collected after 24 h, 40 h, 72 h, 96 h, 120 h, and 144 h depending on the course of the reaction (typically three aliquots per run). Each aliquot was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed.[57]

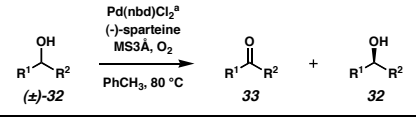


General Procedure for the Oxidative Kinetic Resolution of Secondary Alcohols. Preparative Runs (6.0 mmol) in Table 2.7.1. A 200 mL flask equipped with a magnetic stir bar was charged with powdered molecular sieves (MS3Å, 3.0 g) and flame-dried under vacuum. After cooling under dry N_2, Pd(nbd)Cl_2 (80.8 mg, 0.30 mmol, 0.05 equiv) was added followed by toluene (60.0 mL), and then (–)-sparteine (276 mL, 1.20 mmol, 0.20 equiv). The flask was vacuum-evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. The racemic alcohol (6.00 mmol, 1.0 equiv) was introduced, and the reaction was monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess

values. Aliquots of the reaction mixture (0.2 mL) were collected after 24 h, 40 h, 72 h, 96 h, 120 h, and 144 h depending on the course of the reaction (typically three aliquots per run). Each aliquot was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed. Upon completion of the reaction, the reaction mixture was filtered through a pad of SiO_2 (EtOAc eluent) and purified by column chromatography on SiO_2 (see below for details).

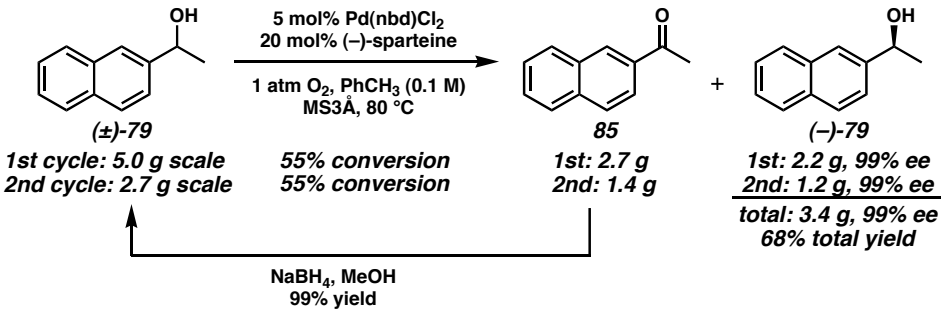
General Procedure for the Oxidative Kinetic Resolution of Secondary Alcohols. Preparative Runs (8.0 mmol) in Table 2.7.1. A 200 mL flask equipped with a magnetic stir bar was charged with powdered molecular sieves (MS3Å, 4.0 g) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (108 mg, 0.40 mmol, 0.05 equiv) was added followed by toluene (80.0 mL), and then (–)-sparteine (368 mL, 1.60 mmol, 0.20 equiv). The flask was vacuum evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. The alcohol (8.00 mmol, 1.0 equiv) was introduced and the reaction monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values. Aliquots of the reaction mixture (0.2 mL) were collected after 24 h, 40 h, 72 h, 96 h, 120 h, and 144 h depending on the course of the reaction (typically three aliquots per run). Each aliquot was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed. Upon completion of the reaction, the reaction mixture was filtered through a pad of SiO_2 (EtOAc eluent) and purified by column chromatography on SiO_2 (see below for details).

