Palladium-Catalyzed Enantioselective Oxidation of Chiral Secondary Alcohols: Access to Both Enantiomeric Series

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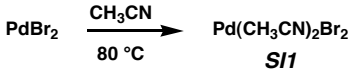
Materials and Methods. Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry, deoxygenated

solvents. Dichloro(sparteine)palladium(II) ($Pd(sparteine)Cl_2$, **4**),[1] bis(trifluoroacetato)(sparteine)palladium(II),[2] dibromo(1,5-cyclooctadiene)palladium(II) ($Pd(COD)Br_2$), and dibromo(norbornadiene)palladium(II) ($Pd(nbd)Br_2$)[3] were prepared as previously reported. Palladium bromide was purchased from Strem Chemicals. (±)-1-(2-Methylphenyl)ethanol ((±)-**SI5**, Table 2, entries 6 and 7) was purchased from Alfa Aesar. (+)-1-Phenylethanol ((+)-**9**) was purchased from Acros Organics. (±)-1-(9-Anthracenyl)ethanol (Table 2, entry 10) was prepared by the method of Snyder.[4] (±)-2-Isobutoxycyclohex-2-en-1-ol (Table 2, entry 11) was prepared by the method of Pattenden.[5] (±)-(*E*)-3-Methyl-4-phenyl-3-buten-2-ol (Table 3, entry 10) was prepared by the method of West.[6] (±)-*syn*,*trans*-1-(2-Phenylcyclopropyl)ethanol[7] ((±)-**SI19**, Table 3, entry 11) and (±)-*anti*,*trans*-1-(2-phenylcyclopropyl)ethanol[8] (Table 3, entry 12) were prepared by the methods of Charette. Other chemicals were prepared as described below or purchased from the Sigma-Aldrich Chemical Company. 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. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled using an IKAmag temperature modulator (heating) or a VWR 1160 refrigerated circulating bath (cooling). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV at 254 nm, *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. 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

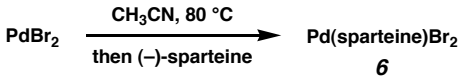
detector using a Chiraldex GTA column (30.0 m x 0.25 mm, purchased from Bodman Industries) at 1.0 mL/min He carrier gas flow. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD, Chiralcel OD-H, Chiralcel OJ, or Chiralcel OB-H column (each is 4.6 mm x 25 cm) 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 or 500 instrument (at 75 or 125 MHz, respectively) 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). Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out by Desert Analytics Laboratory, Tuscon, AZ. X-ray crystal structure analyses were obtained from the California Institute of Technology X-Ray Crystallography Laboratory. The absolute configurations of resolved alcohols were assigned based on comparisons of optical rotations to literature values or by analogy.

Preparation of Palladium Complexes

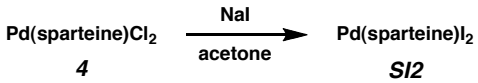


Dibromobis(acetonitrile)palladium(II) (SI1). Palladium bromide (532 mg, 2.0 mmol, 1.0 equiv) was added to acetonitrile (40 mL). The mixture was heated to 80 °C for 1.5 h. Once the solution became clear and orange-red, the reaction was cooled to 23 °C. The mixture was concentrated under reduced pressure to a volume of about 5 mL and then triturated with Et_2O (15

mL). The orange-red solid was filtered, washed with Et_2O (2 x 15 mL), and dried under vacuum to afford **SI1** (661 mg, 95% yield).

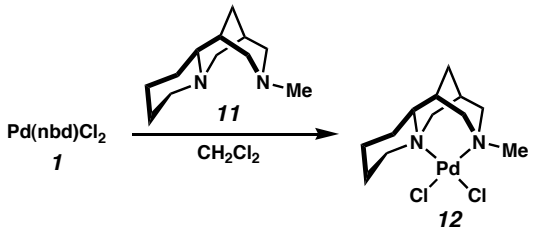


Dibromo(sparteine)palladium(II) (6). Palladium bromide (532 mg, 2.0 mmol, 1.0 equiv) was added to acetonitrile (8 mL). The mixture was heated to 80 °C for 6 h. Once the solution became clear and orange-red, the reaction was cooled to 23 °C. (–)-Sparteine ((–)-**2**, 460 μL, 469 mg, 2.0 mmol, 1.0 equiv) was added dropwise. The reaction immediately formed a dark solution. After stirring 3 h, a brown solid formed. The mixture was triturated with Et_2O (15 mL) and then filtered to afford **6** (791 mg, 79% yield) as a brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (d, *J* = 11.6 Hz, 1H), 4.20-4.15 (m, 1H), 3.97 (br. d, *J* = 12.9 Hz, 1H), 3.52-3.39 (m, 1H), 3.24 (dd, *J* = 14.3, 1.4 Hz, 1H), 2.90-2.77 (comp. m, 2H), 2.45 (dd, *J* = 12.7, 3.0 Hz, 1H), 2.14-1.40 (comp. m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.3, 67.6, 65.5, 64.9, 62.2, 49.1, 35.0, 34.8, 30.3, 28.0, 27.5, 26.0, 24.5, 23.8, 21.4. Anal. calcd for $C_{15}H_{26}Br_2N_2Pd$: C, 35.99; H, 5.23; N, 5.60. Found: C, 35.62; H, 5.15; N, 5.53. A single crystal suitable for X-ray analysis was grown by slow diffusion of hexane into a saturated CH_2Cl_2 solution of **6**.



