Thiourea-Catalyzed Enantioselective Cyanosilylation of Ketones

Douglas E. Fuerst and Eric N. Jacobsen

*Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street,
Cambridge, Massachusetts 02138*

Supporting Information

General Procedures. All cyanosilylation reactions were conducted in round bottomed flasks fitted with rubber septa sealed with Parafilm. All other reactions were performed under an atmosphere of nitrogen in flame-dried round bottomed flasks fitted with rubber septa. Stainless steel syringes or cannulae were used to transfer air and moisture sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh), purchased from EM Science.

Materials. Commercial reagents were used as received with the following exceptions: toluene was distilled from sodium at 760 Torr, dichloromethane was distilled from calcium hydride at 760 Torr, and TMSCN was distilled at 760 Torr.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) were recorded on an Inova-500 (500 MHz) spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl_3 ; δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CHCl_3 ; δ 77.0). Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet) and coupling constant in Hertz (Hz). Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Melting points were measured on a Mel-Temp apparatus and are uncorrected. The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility. Chiral HPLC analysis was performed on a Shimadzu VP-series instrument. Chiral gas chromatography (GC) analysis was performed on a Hewlett-Packard 5890 gas chromatograph using a Chiraldex γ -TA (30 m x 0.25 mm) or Alltech Cyclodex- β (30 m x 0.25 mm) column.

I. Catalyst Optimization.

acetophenone: 93% ee
 100% conv.
 3-hepten-2-one: 72% ee
 75% conv.

acetophenone: 93% ee
 100% conv.
 3-hepten-2-one: 72% ee
 50% conv.

acetophenone: 66% ee
 15% conv.
 3-hepten-2-one: <5% conv.

Heterogeneous @ -40°C

acetophenone: 89% ee
 96% conv.
 3-hepten-2-one: 69% ee
 49% conv.

Heterogeneous @ -40°C

acetophenone: 90% ee
 88% conv.
 3-hepten-2-one: 67% ee
 39% conv.

acetophenone: 65% ee
 87% conv.
 3-hepten-2-one: 47% ee
 34% conv.

acetophenone: 49% ee
 20% conv.

acetophenone: 56% ee
 21% conv.

acetophenone: 76% ee
 95% conv.
 3-hepten-2-one: 53% ee
 57% conv.

acetophenone: <5% conv. 8 d

acetophenone: 93% ee
100% conv.
3-hepten-2-one: 72% ee
100% conv.

acetophenone: 91% ee
100% conv.
3-hepten-2-one: 82% ee
100% conv.

acetophenone: 93% ee
100% conv.
3-hepten-2-one: 81% ee
100% conv.

acetophenone: 95% ee
85% conv.
3-hepten-2-one: 95% ee
65% conv.

acetophenone: 95% ee
75% conv.
3-hepten-2-one: 95% ee
50% conv.

acetophenone: 0% conv.
3-hepten-2-one: 0% conv.

acetophenone: 92% ee
100% conv.
3-hepten-2-one: 75% ee
100% conv.

acetophenone: 91% ee
100% conv.
3-hepten-2-one: 67% ee
100% conv.

acetophenone: 0% conv.
3-hepten-2-one: 0% conv.

acetophenone: 90% ee, 15% conv.
3-hepten-2-one: 82% ee, <5% conv.

acetophenone: 0% conv., w/o CF₃CH₂OH
30% conv., 55% ee w/ CF₃CH₂OH
3-hepten-2-one: 0% conv., w/o CF₃CH₂OH
10% conv. w/ CF₃CH₂OH

II. Catalyst Preparation.

Catalysts **1** and **2** were prepared according to the published procedure.¹

2-isothiocyanato-3,3,*N*-trimethyl-butylamide:

Coupling of (L)-Boc-tert-leucine with methylamine hydrochloride. A 250-mL round bottomed flask was charged with methylamine hydrochloride (0.641 g, 9.50 mmol, 1.1 equiv), diisopropylethylamine (DIPEA, 2.26 mL, 12.96 mmol, 1.5 equiv), and anhydrous dichloromethane (80 mL). 1-Hydroxybenzotriazole hydrate (HOBt, 1.284 g, 9.50 mmol, 1.1 equiv), *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC, 1.820, 9.50 mmol, 1.1 equiv), and (L)-Boc-*tert*-leucine (2.00g, 8.64 mmol, 1.0 equiv) were added in that order. The reaction was stirred for 12 h at 23 °C, then diluted with diethyl ether (150 mL), washed twice with 1M hydrochloric acid (100 mL), twice with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), and dried (Na₂SO₄). Solvent removal in vacuo afforded analytically pure (2,2-dimethyl-1-methylcarbamoyl-propyl)-carbamic acid *tert*-butyl ester as a white solid which was used directly in the next step. **IR** (thin film, cm⁻¹) 3308 (w), 2968 (w), 1687 (m), 1655 (s), 1506 (m), 1367 (m), 1247 (w), 1172 (m), 1073 (w), 1008 (w); **¹H NMR** (500 MHz, CDCl₃) δ 5.69 (br s, 1H), 5.28 (br s, 1H), 3.78 (d, *J*=10.0 Hz, 1H), 2.82 (d, *J*=4.5 Hz, 1H), 1.43 (s, 9H), 0.98 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 171.6, 155.9, 79.5, 62.1, 34.5, 28.3, 26.5, 25.9.

Boc Deprotection. A 4M solution of hydrogen chloride in 1,4-dioxane (20 mL, 9.26 equiv) was added to (2,2-dimethyl-1-methylcarbamoyl-propyl)-carbamic acid *tert*-butyl ester and the resulting solution stirred for 2 h at 23 °C. The solution was concentrated in vacuo and azeotroped with benzene (50 mL) to ensure removal of all excess hydrochloric acid to afford 2-amino-3,3,*N*-trimethyl-butylamide hydrochloride as a foam which was used in the next step without further purification.

