CHAPTER TWO

The Resolution of Important Pharmaceutical Building Blocks by Palladium-Catalyzed Aerobic Oxidation of Secondary Alcohols

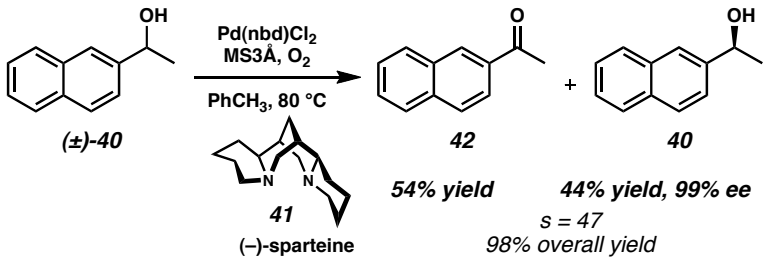
2.1 Background

2.1.1 Introduction

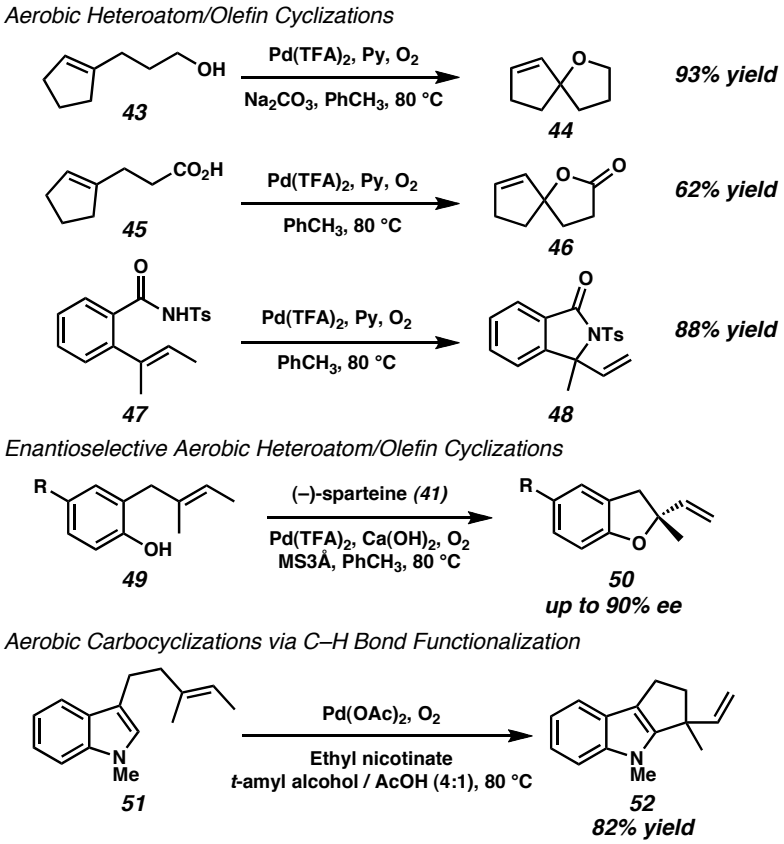
As part of a general program initiated in the area of asymmetric dehydrogenation chemistry, our laboratory recently reported the oxidative kinetic resolution of secondary alcohols. Our method employs a simple palladium dichloride catalyst precursor [Pd(nbd)Cl_2] in conjunction with (–)-sparteine (**41**), which serves as both ligand and base, and molecular oxygen as the stoichiometric oxidant (Scheme 2.1.1).[1,2,3] In this resolution, one enantiomer of a secondary alcohol (e.g., (±)-**40**) is preferentially oxidized to the ketone (e.g., **42**), leaving behind the other, slower-reacting enantiomer of the alcohol (e.g., **40**). The relative reaction rates of each enantiomer, referred to as *selectivity* (k_{rel} or *s*), can be computed from the enantiomeric excess of the alcohol at a given conversion.[4]

This palladium/sparteine system proved useful for the resolution of simple benzylic and allylic alcohols, as well as the desymmetrization of meso-diols, with selectivities ranging from 6.6–47.1 (Scheme 2.1.1).[4] Additionally, the use of dehydrogenative Pd(II) catalysis has been extended to oxidative cyclizations including both heterocyclizations and carbocyclizations (Scheme 2.1.2).[5]

Scheme 2.1.1



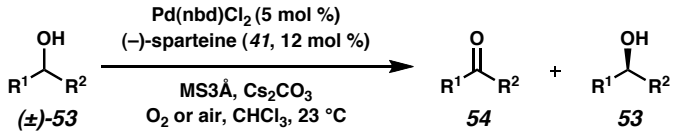
Scheme 2.1.2



Since the initial report,[1a] a number of conceptual improvements to the original oxidative kinetic resolution system have been made that allow a range of secondary alcohols (e.g., **40**) to be resolved with a variety of differing experimental procedures depending on the substrate.[1b,1c] A second method was developed employing Cs_2CO_3 and *t*-

BuOH as additives, which provided generally higher selectivities and shorter reaction times under lower reaction temperatures (Table 2.1.1).[1b] Additionally, a third iteration of our reaction replaced toluene with chloroform, which enabled us to run these transformations at room temperature using ambient air as the stoichiometric oxidant (Table 2.1.2).[1c]

Table 2.1.1



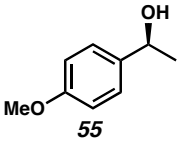
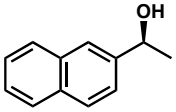
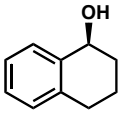
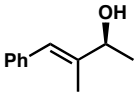
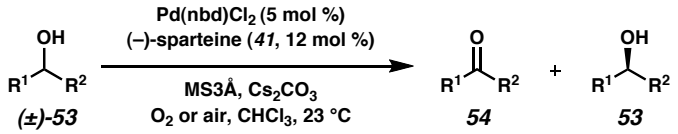
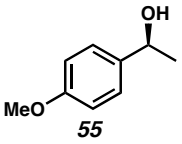
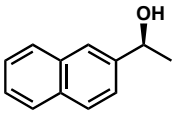
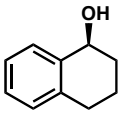
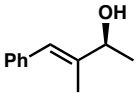
entry	unreacted alcohol, major enantiomer	O_2 source	time	conversion (%)	ee ROH (%)	*s*
1	 *55*	O_2	48 h	62.6	99.9	27.1
		air	24 h	62.3	99.8	25.4
2	 *40*	O_2	48 h	59.3	99.6	31.1
		air	24 h	55.5	98.0	37.3
3	 *56*	O_2	24 h	57.5	98.0	27.6
		air	16 h	60.2	99.6	28.0
4	 *57*	O_2	48 h	62.6	98.7	17.9
		air	44 h	64.7	98.9	15.7