Table 2.7.1 Oxidative kinetic resolution on preparative scale.



entry	racemic alcohol	amount	time	conversion	chromatography eluent	isolated yield of ketone	unreacted alcohol, major enantiomer	isolated yield ROH	ee ROH[b]	s[c,d]
1	R = H	0.977 g (8.00 mmol)	96 h	59.9%	6:1→3:1 hexane/EtOAc	0.535 g (56%)	R = H	0.366 g (37%)	98.7%	23.1
2	R = OMe	1.22 g (8.00 mmol)	96 h	66.6%	6:1→3:1 hexane/EtOAc	0.773 g (64%)	R = OMe	0.392 g (32%)	98.1%	12.3
3	R = F	1.12 g (8.00 mmol)	54 h	63.3%	6:1→3:1 hexane/EtOAc	0.623 g (56%)	R = F	0.361 g (32%)	97.4%	14.4
4	Ar = 1-Naphthyl	1.03 g (6.00 mmol)	192 h	55.9%	6:1→3:1 hexane/EtOAc	0.555 g (54%)	Ar = 1-Naphthyl	0.443 g (43%)	78.4%	9.8
5	Ar = 2-Naphthyl	5.00 g (29.00 mmol)	112 h	55.2%	6:1→3:1 hexane/EtOAc	2.75 g (55%)	Ar = 2-Naphthyl	2.20 g (44%)	99.0%	47.1
6	Ar = *o*-tolyl	1.09 g (8.00 mmol)	144 h	48.4%	6:1→3:1 hexane/EtOAc	0.492 g (46%)	Ar = *o*-tolyl	0.533 g (49%)	68.7%	13.1
7		1.09 g (8.00 mmol)	192 h	59.3%	6:1→4:1 hexane/EtOAc	0.625 g (58%)		0.435 g (40%)	93.1%	14.8
8	n = 1	1.07 g (8.00 mmol)	54 h[e]	67.5%	6:1→3:1 hexane/EtOAc	0.662 g (63%)	n = 1	0.323 g (30%)	93.4%	8.3
9	n = 2	1.19 g (8.00 mmol)	40 h	68.6%	9:1→4:1 hexane/EtOAc	0.796 g (68%)	n = 2	0.370 g (31%)	99.8%	15.8
10		0.973 g (6.00 mmol)	120 h	70.4%	6:1→3:1 hexane/EtOAc	0.671 g (70%)		0.286 g (29%)	91.8%	6.6

[a]5 mol% $Pd(nbd)Cl_2$, 20 mol% (–)-sparteine, 1 atm O_2. [b]The degree of enantiomeric excess was measured directly by chiral HPLC or GC of the recovered alcohols.[58] [c]Selectivity (s) values represent an average of at least two experiments, while conversion and ee values are for specific cases. [d]For each entry, comparable selectivities are observed throughout the course of the run. [e]Experiment performed at 60 °C.



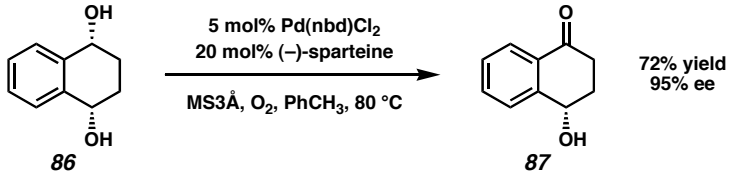
Scale-up Procedure for the Two-Cycle Oxidative Kinetic Resolution of α-methyl-2-naphthalenemethanol 79. 1st cycle: A 500 mL round bottom flask was charged with powdered molecular sieves (MS3Å, 14.5 g) and a magnetic stir bar and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (0.391 g, 1.45 mmol, 0.05 equiv) was added followed by toluene (290 mL), and then (–)-sparteine (1.34 mL, 5.81 mmol, 0.20

equiv). The flask was vacuum evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. Alcohol **(±)-79** (5.00 g, 29.0 mmol, 1.0 equiv) was introduced and the reaction mixture heated at 80 °C for 112 h. Progress of the reaction was monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values by the removal of small aliquots of the reaction mixture (0.2 mL), which were filtered through silica gel (EtOAc eluent), evaporated, and analyzed. After the reaction rate had significantly slowed (112 h, 55% conversion), and aliquot analysis showed a high level of enantiopurity for the remaining alcohol **(–)-79** (99.0% ee), the entire reaction mixture was filtered through a small column of silica gel (5 x 6 cm, EtOAc eluent). The filtrate was evaporated and purified by flash chromatography on silica gel (6:1 to 3:1 hexanes/EtOAc eluent) to provide ketone **85** (R_F = 0.42 in 4:1 hexanes/EtOAc, 2.75 g, 55% yield) and alcohol **(–)-79** (R_F = 0.22 in 4:1 hexanes/EtOAc, 2.20 g, 44% yield, 99.0% ee) as white solids.