Isothiocyanate Formation. A saturated solution of aqueous sodium bicarbonate (90 mL) was added to a solution of 2-amino-3,3,*N*-trimethyl-butylamide hydrochloride (8.64 mmol) in dichloromethane (90 mL) at 0 °C. The mixture was stirred for 10 minutes, stirring stopped, and thiophosgene (0.691 mL, 9.07 mmol, 1.05 equiv) added to the dichloromethane (lower) layer in one portion via syringe. The resulting mixture was stirred (~500 rpm) for 30 minutes at 0 °C. The reaction was then transferred to a separatory funnel and the organic layer removed. The

¹ Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012-10014.

aqueous phase was extracted with dichloromethane (100 mL) and the combined organics dried (Na_2SO_4). Solvent removal in vacuo afforded analytically pure 2-isothiocyanato-3,3,*N*-trimethyl-butamide (1.593g, 99% yield over three steps) as a fluffy white solid that can be stored indefinitely at $-30\text{ }^\circ\text{C}$. **IR** (thin film, cm^{-1}) 3288 (s), 2971 (s), 2873 (w), 2083 (s), 1657 (s), 1572 (m), 1467 (w), 1256 (m), 1162 (w), 668 (w); **^1H NMR** (500 MHz, CDCl_3) δ 6.00 (br s, 1H), 2.87 (d, $J=5.0$ Hz, 1H), 1.09 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 166.7, 70.8, 36.8, 26.6, 26.4; LRMS (ApCI): 187.2 (100%) $[\text{M} + \text{H}]^+$.

General procedure for the preparation of *N,N*-dialkylcyclohexane diamines.

N,N-dipropyl-cyclohexane-1,2-diamine:

(*R,R*)-*N*-(2-Amino-cyclohexyl)-acetamide was prepared according to the procedure of Finney² with commercially available ethyl acetimidate hydrochloride. In our hands this procedure gave a 2:1 – 4:1 mixture of monoacylated:diacylated products that could be readily separated by silica gel chromatography (CH_2Cl_2 : MeOH : Et_3N , 100:10:1). (*R,R*)-*N*-(2-amino-cyclohexyl)-acetamide (0.850 g, 5.44 mmol, 1.0 equiv), propionaldehyde (1.92 mL, 27.2 mmol, 5.0 equiv), and H_2O (1.5 mL) were combined in a 50-mL round bottomed flask with acetonitrile (30 mL) and stirred for 15 minutes. Sodium cyanoborohydride (0.718 g, 11.42 mmol, 2.1 equiv) was added followed by AcOH (1.5 mL) 15 minutes later. After 2 hours, the volatiles were removed in vacuo and the resulting residue transferred to a separatory funnel with ethyl acetate (50 mL) and 1M NaOH (25 mL). The organic layer was washed twice with 1M NaOH (25 mL), brine (25 mL), and dried (Na_2SO_4). The ethyl acetate was removed in vacuo and the crude residue taken up in 4M HCl (30 mL). The resulting solution was refluxed for 12 hours and after cooling to ambient temperature was made basic with 4M NaOH. The aqueous layer was extracted three times with dichloromethane (20 mL), and dried (Na_2SO_4). Solvent removal in vacuo afforded *N,N*-dipropyl-cyclohexane-1,2-diamine (0.940g, 87% yield over two steps) as a pale yellow oil which was used directly in the next step. **IR** (thin film, cm^{-1}) 3356 (br w), 2957 (s), 2929 (s), 2858 (w), 1461 (w), 1379 (w), 1189 (w), 1076 (w), 948 (w), 861 (w); **^1H NMR** (500 MHz, CDCl_3) δ 2.56 (td, $J=4.0$, 10.0 Hz, 1H), 2.39 (m, 2H), 2.29 (m, 2H), 2.08 (m, 1H), 1.98 (m, 1H), 1.77-1.64 (cm, 4H), 1.48-1.36 (cm, 4H), 1.19-1.15 (cm, 5H), 0.87 (t, $J=7.5$, Hz, 6H); **^{13}C NMR** (100 MHz, CDCl_3) δ 66.8, 52.0, 51.3, 35.1, 26.0, 25.1, 22.8, 22.5, 11.9; LRMS (ApCI): 187.2 (100%) $[\text{M} + \text{H}]^+$.

² Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, 41, 8431-8434.

General procedure for thiourea formation.

2-[3-(2-dipropylamino-cyclohexyl)-thioureido]-3,3,*N*-trimethyl-butyramide (**3d**):

2-Isothiocyanato-3,3,*N*-trimethyl-butyramide (0.845 g, 4.54 mmol, 1.0 equiv) was added to a solution of *N,N*-dipropyl-cyclohexane-1,2-diamine (0.900 g, 4.54 mmol, 1.0 equiv) in dichloromethane (20 mL) at 23 °C. The resulting solution was stirred at 23 °C for 30 minutes, then concentrated to ~ 3 mL in vacuo. The resulting solution was loaded onto a silica gel column and chromatographed (100:5 → 100:10, CH₂Cl₂:MeOH) to afford 2-[3-(2-dipropylamino-cyclohexyl)-thioureido]-3,3,*N*-trimethyl-butyramide (1.15 g, 67% yield) as a white foam. **IR** (thin film, cm⁻¹) 3295 (br s), 3076 (w), 2958 (s), 2871 (m), 1651 (s), 1536 (s), 1234 (m), 1079 (w), 913 (w), 734 (m); **¹H NMR** (500 MHz, CDCl₃) δ 6.65 (br s, 1H), 6.16 (br s, 1H), 5.96 (br s, 1H), 4.69 (br s, 1H), 3.51 (br s, 1H), 2.79 (d, *J*=5.0 Hz, 3H), 2.51-2.31 (cm, 6H), 1.89 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.47-1.13 (cm, 8H), 1.04 (s, 9H), 0.87 (t, *J*=7.5, Hz, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ 182.0, 171.2, 66.0, 63.6, 54.9, 51.8, 34.4, 33.0, 26.8, 25.9, 25.4, 24.5, 23.5, 21.9, 11.8; LRMS (ApCI): 385.5 (100%) [M + H]⁺.