Table 2.1.2

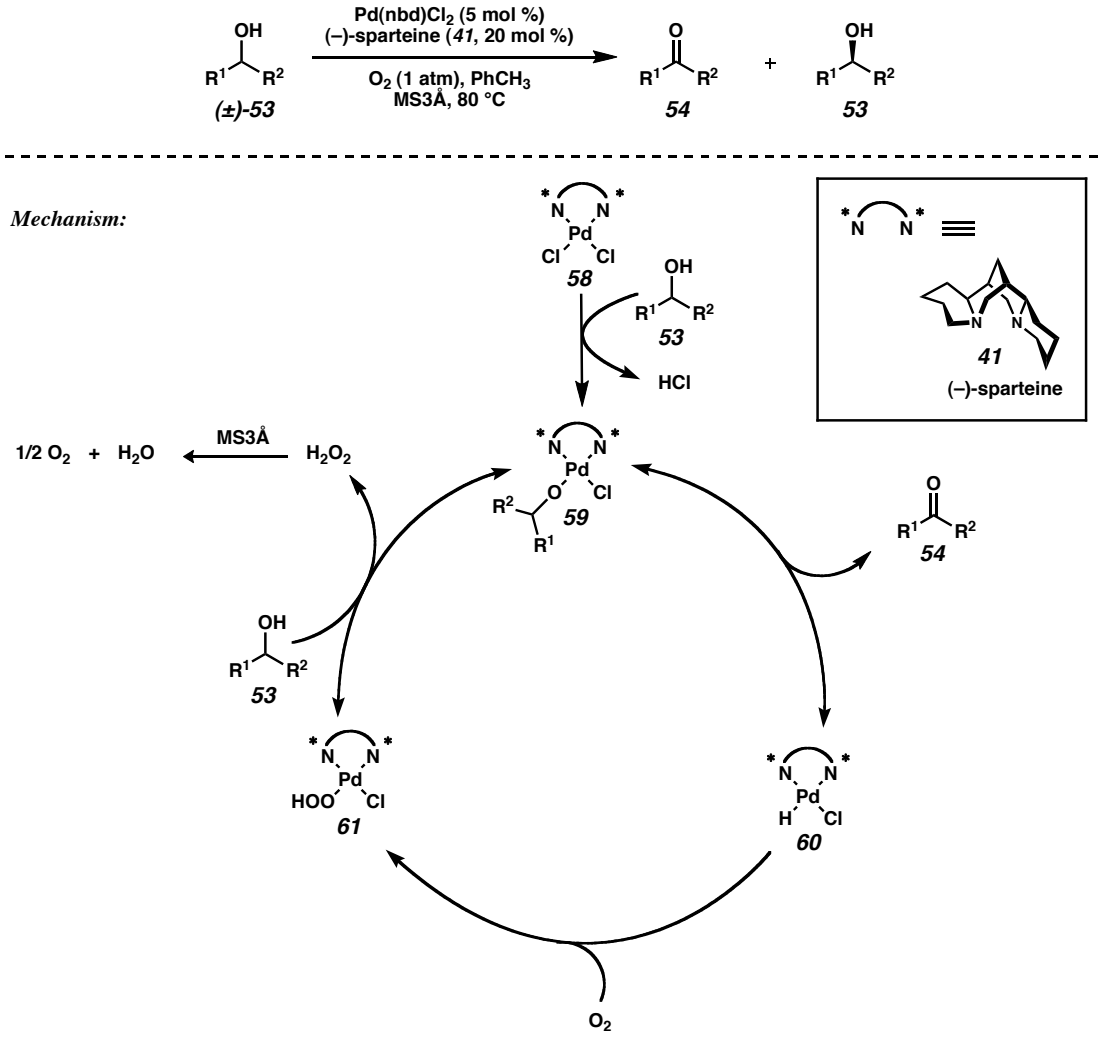


entry	unreacted alcohol, major enantiomer	atm	time	conversion (%)	ee ROH (%)	*s*
1	 *55*	O_2	48 h	62.6	99.9	27.1
		air	24 h	62.3	99.8	25.4
2	 *40*	O_2	48 h	59.3	99.6	31.1
		air	24 h	55.5	98.0	37.3
3	 *56*	O_2	24 h	57.5	98.0	27.6
		air	16 h	60.2	99.6	28.0
4	 *57*	O_2	48 h	62.6	98.7	17.9
		air	44 h	64.7	98.9	15.7

2.1.2 Mechanism of the Pd-Catalyzed Oxidative Kinetic Resolution

The general mechanism envisioned for this reaction is outlined in Scheme 2.1.3.[6] Starting with a palladium(II)-ligand complex (**58**), ligand substitution with a chiral substrate molecule (**53**) affords Pd(II) alkoxide **59**. This complex (**59**) can undergo β-hydride elimination to afford palladium hydride **60**, and generate oxidized substrate molecule **54**. Oxidation of the palladium with molecular oxygen then gives rise to **61**,[7] which can undergo ligand substitution with another substrate molecule (**53**) and continue the catalytic cycle. Finally, the hydrogen peroxide that is produced in the final step is proposed to be disproportionated into oxygen and water via the action of MS3Å.[3]

Scheme 2.1.3



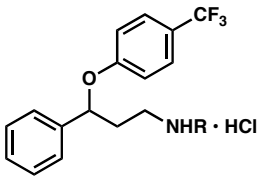
2.2 The Oxidative Kinetic Resolution of Pharmaceutical Building Blocks

2.2.1 Pharmaceutical Targets

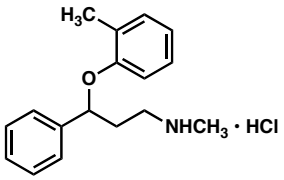
Although this oxidative kinetic resolution system had been optimized and studied in detail, it had primarily only been tested with simple, commercially-available benzylic alcohols. To demonstrate the potential synthetic utility of our palladium-catalyzed enantioselective alcohol oxidation, we investigated the oxidative kinetic resolution of a diverse set of small molecules representing key building blocks of bioactive,

pharmaceutically relevant materials (Figure 2.2.1).[8] These pharmaceutical substances included A) the antidepressants fluoxetine hydrochloride (Prozac®, **62**), norfluoxetine (**63**), tomoxetine (**64**), and nisoxetine (**65**),[9] and B) the orally active leukotriene receptor antagonist montelukast sodium (Singulair®, **66**).[10,11] These compounds were specifically chosen due to the inclusion of a key benzylic or allylic alcohol in the known synthetic routes (i.e., **67**–**70**, Table 2.2.1). We believed that these pharmaceutical agents would represent an ideal testing ground for our new asymmetric methodology.

