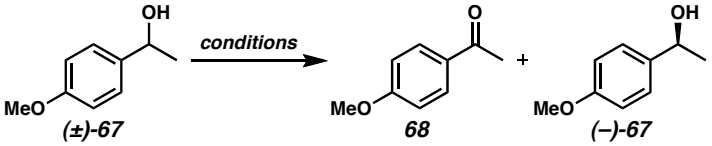
CHAPTER 3

Scope and Applications of the Oxidative Kinetic Resolution of Secondary Alcohols

3.1 Background and Introduction

The previously described methodology for the palladium-catalyzed oxidative kinetic resolution of secondary alcohols has led to the development of four distinct sets of conditions for this process (Table 3.1.1): the original conditions (A) in toluene with no exogenous base,[1] the rate enhanced conditions (B) that take advantage of cesium carbonate and *tert*-butyl alcohol additives,[2] and the chloroform conditions at 23 °C under an atmosphere of either molecular oxygen (C) or ambient air (D).[3,4] 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 alcohols 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 *s* factor 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.[5]

Table 3.1.1 Various conditions for enantioselective alcohol oxidation.



entry	conditions	time	conversion[a]	ee[b]	*s*
A	**$Pd(nbd)Cl_2$ (5 mol%)** **(–)-sparteine (*28*, 20 mol%)** $PhCH_3$ (0.1 M), O_2 MS3Å, 80 °C	96 h	66.6%	98.1%	12
B	**$Pd(nbd)Cl_2$ (5 mol%)** **(–)-sparteine (*28*, 20 mol%)** Cs_2CO_3 (0.5 equiv) *t*-BuOH (1.5 equiv) $PhCH_3$ (0.25 M), O_2 MS3Å, 60 °C	9.5 h	67.4%	99.5%	15
C	**$Pd(nbd)Cl_2$ (5 mol%)** **(–)-sparteine (*28*, 12 mol%)** Cs_2CO_3 (0.4 equiv) $CHCl_3$ (0.25 M), **O_2** MS3Å, 23 °C	48 h	62.6%	99.9%	27
D	**$Pd(nbd)Cl_2$ (5 mol%)** **(–)-sparteine (*28*, 12 mol%)** Cs_2CO_3 (0.4 equiv) $CHCl_3$ (0.25 M), **Air** MS3Å, 23 °C	24 h	62.3%	99.8%	25

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

Initially, the investigated scope of this reaction was limited. A broad survey of secondary alcohols was undertaken in order to evaluate the generality of the conditions toward oxidation and successful resolution. Furthermore, these studies were intended to test the developed selectivity models of the catalyst.[6] Finally, substrate scope exploration would demonstrate the utility of the process, leading to practical applications.

3.2 Substrate Scope of the Palladium-Catalyzed Enantioselective Oxidation

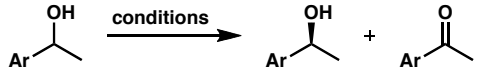
3.2.1 Benzylic Alcohols[†]

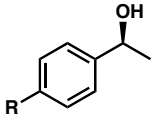
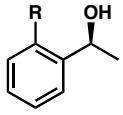
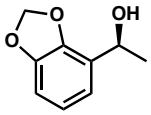
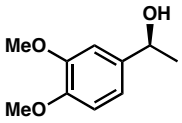
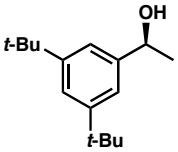
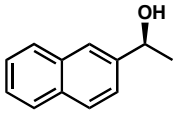
Early substrate scope investigations focused on benzylic alcohols.[1-3] Many members of this class of alcohols are commercially available or readily prepared as

[†] This work was performed in collaboration with Eric M. Ferreira (Ph.D. 2005), Jeffrey T. Bagdanoff (Ph.D. 2005), Daniel D. Caspi (Ph.D. 2008), and Ryan M. McFadden (Ph.D. 2007), graduate students in the Stoltz group at California Institute of Technology.

racemates. In particular, 1-arylethanols are easily accessible. Furthermore, the aryl and methyl groups are sterically and electronically quite different. Thus, the palladium catalyst is highly successful in distinguishing enantiomers in the oxidation, leading to high selectivity across a range of aryl groups (Table 3.2.1). Substrates with electron-rich aromatic rings are the most successful in this transformation. Substitution on the aryl ring at the 3- and 4-positions (entries 1-12, 18, 22-25) is well tolerated. Ortho-substitution leads to much slower rates of oxidation (entries 13-15, 26 and 27), although reactivity improves if the substituent is constrained in a ring (entries 16 and 17). 3,5-substituted aromatic rings, even with bulky substituents, are resolved with excellent *s* factors. Some heteroaromatic substrates (entries 28 and 29) can be resolved to high enantiomeric excesses as well.

Table 3.2.1 Resolution of 1-arylethanols.

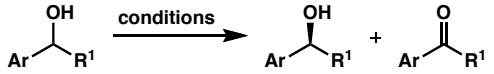


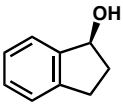
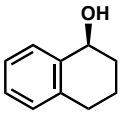
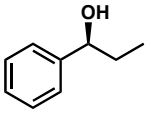
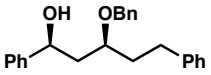
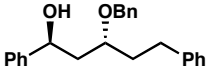
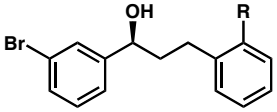
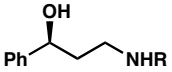
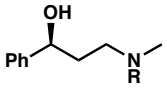
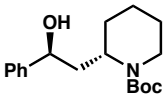
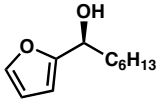
entry	alcohol, major enantiomer		conditions[a]	time	conversion[b]	alcohol ee[c]	*s*
1		***(–)-25***: R = H	A	96 h	59.9%	98.7%	23
2			B	12.5 h	63.9%	99.6%	20
3			C	48 h	59.9%	99.7%	31
4			D	24 h	54.0%	93.3%	30
5		***(–)-67***: R = OMe	A	96 h	66.6%	98.1%	12
6			B	9.5 h	67.4%	99.5%	15
7			C	48 h	62.6%	99.9%	27
8			D	24 h	62.3%	99.8%	25
9		***(–)-71***: R = F	A	54 h	63.3%	97.4%	14
10			B	12.5 h	65.7%	97.4%	12
11			C	48 h	59.3%	98.0%	23
12			D	24 h	56.7%	93.0%	20
13		***(–)-72***: R = Me	A	144 h	48.4%	68.7%	13
14			C	63 h	40.1%	49.2%	11
15		***(–)-73***: R = OMe	C	114 h	58.4%	83.9%	10
16		***(–)-74***	B	15 h	56.5%	99.7%	47
17			C	12 h	55.0%	95.0%	29
18		***(–)-75***	B[d]	18 h	63.8%	98.3%	15
19		***(–)-76***	A	28 h	51.9%	92.7%	44
20			C	24 h	54.3%	98.0%	47
21			D	22 h	53.9%	98.3%	54
22		***(–)-77***	A	112 h	55.2%	99.0%	47
23			B	12 h	66.1%	99.4%	16
24			C	48 h	59.3%	99.6%	31
25			D	24 h	55.5%	98.0%	37
26		***(–)-78***: Ar = 1-Naphthyl	A	192 h	55.9%	78.4%	9.8
27			C	97 h	51.2%	65.9%	8.5
28		***(–)-79***: Ar = 2-Furyl	A	120 h	66.9%	93.8%	8.3
29		***(–)-80***: Ar = 3-Furyl	A	120 h	67.4%	93.5%	8.8

[a] For conditions, see Table 3.1.1. [b] Measured by GC or NMR. [c] Measured by chiral HPLC or chiral GC. [d] Conducted at 40 °C.

Benzylic alcohols with other structural variations are also tolerated by the catalyst system (Table 3.2.2). Cyclic benzylic alcohols are able to be resolved successfully. 1-Indanol (**81**, entries 1-3) is oxidized rapidly, albeit with decreased selectivity, compared to 1-tetralol (**82**, entries 4-7). Alcohols with a variety of β-heteroatom substituents, such as ethers (entries 12 and 13) and protected amines (entries 16-20),[7,8] can be resolved with good selectivity. Other functional groups on the alcohol substrate, including alkyl chains (entries 8-11, 21), a methyl ester (**86**, entry 14), a tertiary alcohol (**87**, entry 15), and even aryl bromides (entries 14 and 15), are tolerated under the reaction conditions.

Table 3.2.2 Resolution of other benzylic alcohols.



entry	alcohol, major enantiomer	conditions[a]	time	conversion[b]	alcohol ee[c]	*s*
1	 ***(+)-81***	A[d]	54 h	67.5%	93.4%	8.3
2		B[e]	12 h	74.0%	99.5%	10
3		C	24 h	68.5%	97.5%	10
4	 ***(+)-82***	A	40 h	68.6%	99.8%	16
5		B[e]	12 h	61.5%	99.0%	21
6		C	24 h	57.5%	98.0%	28
7		D	16 h	60.2%	99.6%	28
8	 ***(–)-83***	A	192 h	59.3%	93.1%	15
9		B[f]	4.5 h	62.8%	98.0%	16
10		C	72 h	62.6%	98.2%	24
11		D	48 h	56.8%	94.9%	22
12	 ***(1S,3S)-84***	C[e]	72 h	57.7%	99.0%	32
13	 ***(1S,3R)-85***	C[e]	72 h	53.0%	88.2%	24
14	 ***(S)-86***: R = CO_2Me	B[f]	4.5 h	62.5%	92.9%	11
15	***(–)-87***: R = $C(OH)Me_2$	B[f]	4.5 h	70.6%	99.9%	15
16	 ***(–)-88***: R = Ac	A	14.5 h	70.0%	97.0%	9.0
17	***(–)-89***: R = Boc	A	24 h	57.5%	93.1%	18
18	 ***(S)-90***: R = Ac	C	24 h	52.3%	82.1%	18
19	***(S)-91***: R = Boc	C	24 h	57.5%	95.1%	21
20	 ***(–)-92***	D	60 h	53.8%	94.2%	33
21	 ***(S)-93***	C	122 h	55.4%	75.4%	9.0

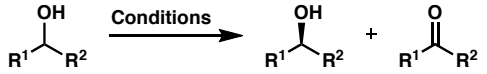
[a-c] See Table 3.2.1 footnotes. [d] Conducted at 60 °C. [e] Conducted at 40 °C. [f] Conducted at 80 °C.

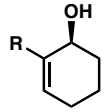
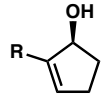
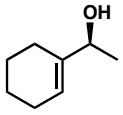
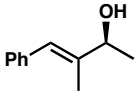
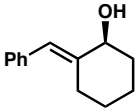
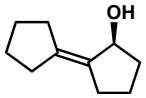
3.2.2 Allylic Alcohols

The broad utility of chiral allylic alcohols in organic synthesis led to an investigation of this important class of molecules next. Conditions in chloroform are particularly effective for these substrates, providing enhanced selectivity over the other

methods (Table 3.2.3). These studies demonstrate the importance of steric factors in determining catalyst selectivity. Cyclohexenols with relatively small substituents (entries 1-4) are oxidized rapidly but with low selectivity. However, the enantiomers of alcohols with larger substituents (entries 5-7) are better distinguished by the catalyst, leading to higher *s* factors. Cyclopentenols (entries 14-24) undergo faster oxidation with lower selectivity than their cyclohexenol counterparts (entries 2-13). Of particular note are vinyl bromides (entries 8-10, 18-20), which decompose rapidly with darkening of the reaction mixture at elevated temperatures, indicating the formation of aggregated Pd(0). Under conditions at 23 °C, on the other hand, little catalyst decomposition is observed and reactions proceed to desirable (50-70%) conversion values. While cyclopentenol **101** is oxidized fast enough to allow moderate resolution at 60 °C with cesium carbonate and *tert*-butyl alcohol (entry 19), cyclohexenol **97** is resolved successfully only at lower temperatures (entries 9 and 10). Alkyl enol ethers are stable in the reactions and are resolved to high enantiomeric excess (entries 11-13, 21-24), providing access to enantioenriched α-hydroxyketone derivatives. The catalyst is also tolerant of a variety of alkene substitution patterns (entries 25-40), again generally displaying higher enantiomer preference in chloroform at 23 °C than in toluene at higher temperatures. Resolution of acyclic allylic alcohols has proven more challenging, though Eric Ferreira and Jeffrey Bagdanoff, graduate students in these laboratories, found that allylic alcohol **104** could be obtained with good selectivity at 23 °C in chloroform (entries 31 and 32).

Table 3.2.3 Resolution of cyclic allylic alcohols.



entry	alcohol, major enantiomer	conditions[a]	time	conversion[b]	alcohol ee[c]	*s*
1	 ***(–)-94***: R = H	A	4 h	63.5%	8.1%	1.2
2	***(–)-95***: R = Me	A	7 h	59.1%	36.6%	2.3
3		B	8 h	78.6%	95.8%	5.4
4		C	24 h	69.3%	84.5%	5.4
5	***(–)-96***: R = *i*-Pr	A	28.5 h	65.9%	95.9%	11
6		B	50 h	64.8%	84.2%	6.7
7		C	31 h	51.2%	74.0%	13
8	***(–)-97***: R = Br	A	73 h	25.7%	30.0%	19
9		C	33 h	63.9%	96.1%	12
10		D	25 h	54.7%	86.3%	16
11	***(S)-98***: R = O*i*-Bu	A	94 h	56.2%	73.1%	7.8
12		B	50 h	34.0%	34.5%	7.1
13		C	74 h	52.2%	85.9%	23
14	 ***(S)-99***: R = Me	C	8 h	66.1%	65.8%	3.7
15	***(–)-100***: R = *i*-Pr	A	25 h	66.6%	76.0%	4.8
16		B	21 h	71.9%	93.0%	6.5
17		C	31 h	76.0%	93.7%	5.5
18	***(S)-101***: R = Br	A	24 h	42.5%	29.4%	3.0
19		B	4 h	75.1%	97.2%	7.0
20		C	24 h	63.6%	75.6%	5.4
21	***(S)-102***: R = O*i*-Bu	A	69 h	68.3%	90.9%	7.1
22		B	50 h	69.8%	99.0%	11
23		C	45 h	65.4%	99.0%	15
24		D	24 h	57.4%	96.9%	17
25	 ***(–)-103***	A	13 h	45.5%	57.4%	9.5
26		B	7.5 h	63.5%	74.1%	5.2
27		C	43 h	63.7%	96.5%	13
28		D	42.5 h	60.5%	91.4%	12
29	 ***(+)-104***	A	120 h	70.4%	91.8%	6.6
30		B	12 h	65.1%	87.9%	7.5
31		C	48 h	62.6%	98.7%	18
32		D	44 h	64.7%	98.9%	16
33	 ***(–)-105***	A	25 h	51.6%	69.1%	9.5
34		B	21 h	57.0%	79.7%	9.5
35		C	45 h	56.8%	90.9%	17
36		D	24 h	62.7%	98.4%	17
37	 ***(+)-106***	A	48 h	53.7%	80.9%	14
38		B	10 h	62.3%	84.2%	7.7
39		C	75 h	57.4%	93.8%	19
40		D	24 h	58.0%	78.0%	8.2

[a-c] See Table 3.2.1 footnotes.

The successful resolution of benzylic alcohols prompted an exploration of aryl substituents on cyclic allylic alcohols. These substrates are readily prepared via Suzuki coupling of arylboronate esters and iodoenones[9] followed by Luche reduction (Scheme 3.2.1).[10] Gratifyingly, subjection of these alcohols to any of our developed kinetic resolution conditions affords highly enantioenriched allylic alcohols (Table 3.2.4).[11] Both electron-rich (entries 9-12) and electron-poor (entries 17-19) 2-aryl substituents lead to excellent selectivity. The lack of a large electronic influence on these resolutions suggests selectivity is primarily due to steric factors. Reactivity, on the other hand, is not adversely affected by the arene substituent. In many cases, these alcohols are oxidized as fast as 2-alkyl substituted alcohols (e.g., **95**, **96**, **99**, and **100**). Even heteroaromatic substitution (entries 28-31) and a larger ring size (entries 32-34) are tolerated, in some cases with exceptionally high selectivity (entry 32, s = 122), albeit with somewhat longer reaction times.

Scheme 3.2.1 Synthesis of 2-arylcycloalkenols.

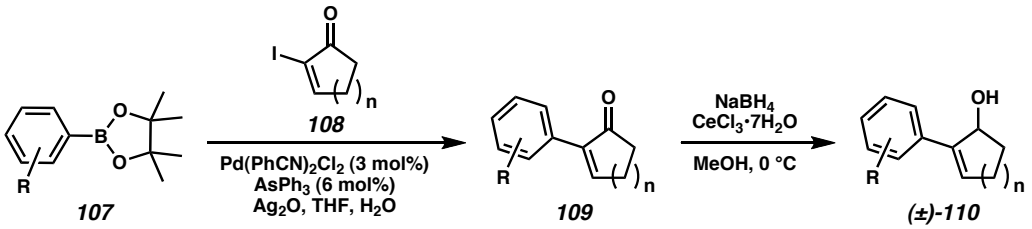
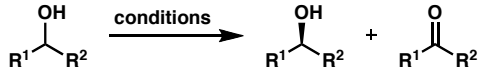
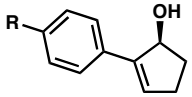
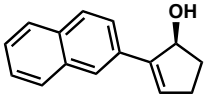
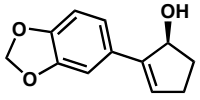
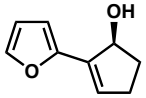
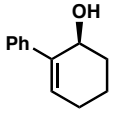


Table 3.2.4 Resolution of 2-arylcycloalkenols.



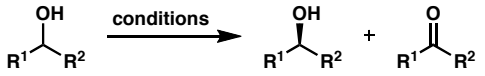
entry	alcohol, major enantiomer	conditions[a]	time	conversion[b]	alcohol ee[c]	*s*
1	 ***(+)-111***: R = H	A	7 h	57.0%	99.7%	44
2		B	1.5 h	52.8%	99.0%	85
3		C	12 h	57.4%	99.0%	33
4		D	10 h	55.8%	99.0%	42
5	***(+)-112***: R = Me	A	10 h	54.8%	92.4%	24
6		B	3.5 h	57.6%	98.8%	31
7		C	11 h	58.8%	99.1%	28
8		D	10 h	55.7%	98.5%	39
9	***(+)-113***: R = OMe	A	31 h	58.0%	99.0%	30
10		B	1.5 h	53.9%	97.3%	46
11		C	24 h	55.0%	92.1%	23
12		D	28.5 h	55.5%	89.0%	17
13	***(+)-114***: R = F	A	10 h	57.4%	99.0%	33
14		B	3.5 h	60.1%	99.0%	24
15		C	11 h	57.9%	98.9%	30
16		D	10 h	58.2%	97.8%	25
17	***(+)-115***: R = CF_3	A	10 h	59.2%	99.0%	26
18		B	1.5 h	62.9%	99.0%	18
19		C	10 h	56.5%	93.6%	21
20	 ***(+)-116***	A	10 h	58.6%	99.0%	28
21		B	1.5 h	53.1%	93.6%	37
22		C	11 h	60.8%	99.0%	22
23		D	10 h	56.1%	99.0%	40
24	 ***(+)-117***	A	24 h	54.1%	99.0%	59
25		B	1.5 h	60.6%	98.8%	22
26		C	10 h	59.4%	98.9%	25
27		D	6 h	56.8%	96.9%	27
28	 ***(+)-118***	A	49 h	54.0%	87.3%	19
29		B	3 h	51.6%	92.1%	45
30		C	72 h	57.0%	95.8%	23
31		D	42.5 h	57.2%	97.6%	27
32	 ***(–)-119***	A	17 h	51.9%	99.0%	122
33		B	3 h	56.9%	97.1%	27
34		C	24 h	55.4%	96.8%	33

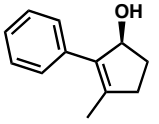
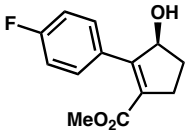
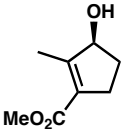
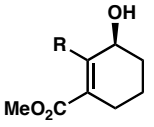
[a-c] See Table 3.2.1 footnotes.