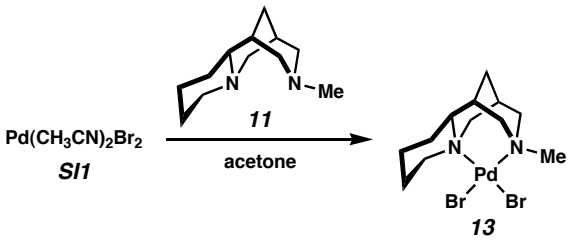
Diiodo(sparteine)palladium(II) (SI2). Sodium iodide (134 mg, 0.89 mmol, 2.1 equiv) was added to a suspension of complex **4** (175 mg, 0.43 mmol, 1.0 equiv) in acetone (10 mL). The dark mixture was stirred at 23 °C for 30 min, after which the solvent was removed under reduced pressure. The solid was washed with copious amounts of H_2O followed by pentane to afford **SI2**

as a dark purple solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (app. dd, *J* = 12.5, 3.2 Hz, 1H), 4.33 (br. d, *J* = 11.7 Hz, 1H), 4.19 (ddd, *J* = 14.4, 13.1, 3.0 Hz, 1H), 3.92 (dt, *J* = 12.4, 2.4 Hz, 1H), 3.75-3.59 (comp. m, 2H), 2.97 (dd, *J* = 12.9, 3.4 Hz, 1H), 2.93-2.79 (comp. m, 2H), 2.54 (dd, *J* = 12.4, 3.1Hz, 1H), 2.17-1.37 (comp. m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.2, 70.2, 66.5, 64.7, 63.8, 48.9, 35.0, 34.9, 29.5, 28.1, 27.3, 26.9, 24.3, 23.6, 21.8; IR (thin film/NaCl): 2935, 1440, 913, 728 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $[C_{15}H_{26}N_2I_2Pd]^+$, 593.9221; found, 593.9242.



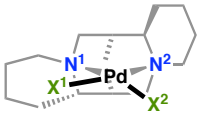
Dichloride Complex 12. To a solution of freshly distilled diamine **11**[9] (194 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added Pd(norbornadiene)Cl_2 (Pd(nbd)Cl_2, **1**, 269 mg, 1.0 mmol, 1.0 equiv). The reaction was allowed to stir 1 h. Then, the volatiles were removed under reduced pressure. The resulting solid was washed with pentane (3 x 5 mL) to afford **12** (310 mg, 83% yield) as a reddish-brown solid: m.p. 183-185 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (dq, *J* = 12.4, 1.7 Hz, 1H), 4.11 (dt, *J* = 12.8, 2.1 Hz, 1H), 3.95 (br. d, *J* = 12.0 Hz, 1H), 3.33 (dq, *J* = 13.0, 1.8 Hz, 1H), 3.10 (qd, *J* = 12.6, 3.6 Hz, 1H), 2.91-2.72 (m, 1H), 2.67 (s, 3H), 2.43 (dd, *J* = 12.6, 2.8 Hz, 1H), 2.38-2.27 (comp. m, 2H), 2.07 (dd, *J* = 13.1, 3.1 Hz, 1H), 2.04-1.94 (m, 1H), 1.91-1.73 (comp. m, 5H), 1.64-1.39 (comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.6, 64.7, 64.4, 64.1, 58.8, 57.0, 34.0, 32.8, 30.2, 29.3, 25.0, 24.2; IR (thin film/NaCl): 2953, 2856, 1454, 1009 cm^{-1}; HRMS-FAB (*m*/*z*): $[M\text{-}Cl]^+$ calcd for $[C_{12}H_{22}N_2ClPd]^+$, 337.0510; found,

337.0503; A single crystal suitable for X-ray analysis was grown by slow diffusion of heptane into a saturated $CHCl_3$ solution of **12**.

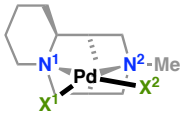


Dibromide Complex 13. To a solution of **SI1** (69.7 mg, 0.20 mmol, 1.0 equiv) in acetone (2 mL) was added a solution of freshly distilled diamine **11** (38.9 mg, 0.20 mmol, 1.0 equiv) in acetone (2 mL). The reaction was allowed to stir 1 h, after which Et_2O (4 mL) was layered over the mixture. The solid was filtered and washed with Et_2O (2 x 2 mL). 1,2-Dichloroethane (4 mL) was added to the solid, and the mixture was stirred vigorously for 4 h. After filtration of the undissolved material, the filtrate was concentrated under reduced pressure to afford **13** (48.4 mg, 53% yield) as a brown solid: m.p. 197-199 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (dq, *J* = 13.0, 1.9 Hz, 1H), 4.15 (br. d, *J* = 12.1 Hz, 1H), 4.04 (dt, *J* = 12.6, 2.2 Hz, 1H), 3.30 (dq, *J* = 12.9, 1.8 Hz, 1H), 3.15 (qd, *J* = 12.3, 3.7 Hz, 1H), 2.95-2.76 (m, 1H), 2.87 (s, 3H), 2.59-2.50 (m, 1H), 2.43 (dd, *J* = 12.5, 2.8 Hz, 1H), 2.37-2.29 (m, 1H), 2.25 (dd, *J* = 13.0, 3.0 Hz, 1H), 2.05 (dd, *J* = 13.1, 3.2 Hz, 1H), 2.02-1.73 (comp. m, 5H), 1.64-1.41 (comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.7, 65.2, 64.7, 64.2, 59.8, 58.8, 34.1, 32.8, 30.1, 29.3, 25.8, 24.2; IR (thin film/NaCl): 2943, 1455, 1008 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $[C_{12}H_{22}Br_2N_2Pd]^+$, 459.9189; found, 459.9198. A single crystal suitable for X-ray analysis was grown by slow diffusion of hexane into a saturated $CHCl_3$ solution of **13**.