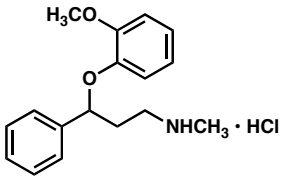
Figure 2.2.1



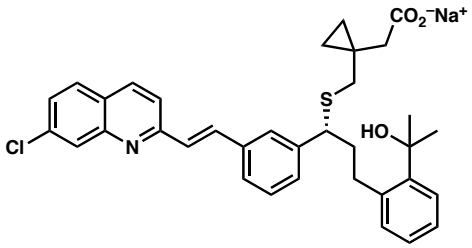
R = CH_3, Fluoxetine·HCl (Prozac®, 62)
R = H, Norfluoxetine·HCl (63)



Tomoxetine (64)



Nisoxetine (65)



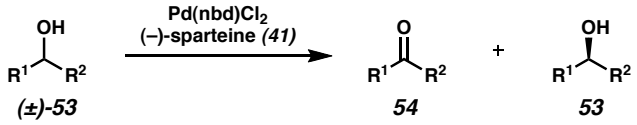
Montelukast Sodium (Singulair®, 66)

2.2.2 Resolution of Pharmaceutical Intermediates

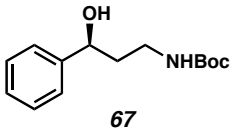
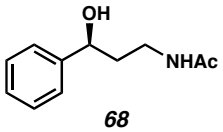
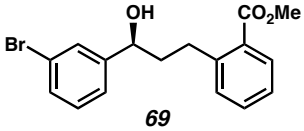
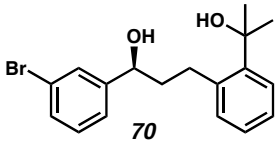
To this end, we prepared a number of key intermediates by literature procedures and subjected them to kinetic resolution using a variety of our palladium-catalyzed aerobic conditions.[12] To our delight, all of the intermediates were resolved to high enantiomeric excess and with good-to-excellent selectivity (*s*) between the *R* and *S* enantiomers (*s* = 9.0–17.9).[4] As shown in Table 2.2.1, the amino alcohol derivatives **67** and **68**, relevant to the antidepressants **62**–**65**, could be resolved under our original conditions, employing $Pd(nbd)Cl_2$, (–)-sparteine (**41**), and O_2.[1a] While acetamide **68** was reasonably selective (*s* = 9), the more synthetically versatile Boc derivative **67** could be resolved with a selectivity factor of nearly 18.

Notably, carbamate **67** could be easily converted to *N*-methyl derivative **71** by reduction with $LiAlH_4$ (78% yield) or to primary amine **72** by treatment with TFA (68% yield), and ketone **73** could be recycled to (±)-**67** by quantitative reduction with $NaBH_4$ (Scheme 2.2.1). Amino alcohol intermediates **71** and **72** could then be converted to pharmaceutically-relevant compounds **62**–**65** using known procedures.[9]

Table 2.2.1

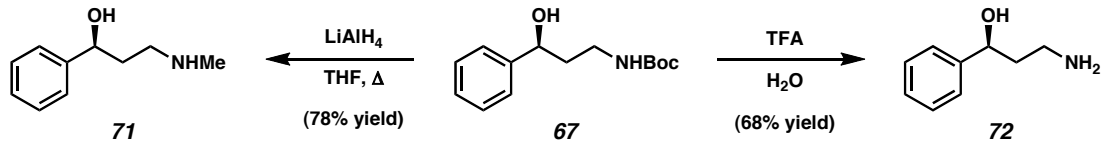


(±)-53 54 53

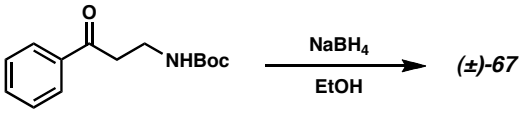
entry	unreacted alcohol, major enantiomer	method[a]	time	conversion (%)	ee ROH (%)[e]	*s*
1	 **67**	A	24 h	57.5[c]	93.1	17.9
2	 **68**	A	14.5 h	70.0[c]	97.0	9.0
3	 **69**	B[b]	4.5 h	62.5[d]	92.9	11.2
4	 **70**	B[b]	4.5 h	70.6[c]	99.9	15.3

[a] Method A: 5 mol % $Pd(nbd)Cl_2$, 20 mol % (–)-sparteine (**41**), MS3Å, O_2 (1 atm), 0.1 M in $PhCH_3$, 80 °C. Method B: 5 mol % $Pd(nbd)Cl_2$, 20 mol % (–)-sparteine (**41**), 0.5 equiv Cs_2CO_3, 1.5 equiv *t*-BuOH, MS3Å, O_2 (1 atm), 0.25 M in $PhCH_3$, 60 °C. [b] Performed at 80 °C. [c] Conversion determined by isolated yield. [d] Conversion determined by ^1H NMR. [e] Enantiomeric excess (ee) determined by chiral HPLC. Total mass recovery in all cases was greater than 85%.

Scheme 2.2.1



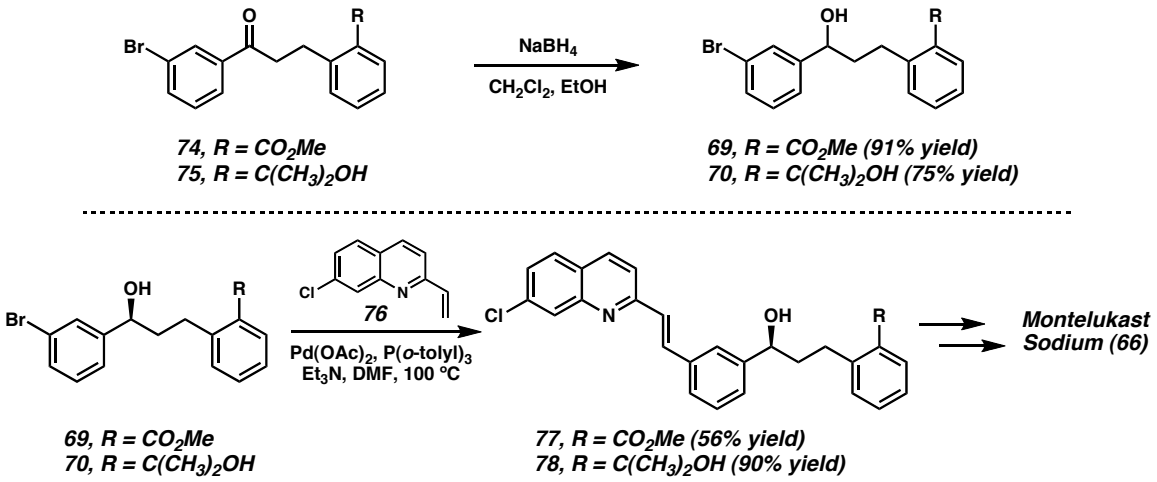
71 67 72



73 (±)-67

The molecules relevant to the Singulair® system also resolved quite efficiently under our conditions (Table 2.2.1, entries 3 and 4). In order to minimize the experimental time involved for the resolution of compounds **69** and **70**, we chose to employ our recently described base-accelerated conditions.[1b] Smooth and rapid kinetic resolution was observed for both substrates (4.5 h) leading to production of the relevant enantiomer en route to Singulair®. Importantly, these resolutions provide a notable example of the functional group compatibility of the rate-accelerated system, as both aryl bromides and benzoate esters are tolerated in the oxidation. Again, the corresponding ketones **74** and **75** could be easily recycled via borohydride reduction. Furthermore, intermolecular Heck reaction of both **69** and **70** provided access to elaborated benzylic alcohols **77** and **78**, intermediates used in the production of montelukast sodium (Scheme 2.2.2).