Substitution at the 3-position of cyclic allylic alcohols was also explored (Table 3.2.5). Again, allylic alcohols with 2-aryl substituents are oxidized rapidly and with exceptionally high selectivity (entries 1-8). 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 9-19). Interestingly, analogous 2-alkyl allylic alcohols unsubstituted at the 3-position oxidize with poor selectivity (cf. Table 3.2.5, entries 9-16 and Table 3.2.3, entries 2-4 and 14).

Table 3.2.5 Resolution of 3-substituted allylic alcohols.



entry	alcohol, major enantiomer	conditions[a]	time	conversion[b]	alcohol ee[c]	*s*
1	 ***(–)-120***	A	4 h	52.9%	99.0%	83
2		B	1 h	53.0%	97.9%	64
3		C	9 h	57.9%	96.9%	23
4		D	6 h	55.4%	94.3%	26
5	 ***(–)-121***	A	4 h	55.6%	99.5%	44
6		B	1 h	55.5%	99.5%	45
7		C	9 h	50.8%	94.7%	83
8		D	20 h	52.8%	98.1%	70
9	 ***(–)-122***	A	8 h	73.3%	98.4%	8.6
10		B	1 h	60.7%	85.2%	9.0
11		C	8 h	74.8%	99.0%	8.7
12		D	8 h	67.6%	93.8%	8.4
13	 ***(–)-123***: R = Me	A	15 h	58.6%	88.4%	12
14		B	7.5 h	65.0%	99.0%	16
15		C	48 h	62.0%	95.1%	13
16		D	42.5 h	64.4%	96.9%	13
17	***(–)-124***: R = Bn	A	24 h	59.5%	87.2%	11
18		C	72 h	61.0%	90.9%	11
19		D	72 h	62.1%	92.5%	11

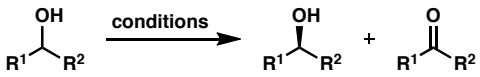
[a-c] See Table 3.2.1 footnotes.

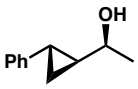
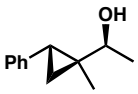
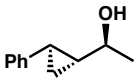
3.2.3 Cyclopropylcarbinyl Alcohols

Other activated racemic alcohols were also explored, such as α-cyclopropylcarbinyl alcohols. A number of substrates were exposed to our oxidative kinetic resolution conditions (Table 3.2.6). Again, the chloroform conditions are especially effective in providing highly selective oxidation (cf. entries 2 and 3, entries 6

and 7). Even 1-cyclopropylethanol (**125**, entries 1-4), with relatively little steric differentiation between alcohol substituents, is able to be resolved to high enantiomeric excess. From the appropriate diastereomerically pure racemates, these resolutions also produce alcohols with three contiguous stereocenters (entries 5-15), including a quaternary stereocenter adjacent to the alcohol (entries 9-11). Furthermore, for entries 5-15, the product ketones are also enantioenriched (Figure 3.2.1). 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.

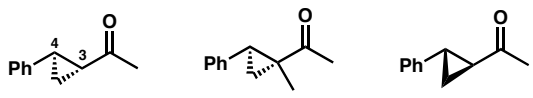
Table 3.2.6 Resolution of cyclopropylcarbinyl alcohols.



entry	alcohol, major enantiomer	conditions[a]	time	conversion[b]	alcohol ee[c]	*s*
1	 *(+)-125*	A	48 h	69.0%	99.0%	12
2		B	22 h	76.4%	96.3%	6.1
3		C	72 h	67.2%	99.0%	13
4		D	68 h	65.9%	95.5%	10
5	 *(+)-126*	A	24 h	68.1%	99.0%	13
6		B	3 h	58.2%	90.5%	14
7		C	25 h	58.6%	99.0%	28
8		D	10.5 h	47.1%	67.4%	14
9	 *(+)-127*	A	23 h	61.5%	77.9%	6.5
10		C	71 h	55.4%	99.0%	45
11		D	38 h	57.3%	89.2%	15
12	 *(–)-128*	A	17 h	65.5%	99.0%	15
13		B	9 h	71.4%	99.0%	10
14		C	24 h	50.8%	76.3%	15
15		D	14.5 h	46.5%	64.3%	13

[a-c] See Table 3.2.1 footnotes.

Figure 3.2.1 Enantioenriched ketones obtained from the resolution.



(–)-129 up to 87% ee

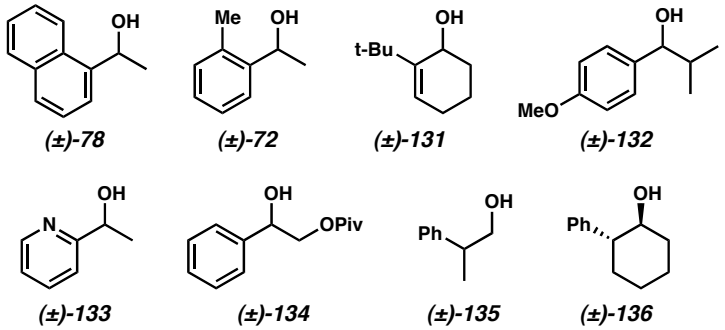
(–)-130 up to 85% ee

(+)-129 up to 74% ee

3.2.4 General Trends and Limitations

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 3.2.2). Benzylic alcohols with ortho-substituents (e.g., (±)-**78** and (±)-**72**) and sterically hindered alcohols such as (±)-**131** and (±)-**132** have dramatically decreased reaction rates. The presence of vicinal heteroatoms (e.g., (±)-**133** and (±)-**134**) impedes the oxidation, presumably through catalyst coordination and deactivation.[12] Finally, unactivated alcohols (e.g., (±)-**135** and (±)-**136**), particularly primary alcohols, are slow to oxidize under any of our developed conditions.[13]

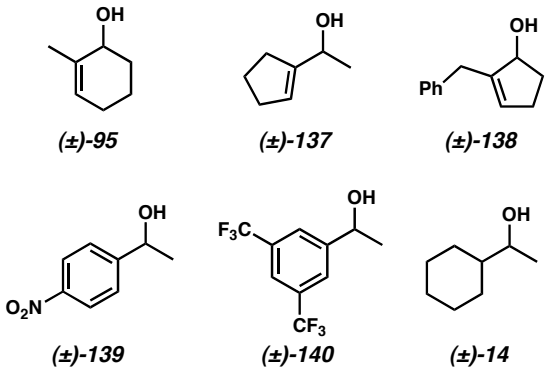
Figure 3.2.2 Alcohols of low reactivity in the oxidation.



In addition to unreactive alcohols, certain classes of alcohols are resolved with poor selectivity (Figure 3.2.3). In some cases, the steric difference between the two alcohol substituents seems too small for the catalyst to adequately distinguish between enantiomers (e.g., (±)-**95**, (±)-**137**, and (±)-**138**). Benzylic alcohols with electron-poor aromatic substituents are much less selectively resolved than their electron-rich counterparts (cf. (±)-**139** and (±)-**140** with Table 3.2.1, entries 5-8 and 19-21, respectively). At least in the case of benzylic alcohols, steric effects alone do not fully

account for these selectivity differences. Saturated alcohols, such as (±)-**14** also tend to display lower selectivity factors in the resolution.

Figure 3.2.3 Alcohols oxidized with low selectivity.

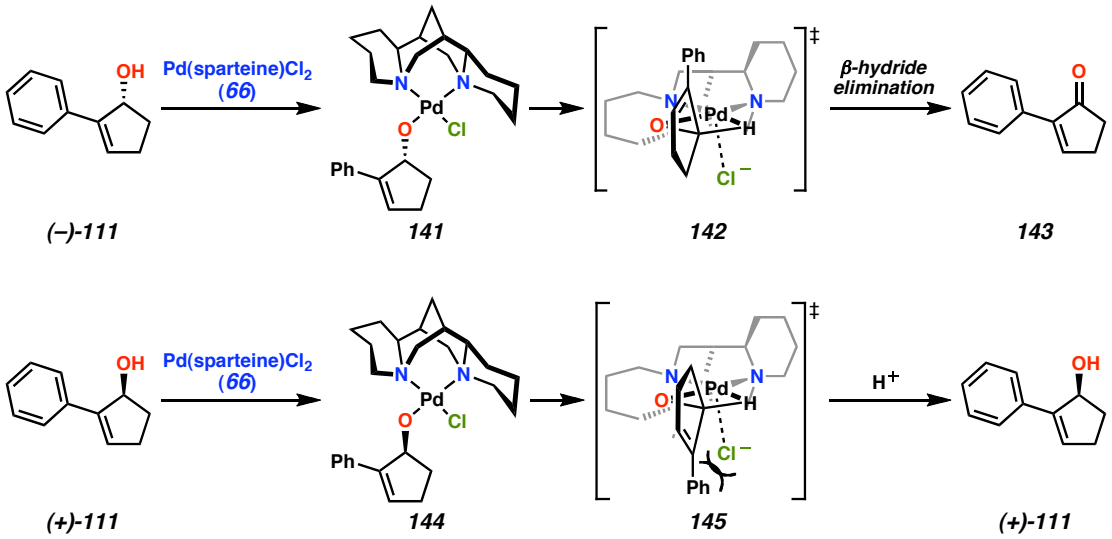


3.2.5 Selectivity Model

Theoretical calculations of the oxidative kinetic resolution by the Goddard group[14] and X-ray crystallographic analysis of a number of palladium complexes by Raissa Trend, a graduate student in these laboratories,[6] have led to a better understanding of the major factors involved in determining the preference of the catalyst for oxidation of one enantiomer of alcohol over the other. Key to high selectivity is a substrate-counterion interaction in the transition state for β-hydride elimination (Scheme 3.2.2). For a racemic mixture of alcohols (±)-**111**, poorly selective alcohol complexation forms a diastereomeric mixture of palladium alkoxides (**141** and **144**). Complex **141** is able to proceed through the β-hydride elimination transition state (**142**) by displacement of the coordinated chloride ion into an apical position of the complex to subsequently generate product ketone **143**. Diastereomeric complex **144**, on the other hand, develops an unfavorable steric interaction in the transition state (**145**), increasing the energy barrier for this process. Substrates such as cyclopentenol (±)-**111** are conformationally restricted

such that the projecting aryl ring is forced into the apical position of the resulting palladium alkoxide. Thus, the *S*-enantiomer has a significantly higher barrier to β-hydride elimination than the *R*-enantiomer, leading to the observed high selectivity factors. Similar steric effects can explain the observed selectivity for other classes of secondary alcohols as well.

Scheme 3.2.2 Model for selectivity of the resolution.

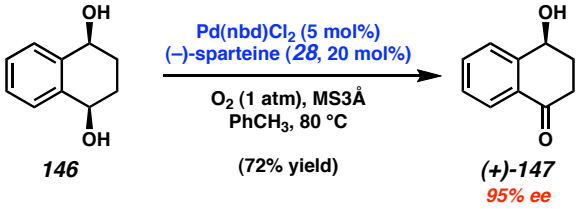


3.3 Applications

3.3.1 *meso*-Diol Desymmetrizations

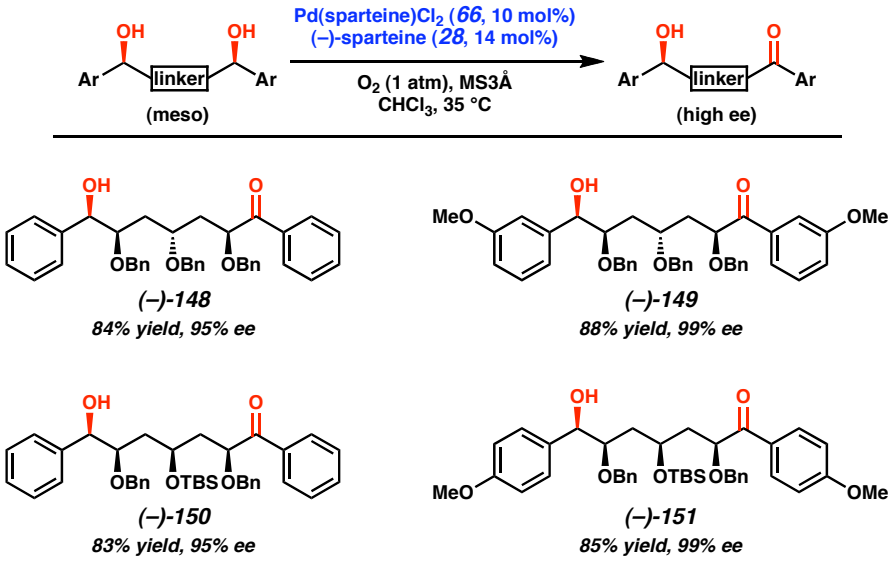
In addition to kinetic resolution, the catalyst system is well suited for selective oxidation of *meso*-diols to hydroxyketones. These reactions have the potential to provide highly enantioenriched products in greater than 50% yield. Eric Ferreira has demonstrated one example of this process with the initially developed resolution conditions (Scheme 3.3.1). Selective oxidation of diol **146** provides hydroxyketone (+)-**147** in 72% yield and 95% ee.[1]

Scheme 3.3.1 Desymmetrization of *meso*-diol **146**.



To further demonstrate the utility of the palladium-catalyzed enantioselective alcohol oxidation, Jeffrey Bagdanoff investigated several *meso*-diol arrays. Exploiting a bidirectional chain synthesis approach,[15,16] four diastereomerically pure *meso*-diols were prepared in a small number of steps. Exposure of these *meso*-diols to catalytic quantities of Pd(sparteine)Cl_2 (**66**) and (–)-sparteine (**28**) under a balloon of oxygen in chloroform provides highly enantioenriched hydroxyketones in excellent yields (Scheme 3.3.2). These reactions establish the absolute configuration of four stereocenters in a single catalytic asymmetric operation, allowing the construction of stereodefined 1,2- and 1,3-bis-ether arrays in high enantiomeric excesses.

Scheme 3.3.2 Desymmetrization of polyether *meso*-diols.

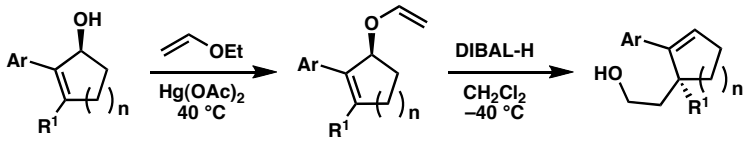


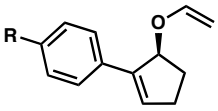
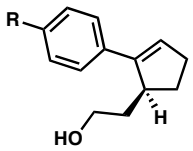
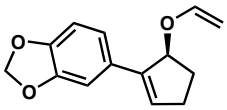
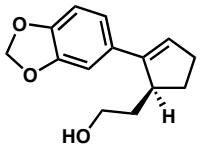
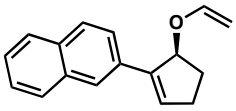
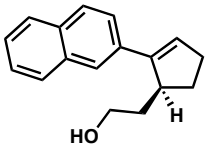
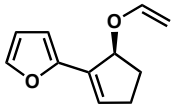
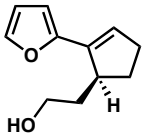
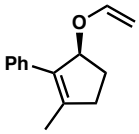
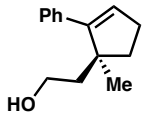
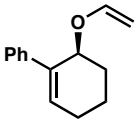
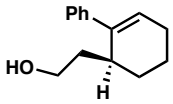
3.3.2 Kinetic Resolution / Claisen Sequence[‡]

To further highlight the utility of the enantioselective alcohol oxidation, the conversion of resolved alcohols into other synthetically useful building blocks was explored. The Claisen rearrangement of 2-aryl allylic alcohols was pursued (Table 3.3.1).[11] Both Ireland-Claisen[17] and Johnson orthoester Claisen conditions[18] did not provide the desired rearrangement products. However, the allylic alcohols can be transformed into the corresponding vinyl ethers by a Hg-catalyzed vinylation procedure. Although yields for this vinylation process are modest, the remainder of the mass balance is predominantly recovered allylic alcohol. Modification of the protocol, including the use of stoichiometric $Hg(OAc)_2$ and variations in temperature and reaction time, do not improve yields.

[‡] This work was performed in collaboration with Dr. Zoltán Novák, a postdoctoral researcher in the Stoltz group at California Institute of Technology.

Table 3.3.1 Claisen rearrangement of allylic alcohols.

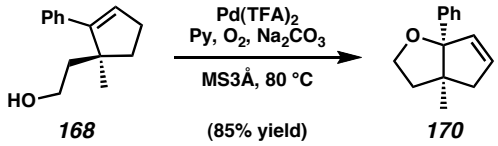


entry	vinyl ether	vinyl ether yield	Claisen product	yield
1		***152***: R = H	43%		***161***: R = H	36%
2		***153***: R = Me	42%		***162***: R = Me	77%
3		***154***: R = OMe	36%		***163***: R = OMe	91%
4		***155***: R = CF_3	37%		***164***: R = CF_3	82%
5		***156***	56%		***165***	76%
6		***157***	47%		***166***	86%
7		***158***	31%		***167***	87%
8		***159***	61%		***168***	82%
9		***160***	16%		***169***	83%

Next, the Claisen rearrangement of these vinyl ethers was investigated. Thermal conditions and treatment with a number of Lewis acids at low temperature lead to competing Claisen and 1,3-rearrangement products. Gratifyingly, exposure of vinyl ethers to DIBAL-H at low temperature induces Claisen rearrangement and subsequent reduction to form the desired primary alcohols in good to excellent yields in most cases. Importantly, because the kinetic resolution is able to produce the starting allylic alcohols

in high enantiomeric excess, the product alcohols are also highly enantioenriched. Even the Claisen rearrangement of vinyl ether **159** to form a quaternary carbon center proceeds in good yield and high enantiomeric excess. Furthermore, alcohol **168** can undergo a second palladium-catalyzed oxidative process developed in our laboratories[19] to form highly enantioenriched tetrahydrofuran **170** containing vicinal, fully substituted stereocenters in 85% yield (Scheme 3.3.3).

Scheme 3.3.3 Oxidative cyclization of a Claisen product.