2-[3-(2-Amino-cyclohexyl)-thioureido]-3,3,*N*-trimethyl-butyramide (**3a**): The general procedure described above was performed on 1.00 mmol scale, using 1.2 equivalents of (*R,R*)-cyclohexane diamine. After 1 hour the reaction mixture was concentrated to ~ 2 mL and the resulting solution was loaded onto a silica gel column and chromatographed (100:5:1, CH₂Cl₂:MeOH:Et₃N) to afford 2-[3-(2-Amino-cyclohexyl)-thioureido]-3,3,*N*-trimethyl-butyramide (211 mg, 71% yield) as a white foam. **IR** (thin film, cm⁻¹) 3284 (br s), 3067 (m), 2937 (s), 2862 (m), 1649 (s), 1546 (s), 1236 (m), 1037 (w), 912 (m), 734 (s); **¹H NMR** (500 MHz, CDCl₃) δ 7.70 (br s, 1H), 6.33 (br s, 1H), 4.64 (s, 1H), 3.92 (br s, 2H), 2.81 (d, *J*=5.0 Hz, 3H), 2.66 (s, 1H), 1.91 (m, 1H), 2.05 (m, 2H), 1.71 (m, 2H), 1.32-1.16 (cm, 4H), 1.04 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 182.9, 172.3, 66.6, 59.2, 54.9, 51.8, 34.6, 34.2, 32.2, 27.0, 26.1, 24.6.

2-[3-(2-Dimethylamino-cyclohexyl)-thioureido]-3,3,*N*-trimethyl-butyramide (**3b**): The general procedure described above was performed on 1.76 mmol scale, using 1.0 equivalent of *N,N*-dimethyl-cyclohexane-1,2-diamine. After 1 hour the reaction mixture was concentrated to ~ 2 mL and the resulting solution was loaded onto a silica gel column and chromatographed (100:5:1, CH₂Cl₂:MeOH:Et₃N) to afford 2-[3-(2-dimethylamino-cyclohexyl)-thioureido]-3,3,*N*-trimethyl-butyramide (516 mg, 89% yield) as a white foam. **IR** (thin film, cm⁻¹) 3292 (br s), 3076 (w), 2937 (s), 2866 (m), 1650 (s), 1545 (s), 1367 (m), 1185 (w), 913 (w), 733 (m); **¹H NMR** (500 MHz, CDCl₃) δ 6.80 (br s, 1H), 6.25 (br s, 1H), 4.73 (br s, 1H), 3.78 (br s, 2H), 2.79 (d, *J*=5.0 Hz, 3H), 2.54 (m, 1H), 2.40 (m, 1H), 2.33 (s, 6H), 1.91 (m,

1H), 1.87 (m, 1H), 1.72 (m, 1H), 1.09-1.01 (cm, 4H), 1.04 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 182.6, 171.5, 67.0, 66.5, 55.4, 40.1, 34.6, 33.0, 27.0, 26.0, 24.9, 24.5, 22.1; LRMS (ApCI): 329.3 (100%) [M + H]⁺.

2-[3-(2-Diethylamino-cyclohexyl)-thioureido]-3,3,N-trimethylbutyramide (**3c**): The general procedure described above was performed on 0.50 mmol scale, using 1.0 equivalent of *N,N*-diethylcyclohexane-1,2-diamine. After 1 hour the entire reaction mixture was loaded onto a silica gel column and chromatographed (100:2:1, CH₂Cl₂:MeOH:Et₃N) to afford 2-[3-(2-diethylamino-cyclohexyl)-thioureido]-3,3,N-trimethylbutyramide (134 mg, 75% yield) as a white foam. **IR** (thin film, cm⁻¹) 3294 (br s), 3078 (w), 2964 (s), 2860 (m), 1650 (s), 1545 (s), 1368 (m), 1236 (w), 915 (w), 733 (m); **¹H NMR** (500 MHz, CDCl₃) δ 6.69 (br s, 1H), 6.27 (br s, 1H), 6.04 (br s, 1H), 3.50 (br s, 1H), 2.79 (d, *J*=5.0 Hz, 3H), 2.60 (m, 2H), 2.52 (m, 1H), 2.35 (m, 2H), 1.88 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.36-1.14 (cm, 4H), 1.05 (s, 9H), 1.03 (t, *J*=6.5 Hz, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ 182.3, 171.8, 66.2, 63.1, 43.6, 34.3, 33.0, 26.9, 26.7, 26.0, 25.4, 24.5, 23.6, 14.0; LRMS (ApCI): 357.3 (100%) [M + H]⁺.

III. Enantioselective Cyanosilylation.

2-Phenyl-2-trimethylsilyloxy-propionitrile: (representative experimental procedure for enantioselective cyanosilylation): A flame-dried 5-mL round bottomed flask equipped with a magnetic stir bar and fitted with a rubber septa was charged sequentially with **3d** (0.0192 g, 0.05 mmol, 5 mol%), acetophenone (0.117 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), and dichloromethane (2.0 mL). The septa was sealed with Parafilm M® and the reaction cooled to -78 °C in an immersion cryo-cool and was stirred for 15 min. 2,2,2-Trifluoroethanol (0.073 mL, 1.00 mmol) was then added via syringe and the reaction stirred at -78 °C for 24 h, after which time the contents of the flasks were put under high vacuum at -78 °C for 5 min. to remove excess HCN. After warming to room temperature, the entire reaction mixture was loaded onto a silica gel column and chromatographed (hexanes:EtOAc, 20:1) to afford 2-phenyl-2-trimethylsilyloxy-propionitrile (210 mg, 96% yield) as a clear colorless oil. The enantiomeric excess was determined to be 97% by chiral GC analysis (γ-TA, 100 °C isothermal, 7 psi): *t_R*(minor) = 14.70 min, *t_R*(major) = 15.31 min; [α]_D²⁵ = -22.3° (c = 1.0, CHCl₃). The absolute configuration was determined to be *R* by comparison with the previously reported optical rotation (lit. [α]_D²⁴ = -21.9° (c = 1.18, CHCl₃, 93% *ee*). All spectroscopic data matches data previously reported by Shibasaki³ as well as Hoveyda and Snapper.⁴

2-phenyl-2-trimethylsilyloxy-butyronitrile: Reaction was performed on a 1.00 mmol scale at -78 °C for 24 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), propiophenone (0.133 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0

³ (a) Hamashima, Y.; Kanai, M.; Shibasaki M. *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413. (b) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909.