Regeneration of alcohol (±)-79. A cooled (0 °C) solution of ketone **85** (2.75 g, 16.2 mmol, 1.0 equiv) in 1:1 CH_2Cl_2/MeOH (16.2 mL) was treated with $NaBH_4$ (733 mg, 19.4 mmol, 1.2 equiv) in four portions over 10 min. The reaction was stirred at 0 °C for 15 min and treated with 1 N HCl solution (30 mL) slowly over 15 min. After the evolution of gas was complete, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, evaporated, and purified by flash chromatography on silica gel (3:1 hexanes/EtOAc eluent) to provide alcohol **(±)-79** (2.76 g, 99% yield) as a white solid, which was used in cycle two.

2nd cycle: A 500 mL round bottom flask was charged with molecular sieves (MS3Å, 8.0 g) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (0.216 g,

0.800 mmol, 0.05 equiv) was added followed by toluene (160 mL), and then (–)-sparteine (0.735 mL, 3.20 mmol, 0.20 equiv). The flask was vacuum evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. Alcohol **(±)-79** (2.76 g, 16.0 mmol, 1.0 equiv) prepared above was introduced and the reaction mixture heated at 80 °C for 96 h. Progress of the reaction was monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values by the removal of small aliquots (0.2 mL), which were filtered through silica gel (EtOAc eluent), evaporated, and analyzed. After the reaction rate had significantly slowed (81 h, 55% conversion), and aliquot analysis showed a high level of enantiopurity for the remaining alcohol **(–)-79** (99.0% ee), the entire reaction mixture was filtered through a small column of silica gel (5 x 6 cm, EtOAc eluent). The filtrate was evaporated and purified by flash chromatography on silica gel (6:1 to 3:1 hexanes/EtOAc eluent) to provide ketone **85** (1.43 g, 54% yield) and alcohol **(–)-79** (1.20 g, 44% yield, 99.0% ee) as white solids. The combination of both cycles provided alcohol **(–)-79** (3.39 g, 68% yield, 99.0% ee).

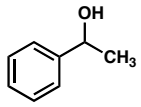
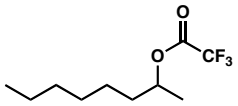
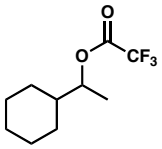
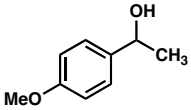
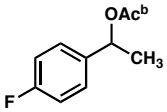
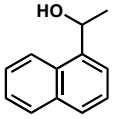
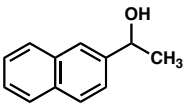


86 *87*

Oxidative Desymmetrization of Meso Diol 86. A 50 mL Schlenk flask equipped with a magnetic stir bar was charged with molecular sieves (MS3Å, 625 mg) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (16.8 mg, 0.0625 mmol, 0.05 equiv) was added followed by toluene (12.5 mL), and then (–)-sparteine (57 mL, 0.25 mmol, 0.20 equiv). The flask was vacuum evacuated and filled with O_2 (3x, balloon),

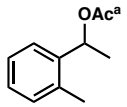
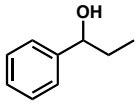
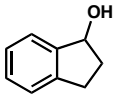
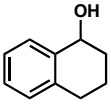
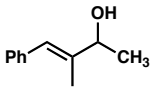
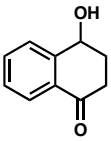
and the reaction mixture was heated to 80 °C for 10 min. Diol **86** (205 mg, 1.25 mmol, 1.0 equiv) was introduced and the reaction monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values. Upon completion of the reaction, the reaction mixture was filtered through a pad of SiO_2 (EtOAc eluent) and purified by column chromatography on SiO_2 (3:1 to 1:1 hexane/EtOAc eluent) to provide hydroxyketone **(+)-87** as an oil (145 mg, 72% yield, 95% ee); $[\alpha]_D^{23}$ +19.6 (*c* 1.0, MeOH).[59] See Table 2.7.2 for details regarding the ee assay.