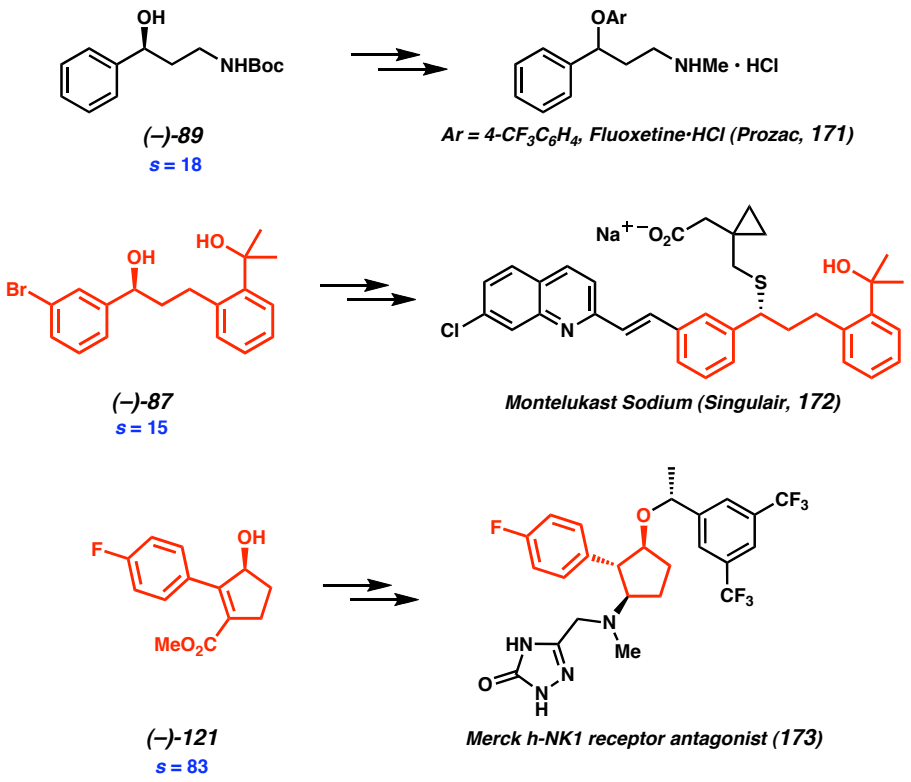


168 **(85% yield)** ***170***

3.3.3 Resolution of Pharmaceutical Intermediates

The wide use of enantioenriched alcohols in synthesis provides numerous applications for the kinetic resolution. A number of alcohols successfully resolved are intermediates in the synthesis of a variety of pharmaceuticals (Scheme 3.3.4).[7,20] Daniel Caspi, a graduate student in these laboratories, successfully resolved Boc-protected γ-aminoalcohol (–)-**89** and bromoarene (–)-**87** to high enantiomeric excess with good corresponding selectivity. Aminoalcohol (–)-**89** can be transformed into an intermediate in the synthesis of a number of antidepressants, including fluoxetine•HCl (Prozac, **171**).[21] Bromoarene (–)-**87** can be converted into a known intermediate in the synthesis of the leukotriene receptor antagonist montelukast sodium (Singulair, **172**).[22] Finally, allylic alcohol (–)-**121**, resolved with an outstanding *s* factor of 83, is an intermediate in the enantioselective synthesis of hNK-1 receptor antagonist **173**.[23]

Scheme 3.3.4 Resolved alcohols as pharmaceutical intermediates.

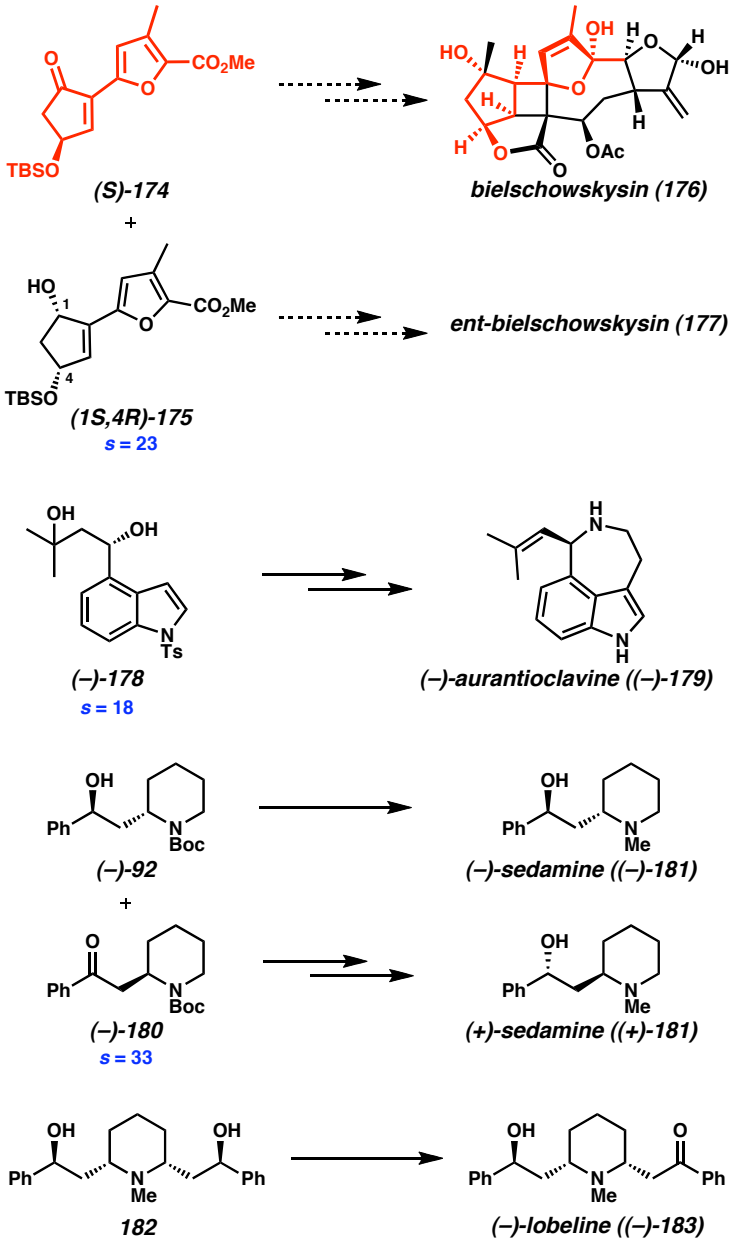


3.3.4 Resolution of Intermediates in Natural Product Syntheses

The palladium-catalyzed oxidative kinetic resolution has also been applied to the construction of enantioenriched secondary alcohols in the context of natural product total synthesis. Michael Meyer, a graduate student in these laboratories, has prepared 2-arylcyclopentenol (±)-**175** en route to the complex gorgonian-derived diterpene bielschowskysin (**176**).[24] Oxidative kinetic resolution of this more functionalized analogue of furan **118** proceeds with excellent selectivity (s = 23) to provide enantioenriched ketone (*S*)-**174** and resolved alcohol (*1S*, *4R*)-**175**. The product ketone maps onto the stereochemically rich cyclopentane and dihydrofuran of bielschowskysin, potentially providing access to this anticancer natural product as a single enantiomer. Furthermore, the alcohol obtained from the resolution has the opposite configuration at

C(4), opening the door to stereodivergent approaches to both enantiomers of bielschowskysin (**176** and **177**) from a single enantioselective oxidation.

Scheme 3.3.5 Enantioselective oxidations for natural product synthesis.



Efforts within these laboratories by postdoctoral researchers Dr. Yeeman Ramtohul and Dr. Shyam Krishnan have demonstrated a successful oxidative kinetic

resolution of indole (±)-**178** using slightly modified conditions in *tert*-butyl alcohol as solvent. Highly enantioenriched indole (–)-**178** has been advanced to the first enantioselective total synthesis of the ergot alkaloid (–)-aurantioclavine ((–)-**179**).[8]

Jeffrey Bagdanoff has prepared piperidine (–)-**92** by enantioselective oxidation of the diastereomerically pure racemate. Boc group reduction affords the natural product (–)-sedamine ((–)-**181**). Enantioenriched ketone (–)-**180** is also obtained from the oxidative kinetic resolution. Diastereoselective ketone reduction and subsequent Boc group reduction provides (+)-sedamine ((+)-**181**). Finally, *meso*-diol **182** undergoes a palladium-catalyzed oxidative desymmetrization to directly afford the nicotinic acetylcholine receptor antagonist alkaloid (–)-lobeline ((–)-**183**).[8]

3.4 Conclusion

Palladium-catalyzed aerobic oxidation is a powerful method for the preparation of enantioenriched secondary alcohols. The development of a number of distinct reaction protocols has allowed the kinetic resolution of a wide range of substrates under mild conditions. Benzylic, allylic, and α-cyclopropyl alcohols can be resolved to high enantiomeric excesses, in many cases with excellent selectivity. Extensive substrate scope studies have revealed general trends in the reactivity and selectivity of the oxidative kinetic resolution, providing a better understanding of this transformation. When diastereomerically pure racemic alcohols are exposed to oxidative kinetic resolution conditions, both enantioenriched alcohols and ketones can be obtained, allowing for enantiodivergent synthetic strategies. These studies have also led to numerous practical applications, including *meso*-diol desymmetrizations, subsequent transformations via Claisen rearrangement, preparation of enantioenriched

pharmaceutically-relevant structures, and intermediates in the total synthesis of a number of natural products. Further efforts to utilize this enantioselective oxidation in complex molecule synthesis are ongoing.

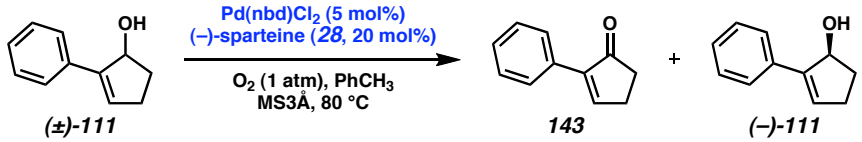
3.5 Experimental Section

3.5.1 Materials and Methods

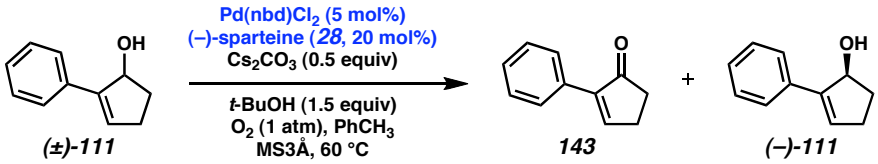
Pd(sparteine)Cl_2 (**66**) was prepared as previously reported.[6] $Pd(PhCN)_2Cl_2$ and $Pd(TFA)_2$ were purchased from Strem Chemicals, Inc., Newburyport, MA. (±)-2-Methylcyclohex-2-enol ((±)-**95**) was prepared by the method of Minehan.[25] (±)-2-Bromocyclohex-2-enol ((±)-**97**) and (±)-2-bromocyclopent-2-enol ((±)-**101**) were prepared by the method of Murphy.[26] (±)-2-Methylcyclopent-2-enol ((±)-**99**) was prepared by the method of Bunnelle.[27] Authentic samples of ketones not commercially available were prepared as for ketone **186** from the corresponding alcohol, unless otherwise noted. Pyridine and Et_3N were distilled over CaH_2. Solvents were dried by passage through an activated alumina column under argon. Powdered 3Å molecular sieves were stored in a 120 °C drying oven until immediately prior to use. Other chemicals were prepared as described below or purchased from the Sigma-Aldrich Chemical Company and used as received. Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry, deoxygenated solvents. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) and preparative TLC were conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV at 254 nm, *p*-anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 32-63 μm) or SiliCycle Silia*Flash* P60 Academic silica gel (particle size 40-63 μm; pore diameter 60 Å) was used for flash column chromatography. Bulb-to-bulb distillations were performed with a Büchi Glass Oven B-585 Kugelrohr. Analytical

achiral GC was performed on an Agilent 6850 GC with FID detector using an Agilent DB-WAX (30.0 m x 0.25 mm) column at 1.0 mL/min He carrier gas flow. Chiral GC was performed on an Agilent 6850 GC with FID detector using a Chiraldex GTA column (30.0 m x 0.25 mm, purchased from Bodman Industries) at 1.0 mL/min He carrier gas flow. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD, Chiralcel OD-H, Chiralcel OJ, Chiralpak AS, or Chiralcel OB-H column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm at 1.0 mL/min mobile phase. ^{1}H NMR spectra were recorded on a Varian Mercury 300 instrument (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported in terms of chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 instrument (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm), multiplicity, and coupling constant (^{19}F, Hz). ^{19}F NMR spectra were recorded on a Varian Mercury 300 instrument (at 282 MHz) and are reported relative to external F_3CCO_2H standard (δ –76.53). Data for ^{19}F NMR spectra are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 or Spectrum BX II spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using a 100 mm path-length cell. The absolute configurations of resolved alcohols were assigned based on comparisons of optical rotations to literature values or by analogy.

3.5.2 General Oxidative Kinetic Resolution Conditions

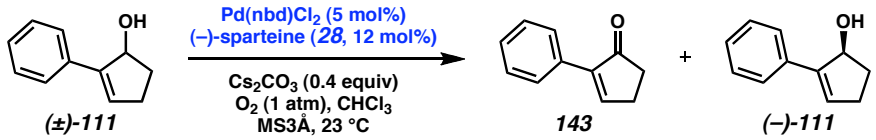


Kinetic Resolution Conditions A.[1] To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, $Pd(nbd)Cl_2$ (6.7 mg, 0.025 mmol, 0.05 equiv) followed by toluene (2.5 mL) and then (–)-sparteine (**28**, 23.0 μL, 0.10 mmol, 0.20 equiv) were added.[28] The reaction tube was then cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). Then, the tube was heated to 80 °C with vigorous stirring under O_2 atmosphere (1 atm, balloon) for 20 min. A solution of (±)-**111** (80.1 mg, 0.50 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in toluene (2.5 mL) was added, and the reaction was allowed to proceed under O_2 atmosphere at 80 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee. Purification of ketone **143** and alcohol (–)-**111** was accomplished by direct chromatography of the crude reaction mixture.



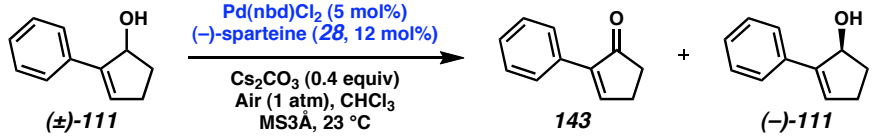
Kinetic Resolution Conditions B.[2] To an oven dried reaction tube with stir bar was added 3Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.050 mmol, 0.05 equiv), followed by toluene (2 mL) and then (–)-sparteine (**28**, 46.0 μL, 0.20 mmol, 0.20 equiv) were added.[28] The reaction tube was cooled to –78 °C, then vacuum

evacuated and purged with O_2 (3x). The tube was heated to 60 °C with vigorous stirring under O_2 atmosphere (1 atm, balloon) for 20 min. Finely powdered Cs_2CO_3 (163 mg, 0.50 mmol, 0.50 equiv) was added, followed by a solution of (±)-**111** (160 mg, 1.0 mmol, 1.0 equiv), anhydrous *t*-BuOH (143 μL, 1.5 mmol, 1.5 equiv), and tridecane (73.2 μL, 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 ketone **143** and alcohol (–)-**111** was accomplished by direct chromatography of the crude reaction mixture.



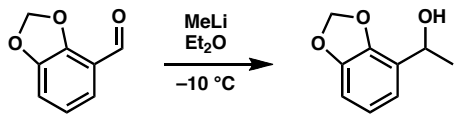
Kinetic Resolution Conditions C.[3] To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, $Pd(nbd)Cl_2$ (6.7 mg, 0.025 mmol, 0.05 equiv), followed by $CHCl_3$ (1 mL)[29] and then (–)-sparteine (**28**, 13.8 μL, 0.06 mmol, 0.12 equiv) were added.[30] The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was allowed to warm to 23 °C and stirred vigorously under O_2 atmosphere (1 atm, balloon) for 15 min. Finely powdered Cs_2CO_3 (65.2 mg, 0.20 mmol, 0.40 equiv) was added, followed by a solution of (±)-**111** (80.1 mg, 0.5 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in $CHCl_3$ (1 mL). The reaction was allowed to proceed under O_2 atmosphere at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee. Purification of ketone **143** and

alcohol (–)-**111** was accomplished by direct chromatography of the crude reaction mixture.



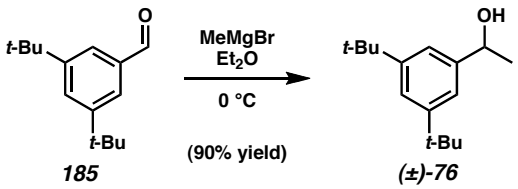
Kinetic Resolution Conditions D.[3] To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After cooling, $Pd(nbd)Cl_2$ (6.7 mg, 0.025 mmol, 0.05 equiv), followed by $CHCl_3$ (1 mL)[29] and then (–)-sparteine (**28**, 13.8 μL, 0.06 mmol, 0.12 equiv) were added.[30] A short tube containing Drierite was attached to the reaction tube. The reaction was stirred vigorously at 23 °C for 15 min. Finely powdered Cs_2CO_3 (65.2 mg, 0.20 mmol, 0.40 equiv) was added, followed by a solution of (±)-**111** (80.1 mg, 0.5 mmol, 1.0 equiv) and tridecane (36.6 μL, 0.15 mmol, 0.30 equiv) in chloroform (1 mL). The reaction was allowed to proceed under an ambient air atmosphere at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion and chiral HPLC for alcohol ee. Purification of ketone **143** and alcohol (–)-**111** was accomplished by direct chromatography of the crude reaction mixture.

3.5.3 Preparative Procedures

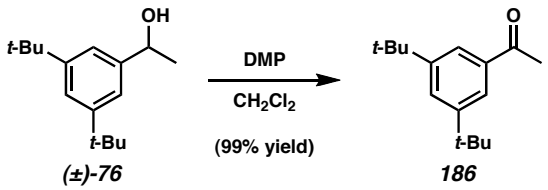


184 *(±)-74*

(±)-1-(Benzo[1,3]dioxol-4-yl)ethanol ((±)-74). A solution of 2,3-(methylenedioxy)benzaldehyde (**184**, 500 mg, 3.05 mmol, 1.0 equiv) in Et_2O (30 mL) was cooled to –10 °C. A solution of methyllithium (1.6 M in Et_2O, 2.48 mL, 3.96 mmol, 1.3 equiv) was added dropwise and the reaction was allowed to warm to 23 °C. The reaction was quenched by addition of crushed ice (10 g) and then saturated aq NH_4Cl (20 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with H_2O (20 mL) and saturated aq NaCl (20 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (9:1→4:1 hexanes:EtOAc) to afford (±)-**74** as an off-white solid: R_f 0.39 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (dd, J = 7.9, 1.7 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.76 (dd, J = 7.2, 1.8 Hz, 1H), 5.97 (d, J = 1.6 Hz, 1H), 5.96 (d, J = 1.5 Hz, 1H), 5.00 (q, J = 6.5 Hz, 1H), 2.11 (br. s, 1H), 1.53 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 143.9, 127.3, 121.8, 118.7, 107.7, 100.9, 66.2, 23.3; IR (thin film/NaCl): 3369, 1460, 1250, 1044 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calcd for $[C_9H_{10}O_3]^+$, 166.0630; found, 166.0630; $[\alpha]_D^{24}$ –26.8° (*c* 1.0, $CDCl_3$; for *S* enantiomer at 99% ee).