⁴ Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009–1012.

mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-phenyl-2-trimethylsilyloxy-butyronitrile (222 mg, 95% yield) as a clear colorless oil. The enantiomeric excess was determined to be 95% by chiral GC analysis (γ -TA, 100 °C isothermal, 7 psi): t_R (minor) = 30.53 min, t_R (major) = 31.67 min; $[\alpha]_D^{25} = -21.5^\circ$ ($c = 1.0$, CHCl_3). All spectroscopic data matches data previously reported by Shibasaki³ as well as Hoveyda and Snapper.⁴

3-Methyl-2-phenyl-2-trimethylsilyloxy-butyronitrile: Reaction was performed on a 1.00 mmol scale at -78°C for 24 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), isobutyrophenone (0.156 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 3-methyl-2-phenyl-2-trimethylsilyloxy-butyronitrile (240 mg, 97% yield) as a clear colorless oil. The enantiomeric excess was determined to be 86% by chiral GC analysis (β -cyclodex, 80 °C isothermal): t_R (major) = 48.65 min, t_R (minor) = 49.63 min; $[\alpha]_D^{25} = -21.4^\circ$ ($c = 1.0$, CHCl_3); **IR** (thin film, cm^{-1}) 2967 (m), 2879 (w), 1492 (w), 1450 (m), 1254 (s), 1214 (m), 1100 (s), 945 (m), 868 (s), 754 (m); **^1H NMR** (500 MHz, CDCl_3) δ 7.49 (m, 2H), 7.40-7.32 (cm, 3H), 2.11 (m, 1H), 1.09 (d, $J=7.0$ Hz, 3H), 0.83 (d, $J=7.0$ Hz, 3H), 0.10 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 140.2, 128.5, 128.2, 125.7, 119.9, 80.1, 41.5, 17.3, 17.1, 0.8.

2-*o*-Tolyl-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 10.00 mmol scale at -78°C for 36 h using 5 mol% **3d** (0.192 g, 0.50 mmol, 5 mol%), 2'-methylacetophenone (1.33 mL, 10.00 mmol), TMSCN (2.94 mL, 22.00 mmol), 2,2,2-trifluoroethanol (0.729 mL, 10.00 mmol), and dichloromethane (20.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-*o*-tolyl-2-trimethylsilyloxy-propionitrile (2.218 g, 95% yield) as a clear colorless oil. The enantiomeric excess was determined to be 98% by chiral GC analysis (γ -TA, 100 °C isothermal, 7 psi): t_R (minor) = 29.16 min, t_R (major) = 31.51 min; $[\alpha]_D^{25} = -24.2^\circ$ ($c = 1.0$, CHCl_3); **IR** (thin film, cm^{-1}) 3067 (w), 2961 (m), 1372 (w), 1255 (s), 1222 (m), 1106 (s), 1069 (m), 991 (s), 848 (s), 458 (w); **^1H NMR** (500 MHz, CDCl_3) δ 7.59 (d, $J=3.5$ Hz, 1H), 7.28-7.21 (cm, 3H), 2.59 (s, 3H), 1.98 (s, 1H), 0.21 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 138.4, 135.5, 132.6, 128.7, 126.0, 125.3, 121.6, 71.7, 30.5, 20.7, 1.1.

2-*p*-Tolyl-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at -78°C for 48 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), 4'-methylacetophenone (0.141 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-*p*-tolyl-2-trimethylsilyloxy-propionitrile (227 mg, 97% yield) as a clear colorless oil. The enantiomeric excess was determined to be 96% by chiral GC analysis (γ -TA, 100 °C isothermal, 7 psi): t_R (minor) = 25.67 min, t_R (major) = 27.10 min; $[\alpha]_D^{25} = -24.0^\circ$ ($c = 1.0$, CHCl_3). All spectroscopic data matches data previously reported by Shibasaki.³

2-(3-Methoxy-phenyl)-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at $-78\text{ }^{\circ}\text{C}$ for 12 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), 3'-methoxyacetophenone (0.141 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-(3-methoxy-phenyl)-2-trimethylsilyloxy-propionitrile (242 mg, 97% yield) as a clear colorless oil. The enantiomeric excess was determined to be 97% by chiral GC analysis (γ -TA, $100\text{ }^{\circ}\text{C}$ isothermal, 7 psi): $t_{\text{R}}(\text{minor}) = 56.78$ min, $t_{\text{R}}(\text{major}) = 58.56$ min; $[\alpha]_{\text{D}}^{25} = -21.8^{\circ}$ ($c = 1.0$, CHCl_3); **IR** (thin film, cm^{-1}) 2995 (w), 2961 (m), 1602 (s), 1488 (s), 1372 (w), 1263 (s), 1119 (s), 1000 (s), 784 (m), 699 (m); **^1H NMR** (500 MHz, CDCl_3) δ 7.31 (t, $J=8.0$ Hz, 1H), 7.13 (m, 1H), 7.09 (m, 1H), 6.88 (m, 1H), 3.83 (s, 3H), 1.85 (s, 3H), 0.20 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 159.7, 143.6, 129.7, 121.5, 116.8, 113.8, 110.5, 71.4, 55.2, 33.5, 1.0; LRMS (CI): 267 (100%) $[\text{M} + \text{NH}_4]^+$.