Measurement of Bond Angles in Pd Complexes



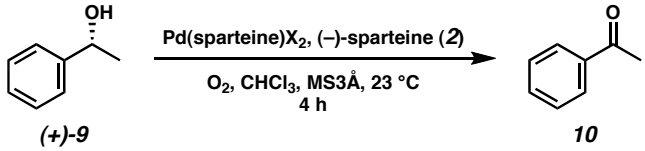
X¹ = X² = Cl: 4
X¹ = X² = OAc: 5
X¹ = X² = Br: 6
X¹ = (R)-α-(trifluoromethyl)benzyloxy, X² = Cl: 7



X¹ = X² = Cl: 12
X¹ = X² = Br: 13

Bond angles were obtained from X-ray structural analyses of single crystals of the appropriate palladium(II) complex. The sum of the six angles around the metal center are defined as the sum of $\angle N^1\text{-Pd-}X^1$, $\angle X^1\text{-Pd-}X^2$, $\angle X^2\text{-Pd-}N^2$, $\angle N^1\text{-Pd-}N^2$, $\angle N^1\text{-Pd-}X^2$, and $\angle X^1\text{-Pd-}N^2$. For an ideal square planar geometry, this sum would be 4(90°) + 2(180°) = 720°. For complex **4**, this sum is 95.65° + 83.09° + 93.44° + 87.51° + 170.06° + 176.24° = 705.99°. The deflection of X^2 (X^1 for **12** and **13**) is defined as the difference between $\angle N^1\text{-Pd-}X^2$ in an ideal square planar complex (180°) and the angle in the appropriate complex. For complex **4**, this X^2 deflection is 180° – 170.06° = 9.94°.

Single Enantiomer Rate Experiments



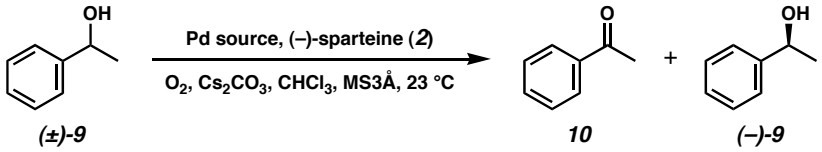
(+)-9 ***10***

X	% conversion
Br	72.0
Cl	38.9
O_2CCF_3	30.3
I	17.5
OAc	7.8

Oxidation of (+)-9 with various Pd(sp)X_2 sources. To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After allowing the tube to cool, the palladium source (0.025 mmol, 0.05 equiv) was added, followed by chloroform (1 mL, ACS reagent grade, stabilized with amylenes) and then (–)-**2** (8.0 μL, 8.2 mg, 0.035 mmol, 0.07 equiv). The reaction

tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was allowed to warm to 23 °C and stirred vigorously under O_2 atmosphere (1 atm, balloon) for 15 min. A solution of (+)-1-phenylethanol ((+)-**9**, 60.4 μL, 61.1 mg, 0.50 mmol, 1.0 equiv) and tridecane (internal GC standard, 36.6 μL, 27.7 mg, 0.15 mmol, 0.30 equiv) in chloroform (1 mL) was added. The reaction was allowed to proceed under O_2 atmosphere at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion to acetophenone (**10**).

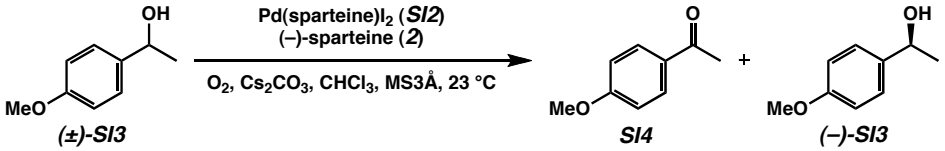
Pd Source Screens



Pd source	time (h)	conv. (%)	alcohol ee (%)	s
$Pd(CH_3CN)_2Br_2$	4.5	59	98	22
$Pd(COD)Br_2$	4.5	59	97	21
$Pd(nbd)Br_2$	4.5	48	76	23
$PdBr_2$	24	52	88	27

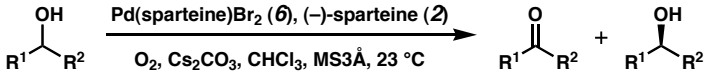
Resolution of (±)-9 with various $PdBr_2$ sources. To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After allowing the tube to cool, the palladium source (0.025 mmol, 0.05 equiv) was added, followed by chloroform (1 mL, ACS reagent grade, stabilized with amylenes) and then (–)-**2** (13.8 μL, 14.1 mg, 0.060 mmol, 0.12 equiv). The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was allowed to warm to 23 °C and stirred vigorously under 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 (±)-**9** (60.3 μL, 61.1 mg, 0.50 mmol, 1.0 equiv) and tridecane (internal

GC standard, 36.6 μL, 27.7 mg, 0.15 mmol, 0.30 equiv) in chloroform (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 to acetophenone (**10**) and chiral HPLC for alcohol ee.

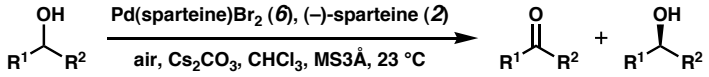


Resolution of (±)-SI3 with Pd(sparteine)I_2 (SI2). To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After allowing the tube to cool, **SI2** (14.9 mg, 0.025 mmol, 0.05 equiv) was added, followed by chloroform (1 mL, ACS reagent grade, stabilized with amylenes) and then (–)-**2** (8.0 μL, 8.2 mg, 0.035 mmol, 0.07 equiv). The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was allowed to warm to 23 °C and stirred vigorously under 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 (±)-2-(4-methoxyphenyl)ethanol ((±)-**SI3**, 0.50 mmol, 1.0 equiv) and tridecane (internal GC standard, 36.6 μL, 27.7 mg, 0.15 mmol, 0.30 equiv) in chloroform (1 mL). The reaction was allowed to proceed under O_2 atmosphere at 23 °C. After 24 h, an aliquot was filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed by GC for conversion (17.6%) and chiral HPLC for alcohol ee (13.4% ee, s = 5.0).