Scheme 2.2.2



2.3 Conclusion

In conclusion, we have employed the palladium-catalyzed aerobic oxidative kinetic resolution of secondary alcohols for the enantioselective preparation of a variety

of pharmaceutical substances including Prozac® (**62**) and Singulair® (**66**). These examples demonstrate the power and utility of the methods to overcome many subtleties of substrate functionality. In this regard, the versatility of this resolution is further demonstrated by the diversity of the substrates chosen for this study, and for the first time this work extends the utility of the resolution to include amino alcohol derivatives and highly functionalized benzylic alcohols. Efforts to develop new catalyst systems and expand the utility and generality of asymmetric aerobic dehydrogenations continue.

2.4 Experimental Section

2.4.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized using a combination of UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. Analytical chiral HPLC was performed on a Chiralcel® OJ or Chiralpak® AD column (each is 4.6 mm x 250 mm) obtained from Daicel Chemical Industries, Ltd. Analytical achiral GC was performed using an Agilent DB-WAX (30.0 m x 0.25 mm) column. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (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. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

2.4.2 Methods of Determination for Enantiomeric Excess and % Conversion

Table 2.4.1. Methods for determination of enantiomeric excess

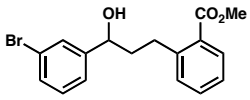
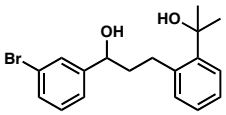
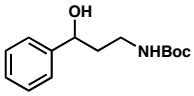
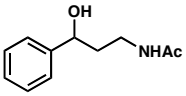
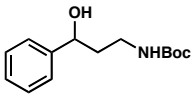
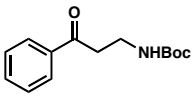
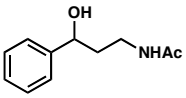
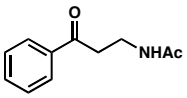
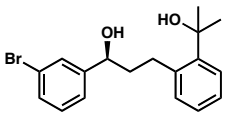
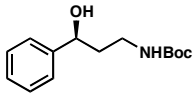
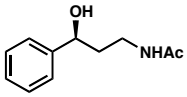
Entry	Substrate	HPLC Assay	Conditions	Retention Time (min)	
				(*R*)-isomer	(*S*)-isomer
1	 ***69***	Chiralpak® AD	5% EtOH/hexanes 1.0 mL/min 254 nm	15.8	17.1
2	 ***70***	Chiralcel® OJ	5% EtOH/hexanes 1.0 mL/min 210 nm	17.8	15.0
3.	 ***67***	Chiralcel® OJ	8% 2-propanol/hexanes 1.0 mL/min 210 nm	10.5	20.1
4	 ***68***	Chiralpak® AD	6% 2-propanol/hexanes 1.0 mL/min 210 nm	27.9	23.8

Table 2.4.2. Methods for determination of % conversion

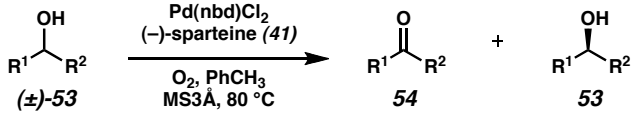
Entry	Substrate	Ketone	GC Conditions	Retention Time (min)	
				Alcohol	Ketone
1	 ***67***	 ***73***	70 °C, 15 min; 7 °C/min to 240 °C; hold 20 min 1.0 mL/min carrier gas flow	48.1	42.2
2	 ***68***	 ***81***	70 °C, 15 min; 7 °C/min to 240 °C; hold 20 min 1.0 mL/min carrier gas flow	53.5	45.1

2.4.3 Optical Rotations of New Compounds

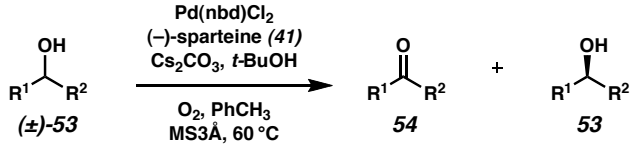
Table 2.4.3. Optical rotations (refer to Table 2.2.1 for relevant % enantiomeric excess)

Entry	Substrate	Rotation
1	 ***70***	$[\alpha]^{26}_{D}$ –31.7° (*c* 1.0, benzene)[13]
2	 ***67***	$[\alpha]^{25}_{D}$ –15.4° (*c* 1.0, $CHCl_3$)[13]
3	 ***68***	$[\alpha]^{25}_{D}$ –23.6° (*c* 1.3, $CHCl_3$)[14]

2.4.4 Representative Procedures for Oxidative Kinetic Resolution

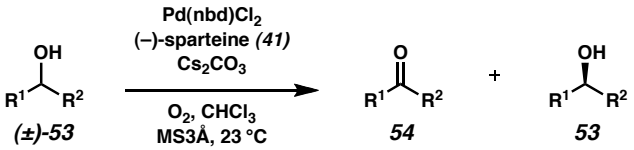


Kinetic Resolution Conditions A: "Original Conditions."[1a] To an oven-dried reaction tube with stir bar was added oven-dried powdered 3Å molecular sieves (250 mg). After cooling, $Pd(nbd)Cl_2$ (6.7 mg, 0.025 mmol) followed by toluene (2.5 mL) and then (–)-sparteine (**41**, 23.4 mg, 23 μL, 0.10 mmol) were added. The reaction tube was then vacuum evacuated and purged with O_2 (3x), and the tube was heated to 80 °C with vigorous stirring under O_2 atmosphere (1 atm) for 20 min. A solution of alcohol **53** (0.50 mmol) in toluene (2.5 mL) was added, and the reaction was allowed to proceed under O_2 atmosphere (1 atm) at 80 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **54** and enantioenriched alcohol **53** was accomplished by direct chromatography of the crude reaction mixture.



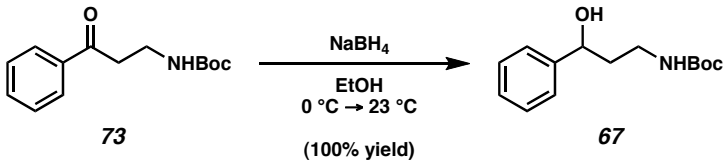
Kinetic Resolution Conditions B: "Rate-Accelerated Conditions."[1b] To an oven-dried reaction tube with stir bar was added oven-dried powdered 3Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.05 mmol), followed by toluene (2 mL) and then (–)-sparteine (**41**, 46.9 mg, 46 μL, 0.20 mmol) were added. The reaction tube was then vacuum evacuated and purged with O_2 (3x), and the tube was heated (60 °C) with vigorous stirring under O_2 atmosphere (1 atm) for 20 min. Finely powdered

anhydrous Cs_2CO_3 (162.9 mg, 0.50 mmol) was added, followed by a solution of alcohol **53** (1.0 mmol), *t*-butanol (111.2 mg, 143 μL, 1.5 mmol) and toluene (2 mL). The reaction was allowed to proceed under O_2 atmosphere (1 atm) at 60 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **54** and enantioenriched alcohol **53** was accomplished by direct chromatography of the crude reaction mixture.