2-(4-Methoxy-phenyl)-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at $-78\text{ }^{\circ}\text{C}$ for 48 h using 10 mol% **3d** (0.0385 g, 0.10 mmol, 10 mol%), 4'-methoxyacetophenone (0.150 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-(4-methoxy-phenyl)-2-trimethylsilyloxy-propionitrile (232 mg, 93% yield) as a clear colorless oil. The enantiomeric excess was determined to be 95% by chiral GC analysis (γ -TA, $100\text{ }^{\circ}\text{C}$ isothermal, 7 psi): $t_{\text{R}}(\text{minor}) = 76.09$ min, $t_{\text{R}}(\text{major}) = 79.99$ min; $[\alpha]_{\text{D}}^{25} = -22.2^{\circ}$ ($c = 1.0$, CHCl_3). All spectroscopic data matches data previously reported by Hoveyda and Snapper.⁴

2-(4-Bromo-phenyl)-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at $-78\text{ }^{\circ}\text{C}$ for 12 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), 4'-bromoacetophenone (0.199 g, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-(4-bromo-phenyl)-2-trimethylsilyloxy-propionitrile (281 mg, 94% yield) as a clear colorless oil. The enantiomeric excess was determined to be 93% by chiral GC analysis (γ -TA, $100\text{ }^{\circ}\text{C}$ isothermal, 7 psi): $t_{\text{R}}(\text{minor}) = 74.80$ min, $t_{\text{R}}(\text{major}) = 82.09$ min; $[\alpha]_{\text{D}}^{25} = -20.1^{\circ}$ ($c = 1.0$, CHCl_3); **IR** (thin film, cm^{-1}) 2962 (m), 2901 (w), 1592 (w), 1488 (s), 1397 (m), 1255 (s), 1227 (s), 1121 (s), 996 (m), 696 (w); **^1H NMR** (500 MHz, CDCl_3) δ 7.52 (m, 2H), 7.42 (m, 2H), 1.83 (s, 3H), 0.19 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 141.2, 131.7, 126.3, 122.7, 121.1, 71.0, 33.4, 1.0.

2-Naphthalen-1-yl-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at $-78\text{ }^{\circ}\text{C}$ for 36 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), 1'-acetonaphthone (0.155 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-naphthalen-1-yl-2-trimethylsilyloxy-propionitrile (246 mg, 91% yield) as a clear colorless oil. The enantiomeric excess was determined to be 95% by chiral GC analysis (γ -TA, $120\text{ }^{\circ}\text{C}$ isothermal, 7 psi): $t_{\text{R}}(\text{minor}) = 89.26$

min, t_R (major) = 91.43 min; $[\alpha]_D^{25} = -29.4^\circ$ ($c = 1.0$, CHCl_3); **IR** (thin film, cm^{-1}) 3054 (w), 2960 (w), 1511 (w), 1254 (s), 1185 (m), 1132 (s), 986 (m), 848 (s), 777 (s), 438 (w); **$^1\text{H NMR}$** (500 MHz, CDCl_3) δ 8.58 (d, $J=8.5$ Hz, 1H), 7.91-7.85 (cm, 2H), 7.58-7.51 (cm, 2H), 7.46 (t, $J=8.5$ Hz, 1H), 2.20 (s, 3H), 0.11 (s, 9H); **$^{13}\text{C NMR}$** (100 MHz, CDCl_3) δ 136.2, 134.9, 130.5, 129.7, 129.5, 126.4, 126.1, 125.9, 125.0, 124.0, 122.1, 73.4, 31.9, 1.2; LRMS (CI): 287 (70%) $[\text{M} + \text{NH}_4]^+$.

2-Naphthalen-2-yl-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at -78°C for 12 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), 2'-acetonaphthone (0.171 g, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-naphthalen-2-yl-2-trimethylsilyloxy-propionitrile (263 mg, 98% yield) as a white solid. The enantiomeric excess was determined to be 97% by chiral HPLC (Chiralcel OJ, 0.5% i-PrOH:hexanes, 0.5 mL/min, $\lambda = 208$ nm): t_R (minor) = 14.02 min, t_R (major) = 16.21 min; $[\alpha]_D^{25} = -14.2^\circ$ ($c = 1.0$, CHCl_3); mp = 59°C . All spectroscopic data matches data previously reported by Shibasaki³ as well as Hoveyda and Snapper.⁴

2-Furan-2-yl-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at -78°C for 48 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), 2-acetylfuran (0.100 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-furan-2-yl-2-trimethylsilyloxy-propionitrile (170 mg, 81% yield) as a clear colorless oil. The enantiomeric excess was determined to be 97% by chiral GC analysis (γ -TA, 80°C isothermal, 7 psi): t_R (major) = 19.66 min, t_R (minor) = 26.05 min; $[\alpha]_D^{25} = -30.9^\circ$ ($c = 1.0$, CHCl_3); **IR** (thin film, cm^{-1}) 3126 (w), 2963 (m), 1499 (w), 1374 (w), 1255 (s), 1163 (s), 1115 (s), 997 (s), 930 (m), 753 (s); **$^1\text{H NMR}$** (500 MHz, CDCl_3) δ 7.42 (dd, $J=1.0, 2.0$ Hz, 1H), 6.50 (dd, $J=1.0, 3.0$ Hz, 1H), 6.39 (dd, $J=2.0, 3.0$ Hz, 1H), 1.93 (s, 3H), 0.09 (s, 9H); **$^{13}\text{C NMR}$** (100 MHz, CDCl_3) δ 151.6, 143.1, 120.2, 110.7, 108.1, 65.9, 28.9, 0.5; LRMS (CI): 227 (100%) $[\text{M} + \text{NH}_4]^+$.

2-Thiophen-2-yl-2-trimethylsilyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at -78°C for 48 h using 10 mol% **3d** (0.0385 g, 0.10 mmol, 10 mol%), 2-acetylthiophene (0.110 mL, 1.00 mmol), TMSCN (0.361 mL, 2.70 mmol), 2,2,2-trifluoroethanol (0.109 mL, 1.50 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-thiophen-2-yl-2-trimethylsilyloxy-propionitrile (199 mg, 88% yield) as a clear colorless oil. The enantiomeric excess was determined to be 97% by chiral GC analysis (β -cyclodex, 80°C isothermal): t_R (major) = 29.39 min, t_R (minor) = 30.12 min; $[\alpha]_D^{25} = -57.6^\circ$ ($c = 1.0$, CHCl_3); **IR** (thin film, cm^{-1}) 3111 (w), 2962 (m), 1353 (w), 1255 (s), 1220 (s), 1148 (s), 1037 (m), 993 (s), 850 (s), 758 (m); **$^1\text{H NMR}$** (500 MHz, CDCl_3) δ 7.31 (dd, $J=1.0, 5.0$ Hz, 1H), 7.20 (dd, $J=1.0, 4.0$ Hz, 1H), 6.98 (dd, $J=4.0, 5.0$ Hz, 1H), 1.98 (s, 3H), 0.19 (s, 9H); **$^{13}\text{C NMR}$** (100 MHz, CDCl_3) δ 146.6, 127.0, 126.3, 125.0, 121.2, 68.6, 33.7, 1.1; LRMS (CI): 243 (100%) $[\text{M} + \text{NH}_4]^+$.