General Oxidative Kinetic Resolution (OKR) Conditions

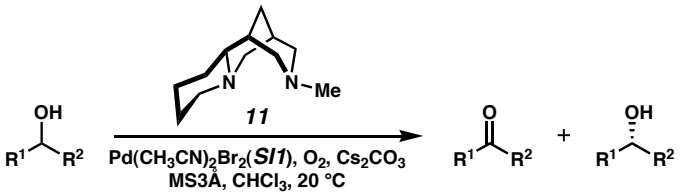


OKR Conditions A: Pd(sparteine)Br_2 Conditions with O_2. To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After allowing the tube to cool, **6** (12.5 mg, 0.025 mmol, 0.05 equiv) was added, followed by chloroform (1 mL, ACS reagent grade, stabilized with amylenes) and then (–)-**2** (8.0 μL, 8.2 mg, 0.035 mmol, 0.07 equiv). The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was allowed to warm to 23 °C and stirred vigorously under 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 the secondary alcohol (0.50 mmol, 1.0 equiv) and tridecane (internal GC standard, 36.6 μL, 27.7 mg, 0.15 mmol, 0.30 equiv) in chloroform (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 the product ketone and enantioenriched secondary alcohol was accomplished by direct chromatography of the crude reaction mixture.

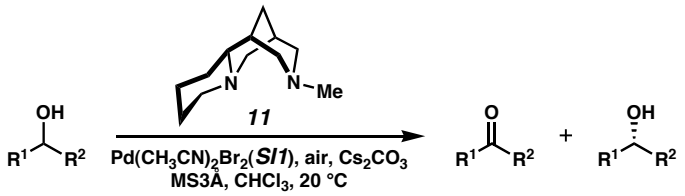


OKR Conditions B: Pd(sparteine)Br_2 Conditions with Ambient Air. To a reaction tube with stir bar was added 3Å molecular sieves (250 mg), **6** (12.5 mg, 0.025 mmol, 0.05 equiv), chloroform (1 mL, ACS reagent grade, stabilized with amylenes), and then (–)-**2** (8.0 μL, 8.2 mg, 0.035 mmol, 0.07 equiv). A tube (2-3 cm) containing Drierite (1 g) was attached, and the reaction was allowed to stir 5 min. Finely powdered Cs_2CO_3 (65.2 mg, 0.20 mmol, 0.40 equiv)

was added, followed by a solution of the secondary alcohol (0.50 mmol, 1.0 equiv) and tridecane (internal GC standard, 36.6 μL, 27.7 mg, 0.15 mmol, 0.30 equiv) in chloroform (1 mL). The reaction was allowed to proceed under 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.

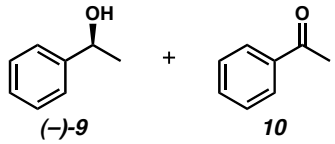


OKR Conditions C: Pd(diamine)Br_2 Conditions with O_2. To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After allowing the tube to cool, **SI1** (8.7 mg, 0.025 mmol, 0.05 equiv) was added, followed by chloroform (1 mL, ACS reagent grade, stabilized with amylenes) and then freshly distilled **11** (9.7 mg, 0.050 mmol, 0.10 equiv). The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was warmed to 20 °C in a circulating bath 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 the secondary alcohol (0.50 mmol, 1.0 equiv) and tridecane (internal GC standard, 36.6 μL, 27.7 mg, 0.15 mmol, 0.30 equiv) in chloroform (1 mL). The reaction was allowed to proceed under O_2 atmosphere at 20 °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 the product ketone and enantioenriched secondary alcohol was accomplished by direct chromatography of the crude reaction mixture.

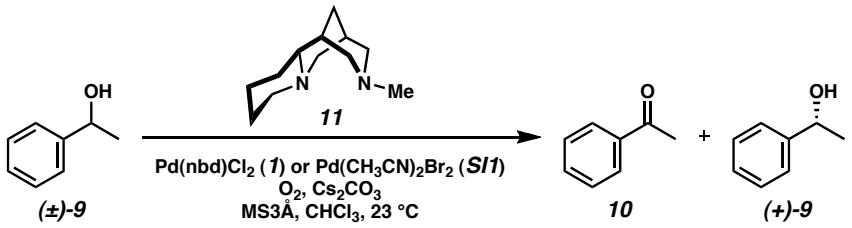


OKR Conditions D: Pd(diamine)Br_2 Conditions with Air. To a reaction tube with stir bar was added 3Å molecular sieves (250 mg), **SI1** (8.7 mg, 0.025 mmol, 0.05 equiv), chloroform (1 mL, ACS reagent grade, stabilized with amylenes), and then freshly distilled **11** (9.7 mg, 0.050 mmol, 0.10 equiv). A tube (2-3 cm) containing Drierite (1 g) was attached, and the reaction was allowed to stir at 20 °C in a circulating bath for 15 min. Finely powdered Cs_2CO_3 (65.2 mg, 0.20 mmol, 0.40 equiv) was added, followed by a solution of the secondary alcohol (0.50 mmol, 1.0 equiv) and tridecane (internal GC standard, 36.6 μL, 27.7 mg, 0.15 mmol, 0.30 equiv) in chloroform (1 mL). The reaction was allowed to proceed under ambient air atmosphere at 20 °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.