Kinetic Resolution Conditions C: "Chloroform Conditions."[1c] To an oven-dried reaction tube with stir bar was added oven-dried powdered 3Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.05 mmol), followed by chloroform (2 mL, stabilized with amylenes) and then (–)-sparteine (**41**, 28.1 mg, 27.6 μL, 0.12 mmol) were added. The reaction tube was then vacuum evacuated and purged with O_2 (3x), and the reaction was stirred vigorously at 23 °C under O_2 atmosphere (1 atm) for 15 min. Finely powdered anhydrous Cs_2CO_3 (130.3 mg, 0.40 mmol) was added, followed by a solution of alcohol **53** (1.0 mmol) in chloroform (2 mL). The reaction was allowed to proceed under O_2 atmosphere (1 atm) at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **54** and enantioenriched alcohol **53** was accomplished by direct chromatography of the crude reaction mixture.

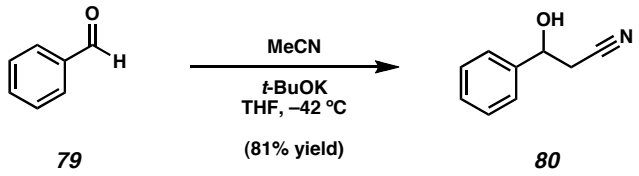
2.4.5 Representative Procedure for Ketone Recycling



73 *67*

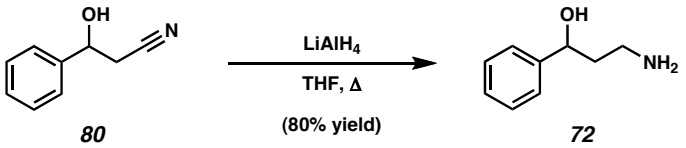
Carbamate 67. To keto-carbamate **73** (113.3 mg, 0.45 mmol) in EtOH (2.0 mL) was added $NaBH_4$ (40.0 mg, 1.0 mmol) at 0 °C. After stirring for 3 h and allowing the reaction to warm to 23 °C, saturated aq. NH_4Cl was added dropwise at 0 °C. The mixture was diluted with EtOAc (1 mL) and H_2O (1 mL) and the phases were partitioned. The aqueous phase was extracted with EtOAc (3 x 1 mL). The organic extracts were combined and passed over a small plug of silica gel (EtOAc eluent). The solvent was removed in vacuo to afford carbamate **67** (113.8 mg, 100% yield).

2.4.6 Preparative Procedures



79 *80*

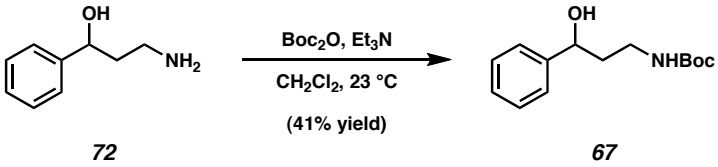
Nitrile 80.[9c] A flask charged with THF (100 mL) and acetonitrile (3.2 mL, 57.1 mmol) was cooled to –42 °C and treated dropwise with a solution of *t*-BuOK (7.1 g, 63.3 mmol) in THF (25 mL). After stirring for 45 min, freshly distilled benzaldehyde (**79**, 5.7 mL, 56.4 mmol) was added dropwise. The reaction was allowed to warm to –15 °C over a 4 h period, and then was quenched by slow addition of saturated aq. NH_4Cl (35 mL). The layers were partitioned, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organics were washed with H_2O (2 x 20 mL) and saturated aq. NaCl (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was flash chromatographed (1:1 Et_2O:hexanes eluent) to give nitrile **80** (6.69 g, 81% yield) as a colorless oil. R_f 0.16 (1:1 Et_2O:hexanes); characterization data for this compound have been previously reported.[9a]



80 *72*

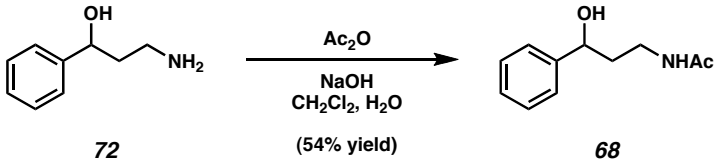
Amino alcohol 72. A flask was charged with a suspension of $LiAlH_4$ (2.92 g, 77.0 mmol) in THF (100 mL). After cooling to 0 °C, the suspension was treated with nitrile **80** (4.54 g, 30.9 mmol) dropwise, and the resulting brown mixture was heated to reflux for 5 h. The reaction was cooled to 0 °C, and quenched by slow addition of H_2O (3

mL), followed by 15% *w*/*v* aq. NaOH (3 mL), and finally by H_2O (9 mL). The crude green sludge was vacuum filtered and washed well with Et_2O. The filtrate was concentrated under reduced pressure to a green oil, and partitioned between EtOAc (100 mL) and 15% *w*/*v* aq. NaOH (30 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated in vacuo to afford amino alcohol **72** (3.74 g, 80% yield) as a dark orange oil, which was used without further purification. R_f 0.0 (1:1 EtOAc:hexanes); characterization data for this compound have been previously reported.[9a]

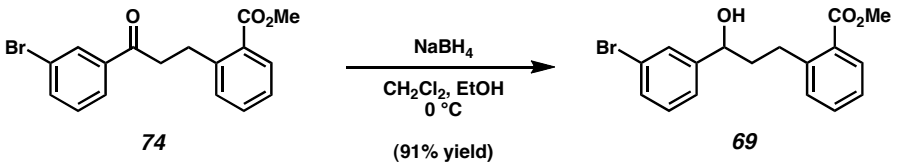


Carbamate 67. To amino alcohol **72** (2.14 g, 14.1 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (2.8 mL, 20.1 mmol) over 1–2 min at 23 °C, followed by Boc_2O (3.09 g, 14.2 mmol). The reaction was stirred for 2 h, then quenched by addition of saturated aq. NH_4Cl (15 mL). The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The organic extracts were combined, washed with saturated aq. $NaHCO_3$ (15 mL), H_2O (15 mL), and saturated aq. NaCl (15 mL), and dried over $MgSO_4$. The crude product was concentrated in vacuo, and passed over a short plug of silica gel (20:1 CH_2Cl_2:MeOH eluent). A solid was precipitated from the residue by treatment with hexanes:Et_2O (10:1, 10 mL), and the solvent was evaporated in vacuo. This material was then recrystallized from hexanes:Et_2O (10:1, 10 mL), filtered, and rinsed with ice-cold pentane (3 x 5 mL) to afford carbamate **67** (1.44 g, 41% yield) as a white solid. R_f 0.60 (7:1 CH_2Cl_2:MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.23 (m, 5H), 4.84 (br s, 1H),

4.77–4.69 (m, 1H), 3.55–3.36 (m, 1H), 3.22–3.09 (m, 1H), 2.94 (br s, 1H), 1.88–1.80 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 144.5, 128.6, 127.6, 125.8, 79.8, 71.9, 39.8, 37.8, 28.6; IR (film) 3360 (br), 1688, 1515, 1281, 1252, 1170 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ calc'd for $C_{14}H_{22}NO_3$, 252.1600; found, 252.1600.