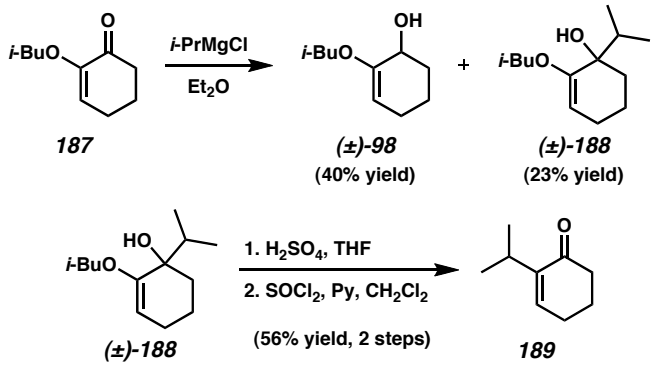


(±)-1-(3,5-Di-*tert*-butylphenyl)ethanol ((±)-76). A solution of 3,5-di-*tert*-butylbenzaldehyde (**185**, 1.09 g, 5.0 mmol, 1.0 equiv) in Et_2O (20 mL) was cooled to 0 °C. A solution of methylmagnesium bromide (3.0 M in Et_2O, 2.5 mL, 7.5 mmol, 1.5 equiv) was added dropwise. The reaction was then quenched by slow addition of saturated aq NH_4Cl (20 mL) and H_2O (10 mL). After warming to 23 °C, the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by passage through a short plug of silica gel (2:1 hexanes:EtOAc) to afford (±)-**76** (1.05 g, 90% yield) as a white solid: R_f 0.45 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, J = 1.9 Hz, 1H), 7.24 (d, J = 1.9 Hz, 1H), 7.24 (d, J = 1.9 Hz, 1H), 4.90 (dq, J = 6.4, 3.2 Hz, 1H), 1.81 (d, J = 3.3 Hz, 1H), 1.52 (d, J = 6.5 Hz, 3H), 1.34 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 145.0, 121.7, 119.6, 71.2, 34.9, 31.5, 25.1; IR (thin film/NaCl): 3335, 2965, 1600, 1363 cm^{-1}; HRMS-FAB (m/z): $[M]^+$ calcd for $[C_{16}H_{26}O]^+$, 234.1984; found, 234.1989; $[\alpha]_D^{24}$ –30.6° (c 0.85, $CHCl_3$; for *S* enantiomer at 98% ee).



General Procedure for the Non-Asymmetric Oxidation of Alcohols to Ketones: 3',5'-Di-*tert*-butylacetophenone (186). To a solution of alcohol (±)-**76** (23.4

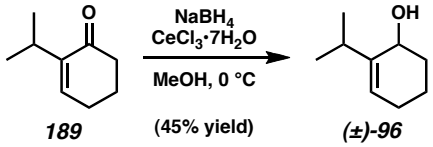
mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 23 °C was added DMP[31] (84.8 mg, 0.20 mmol, 2.0 equiv). After 1 h, the reaction was complete by TLC. The reaction mixture was diluted with 4:1 hexanes:EtOAc (2 mL) and allowed to stir vigorously 20 min to precipitate white solid. Filtration through a short plug of silica gel (4:1 hexanes:EtOAc) afforded ketone **186** (22.9 mg, 99% yield) as a colorless oil. The characterization data matched the data in the literature.[32]



(±)-2-Isobutoxycyclohex-2-enol ((±)-98) and 2-Isopropylcyclohex-2-enone (189). To a solution of isopropylmagnesium chloride (2.0 M in Et_2O, 35.7 mL, 71.3 mmol, 2.0 equiv) in Et_2O (95 mL) was added a solution of 2-isobutoxycyclohex-2-enone[33] (**187**, 6.0 g, 35.7 mmol, 1.0 equiv) in Et_2O (29 mL) over 10 min, such that a gentle reflux was maintained. The reaction was allowed to stir for 45 min, after which it was poured slowly into a mixture of saturated aq NH_4Cl (50 mL), H_2O (50 mL), and crushed ice (50 g). After the ice melted, the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (194:5:1 hexanes:EtOAc:Et_3N) afforded 2-isobutoxy-1-isopropylcyclohex-2-enol ((±)-**188**, 1.72 g, 23% yield) as a colorless oil,

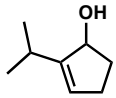
which was carried on immediately to the next step, and 2-isobutoxycyclohex-2-enol ((±)-**98**, 2.45 g, 40% yield) as a colorless oil. The characterization data for (±)-**98** matched the data in the literature.[34]

To a solution of (±)-**188** (1.13 g, 5.33 mmol, 1.0 equiv) in THF (53 mL) was added conc. H_2SO_4 (400 μL). After 30 min, the reaction was quenched by slow addition of saturated aq $NaHCO_3$ (40 mL). The mixture was allowed to stir 20 min (until bubbling ceased) and then was extracted with Et_2O (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. To this crude α-hydroxyketone in CH_2Cl_2 (53 mL) was added pyridine (2.15 mL, 26.6 mmol, 5.0 equiv) and $SOCl_2$ (777 μL, 10.7 mmol, 2.0 equiv). The reaction was allowed to stir at 23 °C for 7 h, after which it was quenched by addition of aq 1 N HCl (40 mL) and allowed to stir a further 10 min. The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration of the filtrate under reduced pressure followed by flash chromatography (49:1 hexanes:EtOAc) and bulb-to-bulb distillation (25 torr, 160-164 °C) afforded 2-isopropylcyclohex-2-enone (**189**, 412 mg, 56% yield from (±)-**188**) as a slightly yellow oil. The characterization data for **189** matched the data in the literature.[35]



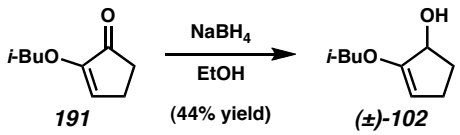
General Procedure for the Reduction of Enones: (±)-2-Isopropylcyclohex-2-enol ((±)-96).[10] To a solution of enone **189** (783 mg, 5.66 mmol, 1.0 equiv) in MeOH (57

mL) at 0 °C was added $CeCl_3 \bullet 7H_2O$ (2.32 g, 6.23 mmol, 1.1 equiv). After allowing the solid to dissolve, $NaBH_4$ (643 mg, 17.0 mmol, 3.0 equiv) was added in small portions over 5 min. After allowing the reaction mixture to warm to 23 °C, the solvent was removed under reduced pressure. H_2O (50 mL) was added, and the slurry was stirred vigorously for 20 min. The mixture was then extracted with EtOAc (4 x 60 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (37:3 hexanes:EtOAc) to afford (±)-**96** (356 mg, 45% yield) as a colorless oil: R_f 0.40 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (t, J = 3.9 Hz, 1H), 4.15 (t, J = 3.6 Hz, 1H), 2.52-2.35 (m, 1H), 2.14-1.88 (comp. m, 2H), 1.85-1.50 (comp. m, 4H), 1.06 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 122.7, 66.0, 32.5, 31.4, 25.5, 23.0, 21.7, 17.8; IR (thin film/NaCl): 3340, 2936, 1461, 1382, 982 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calcd for $[C_9H_{16}O]^+$, 140.1201; found, 140.1198; $[\alpha]_D^{25}$ –24.6° (*c* 1.8, $CHCl_3$; for *S* enantiomer at 96% ee).



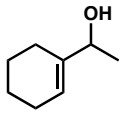
(±)-100

(±)-2-Isopropylcyclopent-2-enol ((±)-100). Prepared as for (±)-**96** from 2-isopropylcyclopent-2-enone[36] (**190**, 2.48 g, 20.0 mmol) to afford, after flash chromatography (94:5:1 hexanes:EtOAc:Et_3N), (±)-**100** (1.08 g, 43% yield) as a slightly yellow oil. The characterization data matched the data in the literature.[37] $[\alpha]_D^{24}$ –27.5° (*c* 0.48, $CHCl_3$; for *S* enantiomer at 92% ee).



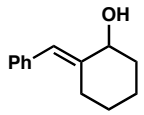
191 *(±)-102*

(±)-2-Isobutoxycyclopent-2-enol ((±)-102). To a solution of 2-isobutoxycyclopent-2-enone[36] (**191**, 1.54 g, 10.0 mmol, 1.0 equiv) in EtOH (absolute, 100 mL) was added $NaBH_4$ (1.14 g, 30.0 mmol, 3.0 equiv). After 2.5 h at 23 °C, the solvent was removed under reduced pressure and H_2O (100 mL) was added. After stirring for 30 min, this mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (96:3:1 hexanes:EtOAc:Et_3N) to afford (±)-**102** (688 mg, 44% yield) as a colorless oil: R_f 0.46 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70-4.62 (m, 1H), 4.59 (t, J = 2.4 Hz, 1H), 3.57-3.47 (comp. m, 2H), 2.45-2.14 (comp. m, 3H), 2.08-1.93 (m, 1H), 1.79-1.68 (m, 1H), 0.96 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 96.9, 76.2, 74.8, 31.2, 28.2, 26.0, 19.5, 19.4; IR (thin film/NaCl): 3392, 2958, 2909, 2871, 1648, 1055 cm^{-1}; HRMS-FAB (m/z): $[M]^+$ calcd for $[C_9H_{16}O_2]^+$, 156.1150; found, 156.1152.



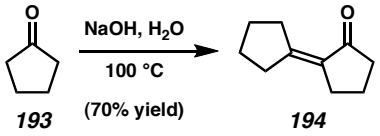
(±)-103

(±)-1-Cyclohexenyl-1-ethanol ((±)-103). Prepared as for (±)-**96** from 1-acetyl-1-cyclohexene (**192**, 3.45 g, 27.8 mmol) to afford, after distillation (22 torr, 86-88 °C) (±)-**103** (2.69 g, 77% yield) as a colorless oil. The characterization data matched the data in the literature.[38] $[\alpha]_D^{25}$ –12.1° (*c* 0.75, $CHCl_3$; for *S* enantiomer at 91% ee) [lit.[39] $[\alpha]_D$ –11.2° (*c* 0.36, $CHCl_3$; *S* enantiomer)].



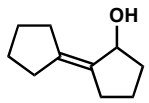
(±)-105

(±)-(*E*)-2-Benzylidenecyclohexanol ((±)-105). Prepared as for (±)-**96** from (*E*)-2-benzylidenecyclohexanone[40] (5.03 g, 27.0 mmol) to afford, after flash chromatography (9:1→17:3→4:1 hexanes:EtOAc), (±)-**105** (4.13 g, 81% yield) as a white solid. The characterization data matched the data in the literature.[41] $[\alpha]_D^{25}$ –36.0° (*c* 1.2, $CHCl_3$; for *S* enantiomer at 96% ee) [lit.[42] $[\alpha]_D^{20}$ –35.2° (*c* 1.2, $CHCl_3$; *S* enantiomer)].



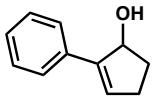
193 *194*

2-Cyclopentylidenecyclopentanone (194). Cyclopentanone (**193**, 10.0 mL, 113 mmol, 2.0 equiv) was added to aq 1 N NaOH (113 mL). The mixture was heated to reflux for 7 h, then cooled to 23 °C and saturated with solid NaCl. After the NaCl dissolved, the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. Distillation (30 torr, 140-142 °C) afforded **194** (5.92 g, 70% yield) as a colorless oil. The characterization data matched the data in the literature.[43]



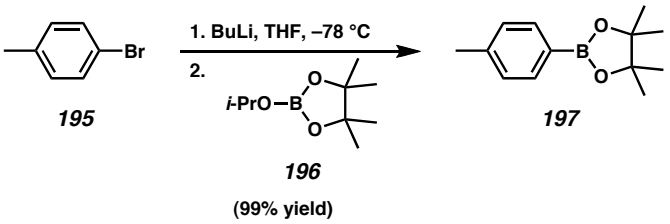
(±)-106

(±)-2-Cyclopentylidenecyclopentanol ((±)-106). Prepared as for (±)-**96** from **194** (1.10 g, 7.32 mmol) to afford, after flash chromatography (9:1 hexanes:EtOAc), (±)-**106** (881 mg, 79% yield) as a white solid. The characterization data matched the data in the literature.[44] $[\alpha]_D^{26}$ +85.3° (*c* 0.99, $CHCl_3$; for *S* enantiomer at 94% ee).

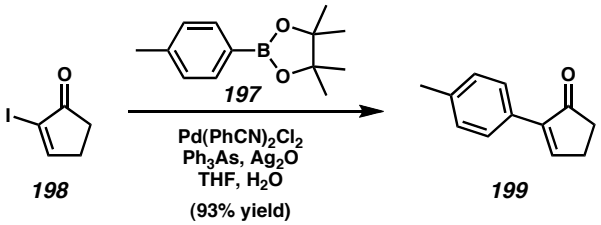


(±)-111

(±)-2-Phenylcyclopent-2-enol ((±)-111). Prepared as for (±)-**96** from 2-phenylcyclopent-2-enone[45,46] (**143**, 218 mg, 1.38 mmol) to afford, after flash chromatography (9:1→4:1→7:3 hexanes:EtOAc), (±)-**111** (196 mg, 89% yield) as a white solid: R_f 0.20 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.54 (comp. m, 2H), 7.39-7.22 (comp. m, 3H), 6.32 (t, *J* = 2.5 Hz, 1H), 5.29-5.21 (m, 1H), 2.74-2.60 (m, 1H), 2.51-2.34 (m, 2H), 2.02-1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 135.1, 130.2, 128.8, 127.8, 126.4, 77.4, 34.3, 30.7; IR (thin film/NaCl): 3220, 2883, 1496, 1322, 1050, 759, 691 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $[C_{11}H_{13}O]^+$, 160.0888; found, 160.0881; $[\alpha]_D^{25}$ +14.0° (*c* 1.4, $CHCl_3$; for *S* enantiomer at 99% ee).

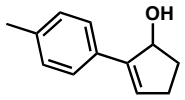


General Procedure for the Preparation of Boronate Esters: 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)toluene (197).[47] A solution of 4-bromotoluene (**195**, 1.23 mL, 10.0 mmol, 1.0 equiv) in THF (67 mL) was cooled to –78 °C. A solution of *n*-butyllithium (2.5 M in hexanes, 4.40 mL, 11.0 mmol, 1.1 equiv) was added dropwise. After stirring 10 min at –78 °C, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**196**, 2.65 mL, 13.0 mmol, 1.3 equiv) was added dropwise. After 10 min, the reaction was quenched at –78 °C with saturated aq NH_4Cl (35 mL) and H_2O (10 mL). After warming to 23 °C, the biphasic mixture was extracted with Et_2O (3 x 60 mL). The combined organic extracts were washed with saturated aq NaCl (30 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (17:3:1 hexanes:EtOAc:Et_3N) to afford **197** (2.17 g, 99% yield) as a slightly yellow oil, which solidified on standing. The characterization data matched the data in the literature.[48]



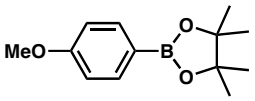
General Procedure for the Arylation of 2-Iodoenones: 2-(4-Tolyl)cyclopent-2-enone (199).[45] 2-Iodocyclopent-2-enone[49] (**198**, 1.46 g, 7.0 mmol, 1.0 equiv), boronic

ester **197** (1.83 g, 8.4 mmol, 1.2 equiv), Ag_2O (2.60 g, 11.2 mmol, 1.6 equiv), Ph_3As (129 mg, 0.42 mmol, 0.06 equiv), and $Pd(PhCN)_2Cl_2$ (81 mg, 0.21 mmol, 0.03 equiv) were added to a solution of THF (18 mL) and H_2O (2.3 mL). A vigorous exothermic reaction occurred. Once the reaction was complete as determined by TLC, it was filtered through Celite (140 mL EtOAc eluent). The filtrate was concentrated under reduced pressure and purified by flash chromatography (9:1 hexanes:EtOAc) to afford enone **199** (1.12 g, 93% yield) as a white solid. The characterization data matched the data in the literature.[50]



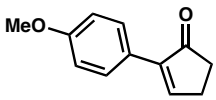
(±)-112

(±)-2-(4-Tolyl)cyclopent-2-enol ((±)-112). Prepared as for (±)-**96** from **199** (1.07 g, 6.18 mmol) to afford, after flash chromatography (9:1→4:1 hexanes:EtOAc), (±)-**112** (827 mg, 77% yield) as a white solid: R_f 0.35 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.26 (t, *J* = 2.5 Hz, 1H), 5.22 (m, 1H), 2.73-2.59 (m, 1H), 2.49-2.32 (m, 2H), 2.34 (s, 3H), 2.01-1.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 137.3, 132.2, 129.5, 129.2, 126.3, 77.4, 34.2, 30.7, 21.4; IR (thin film/NaCl): 3337, 2921, 1512, 1043, 813 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $[C_{12}H_{15}O]^+$, 174.1045; found, 174.1042; $[\alpha]_D^{25}$ +4.5° (*c* 1.6, $CHCl_3$; for *S* enantiomer at 98.5% ee).



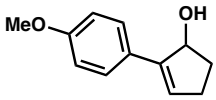
200

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)anisole (200). Prepared as for **197** to afford, after flash chromatography (79:20:1 hexanes:EtOAc:Et_3N), **200** (2.25 g, 80% yield) as a slightly yellow oil. The characterization data matched the data in the literature.[48]



201

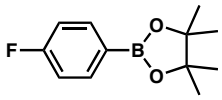
2-(4-Methoxyphenyl)cyclopent-2-enone (201). Prepared as for **199** from **200** to afford, after flash chromatography (4:1 hexanes:EtOAc), **201** (1.05 g, 93%) as a white solid. The characterization data matched the data in the literature.[50]



(±)-113

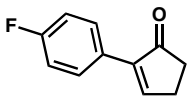
(±)-2-(4-Methoxyphenyl)cyclopent-2-enol ((±)-113). Prepared as for (±)-**96** from **201** (840 mg, 4.46 mmol) to afford, after flash chromatography (9:1→4:1→3:1 hexanes:EtOAc), (±)-**113** (685 mg, 81% yield) as a white solid: R_f 0.30 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.18 (t, J = 2.4 Hz, 1H), 5.19 (m, 1H), 3.81 (s, 3H), 2.72-2.56 (m, 1H), 2.48-2.31 (m, 2H), 2.00-1.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 144.2, 128.1, 127.8, 127.6, 114.2, 77.5, 55.5, 34.3, 30.6; IR (thin film/NaCl): 3249, 2958, 2892, 2846,

1052, 1033, 824 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $[C_{12}H_{14}O_2]^+$, 190.0994; found, 190.0995; $[\alpha]_D^{25}$ +10.6° (*c* 1.9, $CHCl_3$; for *S* enantiomer at 99% ee).



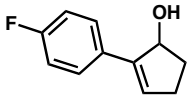
202

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)fluorobenzene (202). Prepared as for **197** to afford, after flash chromatography (17:3:1 hexanes:EtOAc:Et_3N), **202** (2.24 g, 84% yield) as a colorless oil: R_f 0.49 (4:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 2H), 6.78 (m, 2H), 1.05 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (d, *J* = 250.2 Hz), 137.6 (d, *J* = 8.2 Hz), 115.2 (d, *J* = 20.2 Hz), 83.8, 24.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ –108.4; IR (thin film/NaCl): 2979, 1603, 1400, 1362, 1144, 1088 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calcd for $[C_{12}H_{16}BFO_2]^+$, 222.1227; found, 222.1236.



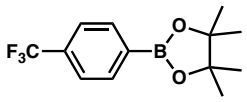
203

2-(4-Fluorophenyl)cyclopent-2-enone (203). Prepared as for **199** from **202** to afford, after flash chromatography (9:1→4:1 hexanes:EtOAc), **203** (1.03 g, 90% yield) as a white solid: R_f 0.30 (7:3 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (t, *J* = 2.9 Hz, 1H), 7.73-7.65 (m, 2H), 7.11-7.02 (m, 2H), 2.75-2.66 (m, 2H), 2.63-2.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 163.0 (d, *J* = 247.8 Hz), 158.8 (d, *J* = 1.4 Hz), 142.6, 129.1 (d, *J* = 8.0 Hz), 128.0 (d, *J* = 3.2 Hz), 115.6 (d, *J* = 21.4 Hz), 35.9, 26.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ –114.1; IR (thin film/NaCl): 1701, 1507, 1224, 834 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calcd for $[C_{11}H_9FO]^+$, 176.0637; found, 176.0631.