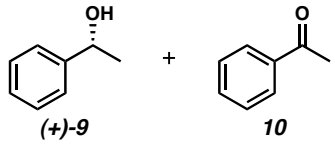
Preparation and Resolution of Racemic Alcohols



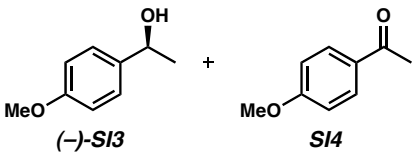
(–)-1-Phenylethanol ((–)-9, Table 2, entry 1). Prepared using OKR conditions A. After 4 h (55.6% conversion), the crude reaction mixture was purified by flash chromatography (4:1 hexanes:Et_2O) to afford (–)-**9** (26.4 mg, 43% yield, 95.6% ee, *s* = 28) and **10** (28.5 mg, 47% yield, 91% total mass recovery).



Resolution of (±)-9 with Diamine 11 and PdX_2 (Scheme 1). To an oven dried reaction tube with stir bar was added 3Å molecular sieves (250 mg). After allowing the tube to cool, the palladium complex **1** or **SI1** (0.025 mmol, 0.05 equiv) was added, followed by chloroform (1 mL, ACS reagent grade, stabilized with amylenes) and then freshly distilled **11** (11.7 mg, 0.060 mmol, 0.12 equiv). The reaction tube was cooled to –78 °C, then vacuum evacuated and purged with O_2 (3x). The reaction was warmed 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 (±)-**9** (60.3 μL, 61.1 mg, 0.50 mmol, 1.0 equiv) and tridecane (internal GC standard, 36.6 μL, 27.7 mg, 0.15 mmol, 0.30 equiv) in chloroform (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.

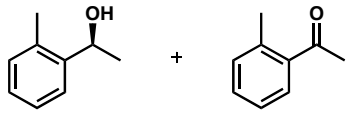


(+)-1-Phenylethanol ((+)-9, Table 3, entry 1). Prepared using OKR conditions C. After 30 h (57.6% conversion), the crude reaction mixture was purified by flash chromatography (4:1 hexanes:Et_2O) to afford (+)-**9** (24.5 mg, 40% yield, 97.1% ee, s = 25) and **10** (30.8 mg, 51% yield, 91% total mass recovery).



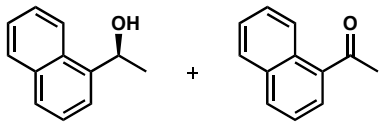
(–)-SI3 *SI4*

(–)-1-(4-Methoxyphenyl)ethanol ((–)-SI3, Table 2, entry 3). Prepared using OKR conditions A. After 4 h (59.4% conversion), the crude reaction mixture was purified by flash chromatography (9:1→7:3 hexanes:EtOAc) to afford (–)-**SI3** (30.9 mg, 41% yield, 95.4% ee, *s* = 17) and **SI4** (43.3 mg, 58% yield, 98% total mass recovery).



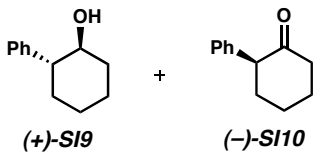
(–)-SI5 *SI6*

(–)-1-(2-Methylphenyl)ethanol ((–)-SI5, Table 2, entry 6). Prepared using OKR conditions A. After 41 h (63.5% conversion), the crude reaction mixture was purified by flash chromatography (9:1→7:3 hexanes:EtOAc) to afford (–)-**SI5** (23.5 mg, 35% yield, 97.1% ee, *s* = 14) and **SI6** (33.2 mg, 50% yield, 84% total mass recovery).

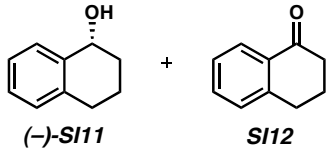


(–)-SI7 *SI8*

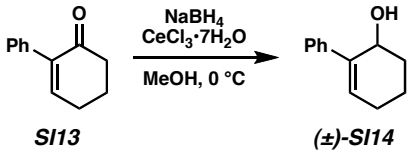
(–)-1-(1-Naphthyl)ethanol ((–)-SI7, Table 2, entry 8). Prepared using OKR conditions A. After 24 h (59.6% conversion), the crude reaction mixture was purified by flash chromatography (9:1→7:3 hexanes:EtOAc) to afford (–)-**SI7** (34.2 mg, 40% yield, 92.5% ee, *s* = 14) and **SI8** (48.4 mg, 57% yield, 97% total mass recovery).



(+)-*trans*-2-Phenylcyclohexanol ((+)-SI9, Table 2, entry 12). Prepared using OKR conditions A. After 49 h (58.0% conversion), the crude reaction mixture was purified by flash chromatography (19:1 hexanes:EtOAc) to afford (+)-**SI9** (34.9 mg, 40% yield, 90.6% ee, s = 15) and (–)-**SI10** (47.4 mg, 54% yield, 64.0% ee, 94% total mass recovery).

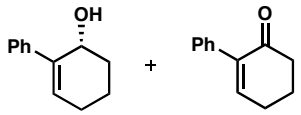


(–)-1-Tetralol ((–)-SI11, Table 3, entry 5). Prepared using OKR conditions C. After 24 h (60.9% conversion), the crude reaction mixture was purified by flash chromatography (9:1→7:3 hexanes:EtOAc) to afford (–)-**SI11** (28.3 mg, 38% yield, 90.2% ee, s = 11) and **SI12** (39.0 mg, 53% yield, 92% total mass recovery).