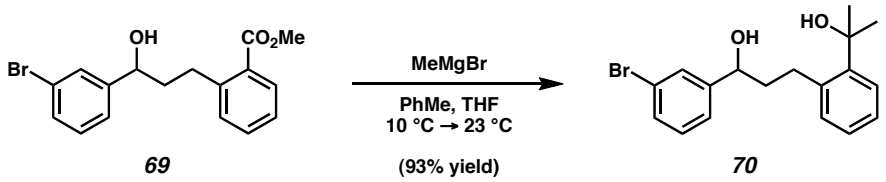


Acetamide 68. To amino alcohol **72** (1.61 g, 10.6 mmol) in CH_2Cl_2 (17 mL) and aq. 1.4 N NaOH (17 mL, 23.8 mmol) was added acetic anhydride (1.3 mL, 13.8 mmol) at 23 °C. After the biphasic reaction was stirred for 5 h, the layers were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were washed with H_2O (15 mL) and saturated aq. NaCl (15 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude material was passed over a short plug of silica gel (20:1 CH_2Cl_2:MeOH eluent). After concentrating to a yellow oil, hexanes:Et_2O (10:1, 10 mL) was added, which precipitated a yellow solid. The solvent was evaporated in vacuo, and the yellow solid was triturated with pentane:Et_2O (12:1), and collected by vacuum filtration to afford acetamide **68** (1.10 g, 54% yield) as a pale yellow solid. R_f 0.50 (9:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 5.96 (br s, 1H), 4.72 (dd, *J* = 7.4, 5.8 Hz, 1H), 3.73–3.59 (m, 1H), 3.28–3.14 (m, 1H), 3.19 (br s, 1H), 1.97 (s, 3H), 1.90–1.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 144.4, 128.6, 127.5, 125.8, 72.0, 39.0, 37.0, 23.3; IR (film): 3295 (br), 1651, 1556 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{11}H_{16}NO_2$, 194.1181; found, 194.1190.



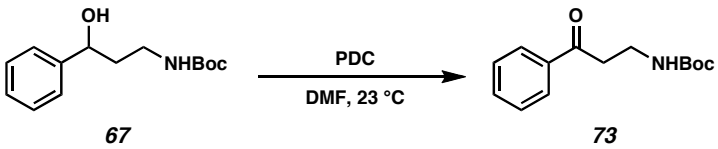
74 *69*

Bromo Methyl Ester 69. To 2-[3-(3-bromophenyl)-3-oxopropyl]benzoic acid methyl ester[15] (**74**, 1.763 g, 5.08 mmol), previously described by Larsen, et al.,[10a] in EtOH (12 mL) and CH_2Cl_2 (12 mL), was added $NaBH_4$ (208.8 mg, 5.52 mmol) portionwise over a 5-min period at 0 °C. The reaction was stirred for 3.5 h at 0 °C, then quenched by slow addition of 0.1 N HCl (45 mL). After stirring 30 min, the mixture was poured over CH_2Cl_2 (75 mL) and the phases were partitioned. The aqueous phase was extracted with CH_2Cl_2 (75 mL), and the organic extracts were combined, washed with H_2O (15 mL) and brine (15 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the crude product was chromatographed (7:1 hexanes:EtOAc eluent) to provide the product as a viscous oil. The residual solvent was removed by lyophilization from benzene to afford bromo methyl ester **69** (1.61 g, 91% yield) as a white-to-off-white solid. R_f 0.44 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (app. dd, J = 8.1, 1.5 Hz, 1H), 7.50 (app. t, J = 1.7 Hz, 1H), 7.46–7.33 (m, 2H), 7.28–7.14 (m, 4H), 4.64 (app. t, J = 6.2 Hz, 1H), 3.87 (s, 3H), 3.16–2.97 (m, 3H), 2.06–1.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 147.2, 143.7, 132.4, 131.2, 130.9, 130.3, 130.0, 129.2, 129.0, 126.2, 124.5, 122.6, 72.6, 52.5, 41.6, 30.4; IR (film) 3460 (br), 1722, 1263, 1083 cm^{-1}; HRMS-EI *m/z*: $[M - H]^+$ calc'd for $C_{17}H_{16}BrO_3$, 347.0283; found, 347.0274.



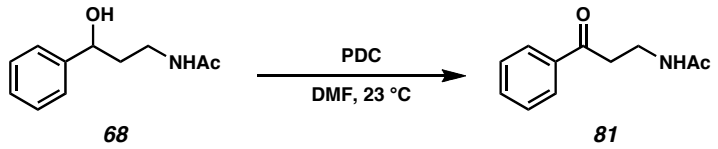
69 *70*

Bromo Diol 70. To bromo methyl ester **69** (1.502 g, 4.30 mmol) in THF (9 mL) and toluene (9 mL) was added MeMgBr (2.78 M in Et_2O, 8.5 mL, 23.4 mmol) in a rapid dropwise fashion at 10 °C. The solution was stirred at 23 °C for 3.5 h after the addition was complete, then quenched by slow addition of saturated aq. NH_4Cl. The resulting mixture was poured over Et_2O (50 mL) and brine (25 mL). The organic phase was dried over $MgSO_4$, and chromatographed (7:1 hexanes:EtOAc → 3:1 hexanes:EtOAc). The fractions containing the methyl ketone (slightly higher R_f than the desired product) were concentrated in vacuo and resubjected to the initial reaction conditions. After purification in the same manner described above, all of the product containing fractions were combined and evaporated in vacuo. The viscous oil was lyophilized from benzene to provide bromo diol **70** (1.39 g, 93% combined yield) as a white-to-off-white solid. R_f 0.33 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (app. s, 1H), 7.37–7.31 (m, 2H), 7.26–7.09 (m, 5H), 4.61 (dd, J = 8.6, 4.1 Hz, 1H), 3.26–3.14 (m, 1H), 3.12–3.01 (m, 1H), 2.21 (br s, 1H), 2.15–1.95 (m, 3H), 1.67 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 144.9, 140.0, 131.4, 130.3, 130.0, 129.1, 127.4, 125.8, 125.6, 124.5, 122.6, 74.5, 72.5, 42.2, 32.4, 32.3, 29.7; IR (film) 3356 (br), 1069 cm^{-1}; HRMS-EI *m/z*: $[M - H]^+$ calc'd for $C_{18}H_{20}BrO_2$, 349.0628; found, 349.0631.