2-(2,4-Dimethyl-thiazol-5-yl)-2-trimethylsilanyloxy-propionitrile: Reaction was performed on a 1.00 mmol scale at $-78\text{ }^{\circ}\text{C}$ for 48 h using 10 mol% **3d** (0.0385 g, 0.10 mmol, 10 mol%), 5-acetyl-2,4-dimethyl-thiazole (0.141 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-(2,4-dimethyl-thiazol-5-yl)-2-trimethylsilanyloxy-propionitrile (220 mg, 87% yield) as a clear colorless oil. The enantiomeric excess was determined to be 97% by chiral GC analysis (γ -TA, $100\text{ }^{\circ}\text{C}$ isothermal, 7 psi): $t_R(\text{minor}) = 46.01\text{ min}$, $t_R(\text{major}) = 47.06\text{ min}$; $[\alpha]_D^{25} = -16.0^{\circ}$ ($c = 1.0$, CHCl_3); **IR** (thin film, cm^{-1}) 2993 (m), 1538 (m), 1256 (s), 1184 (s), 1156 (s), 1056 (m), 980 (s), 854 (s), 638 (w), 564 (w); **^1H NMR** (500 MHz, CDCl_3) δ 2.60 (s, 3H), 2.48 (s, 3H), 1.92 (s, 3H), 0.24 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 163.5, 147.9, 133.1, 120.2, 66.8, 32.1, 19.2, 16.4, 1.3; LRMS (FAB): 255.2 (100%) $[\text{M} + \text{H}]^+$.

2-Methyl-4-phenyl-2-trimethylsilanyloxy-but-3-enenitrile: Reaction was performed on a 1.00 mmol scale at $-78\text{ }^{\circ}\text{C}$ for 12 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), *trans*-4-phenyl-3-buten-2-one (0.146 g, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-methyl-4-phenyl-2-trimethylsilanyloxy-but-3-enenitrile (230 mg, 94% yield) as a clear colorless oil. The enantiomeric excess was determined to be 96% by chiral HPLC (Chiralcel OD, 1.0% *i*-PrOH:hexanes, 0.5 mL/min, $\lambda = 208\text{ nm}$): $t_R(\text{major}) = 9.49\text{ min}$, $t_R(\text{minor}) = 11.13\text{ min}$; $[\alpha]_D^{25} = -61.9^{\circ}$ ($c = 1.0$, CHCl_3). All spectroscopic data matches data previously reported by Shibasaki³ as well as Hoveyda and Snapper.⁴

2-Styryl-2-trimethylsilanyloxy-hexanenitrile: Reaction was performed on a 1.00 mmol scale at $-78\text{ }^{\circ}\text{C}$ for 12 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), *trans*-7-phenyl-6-hepten-5-one (0.188 g, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-styryl-2-trimethylsilanyloxy-hexanenitrile (280 mg, 97% yield) as a white solid. The enantiomeric excess was determined to be 93% by chiral HPLC (Chiralcel OD, 1.0% *i*-PrOH:hexanes, 0.5 mL/min, $\lambda = 208\text{ nm}$): $t_R(\text{major}) = 9.49\text{ min}$, $t_R(\text{minor}) = 11.13\text{ min}$; $[\alpha]_D^{25} = -43.8^{\circ}$ ($c = 1.0$, CHCl_3); mp = $55\text{--}56\text{ }^{\circ}\text{C}$; **IR** (thin film, cm^{-1}) 2959 (m), 2867 (w), 1450 (w), 1254 (m), 1102 (m), 969 (m), 845 (s), 750 (m), 692 (m), 576 (w); **^1H NMR** (500 MHz, CDCl_3) δ 7.43 (m, 2H), 7.37 (m, 2H), 7.32 (m, 1H), 6.90 (d, $J=16.0\text{ Hz}$, 1H), 6.08 (d, $J=16.0\text{ Hz}$, 1H), 1.94 (m, 1H), 1.82 (m, 1H), 1.55 (m, 1H), 1.48–1.34 (cm, 3H), 0.93 (t, $J=7.5\text{ Hz}$, 1H), 0.24 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 135.5, 131.9, 129.1, 129.1, 128.8, 127.1, 120.4, 74.3, 43.3, 26.4, 22.6, 14.2, 1.6; LRMS (FAB): 305 (90%) $[\text{M} + \text{NH}_4]^+$.

2-Methyl-2-trimethylsilanyloxy-hept-3-enenitrile: Reaction was performed on a 1.00 mmol scale at $-78\text{ }^{\circ}\text{C}$ for 48 h using 10 mol% **3d** (0.0385 g, 0.10 mmol, 10 mol%), 3-hepten-2-one (0.136 mL, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL).

The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-methyl-2-trimethylsilyloxy-hept-3-enenitrile (199 mg, 91% yield) as a clear colorless oil. The enantiomeric excess was determined to be 89% by chiral GC analysis (γ -TA, 70 °C isothermal, 7 psi): t_R (minor) = 24.96 min, t_R (major) = 26.01 min; $[\alpha]_D^{25} = +3.6^\circ$ (c = 1.0, CHCl₃); **IR** (thin film, cm⁻¹) 2962 (s), 2935 (m), 1457 (w), 1372 (w), 1255 (s), 1204 (m), 1113 (s), 1005 (s), 973 (s), 758 (m); **¹H NMR** (500 MHz, CDCl₃) δ 6.00 (dt, $J=7.0, 15.5$ Hz, 1H), 5.45 (dt, $J=1.5, 15.5$ Hz, 1H), 2.06 (m, 2H), 1.62 (s, 3H), 1.43 (m, 2H), 0.92 (t, $J=7.0$ Hz, 3H), 0.20 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 132.6, 130.9, 121.0, 69.8, 33.8, 30.9, 21.8, 13.7, 1.4; LRMS (FAB): 212.3 (100%) [M + H]⁺.