Table 2.7.2 Methods utilized for the determination of enantiomeric excess.

entry	Substrate	ee Assay	Conditions	Retention Time of (*R*) isomer (min)	Retention Time of (*S*) isomer (min)
1	 *20*	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	10.69	13.37
2	 *124*	GC Chiraldex G-TA	50 °C, 0 min 5 °C/min to 200 °C 1.0 mL/min carrier gas flow	7.72[a]	7.94[a]
3	 *125*	GC Chiraldex G-TA	50 °C, 25 min 5 °C/min to 200 °C 1.0 mL/min carrier gas flow	30.17[a]	30.45[a]
4	 *76*	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	14.60	16.52
5	 *126*	GC Chiraldex B-DM	50 °C, 0 min 5 °C/min to 200 °C 1.0 mL/min carrier gas flow	16.41	15.78
6	 *78*	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	31.99	18.96
7	 *79*	HPLC Chiralcel OJ	4% 2-propanol/hexane 1.0 mL/min	38.69	31.32

a. Prepared by reaction of the alcohol with TFAA; absolute configuration not determined.
b. Prepared by reaction of the alcohol with Ac_2O and pyridine.

Table 2.7.2 (continued)

entry	Substrate	ee Assay	Conditions	Retention Time of (*R*) isomer (min)	Retention Time of (*S*) isomer (min)
8	 *127*	GC Chiraldex B-DM	85 °C, 45 min 1.0 mL/min carrier gas flow	42.17	40.71
9	 *81*	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	11.15	13.23
10	 *82*	HPLC Chiralcel OJ	3% EtOH/hexane 1.0 mL/min	17.35	14.76
11	 *83*	HPLC Chiralcel AS	2% EtOH/hexane 1.0 mL/min	15.55	12.68
12	 *84*	HPLC Chiralcel OD-H	4% 2-propanol/hexane 1.0 mL/min	13.44	15.44
13	 *87*	HPLC Chiralcel AS	6% 2-propanol/hexane 1.0 mL/min	37.97	30.44

a. Prepared by reaction of the alcohol with Ac_2O and pyridine.

Table 2.7.3 Selected experimental data for the determination of conversion, enantiomeric excess, and selectivity (s).

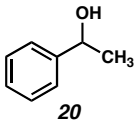
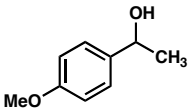
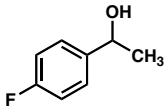
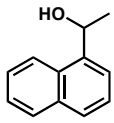
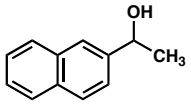
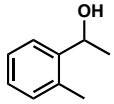
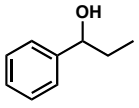
entry	Substrate	time (h)	% Conversion	Measured %ee, unreacted ROH	s
1	 *20*	19 40 96 96	35.7 47.4 59.9 57.1	48.6 75.7 98.7 96.6	24.3 26.1 23.1 24.8
2	 *76*	40 96 96 96 120	50.8 64.8 66.6 65.8 66.0	72.5 97.6 98.1 98.3 98.9	12.2 13.1 12.3 13.3 14.3
3	 *77*	48 54 60 72	63.9 63.3 65.7 65.2	96.1 97.4 96.9 97.9	12.3 14.4 11.6 13.2
4	 *78*	40 144 144 168 192	26.5 47.4 47.4 54.5 55.9	27.3 62.2 61.8 76.6 78.4	9.4 10.2 10.0 10.2 9.8
5	 *79*	81 112	55.1 55.2	99.0 99.0	48.0 47.1
6	 *80*	96 96 144 144	34.2 40.5 39.5 48.4	41.6 52.0 48.7 68.7	13.5 12.5 11.1 13.1
7	 *81*	40 48 96 96 192	30.3 41.6 57.2 55.7 59.3	34.4 55.0 89.0 86.8 93.1	12.0 13.4 14.4 15.0 14.8