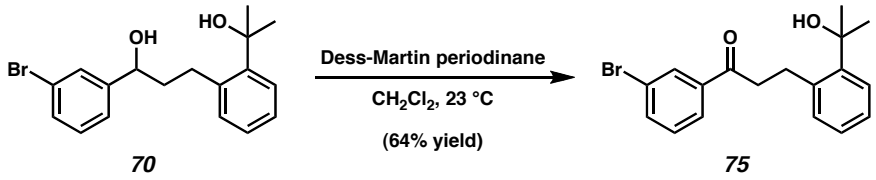
67 *73*

Keto-Carbamate 73. To carbamate **67** (27.5 mg, 0.11 mmol) in DMF (2 mL) was added pyridinium dichromate (237 mg, 0.63 mmol) at 23 °C. After 10 h, the reaction mixture was diluted in Et_2O (5 mL) and brine (5 mL), and the phases were partitioned. The aqueous phase was extracted with Et_2O (2 x 5 mL), and the organic extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (20:1 → 10:1 hexanes:EtOAc eluent) to afford keto-carbamate **73** as a solid, which was used as an authentic standard to confirm the oxidative kinetic resolution product of carbamate **67**. R_f 0.50 (1:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.90 (m, 2H), 7.61–7.51 (m, 1H), 7.49–7.39 (m, 2H), 5.13 (br s, 1H), 3.53 (q, J = 5.9 Hz, 2H), 3.19 (t, J = 5.5 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 156.1, 136.7, 133.6, 128.8, 128.1, 79.3, 38.8, 35.6, 28.5; IR (film) 1682, 1506, 1172 cm^{-1}; HRMS-FAB m/z: $[M + H]^+$ calc'd for $C_{14}H_{20}NO_3$, 250.1443; found, 250.1441.



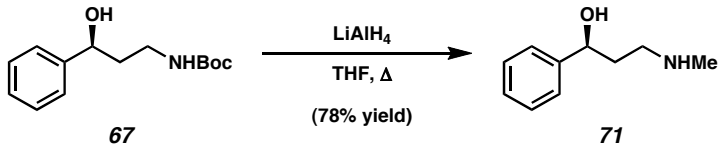
68 *81*

Keto-Acetamide 81. Compound **81** was prepared in an analogous manner to keto-carbamate **73**. The characterization data for this compound have been previously reported by Knochel.[16]



70 *75*

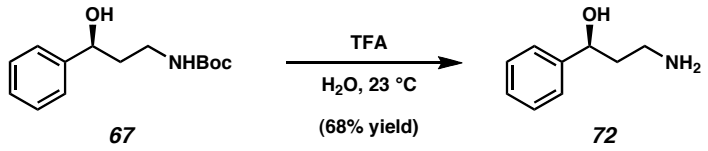
Bromo Hydroxy Propanone 75. To bromo diol **70** (51.6 mg, 0.15 mmol) in CH_2Cl_2 (2.5 mL) was added Dess-Martin periodinane (70.7 mg, 0.17 mmol). The mixture was stirred for 3 h at 23 °C, and then chromatographed directly (1:1 Et_2O:pentane eluent) to provide bromo hydroxy propanone **75** (33.0 mg, 64% yield) as a solid. This product was used as an authentic standard to confirm the oxidative kinetic resolution product of bromo diol **70**. R_f 0.60 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 8.06 (app. t, *J* = 1.7 Hz, 1H), 7.86–7.81 (m, 1H), 7.57 (app. ddd, 1H, *J* = 7.7, 1.6, 1.1 Hz, 1H), 7.25–7.20 (m, 1H), 7.11–6.98 (m, 3H), 6.65 (app. td, *J* = 10.8, 3.9 Hz), 3.43 (app. t, *J* = 7.7 Hz, 2H), 2.98–2.91 (m, 2H), 1.44–1.41 (m, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.1, 146.4, 140.5, 139.5, 136.0, 132.2, 131.8, 130.6, 127.7, 127.1, 126.4, 126.4, 123.4, 73.8, 42.4, 32.6 (2C), 29.2; IR (film) 3452 (br), 1684, 1198 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ for $C_{18}H_{20}O_2Br$ calc'd, 347.0647; found, 347.0632.



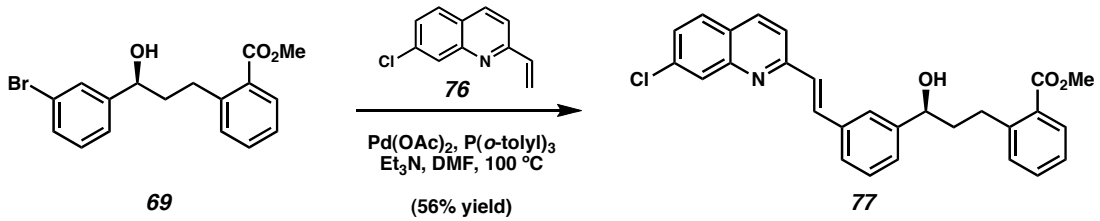
67 *71*

(*S*)-Methyl Amine 71. To a suspension of $LiAlH_4$ (56.8 mg, 1.5 mmol) in THF (1.5 mL) was added enantioenriched carbamate **67** (47.5 mg, 0.19 mmol). The reaction was heated to reflux for 5.5 h, and then quenched at 0 °C by slow addition of H_2O (50 μL), followed by 15% *w/v* aq. NaOH (50 μL), and finally by H_2O (150 μL). The mixture was filtered, and the filter cake was rinsed well with Et_2O. The filtrate was evaporated

under reduced pressure, diluted in CH_2Cl_2 (1 mL), washed with saturated aq. NaCl (0.5 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, which provided methyl amine **71** (24.5 mg, 78% yield) as an oil. $[\alpha]^{26}_D$ –33.7° (*c* 0.81, $CHCl_3$). lit[17]: $[\alpha]^{23}_D$ –37.4° (*c* 1%, $CHCl_3$).

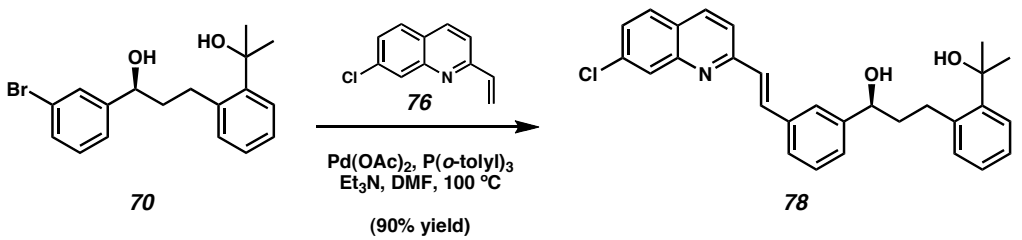


(*S*)-Amino Alcohol 72. To enantioenriched carbamate **67** (25.2 mg, 0.1 mmol) was added a mixture of trifluoroacetic acid (1.0 mL) and H_2O (0.2 mL). The solution was stirred at 23 °C for 48 h, and then the volatiles were removed in vacuo. The aqueous residue was made basic using 5 N aq. NaOH (1 mL), and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford title compound **72** (10.2 mg, 68% yield) as a solid. Characterization data for this compound have been previously reported.[9a] $[\alpha]^{25}_D$ –40.5 ° (*c* 0.5, MeOH). lit:[9a] $[\alpha]^{25}_D$ –43.65° (*c* 1, MeOH).