2-Bromo-1-trimethylsilyloxy-cyclohex-2-enecarbonitrile: Reaction was performed on a 1.00 mmol scale at -78 °C for 12 h using 5 mol% **3d** (0.0192 g, 0.05 mmol, 5 mol%), 2-bromo-2-cyclohexen-1-one (0.173 g, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 2-bromo-1-trimethylsilyloxy-cyclohex-2-enecarbonitrile (261 mg, 95% yield) as a white solid. The enantiomeric excess was determined to be 97% by chiral GC analysis (γ -TA, 110 °C isothermal, 7 psi): t_R (minor) = 35.33 min, t_R (major) = 37.74 min; $[\alpha]_D^{25} = +20.3^\circ$ (c = 1.0, CHCl₃); mp = 63-64 °C; **IR** (thin film, cm⁻¹) 2964 (m), 2940 (m), 1332 (w), 1253 (s), 1187 (w), 1132 (s), 993 (m), 847 (s), 758 (m), 638 (w); **¹H NMR** (500 MHz, CDCl₃) δ 6.00 (t, $J=4.5$ Hz, 1H), 2.25 (m, 1H), 2.17-2.10 (cm, 3H), 1.87-1.82 (cm, 2H), 0.31 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃) δ 135.2, 121.8, 120.1, 70.8, 39.1, 27.2, 18.1, 1.2.

1-Trimethylsilyloxy-indan-1-carbonitrile: Reaction was performed on a 1.00 mmol scale at -78 °C for 48 h using 10 mol% **3d** (0.0385 g, 0.10 mmol, 10 mol%), 1-indanone (0.132 g, 1.00 mmol), TMSCN (0.294 mL, 2.20 mmol), 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford 1-trimethylsilyloxy-indan-1-carbonitrile (225 mg, 97% yield) as a clear colorless oil. The enantiomeric excess was determined to be 91% by chiral GC analysis (γ -TA, 100 °C isothermal, 7 psi): t_R (minor) = 55.57 min, t_R (major) = 57.72 min; $[\alpha]_D^{25} = -35.7^\circ$ (c = 1.0, CHCl₃).

Phenyl-trimethylsilyloxy-acetonitrile: Reaction was performed on a 1.00 mmol scale at -78 °C for 2 h using 1 mol% **3d** (0.0039 g, 0.010 mmol, 1.0 mol%), benzaldehyde (0.102 mL, 1.00 mmol), TMSCN (0.188 mL, 1.40 mmol), 2,2,2-trifluoroethanol (0.015 mL, 0.20 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography (hexanes:EtOAc, 20:1) to afford phenyl-trimethylsilyloxy-acetonitrile (126 mg, 61% yield) as a clear colorless oil. The enantiomeric excess was determined to be 96% by chiral GC analysis (γ -TA, 100 °C isothermal, 7 psi): t_R (minor) = 25.35 min, t_R (major) = 27.49 min.

4-Phenyl-2-trimethylsilyloxy-but-3-enenitrile: Reaction was performed on a 1.00 mmol scale at -78 °C for 2 h using 1 mol% **3d** (0.0039 g, 0.010 mmol, 1.0 mol%), *trans*-cinnamaldehyde (0.126 mL, 1.00 mmol), TMSCN (0.188 mL, 1.40 mmol), 2,2,2-trifluoroethanol (0.015 mL, 0.20 mmol), and dichloromethane (2.0 mL). The product was purified by silica gel flash chromatography

(hexanes:EtOAc, 20:1) to afford 4-phenyl-2-trimethylsilanyloxy-but-3-enenitrile (160 mg, 69% yield) as a clear colorless oil. The enantiomeric excess was determined to be 93% by chiral GC analysis (γ -TA, 100 °C isothermal, 7 psi): t_R (minor) = 49.88 min, t_R (major) = 51.14 min.

IV. Recycling of catalyst **3d**.

The cyanosilylation of 2'-methylacetophenone was run as described above on 10.0 mmol scale using 5 mol% **3d** (192 mg). After the cyanosilylated product eluted from the silica gel column (hexanes:EtOAc, 20:1), **3d** was eluted from the column (CH₂Cl₂:MeOH:Et₃N, 100:5:1) and recovered in 96% yield. After solvent removal in vacuo, the recovered catalyst was azeotroped with dichloromethane and put under high vacuum three times to ensure removal of all Et₃N. Recovered **3d** was then used in a subsequent cyanosilylation of 2'-methylacetophenone on 0.2 mmol scale using 5 mol% **3d** (3.8 mg) to afford 2-*o*-tolyl-2-trimethylsilanyloxy-propionitrile (0.042 mg, 91% yield, 98% ee).

V. Preparation of racemic samples for GC and HPLC analysis.

To a solution of ketone (1.00 mmol) in acetonitrile (1 mL) at 23 °C was added trimethylamine *N*-oxide (0.015 g, 0.20 mmol) and TMSCN (0.200 mL, 1.50 mmol). The solution was allowed to stir until all of the starting ketone was consumed, then the entire reaction mixture was loaded onto a silica gel column and chromatographed as described above.