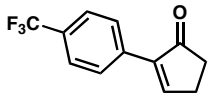
(±)-114

(±)-2-(4-Fluorophenyl)cyclopent-2-enol ((±)-114). Prepared as for (±)-**96** from **203** (933 mg, 5.29 mmol) to afford, after flash chromatography (9:1→4:1 hexanes:EtOAc), (±)-**114** (792 mg, 84% yield) as a white solid: R_f 0.31 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.50 (m, 2H), 7.07-6.98 (m, 2H), 6.24 (t, *J* = 2.5 Hz, 1H), 5.20 (m, 1H), 2.73-2.59 (m, 1H), 2.50-2.34 (comp. m, 2H), 2.01-1.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, *J* = 246.6 Hz), 143.7, 131.3 (d, *J* = 3.1 Hz), 129.9 (d, *J* = 1.8 Hz), 128.0 (d, *J* = 8.0 Hz), 115.6 (d, *J* = 21.5 Hz), 77.6, 34.4, 30.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ –115.8; IR (thin film/NaCl): 3218, 1510, 1237, 1050, 834 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $[C_{11}H_{11}FO]^+$, 178.0794; found, 178.0786; $[\alpha]_D^{25}$ +12.8° (*c* 2.2, $CHCl_3$; for *S* enantiomer at 99% ee).



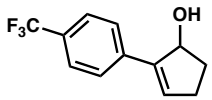
204

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzotrifluoride (204). Prepared as for **197** to afford, after flash chromatography (17:3:1 hexanes:EtOAc:Et_3N), **204** (3.13 g, 96% yield) as an off-white solid. The characterization data matched the data in the literature.[51]



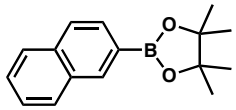
205

2-(4-Trifluoromethylphenyl)cyclopent-2-enone (205). Prepared as for **199** from **204** to afford, after flash chromatography (9:1 hexanes:EtOAc), **205** (1.14 g, 84% yield) as a white solid: R_f 0.37 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (t, *J* = 2.9 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 2H), 2.79-2.72 (m, 2H), 2.66-2.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 160.5, 142.4, 135.1, 130.2 (q, *J* = 32.5 Hz), 127.3, 125.3 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.1 Hz), 35.7, 26.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.7; IR (thin film/NaCl): 3066, 1692, 1332, 1112, 847 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $[C_{12}H_9F_3O]^+$, 226.0606; found, 226.0608.



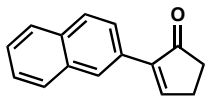
(±)-115

(±)-2-(4-Trifluoromethylphenyl)cyclopent-2-enol ((±)-115). Prepared as for (±)-**96** from **205** (1.14 g, 5.00 mmol) to afford, after flash chromatography (9:1→4:1 hexanes:EtOAc), (±)-**115** (887 mg, 77% yield) as a white solid: R_f 0.34 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.43 (t, *J* = 2.6 Hz, 1H), 5.24 (m, 1H), 2.77-2.62 (m, 1H), 2.54-2.37 (m, 2H), 2.02-1.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 138.4, 132.6, 127.7, 126.3, 125.4 (q, *J* = 3.8 Hz), 77.1, 34.1, 30.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.5; IR (thin film/NaCl): 3239, 1326, 1112, 827 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $[C_{12}H_{12}OF_3]^+$, 228.0762; found, 228.0752; $[\alpha]_D^{25}$ +16.0° (*c* 2.5, $CHCl_3$; for *S* enantiomer at 99% ee).



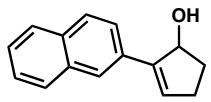
206

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (206). Prepared as for **197** to afford, after flash chromatography (17:3:1 hexanes:EtOAc:Et_3N), **206** (2.87 g, 94% yield) as an off-white solid. The characterization data matched the data in the literature.[48]



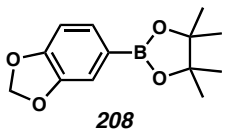
207

2-(2-Naphthyl)cyclopent-2-enone (207). Prepared as for **199** from **206** to afford, after flash chromatography (9:1 hexanes:EtOAc), **207** (180 mg, 86% yield) as an off-white solid: R_f 0.33 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.96 (t, J = 3.0 Hz, 1H), 7.93-7.78 (comp. m, 3H), 7.71 (dd, J = 8.6, 1.7 Hz, 1H), 7.52-7.44 (comp. m, 2H), 2.80-2.73 (m, 2H), 2.69-2.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 159.4, 143.3, 133.5, 133.4, 129.2, 128.8, 128.3, 127.8, 126.6, 126.5, 126.4, 125.0, 36.2, 26.5; IR (thin film/NaCl): 1690, 1311, 748, 475 cm^{-1}; HRMS-FAB (m/z): $[M]^+$ calcd for $[C_{15}H_{12}O]^+$, 208.0888; found, 208.0889.



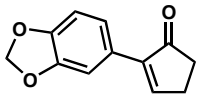
(±)-116

(±)-2-(2-Naphthyl)cyclopent-2-enol ((±)-116). Prepared as for (±)-**96** from **207** (1.90 g, 9.14 mmol) to afford, after flash chromatography (9:1→4:1 hexanes:EtOAc), (±)-**116** (1.67 g, 87% yield) as a white solid: R_f 0.37 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.87-7.67 (comp. m, 4H), 7.50-7.40 (comp. m, 2H), 6.45 (t, J = 2.5 Hz, 1H), 5.37 (m, 1H), 2.80-2.65 (m, 1H), 2.56-2.38 (m, 2H), 2.07-1.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 133.9, 133.0, 132.4, 130.9, 128.5, 128.4, 127.9, 126.4, 126.1, 125.0, 124.8, 77.4, 34.4, 30.9; IR (thin film/NaCl): 3385, 1044, 819, 476 cm^{-1}; HRMS-FAB (m/z): $[M + H]^+$ calcd for $[C_{15}H_{15}O]^+$, 210.1045; found, 210.1043; $[\alpha]_D^{25}$ +46.4° (c 2.0, $CHCl_3$; for S enantiomer at 99% ee).



208

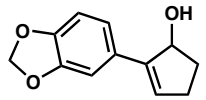
5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzodioxole (208). Prepared as for **197** to afford, after flash chromatography (17:3:1 hexanes:EtOAc:Et_3N), **208** (2.43 g, 99% yield) as an off-white solid. The characterization data matched the data in the literature.[52]



209

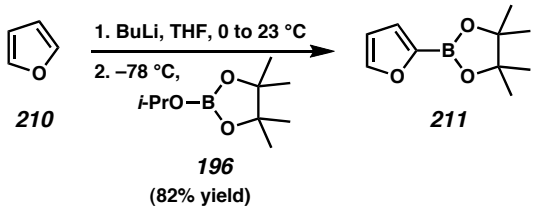
2-(Benzo[1,3]dioxol-5-yl)cyclopent-2-enone (209). Prepared as for **199** from **208** to afford, after flash chromatography (17:3→4:1→7:3 hexanes:EtOAc), **209** (1.37 g,

90% yield) as a white solid: R_f 0.30 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (t, *J* = 2.9 Hz, 1H), 7.27-7.19 (comp. m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.96 (s, 2H), 2.71-2.65 (m, 2H), 2.61-2.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 157.8, 147.8, 143.0, 125.8, 121.1, 108.5, 107.6, 101.2, 36.0, 26.2; IR (thin film/NaCl): 1695, 1488, 1240, 1035, 806 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calcd for $[C_{12}H_{10}O_3]^+$, 202.0630; found, 202.0623.

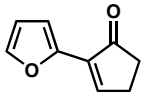


(±)-117

(±)-2-(Benzo[1,3]dioxol-5-yl)cyclopent-2-enol ((±)-117). Prepared as for (±)-(±)-**96** from **209** (1.21 g, 6.00 mmol) to afford, after flash chromatography (9:1→17:3→4:1 hexanes:EtOAc), (±)-**117** (1.03 g, 84% yield) as a white solid: R_f 0.27 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08-7.03 (comp. m, 2H), 6.82-6.76 (m, 1H), 6.16 (t, *J* = 2.5, 1H), 5.95 (s, 2H), 5.15 (m, 1H), 2.71-2.57 (m, 1H), 2.47-2.30 (m, 2H), 1.99-1.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 147.1, 144.3, 129.5, 128.8, 120.0, 108.5, 106.8, 101.2, 77.5, 34.3, 30.6; IR (thin film/NaCl): 3354, 2894, 1490, 1503, 1226, 1041, 937 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $[C_{12}H_{13}O_3]^+$, 204.0787; found, 204.0793; $[\alpha]_D^{25}$ +9.6° (*c* 1.6, $CHCl_3$; for *S* enantiomer at 99% ee).



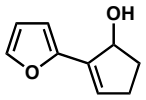
2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-furan (211). A solution of furan (**210**, 1.75 mL, 24.0 mmol, 1.2 equiv) in THF (120 mL) was cooled to 0 °C. A solution of *n*-butyllithium (2.26 M in hexanes, 8.84 mL, 20.0 mmol, 1.0 equiv) was added dropwise. The reaction was allowed to stir 30 min at 0 °C and 30 min at 23 °C, after which it was cooled to –78 °C. Borolane **196** (6.36 mL, 31.2 mmol, 1.3 equiv) was added dropwise. After stirring 10 min, the reaction was allowed to warm to 23 °C and was quenched by addition of saturated aq NH_4Cl (50 mL) and H_2O (10 mL). The mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. Bulb-to-bulb distillation (0.1 torr, 90-95 °C) afforded **211** (3.17 g, 82% yield) as a colorless oil. The characterization data matched the data in the literature.[53]



212

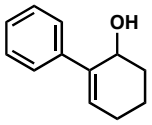
2-(2-Furyl)cyclopent-2-enone (212). Prepared as for **199** from **211** to afford, after flash chromatography (19:1→17:3 hexanes:EtOAc), **212** (1.09 g, 55% yield) as an off-white solid: R_f 0.51 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (t, J = 3.1 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.04 (d, J = 3.5 Hz, 1H), 6.44 (dd, J = 3.5, 1.7 Hz, 1H), 2.77-2.71 (m, 2H), 2.56-2.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 154.2,

147.1, 142.5, 134.9, 111.6, 109.4, 35.5, 26.9; IR (thin film/NaCl): 1706, 1326, 1132, 747 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calcd for $[C_9H_8O_2]^+$, 148.0524; found, 148.0521.



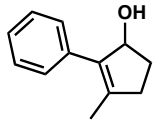
(±)-118

(±)-2-(2-Furyl)cyclopent-2-enol ((±)-118). Prepared as for (±)-**96** from **212** (961 mg, 6.49 mmol) to afford, after flash chromatography (19:1→9:1→4:1 hexanes:EtOAc), (±)-**118** (793 mg, 81% yield) as an off-white solid: R_f 0.26 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.6 Hz, 1H), 6.43 (d, *J* = 3.4 Hz, 1H), 6.40 (dd, *J* = 3.3, 1.7 Hz, 1H), 5.11 (m, 1H), 2.74-2.60 (m, 1H), 2.49-2.30 (m, 2H), 1.95-1.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 142.0, 135.7, 128.4, 111.4, 106.8, 77.3, 55.9, 30.8; IR (thin film/NaCl): 3344, 2934, 2849, 1044, 928, 733 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $[C_9H_{11}O_2]^+$, 150.0681; found, 150.0680; $[\alpha]_D^{25}$ +30.9° (*c* 1.1, $CHCl_3$; for *S* enantiomer at 99% ee).



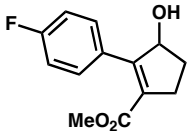
(±)-119

(±)-2-Phenylcyclohex-2-enol ((±)-119). Prepared as for (±)-**96** from 2-phenylcyclohex-2-enone[45] (**213**, 2.70 g, 15.7 mmol) to afford, after filtration through a short plug of silica gel (1:1 hexanes:EtOAc), (±)-**119** (2.22 g, 81% yield) as an off-white solid. The characterization data matched the data in the literature.[54] $[\alpha]_D^{25}$ –109.5° (*c* 1.3, $CHCl_3$; for *S* enantiomer at 99% ee) [lit.[55] $[\alpha]_D$ +114.5° (*c* 1.6, $CHCl_3$; *R* enantiomer)].



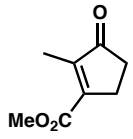
(±)-120

(±)-2-Phenyl-3-methylcyclopent-2-enol ((±)-120). Prepared as for (±)-**96** from 2-phenyl-3-methylcyclopent-2-enone[56] (**214**, 3.82 g, 22.2 mmol) to afford, after flash chromatography (9:1→4:1 hexanes:EtOAc), (±)-**120** (3.25 g, 84% yield) as a slightly yellow oil, which solidified to a white solid on standing: R_f 0.24 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.22 (comp. m, 5H), 5.16 (br. d, J = 5.5 Hz, 1H), 2.74-2.58 (m, 1H), 2.44-2.30 (m, 2H), 1.87-1.75 (m, 1H), 1.85 (d, J = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 138.5, 136.7, 128.6, 128.5, 126.9, 80.5, 36.9, 32.7, 15.9; IR (thin film/NaCl): 3370, 2930, 1442, 699 cm^{-1}; HRMS-FAB (m/z): $[M + H]^+$ calcd for $[C_{10}H_{15}O]^+$, 174.1045; found, 174.1037; $[\alpha]_D^{25}$ –2.4° (*c* 1.2, $CHCl_3$; for *S* enantiomer at 99% ee).



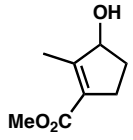
(±)-121

Fluorophenylcarboxylate (±)-121. Prepared as for (±)-**96** from methyl 2-(4-fluorophenyl)-3-oxocyclopent-1-enecarboxylate[23a] (**215**, 125 mg, 0.53 mmol) to afford, after flash chromatography (4:1 hexanes:EtOAc), (±)-**121** (103 mg, 82% yield) as a slightly yellow oil: R_f 0.11 (4:1 hexanes:EtOAc). The characterization data matched the data in the literature.[23a] $[\alpha]_D^{22}$ –37.2° (*c* 0.1, MeOH; for *S* enantiomer at 99% ee) [lit.[23a] $[\alpha]_D$ –186.6° (*c* 0.01, MeOH; *S* enantiomer)].



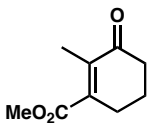
216

Methyl 2-Methyl-3-oxocyclopent-1-enecarboxylate (216). Prepared according to the procedure of Kuethe:[23a] R_f 0.26 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 2.84-2.76 (m, 2H), 2.55-2.48 (m, 2H), 2.09 (t, J = 2.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 166.1, 154.4, 147.7, 52.3, 34.1, 26.6, 10.0; IR (thin film/NaCl): 1713, 1438, 1226, 1076 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $[C_8H_{10}O_3]^+$, 154.0630; found, 154.0626.



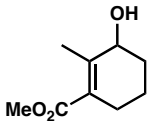
(±)-122

(±)-Methyl 3-Hydroxy-2-methylcyclopent-1-enecarboxylate ((±)-122). Prepared as for (±)-**96** from **216** (2.35 g, 15.2 mmol) to afford, after flash chromatography (7:3 hexanes:EtOAc), (±)-**122** (2.06 g, 87% yield) as a colorless oil: R_f 0.10 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (t, J = 6.9 Hz, 1H), 3.75 (s, 3H), 2.75-2.62 (m, 1H), 2.53-2.25 (comp. m, 2H), 2.13 (s, 3H), 1.71-1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 155.2, 128.9, 81.2, 51.4, 32.2, 30.4, 36.9, 13.5; IR (thin film/NaCl): 3419, 2951, 1715, 1436, 1220, 1054 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $[C_8H_{12}O_3]^+$, 156.0787; found, 156.0780; $[\alpha]_D^{25}$ –57.0° (*c* 0.82, $CHCl_3$; for *S* enantiomer at 99% ee).



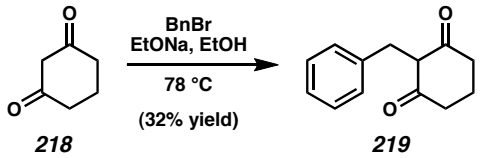
217

Methyl 2-Methyl-3-oxocyclohex-1-enecarboxylate (217). Prepared according to the procedure of Kuethe:[23a] R_f 0.24 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 2.61-2.53 (m, 2H), 2.51-2.44 (m, 2H), 2.07-1.97 (m, 2H), 1.94 (t, J = 2.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 169.0, 144.4, 137.4, 52.2, 38.0, 27.5, 22.4, 12.8; IR (thin film/NaCl): 2954, 1727, 1682, 1435, 1232, 1052 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $[C_9H_{12}O_3]^+$, 168.0787; found, 168.0786.

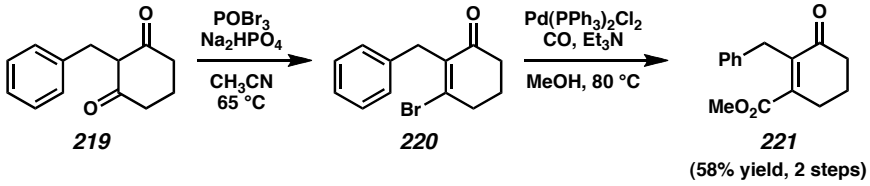


(±)-123

(±)-Methyl 3-Hydroxy-2-methylcyclohex-1-enecarboxylate ((±)-123). Prepared as for (±)-**96** from **217** (4.66 g, 27.7 mmol) to afford, after filtration through a short plug of silica gel (1:1 hexanes:EtOAc), (±)-**123** (4.71 g, 99% yield) as a colorless oil: R_f 0.12 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (t, J = 4.5 Hz, 1H), 3.74 (s, 3H), 2.41-2.12 (comp. m, 2H), 2.07 (t, J = 2.1 Hz, 3H), 1.82-1.60 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 144.0, 127.8, 69.8, 51.6, 31.6, 27.0, 18.7, 18.1; IR (thin film/NaCl): 3424, 2945, 1718, 1435, 1215, 1061 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $[C_9H_{14}O_3]^+$, 170.0943; found, 170.0938; $[\alpha]_D^{25}$ –72.3° (*c* 0.95, $CHCl_3$; for *S* enantiomer at 97% ee).