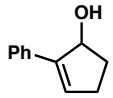
General Reduction of Enones: (±)-2-Phenylcyclohex-2-enol ((±)-SI14).[10] To a solution of 2-phenylcyclohex-2-enone[11] (**SI13**, 2.70 g, 15.7 mmol, 1.0 equiv) in MeOH (160 mL) at 0 °C was added $CeCl_3 \bullet 7H_2O$ (6.42 g, 17.2 mmol, 1.1 equiv). After allowing the solid to dissolve, $NaBH_4$ (2.37 g, 62.6 mmol, 4.0 equiv) was added in small portions over 5 min. The reaction mixture was allowed to warm to 23 °C, and the solvent was removed under reduced pressure. H_2O (125 mL) was added, and the slurry was stirred vigorously for 20 min. The mixture was then

extracted with EtOAc (4 x 150 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by filtration through a short plug of silica gel (1:1 hexanes:EtOAc) to afford (±)-**SI14** (2.22 g, 81% yield) as an off-white solid. Characterization data have been previously reported.[12]



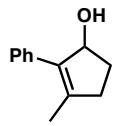
(+)-SI14 *SI13*

(+)-2-Phenylcyclohex-2-enol ((+)-SI14, Table 3, entry 6). Prepared using OKR conditions C. After 46 h (56.8% conversion), the crude reaction mixture was purified by flash chromatography (19:1→4:1 hexanes:EtOAc) to afford (+)-**SI14** (37.6 mg, 43% yield, 90.7% ee, *s* = 17) and **SI13** (45.8 mg, 53% yield, 96% total mass recovery).



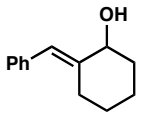
(±)-SI15

(±)-2-Phenylcyclopent-2-enol ((±)-SI15, Table 3, entry 7). Prepared as for (±)-**SI14** from 2-phenylcyclopent-2-enone[11] (218 mg, 1.38 mmol) to afford, after flash chromatography (9:1→4:1→7:3 hexanes:EtOAc), (±)-**SI15** (196 mg, 89% yield) as a white solid. Characterization data have been previously reported.[12]



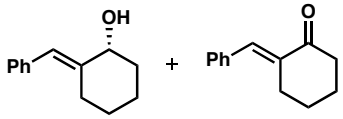
(±)-SI16

(±)-2-Phenyl-3-methylcyclopent-2-enol ((±)-SI16, Table 3, entry 8). Prepared as for (±)-**SI14** from 2-phenyl-3-methylcyclopent-2-enone[13] (3.82 g, 22.2 mmol) to afford, after flash chromatography (9:1→4:1 hexanes:EtOAc), (±)-**SI16** (3.25 g, 84% yield) as a slightly yellow oil, which solidified to a white solid on standing. Characterization data have been previously reported.[12]



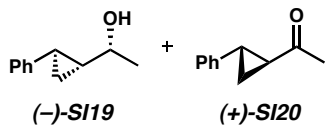
(±)-SI17

(±)-(*E*)-2-Benzylidenecyclohexanol ((±)-SI17). Prepared as for (±)-**SI14** from (*E*)-2-benzylidenecyclohexanone (**SI18**)[14] (5.03 g, 27.0 mmol) to afford, after flash chromatography (9:1→17:3→4:1 hexanes:EtOAc), (±)-**SI17** (4.13 g, 81% yield) as a white solid. The characterization data matched the data in the literature.[15]



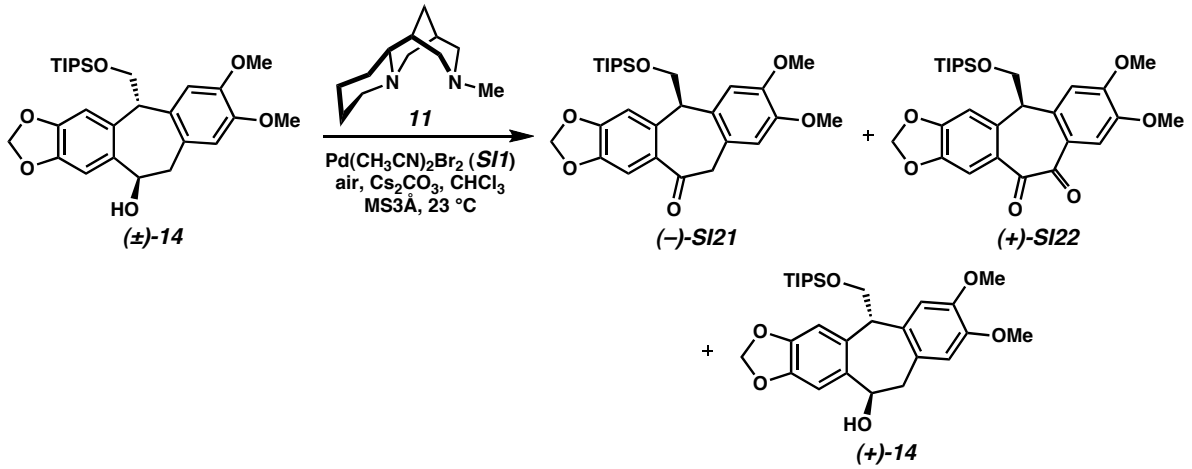
(+)-SI17 ***SI18***

(+)-(*E*)-2-Benzylidenecyclohexanol ((+)-SI17, Table 3, entry 9). Prepared using OKR conditions C. After 46 h (59.3% conversion), the crude reaction mixture was purified by flash chromatography (9:1 hexanes:EtOAc) to afford (+)-**SI17** (36.3 mg, 39% yield, 90.6% ee, s = 13) and **SI18** (51.2 mg, 55% yield, 94% total mass recovery).



(–)-SI19 *(+)-SI20*

(–)-*syn*,*trans*-1-(2-Phenylcyclopropyl)ethanol ((–)-SI19, Table 3, entry 11). Prepared using OKR conditions C. After 32 h (59.0% conversion), the crude reaction mixture was purified by flash chromatography (4:1 hexanes:EtOAc) to afford (–)-**SI19** (32.1 mg, 40% yield, 90.2% ee, *s* = 13) and (+)-**SI20** (42.3 mg, 53% yield, 64.1% ee, 92% total mass recovery).