Table 2.7.3 (continued)

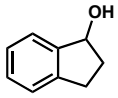
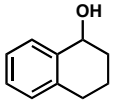
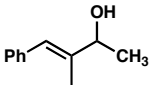
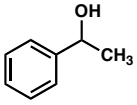
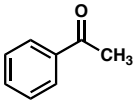
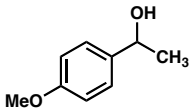
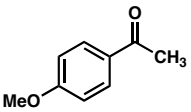
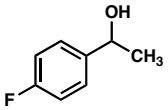
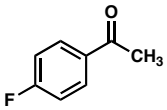
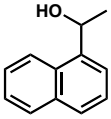
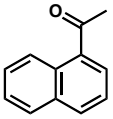
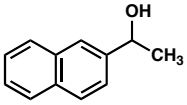
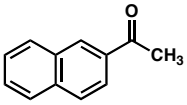
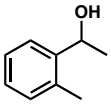
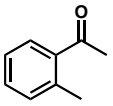
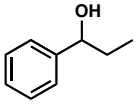
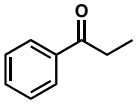
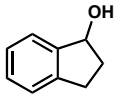
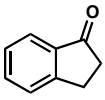
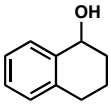
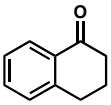
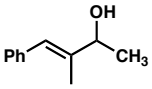
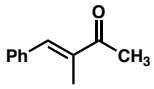
entry	Substrate	time (h)	% Conversion	Measured %ee, unreacted ROH	s
8	 *82*	48 54 96	65.2 67.5 68.0	92.5 93.4 90.0	9.1 8.3 6.9
9	 *83*	40 40 48 96 96	68.6 59.9 67.6 68.7 69.3	99.8 95.2 99.7 99.9 99.9	15.8 16.1 15.9 17.2 16.6
10	 *84*	40 96 120 144	46.0 66.2 70.4 68.4	54.5 85.9 91.8 90.7	7.7 6.6 6.6 7.0

Table 2.7.4 Methods utilized for the determination of % conversion.

entry	alcohol	ketone	GC Conditions[a]	Retention Time of alcohol (min)	Retention Time of ketone (min)
1	 ***20***	 ***21***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	29.03	26.02
2	 ***76***	 ***128***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	34.82	33.90
3	 ***77***	 ***129***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	29.82	25.93
4	 ***78***	 ***130***	70 °C, 0 min; 3.0 °C/min to 270 °C 1.0 mL/min carrier gas flow	50.74	44.91
5	 ***79***	 ***85***	70 °C, 0 min; 3.0 °C/min to 270 °C 1.0 mL/min carrier gas flow	36.17	35.96
6	 ***80***	 ***131***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	31.01	26.68
7	 ***81***	 ***132***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	30.06	27.43

[a]All assays performed on Agilent DB-WAX column.

Table 2.7.4 (continued)

entry	alcohol	ketone	GC Conditions[a]	Retention Time of alcohol	Retention Time of ketone
8	 ***82***	 ***133***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	33.12	32.20
9	 ***83***	 ***134***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	34.90	33.39
10	 ***84***	 ***135***	70 °C, 15 min; 5.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	25.37	23.04

[a]All assays performed on Agilent DB-WAX column.

2.8 Notes and References

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1999, pp 1234-1249. (b) Luzzio, F. A. *Org. React*. **1998**, *53*, 1-221. (c) Tidwell, T. T. *Org. React*. **1990**, *39*, 297-572. (d) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph Series; American Chemical Society: Washington, D.C., 1990.

(2) Portions of this research have been described in a previous communication. See, Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc*. **2001**, *123*, 7725-7726.

(3) Simultaneous to our work, a related system was reported by Sigman. See, (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc*. **2001**, *123*, 7475-7476.

(4) For an excellent discussion on nonenzymatic kinetic resolutions, see, Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal*. **2001**, *343*, 5-26.

(5) For a monograph describing enzymatic approaches to kinetic resolution, see, Wong, C. -H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, U.K., 1994.

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