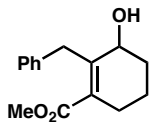
2-Benzylcyclohexane-1,3-dione (219). Prepared by modification of a procedure from Hewett.[57] Na (3.45 g, 150 mmol, 1.5 equiv) was added to EtOH (absolute, 200 mL). After all of the metal dissolved, cyclohexane-1,3-dione (**218**, 11.2 g, 100 mmol, 1.0 equiv) was added, followed by benzyl bromide (23.8 mL, 200 mmol, 2.0 equiv). The reaction was heated to reflux for 13 h. After cooling to 23 °C, the volatiles were removed under reduced pressure. Et_2O (100 mL) was added, and the mixture was extracted with 1 N NaOH (2 x 100 mL). The combined aqueous extracts were cooled to 0 °C and acidified to pH 1.5 by dropwise addition of conc. H_2SO_4. After addition of saturated aq NaCl (50 mL), the mixture was allowed to stand at 0 °C for 5 min. The solid was filtered to afford **219** (6.51 g, 32% yield) as a tan solid. The characterization data matched the data in the literature.[58]



Methyl 2-Benzyl-3-oxocyclohex-1-enecarboxylate (221). Prepared according to the procedure of Kuethe.[23a] To a mixture of **219** (2.02 g, 10.0 mmol, 1.0 equiv) and Na_2HPO_4 (710 mg, 5.0 mmol, 0.5 equiv) in CH_3CN (15 mL) was added a solution of $POBr_3$ (2.15 g, 7.5 mmol, 0.75 equiv) in CH_3CN (5 mL). The reaction was heated to 65 °C for 24 h. After cooling to 23 °C, H_2O (6 mL) was added slowly to quench the reaction. After evaporation of CH_3CN under reduced pressure, H_2O (40 mL) and

saturated aq NaCl (20 mL) were added. The mixture was extracted with EtOAc (4 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (9:1→17:3 hexanes:Et_2O) to afford 2-benzyl-3-bromocyclohex-2-enone (**220**), which was used directly in the next step.

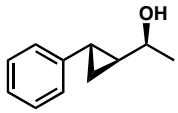
To a solution of this bromide in MeOH (12.5 mL) was added $Pd(PPh_3)_2Cl_2$ (132 mg, 0.19 mmol, 0.03 equiv) followed by Et_3N (1.75 mL, 1.27 g, 12.5 mmol, 2.0 equiv) in a steel bomb. The reaction was pressurized with carbon monoxide (100 psi) and heated to 80 °C behind a blast shield for 21 h. After cooling to 23 °C and venting the carbon monoxide, the reaction was diluted with Et_2O (70 mL) and filtered through a short plug of Celite (Et_2O eluent). The filtrate was concentrated under reduced pressure and purified by flash chromatography (17:3 hexanes:Et_2O) to afford **221** (1.42 g, 58% yield from **219**) of an off-white solid: R_f 0.45 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.10 (comp. m, 5H), 3.81 (br. s, 2H), 3.78 (s, 3H), 2.63 (t, J = 6.0 Hz, 2H), 2.47 (app. t, J = 6.7 Hz, 2H), 2.04 (tt, J = 6.7, 6.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 168.7, 145.6, 139.4, 129.6, 128.7, 128.2, 126.0, 52.2, 38.0, 31.9, 27.7, 22.0; IR (thin film/NaCl): 2951, 1726, 1681, 1255, 1238 cm^{-1}; HRMS-FAB (m/z): $[M]^+$ calcd for $[C_{15}H_{16}O_3]^+$, 244.1100; found, 244.1100.



(±)-124

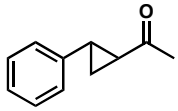
(±)-Methyl 3-Hydroxy-2-benzylcyclohex-1-enecarboxylate ((±)-124). Prepared as for (±)-**96** from **221** (2.02 g, 8.3 mmol) to afford, after flash chromatography (3:2

hexanes:Et_2O), (±)-**124** (1.42 g, 70% yield) as a colorless oil: R_f 0.29 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.17 (comp. m, 5H), 4.03 (br. s, 1H), 4.00 (d, *J* = 14.3 Hz, 1H), 3.75 (s, 3H), 3.69 (dt, *J* = 14.4, 2.0 Hz, 1H), 2.50-2.38 (m, 1H), 2.34-2.20 (m, 1H), 1.81-1.57 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 143.9, 139.4, 129.7, 128.9, 128.5, 126.2, 66.2, 51.7, 36.9, 31.2, 27.1, 17.5; IR (thin film/NaCl): 3412, 2943, 1715, 1234 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calcd for $[C_{15}H_{18}O_3]^+$, 246.1256; found, 246.1251; $[\alpha]_D^{24}$ –226.3° (*c* 1.83, $CHCl_3$; for *S* enantiomer at 96% ee).



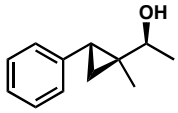
(±)-126

(±)-*syn,trans*-1-(2-Phenylcyclopropyl)ethanol ((±)-126). Prepared by the method of Charette.[59] The characterization data matched the data in the literature.[60] $[\alpha]_D^{24}$ +44.1° (*c* 1.1, $CHCl_3$; for (1*S*, 1'*S*, 2'*S*) enantiomer at 90% ee).



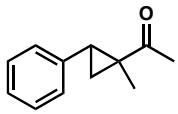
(±)-129

(±)-*trans*-1-(2-Phenylcyclopropyl)ethanone ((±)-129). Prepared as for **186** from (±)-**126** (16.5 mg, 0.10 mmol) to afford (±)-**129** (15.9 mg, 97% yield) as a colorless oil. The characterization data matched the data in the literature.[61] $[\alpha]_D^{24}$ –275.5° (*c* 0.59, $CHCl_3$; for (1'*R*, 2'*R*) enantiomer at 57% ee) [lit.[61] $[\alpha]_D^{20}$ +116.2° (*c* 0.785, $CHCl_3$; for (1'*S*, 2'*S*) enantiomer)].



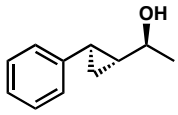
(±)-127

(±)-*syn,trans*-1-(1-Methyl-2-phenylcyclopropyl)ethanol ((±)-127). Prepared by the method of Charette.[59] The characterization data matched the data in the literature. $[\alpha]_D^{24}$ +2.1° (*c* 1.5, $CHCl_3$; for (1*S*, 1'*S*, 2'*R*) enantiomer at 89% ee).



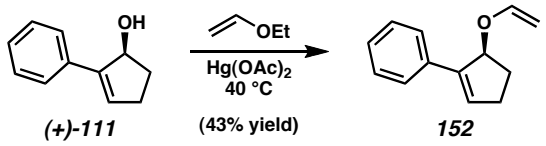
(±)-130

(±)-*trans*-1-(1-Methyl-2-phenylcyclopropyl)ethanone ((±)-130). Prepared as for **186** from (±)-**127** (17.6 mg, 0.10 mmol) to afford (±)-**130** (6.2 mg, 36% yield) as a colorless oil. The characterization data matched the data in the literature.[62] $[\alpha]_D^{25}$ –152.1° (*c* 1.59, abs. EtOH; for (1'*R*, 2'*S*) enantiomer at 74% ee) [lit.[62] $[\alpha]_D^{25}$ +173.3° (*c* 2, abs. EtOH; for (1'*S*, 2'*R*) enantiomer)].

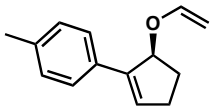


(±)-128

(±)-*anti,trans*-1-(2-Phenylcyclopropyl)ethanol ((±)-128). Prepared by the method of Charette.[63] The characterization data matched the data in the literature.[64] $[\alpha]_D^{24}$ –60.1° (*c* 1.0, $CHCl_3$; for (1*S*, 1'*R*, 2'*R*) enantiomer at 94% ee) [lit.[64] $[\alpha]_D$ +64.2° (*c* 1.0, $CHCl_3$; for (1*R*, 1'*S*, 2'*S*) enantiomer)].

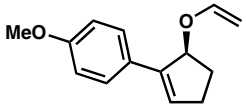


General Procedure for the Vinylation of Allylic Alcohols: Vinyl Ether 152. To a solution of cyclopentenol (+)-**111** (36.5 mg, 0.23 mmol, 1.0 equiv) in freshly distilled ethyl vinyl ether (3 mL) was added $Hg(OAc)_2$ (20.3 mg, 0.064 mmol, 0.28 equiv). The reaction was sealed with a teflon cap and heated to 40 °C for 120 h. The reaction was cooled to 23 °C, and K_2CO_3 (anhydrous, 173 mg, 1.25 mmol, 5.5 equiv) was added. The suspension was stirred for 30 min then filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (250:7→10:1 hexanes:EtOAc) to afford recovered cyclopentenol (+)-**111** (20.1 mg, 55% yield) and vinyl ether **152** (18.5 mg, 43% yield) as a colorless oil: R_f 0.55 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.46 (comp. m, 2H), 7.35-7.22 (comp. m, 3H), 6.50-6.43 (m, 2H), 5.37 (dt, J = 6.9, 2.4 Hz, 1H), 4.35 (dd, J = 14.4, 1.8 Hz, 1H), 4.11 (dd, J = 6.6, 1.5 Hz, 1H), 2.76-2.64 (m, 1H), 2.54-2.26 (m, 2H), 2.15-2.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 141.1, 134.6, 132.0, 128.4, 127.3, 125.9, 88.3, 83.1, 31.0, 30.1; IR (thin film/NaCl): 3057, 2934, 2846, 1632, 1610, 1496, 1447, 1358, 1318, 1188, 1048, 1032, 962, 822 cm^{-1}; HRMS-ES (m/z): $[M]^+$ calcd for $[C_{13}H_{14}O]^+$, 186.1045; found, 186.1042; $[\alpha]_D^{25}$ +32.5° (c 0.38, CH_2Cl_2).



153

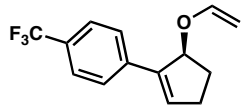
Vinyl Ether 153. Prepared as for **152** from (+)-**112** (100 mg, 0.57 mmol) to afford, after flash chromatography (125:2→10:1 hexanes:EtOAc), cyclopentenol (+)-**112** (48 mg, 48% yield) and **153** (48 mg, 42% yield) as a colorless oil: R_f 0.57 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 6.3 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.52 (dd, *J* = 14.4, 6.9 Hz, 1H), 6.42 (t, *J* = 2.4 Hz, 1H), 5.37 (dt, *J* = 7.2, 2.4 Hz, 1H), 4.37 (dd, *J* = 14.4, 1.8 Hz, 1H), 4.12 (dd, *J* = 6.6, 1.8 Hz, 1H), 2.74-2.65 (m, 1H), 2.54-2.43 (m, 1H), 2.36 (s, 3H), 2.39-2.27 (m, 1H), 2.16-2.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 141.0, 137.0, 131.8, 131.0, 129.1, 125.9, 88.3, 83.1, 31.0, 30.1, 21.2; IR (thin film/NaCl): 2921, 2849, 1631, 1609, 1513, 1449, 1352, 1317, 1187, 1048, 1030, 963, 813 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{16}O]^+$, 200.1201; found, 200.1201; $[\alpha]_D^{25}$ +20.8° (*c* 0.16, CH_2Cl_2).



154

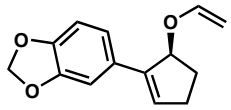
Vinyl Ether 154. Prepared as for **152** from (+)-**113** (100 mg, 0.53 mmol) to afford, after flash chromatography (60:1→10:1 hexanes:EtOAc), cyclopentenol (+)-**113** (61 mg, 61% yield) and **154** (41 mg, 36% yield) as a colorless oil: R_f 0.52 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.7 Hz, 2H). 6.89 (d, *J* = 9.0 Hz, 2H), 6.51 (dd, *J* = 14.4, 6.9 Hz, 1H), 6.33 (t, *J* = 2.7 Hz, 1H), 5.37 (dt, *J* = 7.2, 2.1 Hz, 1H), 4.36 (dd, *J* = 14.4, 2.1 Hz, 1H), 4.11 (dd, *J* = 6.6, 1.8 Hz, 1H), 3.81 (s, 3H),

2.75-2.62 (m, 1H), 2.52-2.42 (m, 1H), 2.38-2.56 (m, 1H), 2.14-2.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 150.1, 140.5, 129.9, 127.4, 127.2, 113.8, 88.3, 83.3, 55.2, 30.9, 30.1; IR (thin film/NaCl): 2918, 2848, 2359, 2340, 1632, 1609, 1512, 1463, 1353, 1317, 1269, 1257, 1180, 1112, 1036, 963, 891, 824 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{16}O_2]^+$, 216.1150; found, 216.1155; $[\alpha]_D^{26}$ +18.8° (*c* 0.43, CH_2Cl_2).



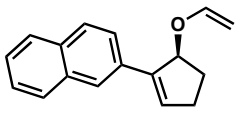
155

Vinyl Ether 155. Prepared as for **152** from (+)-**115** (100 mg, 0.44 mmol) to afford, after preparative TLC (10:1 hexanes:EtOAc), cyclopentenol (+)-**115** (57 mg, 57% yield) and **155** (41.7 mg, 37% yield) as a colorless oil: R_f 0.59 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 4H), 6.58 (t, *J* = 2.7 Hz, 1H), 6.50 (dd, *J* = 14.4, 6.6 Hz, 1H), 5.37 (dt, *J* = 7.2, 2.1 Hz, 1H), 4.37 (dd, *J* = 14.1, 1.8 Hz, 1H), 4.15 (dd, *J* = 6.6, 1.8 Hz, 1H), 2.80-2.67 (m, 1H), 2.58-2.47 (m, 1H), 2.42-2.30 (m, 1H), 2.17-2.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 140.2, 134.6, 126.2, 125.5, 125.4, 125.3, 125.3, 88.8, 82.9, 31.2, 30.0; IR (thin film/NaCl): 2917, 2846, 2141, 1731, 1660, 1633, 1614, 1507, 1414, 1365, 1317, 1246, 1190, 1164, 1122, 1071, 1033, 1016, 963, 829, 733 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{13}OF_3]^+$, 254.0919; found, 254.0913; $[\alpha]_D^{26}$ +31.0° (*c* 0.32, CH_2Cl_2).



156

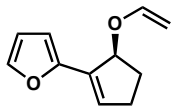
Vinyl Ether 156. Prepared as for **152** from (+)-**117** (100 mg, 0.49 mmol) to afford, after flash chromatography (125:2→10:1 hexanes:EtOAc), cyclopentenol (+)-**117** (36.6 mg, 37% yield) and **156** (63.3 mg, 56% yield) as a colorless oil: R_f 0.61 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 1.8 Hz, 1H), 6.97 (dd, *J* = 13.8, 1.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.49 (q, *J* = 6.9 Hz, 1H), 6.30 (t, *J* = 2.4 Hz, 1H), 5.94 (s, 2H), 5.29 (dt, *J* = 7.2, 2.4 Hz, 1H), 4.35 (dd, *J* = 14.4, 2.1 Hz, 1H), 4.11 (dd, *J* = 6.9, 1.8 Hz, 1H), 2.73-2.61 (m, 1H), 2.51-2.40 (m, 1H), 2.37-2.25 (m, 1H), 2.13-2.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 147.7, 146.9, 140.6, 130.6, 119.7, 108.2, 106.4, 100.9, 88.4, 83.2, 30.9, 30.0; IR (thin film/NaCl): 2898, 2849, 2359, 2340, 1632, 1610, 1503, 1490, 1447, 1366, 1317, 1227, 1187, 1106, 1040, 969, 936, 889, 808 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{14}O_3]^+$, 230.0943; found, 230.0933. $[\alpha]_D^{26}$ +20.8° (*c* 0.075, CH_2Cl_2).



157

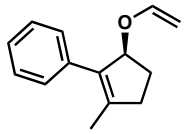
Vinyl Ether 157. Prepared as for **152** from (+)-**116** (100 mg, 0.48 mmol) to afford, after preparative TLC (10:1 hexanes:EtOAc), cyclopentenol (+)-**116** (47.5 mg, 48% yield) and **157** (53 mg, 47% yield) as a colorless oil: R_f 0.71 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.80 (comp. m, 4H), 7.70-7.67 (m, 1H), 7.51-7.43 (comp. m, 2H), 6.61 (t, *J* = 2.7 Hz, 1H), 6.58 (dd, *J* = 14.4, 6.9 Hz, 1H), 5.51 (dt, *J* = 7.2,

2.7 Hz, 1H), 4.43 (dd, *J* = 14.1, 1.8 Hz, 1H), 4.18 (dd, *J* = 6.9, 1.8 Hz, 1H), 2.83-2.71 (m, 1H), 2.60-2.49 (m, 1H), 2.44-2.32 (m, 1H), 2.23-2.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 141.1, 133.5, 1327, 131.9, 128.3, 127.9, 127.5, 126.0, 125.8, 124.7, 124.3, 88.5, 83.1, 31.2, 30.1; IR (thin film/NaCl): 3282, 3055, 2929, 2848, 1632, 1610, 1507, 1449, 1317, 1187, 1048, 1030, 963, 947, 894, 815, 746, 665 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{17}H_{16}O]^+$, 236.1201; found, 236.1207; $[\alpha]_D^{26}$ +48.7° (*c* 0.53, CH_2Cl_2).



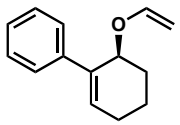
158

Vinyl Ether 158. Prepared as for **152** from (+)-**118** (82.3 mg, 0.55 mmol) to afford, after flash chromatography (125:2→10:1 hexanes:EtOAc), cyclopentenol (+)-**118** (53.2 mg, 65% yield) and **158** (30.3 mg, 31% yield) as a colorless oil: R_f 0.72 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.8 Hz, 1H), 6.49 (q, *J* = 6.6 Hz, 1H), 6.39 (dd, *J* = 3.6, 2.1 Hz, 1H), 6.36 (t, *J* = 3.0 Hz, 1H), 6.30 (d, *J* = 3.3 Hz, 1H), 5.23 (dt, *J* = 7.2, 2.7 Hz, 1H), 4.34 (dd, *J* = 14.4, 1.8 Hz, 1H), 4.10 (dd, *J* = 6.9, 1.8 Hz, 1H), 2.75-2.63 (m, 1H), 2.53-2.42 (m, 1H), 2.37-2.25 (m, 1H), 2.09-1.99 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 150.2, 141.9, 132.2, 130.1, 111.1, 106.9, 88.5, 83.3, 31.1, 30.1; IR (thin film/NaCl): 2924, 2850, 1633, 1611, 1487, 1349, 1317, 1189, 1153, 1051, 1028, 962, 916, 884, 806 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{11}H_{12}O_2]^+$, 176.0837; found, 176.0842; $[\alpha]_D^{25}$ +39.1° (*c* 0.35, CH_2Cl_2).



159

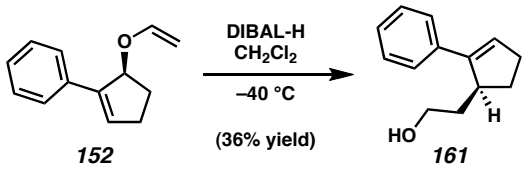
Vinyl Ether 159. Prepared as for **152** from (–)-**120** (428 mg, 2.47 mmol) to afford, after flash chromatography (200:1→100:1→10:1 hexanes:EtOAc), cyclopentenol (–)-**120** (140 mg, 33% yield) and **159** (301 mg, 61% yield) as a colorless oil: R_f 0.69 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.36 (comp. m, 4H), 7.31-7.24 (m, 1H), 6.45 (dd, *J* = 13.8, 6.3 Hz, 1H), 5.25 (br. d, *J* = 6.9 Hz, 1H), 4.31 (dd, *J* = 14.4, 1.8 Hz, 1H), 4.04 (dd, *J* = 6.6, 1.5 Hz, 1H), 2.79-2.68 (m, 1H), 2.48-2.22 (m, 2H), 2.06-1.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 142.3, 136.4, 134.7, 128.2, 128.1, 126.6, 88.0, 87.1, 37.1, 28.9, 15.7; IR (thin film/NaCl): 3055, 3029, 2975, 2938, 2912, 2845, 1631, 1608, 1492, 1444, 1379, 1350, 1317, 1189, 1099, 1058, 1016, 989, 964, 872, 816 cm^{-1}. HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{16}O]^+$, 200.1201; found, 200.1213; $[\alpha]_D^{26}$ +6.1° (*c* 0.80, CH_2Cl_2).