(±)-14 *(–)-SI21* *(+)-SI22* *(+)-14*

Resolution of (±)-14 with Diamine 11 and $Pd(CH_3CN)_2Br_2$ in Air: Hydroxysilane (+)-14 (Scheme 2). To a mixture of 3Å molecular sieves (125 mg) and **SI1** (7.0 mg, 0.020 mmol, 0.20 equiv) was added a solution of freshly distilled **11** (7.8 mg, 0.040 mmol, 0.40 equiv) in chloroform (0.5 mL, ACS reagent grade, stabilized with amylenes) in a 1 dram vial with septum. A 16-gauge needle was inserted in the septum to allow in ambient air, and the reaction was maintained at 23 °C and stirred vigorously for 15 min. Finely powdered Cs_2CO_3 (32.6 mg, 0.10 mmol, 1.0 equiv) was added, followed by a solution of hydroxysilane (±)-**14**[16] (50.1 mg, 0.10 mmol, 1.0 equiv) and 1,4-bis(trimethylsilyl)benzene (internal NMR standard, 4.4 mg, 0.020 mmol, 0.20 equiv) in chloroform (0.5 mL). The reaction was allowed to proceed under ambient

air atmosphere at 23 °C. After 67 h, the reaction mixture was filtered through a small plug of silica gel (EtOAc eluent), concentrated under reduced pressure, and analyzed by ^{1}H NMR (C_6D_6, relaxation time = 10 s) for conversion (55.6% conversion based on internal standard). The resulting oil was purified by flash chromatography (7:3→1:1 hexanes:Et_2O), followed by preparative TLC (3:2 hexanes:EtOAc) to afford ketosilane (–)-**SI21** (15.0 mg, 30% yield, 80.3% ee), diketosilane (+)-**SI22** (7.5 mg, 15% yield, 84.8% ee), and hydroxysilane (+)-**14** (22.4 mg, 45% yield, 95.3% ee, s = 27).

Methods for Determination of Conversion

Conversion values for (±)-1-(9-anthacenyl)ethanol (Table 2, entry 10) and (±)-(*E*)-2-benzylidenecyclohexanol ((±)-**SI17**, Table 3, entry 9) were determined relative to product ketone by ^{1}H NMR of a reaction aliquot after filtration through a short plug of silica gel. Conversion values for (±)-**14** were determined relative to 1,4-bis(trimethylsilyl)benzene as internal standard 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 S-1) relative to tridecane as internal standard.

Table S-1. Methods for the Determination of % Conversion

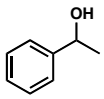
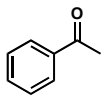
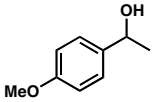
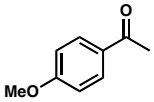
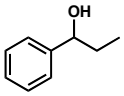
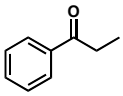
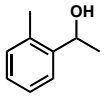
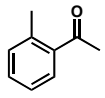
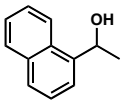
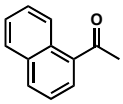
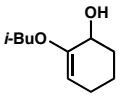
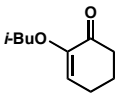
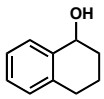
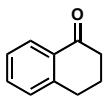
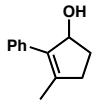
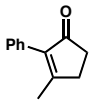
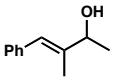
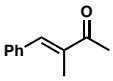
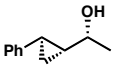
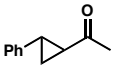
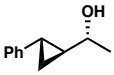
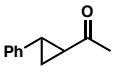
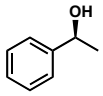
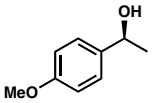
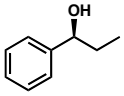
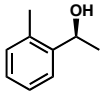
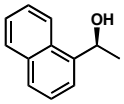
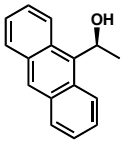
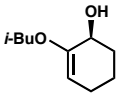
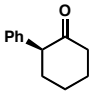
entry	alcohol	ketone	GC conditions	alcohol retention time (min)	ketone retention time (min)
1	 (±)-9	 10	100 °C, 5 min; Ramp 13 °C/min	10.6	8.9
2	 (±)-SI3	 SI4	100 °C, 5 min; Ramp 13 °C/min	14.4	13.9
3			100 °C, 5 min; Ramp 13 °C/min	11.5	10.0
4	 (±)-SI5	 SI6	100 °C, 5 min; Ramp 13 °C/min	12.9	10.5
5	 (±)-SI7	 SI8	100 °C, 5 min; Ramp 13 °C/min to 240 °C 240 °C, 5 min	19.2	17.1
6			100 °C, 5 min; Ramp 13 °C/min	10.6	12.2
7	 (±)-SI9	 (±)-SI10	100 °C, 5 min; Ramp 13 °C/min	14.2	14.9
8	 (±)-SI11	 SI12	100 °C, 5 min; Ramp 13 °C/min	14.5	13.6
9	 (±)-SI14	 SI13	100 °C, 5 min; Ramp 13 °C/min to 240 °C 240 °C, 5 min	15.8	16.1

Table S-1 continued.