Chiral GC : γ-TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	14.710	50580	7394	MM	0.114	49.9257
2	15.266	50730	7546	MM	0.112	50.0743

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	14.702	1310	201	MM	0.109	1.6036
2	15.312	80387	11234	MM	0.119	98.3964

Chiral GC : γ-TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	30.658	86750	5288	MF	0.273	49.8877
2	31.666	87141	5626	FM	0.258	50.1123

Sig. 1 in C:\PEAK\DEF\5-71.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	30.527	2251	163	MM	0.230	2.5066
2	31.669	87541	5611	MM	0.260	97.4934

Chiral GC : β -cyclodextr, 80 °C isothermal

Sig. 1 in C:\PEAK\EXPORT1\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	48.695	107202	3342	MF	0.535	49.8377
2	49.844	107901	3606	FM	0.499	50.1623

Sig. 1 in C:\PEAK\EXPORT1\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	48.647	224037	7007	MF	0.533	93.0669
2	49.631	16690	602	FM	0.462	6.9331

Chiral GC : γ -TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	29.217	35297	2695	MM	0.218	49.9228
2	31.372	35406	2587	MM	0.228	50.0772

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	29.157	1456	110	MM	0.221	1.1118
2	31.509	129499	7740	MM	0.279	98.8882

Chiral GC : γ -TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	25.723	82667	6276	MM	0.220	49.9784
2	27.020	82738	6455	MM	0.214	50.0216

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	25.671	1761	151	MM	0.194	1.8559
2	27.100	93105	7086	MM	0.219	98.1441

Chiral GC : γ -TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	57.132	71025	2351	MM	0.503	49.9079
2	58.721	71287	2567	MM	0.463	50.0921

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	56.780	1069	42	MM	0.428	1.3495
2	58.702	78148	2701	MM	0.482	98.6505

Chiral GC : γ -TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	76.220	40924	1171	MM	0.582	49.9887
2	79.681	40943	1168	MM	0.584	50.0113

Sig. 1 in C:\PEAK\DEF\5-67.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	76.093	2149	62	MM	0.582	2.3971
2	79.986	87482	2210	MM	0.660	97.6029

Chiral GC : γ -TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	74.993	72756	1953	MM	0.621	50.0714
2	82.076	72548	1985	MM	0.609	49.9286

Sig. 1 in C:\PEAK\DEF\5-41.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	74.800	2614	81	MM	0.538	3.7383
2	82.086	67303	1880	MM	0.597	96.2617

Chiral GC : γ -TA, 120 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	89.668	43846	1013	MF	0.721	49.7368
2	91.509	44310	1101	FM	0.670	50.2632

Sig. 1 in C:\PEAK\DEF\5-93.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	89.264	1585	40	MM	0.658	2.5254
2	91.433	61165	1420	MM	0.718	97.4746

Chiral HPLC : Chiralcel OJ, 0.5% i-PrOH:hexanes, 0.5 mL/min

SPD-10Avp Ch1-208nm Results

Retention Time	Area	Area Percent
14.367	38688866	49.489
16.500	39488582	50.511
Totals	78177448	100.000

SPD-10Avp Ch1-208nm Results

Retention Time	Area	Area Percent
14.042	1863139	1.512
16.208	121348787	98.488
Totals	123211926	100.000

Chiral GC : γ -TA, 80 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	19.861	81522	7212	MM	0.188	49.8775
2	25.724	81923	3980	MM	0.343	50.1225

Sig. 1 in C:\PEAK\DEF\5-47.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	19.657	108899	9189	MM	0.198	98.6889
2	26.049	1447	131	MM	0.184	1.3111

Chiral GC : β -cyclodex, 80 °C isothermal

Sig. 1 in C:\PEAK\EXPORT1\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	29.446	155171	8301	MF	0.312	49.9848
2	30.173	155265	8734	FM	0.296	50.0152

Sig. 1 in C:\PEAK\EXPORT1\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	29.390	271316	14999	MF	0.301	98.7907
2	30.121	3321	187	FM	0.296	1.2093

Chiral GC : γ -TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	45.604	60081	2660	MF	0.376	49.6133
2	46.712	61018	2848	FM	0.357	50.3867

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	46.007	1446	65	MF	0.369	1.7503
2	47.055	81155	3651	FM	0.371	98.2497

Chiral HPLC : Chiralcel OD, 1.0% i-PrOH:hexanes, 0.5 mL/min

SPD-10Avp Ch1-208nm Results

Retention Time	Area	Area Percent
9.275	21883343	49.974
10.408	21904020	50.021
Totals	43789625	100.000

SPD-10Avp Ch1-208nm Results

Retention Time	Area	Area Percent
9.492	60264176	97.949
11.133	1262133	2.051
Totals	61526309	100.000

Chiral HPLC : Chiralcel OD, 1.0% i-PrOH:hexanes, 0.5 mL/min

SPD-10Avp Ch1-208nm Results

Retention Time	Area	Area Percent
7.692	15979076	49.827
8.608	16088284	50.167
Totals	32069179	100.000

SPD-10Avp Ch1-208nm Results

Retention Time	Area	Area Percent
7.758	47345287	96.402
8.683	1767136	3.598
Totals	49112423	100.000

Chiral GC : γ -TA, 70 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	25.035	94254	8149	MM	0.193	49.9646
2	26.106	94387	7632	MM	0.206	50.0354

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	24.963	6867	632	MM	0.181	5.7539
2	26.007	112472	9164	MM	0.205	94.2461

Chiral GC : γ -TA, 110 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	35.298	14462	959	MM	0.251	49.8806
2	37.704	14531	916	MM	0.264	50.1194

Sig. 1 in C:\PEAK\DEF\5-89.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	35.332	489	35	MM	0.235	1.6161
2	37.739	29773	1848	MM	0.268	98.3839

Chiral GC : γ -TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	55.996	119370	3707	MM	0.537	49.9726
2	57.900	119500	4191	MM	0.475	50.0274

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	55.567	5786	219	MM	0.440	4.7380
2	57.723	116341	4052	MM	0.479	95.2620

Chiral GC : γ-TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	25.486	68158	5508	MM	0.206	49.9527
2	27.474	68287	5670	MM	0.201	50.0473

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	25.351	2598	227	MM	0.191	2.0991
2	27.491	121147	9318	MM	0.217	97.9009

Chiral GC : γ -TA, 100 °C isothermal, 7 psi

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	50.069	68628	2267	MF	0.504	49.9422
2	51.036	68787	2704	FM	0.424	50.0578

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	49.878	3837	139	MF	0.460	3.6465
2	51.139	101393	3391	FM	0.498	96.3535