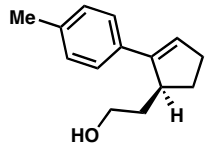
160

Vinyl Ether 160. Prepared as for **152** from (–)-**119** (174.1 mg, 1.00 mmol) to afford, after flash chromatography (125:2→10:1 hexanes:EtOAc), cyclopentenol (–)-**119** (98 mg, 56% yield) and **160** (31 mg, 16% yield) as a colorless oil: R_f 0.72 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.22 (comp. m, 5H), 6.43 (dd, *J* = 14.1, 6.6 Hz, 1H), 6.35 (t, *J* = 3.3 Hz, 1H), 4.78 (t, *J* = 3.0 Hz, 1H), 4.41 (dd, *J* = 14.1, 1.5 Hz, 1H), 4.08 (dd, *J* = 6.6, 1.8 Hz, 1H), 2.40-2.30 (m, 1H), 2.25-2.14 (m, 2H), 1.91-1.64

(comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 140.4, 135.6, 130.6, 128.3, 126.9, 125.6, 88.5, 72.5, 27.6, 25.9, 16.8; IR (thin film/NaCl): 3023, 2933, 2865, 2829, 2359, 2340, 1632, 1610, 1496, 1445, 1376, 1355, 1330, 1312, 1260, 1185, 1094, 1062, 1011, 977, 946, 917, 870, 813, 756, 695 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{16}O]^+$, 200.1201; found, 200.1207; $[\alpha]_D^{25}$ –115.8° (*c* 0.17, CH_2Cl_2).

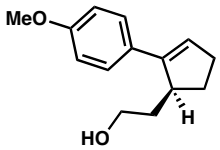


General Procedure for Claisen Rearrangement: Primary Alcohol 161. To a solution of vinyl ether **152** (7.6 mg, 0.041 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at –40 °C was added DIBAL-H (1 M in $PhCH_3$, 45 μL, 0.045 mmol, 1.1 equiv) dropwise. The reaction mixture was allowed to warm to 23 °C and to stir 2 h, after which it was quenched with excess Na_2SO_4•$10H_2O$. The suspension was stirred 30 min and filtered, and the filtrate was concentrated under reduced pressure. Purification by preparative TLC (9:2 hexanes:EtOAc) to afford primary alcohol **161** (2.8 mg, 36% yield): R_f 0.16 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (comp. m, 5H), 5.80 (t, *J* = 2.4 Hz, 1H), 3.75-3.58 (m, 2H), 2.42-2.35 (m, 2H), 2.10-2.01 (m, 1H), 1.89-1.77 (comp. m, 3H), 1.34 (s, 1H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 137.9, 128.9, 128.1, 127.3, 126.6, 60.7, 48.7, 48.5, 39.2, 30.1, 26.8; IR (thin film/NaCl): 3369, 3054, 2951, 2866, 1598, 1492, 1453, 1376, 1099, 1054, 1020, 759, 700 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{18}O]^+$, 202.1358; found, 202.1355; $[\alpha]_D^{25}$ +27.5° (*c* 0.66, CH_2Cl_2; for *S* enantiomer at 87% ee).



162

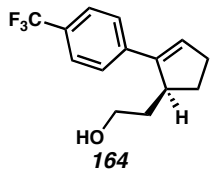
Primary Alcohol 162. Prepared as for **161** from **153** (40.9 mg, 0.21 mmol) to afford, after preparative TLC (9:2 hexanes:EtOAc), primary alcohol **162** (32 mg, 77% yield) as a colorless oil: R_f 0.15 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.02-6.00 (m, 1H), 3.73-3.65 (m, 2H), 3.26 (m, 1H), 2.52-2.44 (m, 2H), 2.34 (s, 3H), 2.26-2.13 (m, 1H), 1.94-1.74 (m, 2H), 1.55-1.43 (m, 1H), 1.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 136.6, 129.1, 126.0, 125.8, 61.7, 41.5, 36.5, 31.5, 29.8, 21.1; IR (thin film/NaCl): 3337, 3048, 3023, 2936, 2844, 1901, 1617, 1566, 1511, 1437, 1379, 1335, 1307, 1185, 1111, 1056, 1019, 981, 879, 803 cm^{-1}; HRMS-ES (m/z): $[M]^+$ calcd for $[C_{14}H_{18}O]^+$, 202.1358; found, 202.1353; $[\alpha]_D^{24}$ +51.5° (c 0.075, CH_2Cl_2; for *S* enantiomer at 96.8% ee).



163

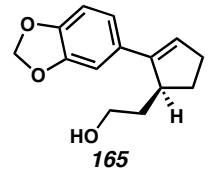
Primary Alcohol 163. Prepared as for **161** from **154** (38.5 mg, 0.18 mmol) to afford, after preparative TLC (9:2 hexanes:EtOAc), primary alcohol **163** (35.2 mg, 91% yield) as a colorless oil: R_f 0.15 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.94 (s, 1H), 3.80 (s, 3H), 3.72-3.64 (m, 2H), 3.26 (br. s, 1H), 2.50-2.44 (m, 2H), 2.24-2.11 (m, 1H), 1.92-1.73 (m, 2H), 1.54-1.42 (m, 1H), 1.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 145.6, 128.9, 127.2, 124.7, 113.7, 61.7, 55.2, 41.6, 36.4, 31.4, 29.8; IR (thin film/NaCl): 3392, 2934, 2836,

1607, 1510, 1462, 1441, 1294, 1252, 1178, 1037, 804 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{18}O_2]^+$, 218.1307; found, 218.1299; $[\alpha]_D^{25}$ +66.9° (*c* 0.27, CH_2Cl_2; for *S* enantiomer at 98.6% ee).



164

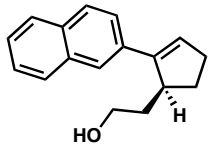
Primary Alcohol 164. Prepared as for **161** from **155** (41.1 mg, 0.16 mmol) to afford, after preparative TLC (9:2 hexanes:EtOAc), primary alcohol **164** (34.0 mg, 82% yield) as a colorless oil: R_f 0.18 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.4, 21.6 Hz, 4H), 6.17 (s, 1H), 3.72-3.67 (m, 2H), 3.30 (br. s, 1H), 2.52-2.50 (m, 2H), 2.29-2.16 (m, 1H), 1.90-1.78 (m, 2H), 1.52-1.42 (m, 1H), 1.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 139.8, 129.4, 126.3, 125.4, 125.4, 125.3, 61.5, 41.5, 36.3, 31.6, 29.7; IR (thin film/NaCl): 3368, 2937, 2846, 1615, 1412, 1326, 1164, 1123, 1110, 1069, 1015, 850, 831, 815 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{15}OF_3]^+$, 256.1075; found, 256.1073; $[\alpha]_D^{26}$ +48.5° (*c* 0.20, CH_2Cl_2; for *S* enantiomer at 97.1% ee).



165

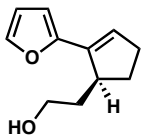
Primary Alcohol 165. Prepared as for **161** from **156** (63.4 mg, 0.28 mmol) to afford, after preparative TLC (9:2 hexanes:EtOAc), primary alcohol **165** (49 mg, 76% yield) as a colorless oil: R_f 0.22 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.89 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.78 (d, *J* = 8.4 Hz), 5.94 (s, 2H), 5.93 (s,

1H), 3.72-3.64 (m, 2H), 3.32 (br. s, 1H), 2.49-2.43 (m, 2H), 2.23-2.11 (m, 1H), 1.92-1.73 (m, 2H), 1.54-1.42 (m, 1H), 1.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 146.5, 145.8, 130.6, 125.4, 119.6, 108.1, 106.6, 100.9, 61.6, 41.7, 36.3, 31.3, 29.7; IR (thin film/NaCl): 3350, 3041, 2935, 2888, 2777, 2063, 1850, 1604, 1503, 1489, 1443, 1356, 1223, 1126, 1104, 1040, 986, 937, 862, 806 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{16}O_3]^+$, 232.1100; found, 232.1091; $[\alpha]_D^{24}$ +62.2° (*c* 0.27, CH_2Cl_2; for *S* enantiomer at 93.1% ee).



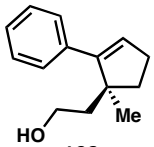
166

Primary Alcohol 166. Prepared as for **161** from **157** (45.3 mg, 0.19 mmol) to afford, after preparative TLC (9:2 hexanes:EtOAc), primary alcohol **166** (39.0 mg, 86% yield) as a colorless oil: R_f 0.24 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.78 (comp. m, 4H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.49-7.41 (m, 1H), 6.22 (s, 1H), 3.80 (s, 3H), 3.72 (t, *J* = 5.1 Hz, 2H), 3.41 (br. s, 1H), 2.62-2.46 (m, 2H), 2.31-2.18 (m, 1H), 2.10-1.81 (m, 2H), 1.61-1.49 (m, 1H), 1.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 133.6, 133.5, 132.5, 128.0, 127.9, 127.52, 127.46, 126.1, 125.6, 124.8, 124.5, 61.7, 41.5, 36.4, 31.6, 29.8; IR (thin film/NaCl): 3369, 3055, 2933, 2847, 1627, 1595, 1505, 1435, 1354, 1273, 1197, 1145, 1128, 1056, 989, 962, 946, 893, 858, 812, 747 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{17}H_{18}O]^+$, 238.1358; found, 238.1354; $[\alpha]_D^{25}$ +25.4° (*c* 0.47, CH_2Cl_2; for *S* enantiomer at 98.8% ee).



167

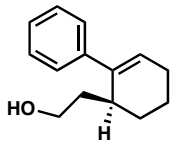
Primary Alcohol 167. Prepared as for **161** from **158** (27.0 mg, 0.15 mmol) to afford, after preparative TLC (9:2 hexanes:EtOAc), primary alcohol **167** (23.8 mg, 87% yield) as a colorless oil: R_f 0.21 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 1.5 Hz), 6.38 (dd, J = 3.3, 1.8 Hz, 1H), 6.26 (d, J = 3.3 Hz), 6.07 (s, 2H), 3.77-3.67 (m, 2H), 3.09 (br. s, 1H), 2.60-2.37 (m, 2H), 2.19-2.09 (m, 1H), 2.02-1.91 (m, 1H), 1.83-1.74 (m, 1H), 1.68-1.54 (m, 2H), 1.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 141.4, 136.6, 125.4, 110.9, 105.8, 61.6, 41.6, 36.7, 31.3, 29.8; IR (thin film/NaCl): 3368, 2938, 2873, 1654, 1487, 1459, 1329, 1056, 1008, 920, 885, 800, 733, 681 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{11}H_{14}O_2]^+$, 178.0994; found, 178.0995; $[\alpha]_D^{24}$ +23.4° (*c* 0.29, CH_2Cl_2; for *S* enantiomer at 48.6% ee).[65]



168

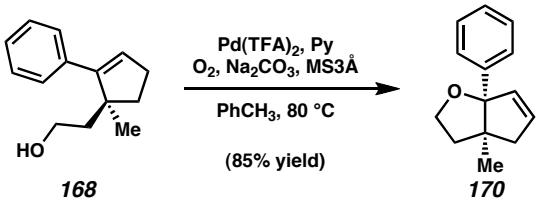
Primary Alcohol 168. Prepared as for **161** from **159** (39.9 mg, 0.20 mmol) to afford, after preparative TLC (4:1 hexanes:EtOAc), primary alcohol **168** (32.9 mg, 82% yield) as a colorless oil: R_f 0.12 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (comp. m, 5H), 5.80 (t, J = 2.4 Hz, 1H), 3.75-3.58 (m, 2H), 2.42-2.35 (m, 2H), 2.10-2.01 (m, 1H), 1.89-1.77 (comp. m, 3H), 1.34 (s, 1H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 137.9, 128.9, 128.1, 127.3, 126.6, 60.7, 48.7, 48.5, 39.2, 30.1, 26.8; IR (thin film/NaCl): 3369, 3054, 2951, 2866, 1598, 1492, 1453, 1376, 1099, 1054,

1020, 759, 700 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{18}O]^+$, 202.1358; found, 202.1355; $[\alpha]_D^{25}$ +27.5° (*c* 0.66, CH_2Cl_2; for *S* enantiomer at 87% ee).



169

Primary Alcohol 169. Prepared as for **161** from **160** (32.4 mg, 0.16 mmol) to afford, after preparative TLC (9:2 hexanes:EtOAc), primary alcohol **169** (27.1 mg, 83% yield) as a colorless oil: R_f 0.29 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.21 (comp. m, 5H), 5.92 (t, *J* = 4.2 Hz, 1H), 3.59 (t, *J* = 6.0 Hz, 2H), 2.89 (br. s, 1H), 2.21-2.15 (m, 2H), 1.87-1.43 (comp. m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 141.7, 128.3, 126.5, 126.5, 126.2, 61.2, 36.5, 30.0, 27.3, 26.0, 18.5; IR (thin film/NaCl): 3351, 3021, 2930, 2861, 2832, 1639, 1598, 1493, 1443, 1430, 1058, 1032, 1013, 986, 757, 698 cm^{-1}; HRMS-ES (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{18}O]^+$, 202.1358; found, 202.1358; $[\alpha]_D^{25}$ +107.2° (*c* 0.050, CH_2Cl_2; for *S* enantiomer at 97.0% ee).



168 ***170***

Tetrahydrofuran 170. To an oven-dried reaction tube with stir bar was added oven-dried powdered 3 Å molecular sieves (120 mg). After cooling, $Pd(TFA)_2$ (4.1 mg, 0.012 mmol, 0.10 equiv), anhydrous Na_2CO_3 (52.6 mg, 0.50 mmol, 4.0 equiv), followed by $PhCH_3$ (2.5 mL), pyridine (4.0 μL, 0.050 mmol, 0.40 equiv), and alcohol **168** (25.1

mg, 0.12 mmol, 1.0 equiv). The reaction vessel was then cooled to –78 °C, vacuum evacuated, and purged with O_2 (3 x). The reaction was then heated to 80 °C with vigorous stirring under O_2 (1 atm). After 15.5 h, the reaction was complete by TLC analysis. The reaction was cooled to 23 °C, filtered through a short plug of silica gel (EtOAc eluent), and concentrated under reduced pressure to afford tetrahydrofuran **170** (21.0 mg, 85% yield) as a colorless oil. Further purification by preparative TLC (4:1 hexanes:EtOAc) afforded an analytically pure sample: R_f 0.62 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.20 (comp. m, 5H), 6.07 (ddd, *J* = 5.8, 2.4, 2.4 Hz, 1H), 5.65 (ddd, *J* = 5.8, 2.1, 2,1 Hz, 1H), 4.07 (ddd, *J* = 8.6, 6.8, 4.3 Hz, 1H), 3.82 (ddd, *J* = 8.6, 8,6, 6.2 Hz, 1H), 2.53 (ddd, *J* = 17.3, 2.2, 2.2 Hz, 1H), 2.34 (ddd, *J* = 17.3, 2.2, 2.2 Hz, 1H), 1.96 (ddd, *J* = 12.0, 6.1, 4.4 Hz, 1H), 1.89 (ddd, *J* = 11.9, 8.6, 6.8 Hz, 1H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 134.6, 133.4, 128.0, 127.0, 126.2, 100.0, 65.9, 51.4, 47.6, 43.6, 25.5; IR (thin film/NaCl): 2956, 1722, 1492, 1448, 1047 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calcd for $[C_{14}H_{16}O]^+$, 200.1201; found, 200.1203; $[\alpha]_D^{26}$ –16.1° (*c* 1.6, CH_2Cl_2; for (*S*, *S*) enantiomer at 86% ee).

3.5.4 Methods for Determination of Conversion

Conversion values for **105**, **113**, **114**, and **124** were determined by ^{1}H NMR of a reaction aliquot after filtration through a short plug of silica gel. All other conversions were determined by GC (Table 3.5.1 or Chapter 2) relative to internal standard (tridecane).

Table 3.5.1 Methods for determination of conversion.

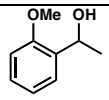
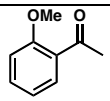
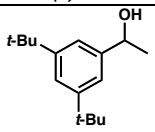
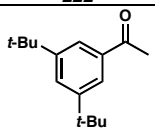
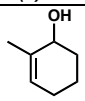
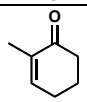
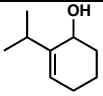
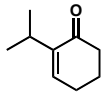
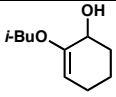
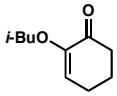
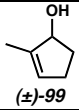
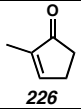
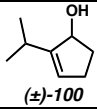
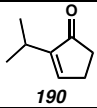
entry	alcohol	ketone	GC conditions	alcohol retention time (min)	ketone retention time (min)
1	 (±)-73	 222	100 °C, 5 min; Ramp 13 °C/min	13.5	12.7
2	 (±)-76	 186	100 °C, 5 min; Ramp 13 °C/min	13.5	12.6
3	 (±)-94	 223	70 °C, 15 min; Ramp 7 °C/min	21.8	20.4
4	 (±)-95	 224	70 °C, 15 min; Ramp 7 °C/min	23.4	20.5
5	 (±)-96	 189	100 °C, 5 min; Ramp 13 °C/min	9.0	7.8
6	 (±)-97	 225	70 °C, 15 min; Ramp 7 °C/min	28.7	31.2
7	 (±)-98	 187	100 °C, 5 min; Ramp 13 °C/min	10.6	12.2
8	 (±)-99	 226	70 °C, 15 min; Ramp 7 °C/min	19.8	17.8
9	 (±)-100	 190	100 °C, 5 min; Ramp 13 °C/min	8.0	7.4