10	 ***(±)-SI15***		100 °C, 5 min; Ramp 13 °C/min to 240 °C 240 °C, 5 min	15.8	16.1
11	 ***(±)-SI16***		100 °C, 5 min; Ramp 13 °C/min to 240 °C 240 °C, 5 min	15.1	16.6
12			100 °C, 5 min; Ramp 13 °C/min	14.1	13.1
13	 ***(±)-SI19***	 ***(±)-SI20***	100 °C, 5 min; Ramp 13 °C/min	14.2	13.1
14		 ***(±)-SI20***	100 °C, 5 min; Ramp 13 °C/min	14.1	13.1

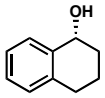
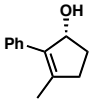
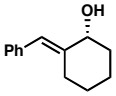
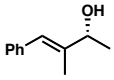
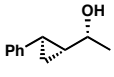
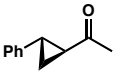
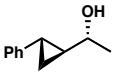
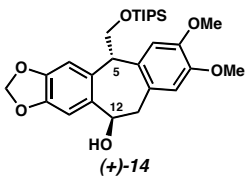
Methods for Determination of Enantiomeric Excess

Table S-2. Methods for Determination of Enantiomeric Excess

entry	alcohol	ee assay and column	assay conditions	(*S*) enantiomer retention time (min)	(*R*) enantiomer retention time (min)
1	 *(–)-9*	HPLC OJ	4% *i*PrOH/hexanes	17.8	20.8
2	 *(–)-SI3*	HPLC OD-H	3% EtOH/hexanes	15.7	16.7
3		HPLC OD-H	3% EtOH/hexanes	17.6	12.0
4	 *(–)-SI5*	HPLC AD	3% EtOH/hexanes	13.1	11.2
5	 *(–)-SI7*	HPLC OD-H	8% EtOH/hexanes	12.6	18.4
6		HPLC AD	5% EtOH/hexanes	17.6	27.9
7		GC GTA	80 °C isothermal	53.4	52.5
8	 *(+)-SI9*	HPLC AD	4% EtOH/hexanes	28.1[a]	18.8
9	 *(–)-SI10*	HPLC OB-H	3% EtOH/hexanes	18.1	23.2

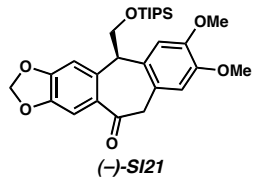
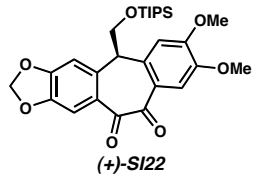
[a] Retention time for (*1S*, *2R*) enantiomer (shown).

Table S-2 continued.

10	 *(–)-SI11*	HPLC OB-H	3% *i*PrOH/hexanes	21.3	12.2
11	 *(+)-SI14*	HPLC AD	3% EtOH/hexanes	21.9	16.4
12	 *(–)-SI15*	HPLC OD-H	3% EtOH/hexanes	23.3	18.5
13	 *(+)-SI16*	HPLC OB-H	3% EtOH/hexanes	9.6	7.9
14	 *(+)-SI17*	HPLC OD-H	4% EtOH/hexanes	12.4	10.3
15		HPLC OD-H	3% *i*PrOH/hexanes	17.9	15.6
16	 *(–)-SI19*	HPLC OD-H	2% EtOH/hexanes	15.1	17.8[b]
17	 *(+)-SI20*	HPLC OD-H	2% EtOH/hexanes	7.9[c]	8.5
18		HPLC OD-H	2% EtOH/hexanes	20.7	14.6[d]
19	 *(+)-14*	HPLC AD	5% EtOH/hexanes	11.6	20.5[e]

[b] Retention time for (*1R*, *1'R*, *2'R*) enantiomer (shown). [c] Retention time for (*1'S*, *2'S*) enantiomer (shown). [d] Retention time for (*1R*, *1'S*, *2'S*) enantiomer (shown). [e] Retention time for (*5R*, *12R*) enantiomer (shown, isopavine numbering).

Table S-2 continued.

20	 *(–)-SI21*	HPLC AD	5% EtOH/hexanes	9.9	21.0
21	 *(+)-SI22*	HPLC AD	5% EtOH/hexanes	23.1	60.1

References

[1] R. M. Trend, B. M. Stoltz, *J. Am. Chem. Soc*. **2004**, *126*, 4482-4483.
[2] R. M. Trend, Y. K. Ramtohul, B. M. Stoltz, *J. Am. Chem. Soc*. **2005**, *127*, 17778-17788.
[3] D. Drew, J. R. Doyle, *Inorg. Synth*. **1972**, Vol. XIII, 53-55.
[4] A. Sanyal, J. K. Snyder, *Org. Lett*. **2000**, *2*, 2527-2530.
[5] M. J. Begley, M. Ladlow, G. Pattenden, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1095-1106.
[6] T. N. Grant, F. G. West, *J. Am. Chem. Soc*. **2006**, *128*, 9348-9349.
[7] A. B. Charette, H. Lebel, *J. Org. Chem*. **1995**, *60*, 2966-2967.
[8] A. B. Charette, M.-C. Lacasse, *Org. Lett*. **2002**, *4*, 3351-3353.
[9] A. J. Dixon, M. J. McGrath, P. O'Brien, *Org. Synth*. **2006**, *83*, 141-154.
[10] J.-L. Luche, L. Hahn-Rodriguez, P. Crabbé, *J. Chem. Soc., Chem. Commun*. **1978**, 601-602.
[11] F. S. Ruel, M. P. Braun, W. S. Johnson, *Org. Synth*. **2004**, Collect. Vol. X, 467-471.
[12] D. C. Ebner, Z. Novák, B. M. Stoltz, *Synlett* **2006**, 3533-3539.
[13] A. Padwa, T. J. Blacklock, D. Getman, N. Hatanaka, R. Loza, *J. Org. Chem*. **1978**, *43*, 1481-1492.
[14] J. D. Billimoria, *J. Chem. Soc*. **1955**, 1126-1129.
[15] A. Grau-Martinez, D. P. Curran, *Tetrahedron* **1997**, *53*, 5679-5698.
[16] U. K. Tambar, D. C. Ebner, B. M. Stoltz, *J. Am. Chem. Soc*. **2006**, *128*, 11752-11753.