(*S*)-Chloroquinoline Methyl Ester 77.[10b,18] To enantioenriched bromo methyl ester **69** (83.8 mg, 0.24 mmol) was added $Pd(OAc)_2$ (3.0 mg, 0.013 mmol), P(*o*-tolyl)$_3$ (12.7 mg, 0.042 mmol), 2-ethenyl-7-chloroquinoline[10a] (**76**, 47.0 mg, 0.25 mmol), and

DMF (0.7 mL). The dark mixture was degassed three times using the freeze-pump-thaw technique, and then Et_3N (93 μL, 0.67 mmol) was added. The reaction was heated to 100 °C for 3 h, then cooled to 23 °C. The crude mixture was diluted with EtOAc (2 mL) and H_2O (2 mL). The phases were partitioned, and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried by passage over a short plug of silica gel (EtOAc eluent), and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (5:1 hexanes:EtOAc eluent). Desired chloroquinoline methyl ester **77** (62.0 mg, 56% yield) was obtained as a solid after evaporation of solvent under reduced pressure, and lyophilization from benzene. R_f 0.21 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) 8.35 (app. d, J = 1.6 Hz, 1H), 7.92–7.85 (m, 2H), 7.68 (s, 1H), 7.43–7.36 (m, 3H), 7.29–6.89 (m, 8H), 4.67 (t, J = 5.8 Hz, 1H), 3.43 (s, 3H), 3.30–3.10 (m, 2H), 2.65 (br s, 1H), 2.11 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6, 27/28 C) 168.5, 157.5, 149.7, 146.9, 145.1, 137.2, 136.1, 136.0, 132.7, 131.9, 131.5, 130.2, 129.3, 129.3, 129.1, 128.9, 127.3, 127.1, 126.7, 126.5, 126.2, 125.7, 120.6, 73.6, 52.0, 42.5, 31.2; IR (film) 3407 (br), 1719, 1607, 1497, 1258 cm^{-1}; HRMS-FAB *m/z*: [M + H]$^+$ calc'd for $C_{28}H_{25}NO_3Cl$, 458.1523; found, 458.1517. lit (*R*)-**77**:[10b] $[\alpha]^{22}_D$ +28.3° (99.5% ee, *c* 1, $CHCl_3$). The absolute configuration of **77** was determined by optical rotation and chiral HPLC,[19] and no degradation of enantiopurity was observed in the conversion of starting material (**69**) to product (**77**).



(*S*)-Chloroquinoline Diol 78.[18,19] To enantioenriched bromo diol **70** (41.6 mg, 0.12 mmol) was added $Pd(OAc)_2$ (1.9 mg, 0.008 mmol), P(*o*-tolyl)$_3$ (10.8 mg, 0.035 mmol), 2-ethenyl-7-chloroquinoline[10a] (**76**, 23.9 mg, 0.12 mmol), and DMF (0.35 mL). The dark mixture was degassed three times using the freeze-pump-thaw technique, and then Et_3N (40 μL, 0.29 mmol) was added. The reaction was heated to 100 °C for 3 h, then cooled to 23 °C. The crude mixture was chromatographed directly (9:1 hexanes:EtOAc → 3:1 hexanes:EtOAc eluent). Desired chloroquinoline diol **78** (49.2 mg, 90% yield) was obtained as a solid after evaporation of solvent under reduced pressure and lyophilization from benzene. R_f 0.11 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) 8.32 (app. d, J = 1.6 Hz, 1H), 7.82 (app. d, J = 16.5 Hz, 1H), 7.69 (app. s, 1H), 7.42–7.31 (m, 4H), 7.29–7.00 (m, 8H), 4.68 (dd, J = 8.2, 4.4 Hz, 1H), 3.97 (br s, 1H), 3.45–3.32 (m, 1H), 3.21–3.10 (m, 1H), 2.96 (br s, 1H), 2.23–2.09 (m, 2H), 1.50 (s, 1H), 1.48 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6, 28/29 C) 157.5, 149.5, 146.8, 146.1, 141.1, 137.1, 136.2, 136.0, 135.9, 132.2, 129.3, 129.3, 129.0, 129.0, 128.9, 127.8, 127.3, 126.8, 126.3, 126.2, 125.8, 120.4, 74.3, 73.4, 43.0, 32.6, 32.4, 30.4; IR (film) 3361 (br), 1607, 1498 cm^{-1}; HRMS-FAB m/z: $[M + H]^+$ calc'd for $C_{29}H_{29}NO_2Cl$, 458.1887; found, 458.1886. The absolute configuration of **78** was determined by chiral HPLC,[19] and no degradation of enantiopurity was observed in the conversion of starting material (**70**) to product (**78**).

2.5 Notes and References

(1) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726. (b) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835–837. (c) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353–357.

(2) Simultaneous to our publication, a related system was reported; see: Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476.

(3) The kinetic resolutions in references 1 and 2 were based on a non-asymmetric alcohol oxidation employing $Pd(OAc)_2$, pyridine, and O_2, see: Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755.

(4) The selectivity factor (*s*) was determined using the equation: $s = k_{rel}$(fast/slow) = ln[(1 - C)(1 - ee)]/ln[(1 - C)(1 + ee)], where C = conversion. For an excellent discussion of kinetic resolutions, 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.

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(7) For recent discussions concerning the mechanistic details of Pd oxidation by molecular oxygen, see: (a) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612–6615. (b) Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 4410–4422. (c) Chowdhury, S.; Rivalta, I.; Russo, N.; Sicilia, E. *Chem. Phys. Lett.* **2007**, *443*, 183–189. (d) Keith, J. M.; Goddard, W. A., III; Oxgaard, J. *J. Am. Chem. Soc.* **2007**, *129*, 10361–10369.

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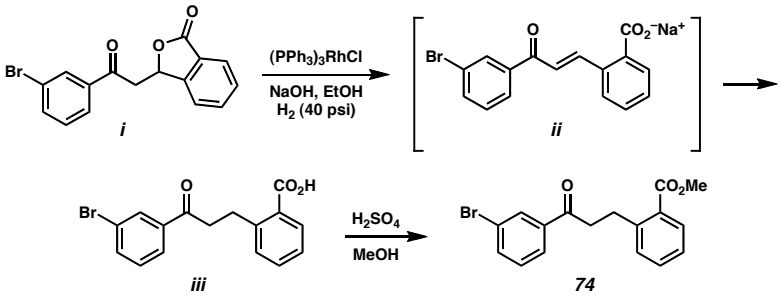
(12) Substrates were tested under all of the available oxidative kinetic resolution protocols (see reference 1), and the best results are reported.

(13) The absolute configurations of **67** and **70** were assigned by conversion to known compounds (**67** → **72** and **70** → **78**).

(14) The absolute configuration of **68** was assigned by analogy to known compounds.

(15) In our hands, the reported benzofuranone reduction with Wilkinson's catalyst[10a] (**i** → **ii** → **iii**) did not proceed as described unless the starting material was further purified. This could be accomplished by filtering benzofuranone **i** in boiling EtOAc to remove insoluble impurities. Additionally, the product obtained after the benzofuranone reduction did not match the reported values for benzoic acid **iii**; however, brief exposure to acidic MeOH (conditions for the subsequent esterification reaction, **iii** → **74**) quantitatively converted it to the reported compound (**iii**).



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(18) The NMR characterization data have been previously reported in $CDCl_3$. In our hands, these compounds slowly decomposed in $CDCl_3$, so we have reported these data in C_6D_6.

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