Table 3.5.1 continued

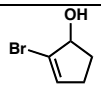
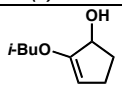
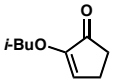
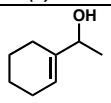
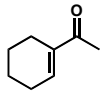
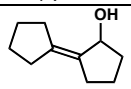
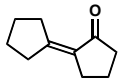
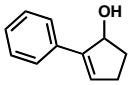
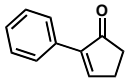
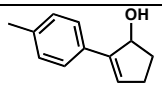
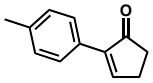
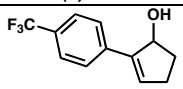
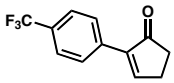
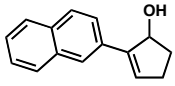
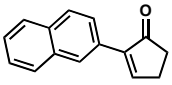
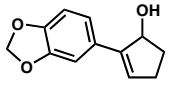
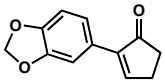
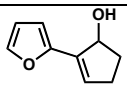
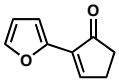
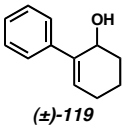
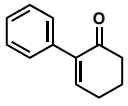
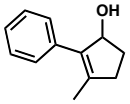
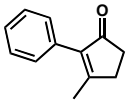
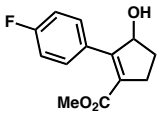
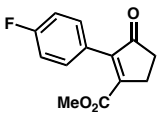
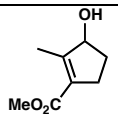
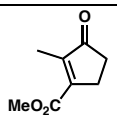
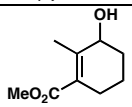
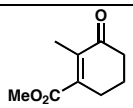
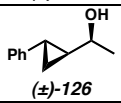
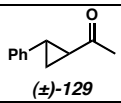
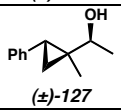
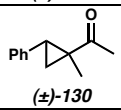
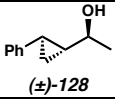
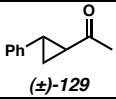
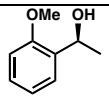
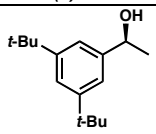
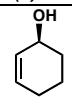
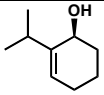
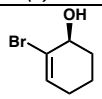
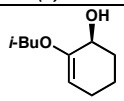
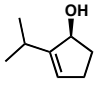
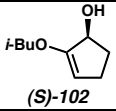
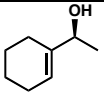
entry	alcohol	ketone	GC conditions	alcohol retention time (min)	ketone retention time (min)
10	 (±)-101	 227	70 °C, 15 min; Ramp 7 °C/min	28.6	30.6
11	 (±)-102	 191	100 °C, 5 min; Ramp 13 °C/min	10.3	11.8
12	 (±)-103	 192	100 °C, 5 min; Ramp 13 °C/min	9.3	8.7
13	 (±)-106	 194	70 °C, 15 min; Ramp 7 °C/min	29.5	29.7
14	 (±)-111	 143	100 °C, 5 min; Ramp 13 °C/min to 240 °C; 240 °C, 5 min	15.8	16.1
15	 (±)-112	 199	70 °C, 15 min; Ramp 7 °C/min	37.2	37.7
16	 (±)-115	 205	70 °C, 15 min; Ramp 7 °C/min	35.8	35.3
17	 (±)-116	 207	70 °C, 15 min; Ramp 7 °C/min to 240 °C; 240 °C, 20 min	53.3	55.4
18	 (±)-117	 209	70 °C, 15 min; Ramp 7 °C/min to 240 °C; 240 °C, 20 min	46.9	48.6
19	 (±)-118	 212	70 °C, 15 min; Ramp 7 °C/min	33.4	32.8
20	 (±)-119	 213	100 °C, 5 min; Ramp 13 °C/min to 240 °C; 240 °C, 5 min	15.8	16.1
21	 (±)-120	 214	100 °C, 5 min; Ramp 13 °C/min to 240 °C; 240 °C, 5 min	15.1	16.6

Table 3.5.1 continued

entry	alcohol	ketone	GC conditions	alcohol retention time (min)	ketone retention time (min)
22	 ***(±)-121***	 ***215***	70 °C, 15 min; Ramp 7 °C/min to 240 °C; 240 °C, 20 min	42.3	40.3
23	 ***(±)-122***	 ***216***	100 °C, 5 min; Ramp 13 °C/min	14.0	12.0
24	 ***(±)-123***	 ***217***	100 °C, 5 min; Ramp 13 °C/min	15.1	13.2
25	 ***(±)-125***	 ***228***	50 °C; Ramp 3 °C/min	7.4	5.0
26	 ***(±)-126***	 ***(±)-129***	100 °C, 5 min; Ramp 13 °C/min	14.2	13.1
27	 ***(±)-127***	 ***(±)-130***	70 °C, 15 min; Ramp 7 °C/min	33.2	31.3
28	 ***(±)-128***	 ***(±)-129***	100 °C, 5 min; Ramp 13 °C/min	14.1	13.1

3.5.5 Methods for Determination of Enantiomeric Excess

Table 3.5.2 Methods for determination of enantiomeric excess.

entry	compound (major enantiomer)	ee assay and column	assay conditions	(*S*) enantiomer retention time (min)	(*R*) enantiomer retention time (min)
1	 *(–)-73*	HPLC OB-H	3% EtOH/hexanes	11.5	21.4
2	 *(–)-76*	HPLC AD	0.25% *i*PrOH/hexanes	16.8	15.1
3[a]	 *(–)-94*	HPLC OJ	2% EtOH/hexanes	14.0	12.2
4[a]	 *(–)-95*	HPLC AD	1% EtOH/hexanes	9.7	8.9
5	 *(–)-96*	GC GTA	50 °C Ramp 1 °C/min	34.6	37.0
6[a]	 *(–)-97*	HPLC AD	1% EtOH/hexanes	16.7	15.3
7	 *(S)-98*	GC GTA	80 °C isothermal	53.4	52.5
8[a]	 *(S)-99*	HPLC OJ	1% EtOH/hexanes	12.0	13.2
9	 *(–)-100*	GC GTA	70 °C Ramp 1 °C/min	15.8	17.8
10[a]	 *(S)-101*	HPLC OJ	1% EtOH/hexanes	26.2	28.8
11	 *(S)-102*	GC GTA	80 °C isothermal	27.6	25.7
12	 *(–)-103*	GC GTA	50 °C Ramp 3 °C/min	18.7	19.0

[a] Assayed as the *p*-NBz derivative by treatment of the aliquot with *p*-NBzCl and DMAP in CH_2Cl_2.

Table 3.5.2 continued

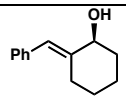
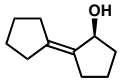
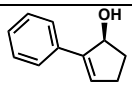
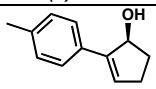
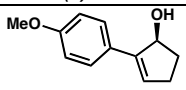
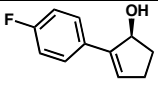
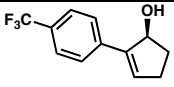
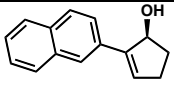
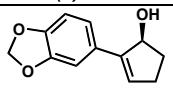
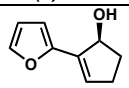
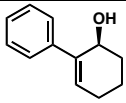
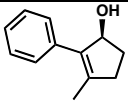
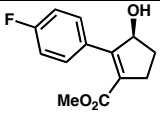
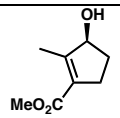
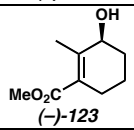
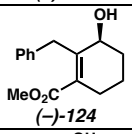
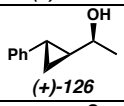
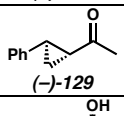
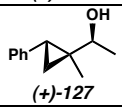
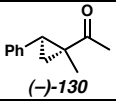
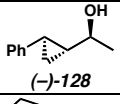
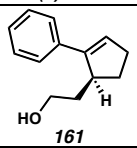
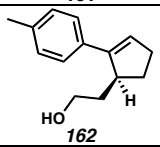
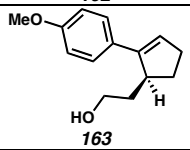
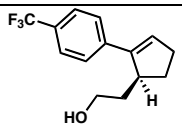
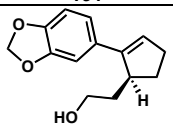
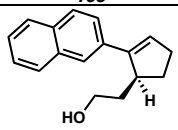
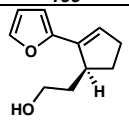
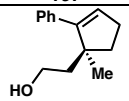
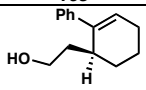
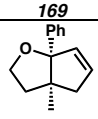
entry	compound (major enantiomer)	ee assay and column	assay conditions	(*S*) enantiomer retention time (min)	(*R*) enantiomer retention time (min)
13	 *(–)-105*	HPLC OD-H	4% EtOH/hexanes	12.4	10.3
14	 *(+)-106*	GC GTA	70 °C Ramp 1 °C/min	36.3	35.7
15	 *(+)-111*	HPLC OD-H	3% EtOH/hexanes	23.3	18.5
16	 *(+)-112*	HPLC OB-H	8% EtOH/hexanes	14.4	7.5
17	 *(+)-113*	HPLC AS	4% EtOH/hexanes	11.5	15.9
18	 *(+)-114*	HPLC OB-H	4% EtOH/hexanes	11.0	9.1
19	 *(+)-115*	HPLC OD-H	2% EtOH/hexanes	15.3	14.0
20	 *(+)-116*	HPLC AS	3% EtOH/hexanes	11.4	13.2
21	 *(+)-117*	HPLC OB-H	10% EtOH/hexanes	26.8	11.0
22	 *(+)-118*	HPLC AD	4% EtOH/hexanes	21.3	17.7
23	 *(–)-119*	HPLC AD	3% EtOH/hexanes	21.9	16.4
24	 *(–)-120*	HPLC OB-H	3% EtOH/hexanes	9.6	7.9
25	 *(–)-121*	HPLC OB-H	5% EtOH/hexanes	18.2	22.3

Table 3.5.2 continued

entry	compound (major enantiomer)	ee assay and column	assay conditions	(*S*) enantiomer retention time (min)	(*R*) enantiomer retention time (min)
26	 *(−)-122*	HPLC AD	3% EtOH/hexanes	23.0	26.0
27	 *(−)-123*	HPLC OB-H	2% *i*PrOH/hexanes	20.8	22.9
28	 *(−)-124*	HPLC OD-H	4% EtOH/hexanes	10.2	11.5
29	 *(+)-125*	GC GTA	40 °C isothermal	10.8	11.3
30	 *(+)-126*	HPLC OD-H	2% EtOH/hexanes	15.1[b]	17.8
31	 *(−)-129*	HPLC OD-H	2% EtOH/hexanes	7.9	8.5[c]
32	 *(+)-127*	HPLC OD-H	3% EtOH/hexanes	8.8[d]	10.1
33	 *(−)-130*	HPLC OD-H	3% EtOH/hexanes	6.9	7.5[e]
34	 *(−)-128*	HPLC OD-H	2% EtOH/hexanes	20.7[f]	14.6
35	 *161*	HPLC OJ	2% EtOH/hexanes	32.6	22.8
36	 *162*	HPLC OJ	2% EtOH/hexanes	13.4	15.3
37	 *163*	HPLC OJ	4% EtOH/hexanes	13.6	16.2

[b] Retention time for the (1*S*, 1'*S*, 2'*S*) enantiomer (shown). [c] Retention time for the (1'*R*, 2'*R*) enantiomer (shown). [d] Retention time for the (1*S*, 1'*S*, 2'*R*) enantiomer (shown). [e] Retention time for the (1'*R*, 2'*S*) enantiomer (shown). [f] Retention time for the (1*S*, 1'*R*, 2'*R*) enantiomer (shown).

Table 3.5.2 continued

entry	compound (major enantiomer)	ee assay and column	assay conditions	(*S*) enantiomer retention time (min)	(*R*) enantiomer retention time (min)
38	 **164**	HPLC OJ	2% *i*PrOH/hexanes	21.6	18.5
39	 **165**	HPLC OJ	4% EtOH/hexanes	17.8	21.1
40	 **166**	HPLC OJ	4% EtOH/hexanes	12.7	14.1
41	 **167**	HPLC OJ	4% EtOH/hexanes	12.3	10.9
42	 **168**	HPLC OD-H	3% EtOH/hexanes	13.1	10.7
43	 **169**	HPLC OJ	2% EtOH/hexanes	14.2	19.2
44	 **170**	GC GTA	100 °C Ramp 1 °C/min	28.8[g]	29.2

[g] Retention time for the (*S*, *S*) enantiomer (shown).

3.6 Notes and References

(1) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725-7726.

(2) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835-837.

(3) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 353-357.

(4) The selectivity factor (*s*) was determined using the following equation: $s = \frac{\ln[(1-conv)(1-ee_{alc})]}{\ln[(1-conv)(1+ee_{alc})]}$, where ee_{alc} is the ee of the recovered alcohol and *conv* is the total conversion of alcohol to ketone, see: Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley & Sons: New York, 1988; Vol. 18, pp 249-330.

(5) For a brief discussion of the substrate scope of the oxidative kinetic resolution, see: Stoltz, B. M.; Ebner, D. C. Kinetic Resolution by Enantioselective Aerobic Oxidation of Alcohols. In *Handbook of C–H Transformation*, Dyker, G., Ed.; Wiley-VCH: New York, 2005; Vol. 2, pp 393-401.

(6) Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 4482-4483.

(7) Caspi, D. D.; Ebner, D. C.; Bagdanoff, J. T.; Stoltz, B. M. *Adv. Synth. Catal.* **2004**, *346*, 185-189.

(8) Krishnan, S.; Ramtohul, Y. K.; Bagdanoff, J. T.; Ebner, D. C.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* in press.

(9) Ruel, F. S.; Braun, M. P.; Johnson, W. S. *Organic Syntheses*; Wiley & Sons: New York, 2004; Collect. Vol. X, pp 467-471.

(10) Luche, J. L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 601-602.

(11) Ebner, D. C.; Novák, Z.; Stoltz, B. M. *Synlett* **2006**, 3533-3539.

(12) Low reactivity was also observed in a related system, see: Sayyed, I. A.; Kumar, N. S. C. R.; Sudalai, A. *Indian J. Chem., Sect. B* **2005**, *44B*, 1533-1535.

(13) For palladium-catalyzed alcohol oxidation conditions that allow the resolution of some saturated alkyl alcohols, see: Mandal, S. K.; Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 4600-4603.

(14) Nielsen, R. J.; Keith, J. M.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2004**, *126*, 7967-7974.

(15) For discussions on synthetic approaches based on bidirectional chain synthesis, see: (a) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9-17. (b) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718-4720.

(16) For examples of bidirectional synthesis/terminus differentiation in natural products synthesis, see: (a) Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1637-1639. (b) Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360-3361. (c) Schreiber, S.

L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15-16. (d) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657-9659.

(17) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.

(18) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741-743.

(19) (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892-2895. (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778-17788.

(20) Related oxidative kinetic resolutions en route to pharmaceutical agents have been reported, see: (a) Ali, I. S.; Sudalai, A. *Tetrahedron Lett.* **2002**, *43*, 5435-5436. (b) Thakur, V. V.; Sudalai, A. *Indian J. Chem., Sect. B* **2005**, *44B*, 557-562.

(21) (a) Mitchell, D.; Koenig, T. M. *Synth. Commun.* **1995**, *25*, 1231-1238. (b) Kumar, A.; Ner, D. H.; Dike, S. Y. *Tetrahedron Lett.* **1991**, *32*, 1901-1904. (c) Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339-1342. (d) Ali, I. S.; Sudalai, A. *Tetrahedron Lett.* **2002**, *43*, 5435-5436. (e) Kumar, A.; Ner, D. H.; Dike, S. *Ind. J. Chem. B* **1992**, *31*, 803-809, and references therein.

(22) (a) Larsen, R. D.; Corley, E. G.; King, A. O.; Carroll, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398-3405. (b) King, A. O.; Corley, E. G.; Anderson, R.

K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; Labelle, M.; Prasit, P.; Zamboni, R. J. *J. Org. Chem.* **1993**, *58*, 3731-3735. (c) Bhupathy, M.; McNamara, J. M.; Sidler, D. R.; Volante, R. P.; Bergan, J. J. (Merck & Co., Inc.). World Patent 95/18107, 1995. (d) Bhupathy, M.; McNamara, J. M.; Sidler, D. R.; Volante, R. P.; Bergan, J. J. (Merck & Co., Inc.). U. S. Patent 5,614,632, 1997, and references therein.

(23) (a) Kuethe, J. T.; Wong, A.; Wu, J.; Davies, I. W.; Dormer, P. G.; Welch, C. J.; Hillier, M. C.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5993-6000. (b) Desai, R. C.; Cicala, P.; Meurer, L. C.; Finke, P. E. *Tetrahedron Lett.* **2002**, *43*, 4569-4570, and references therein.

(24) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661-1664.

(25) Baker, L.; Minehan, T. *J. Org. Chem.* **2004**, *69*, 3957-3960.

(26) Murphy, J. A.; Scott, K. A.; Sinclair, R. S.; Martin, C. G.; Kennedy, A. R.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2395-2408.

(27) Bunnelle, W. H.; Isbell, T. A. *J. Org. Chem.* **1992**, *57*, 729-740.

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

([29]) $CHCl_3$ stabilized with amylenes. $CHCl_3$ stabilized with EtOH must be distilled prior to use.

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

(31) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.

(32) Zhang, L.; Nadzan, A. M.; Heyman, R. A.; Love, D. L.; Mais, D. E.; Croston, G.; Lamph, W. W.; Boehm, M. F. *J. Med. Chem.* **1996**, *39*, 2659-2663.

(33) Pattenden, G.; Whybrow, D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3147-3149.

(34) Begley, M. J.; Ladlow, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1095-1106.

(35) Birch, A. J.; Slobbe, J. *Aust. J. Chem.* **1977**, *30*, 1045-1049.

(36) Ansell, M. F.; Ducker, J. W. *J. Chem. Soc.* **1959**, 329-331.

(37) Little, R. D.; Brown, L. M.; Masjedizadeh, M. R. *J. Am. Chem. Soc.* **1992**, *114*, 3071-3075.

(38) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975-984.

(39) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640-5644.

(40) Billimoria, J. D. *J. Chem. Soc.* **1955**, 1126-1129.

(41) Grau-Martinez, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 5679-5698.

(42) Fogliato, G.; Fronza, G.; Fuganti, C.; Lanati, S.; Rallo, R.; Rigoni, R.; Servi, S. *Tetrahedron* **1995**, *51*, 10231-10240.

(43) Schick, H.; Mahrwald, R. *Synthesis* **1990**, 592-595.

(44) Dang, H.-S.; Davies, A. G.; Davison, I. G. E.; Schiesser, C. H. *J. Org. Chem.* **1990**, *55*, 1432-1438.

(45) Ruel, F. S.; Braun, M. P.; Johnson, W. S. *Organic Syntheses*; Wiley & Sons: New York, 2004; Collect. Vol. X, pp 467-471.

(46) Felpin, F. X. *J. Org. Chem.* **2005**, *70*, 8575-8578.

(47) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179-13184.

(48) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164-168.

(49) Negishi, E.-i.; Tan, Z.; Liou, S.-Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197-10207.

(50) Pour, M; Spulák, M; Balsánek, V.; Kunes, J.; Kubanová, P.; Buchta, V. *Bioorg. Med. Chem.* **2003**, *11*, 2843-2866.

(51) Fürstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541-543.

(52) Steinke, N.; Frey, W.; Baro, A.; Laschat, S.; Drees, C.; Nimtz, M.; Hägele, C.; Giesselmann, F. *Chem.–Eur. J.* **2006**, *12*, 1026-1035.

(53) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263-14278.

(54) Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 2579-2581.

(55) Ito, S.; Kasai, M.; Ziffer, H.; Silverton, J. V. *Can. J. Chem.* **1987**, *65*, 574-582.

(56) Padwa, A.; Blacklock, T. J.; Getman, D.; Hatanaka, N.; Loza, R. *J. Org. Chem.* **1978**, *43*, 1481-1492.

(57) Hewett, C. L. *J. Chem. Soc.* **1936**, 50-52.

(58) Correa, J.; Mainero, R. M. *J. Org. Chem.* **1969**, *34*, 2192-2195.

(59) Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966-2967.

(60) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12160-12167.

(61) Barluenga, J.; Bernad, P. L., Jr.; Concellón, J. M.; Piñera-Nicolás, A.; García-Granda, S. *J. Org. Chem.* **1997**, *62*, 6870-6875.

(62) DePuy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347-3354.

(63) Charette, A. B.; Lacasse, M.-C. *Org. Lett.* **2002**, *4*, 3351-3353.

(64) Charette, A. B.; Lebel, H.; Gagnon, A. *Tetrahedron* **1999**, *55*, 8845-8856.

(65) The decreased enantiomeric excess for this substrate is presumably due to competing 1,3-rearrangement, leading to partial racemization.