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Catalytic Enantioselective Acylation of (Silyloxy)nitrile Anions

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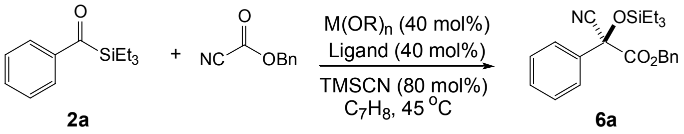
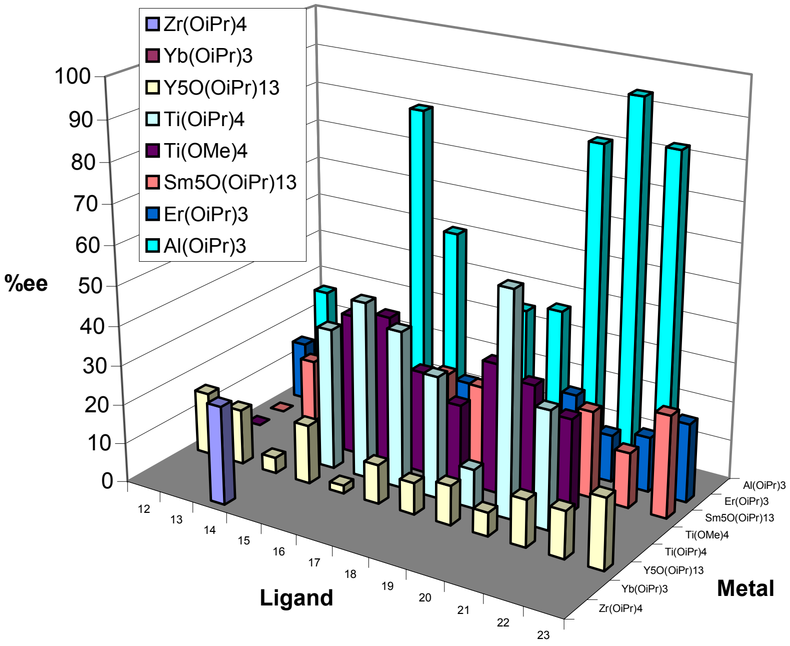
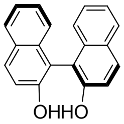
Experimental Section

Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on the following instruments: Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) and Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometers with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.23 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constants (Hz), and integration. Enantiomeric excesses were obtained using a Berger Supercritical Fluid Chromatograph model FCM 1100/1200 equipped with an Agilent 1100 series UV-Vis detector using one of the three following chiral HPLC columns: Chiralcel Chiralpak AD or OD columns or a Regis Pirkle Whelk-O 1 column. Samples were eluted with SFC grade CO_2 and the indicated percentage of MeOH. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent Technologies silica gel 60 (32-63 µm). All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. Yields and enantiomeric excesses are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Diethyl ether, tetrahydrofuran, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use.[1] Dithianes were prepared from the corresponding aldehydes using Graham's procedure.[2] Preparation of new acylsilanes are reported herein or have been reported in a previous communication. Racemic standards of compounds **6a-6j** were prepared as described in a previous communication.[3] Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. **CAUTION:** Trimethylsilylcyanide is toxic and releases HCN upon exposure to acid. While we have encountered no problems in the chemistry described herein, we regularly employ an HCN detector (BW Technologies, Ltd.) in manipulations involving cyanide reagents as a precautionary measure. Reactions should be conducted in a well-ventilated fume hood.



Enantioselective catalyst screen for reaction of acylsilane 2a with benzylcyanoformate. All subsequent manipulations were performed in a dry box to exclude moisture. 200 μL of a 0.045 M solution (0.0091 mmol) of each ligand in toluene was added by pipette to each individual vial containing 0.0091 mmol of metal alkoxide ($M(OR)_n$). This solution was allowed to stir for 30 min and then the solvent was removed under reduced pressure. An additional 200 μL of toluene was added to each vial and this solvent was also removed under reduced pressure (this step is to insure complete alcohol removal). 0.9 mL of a solution of the acylsilane (0.023 mmol), cyanoformate (0.091 mmol), and TMSCN (0.018 mmol) was added to each vial. The reactions were allowed to stir for 72 h in the dry box. Next, the reactions were removed from the glove box and a solution of 1M NaOH (~0.1 mL) was added to each vial to insure excess cyanoformate hydrolysis. Each reaction was filtered through a pad of SiO_2 with the aid of Et_2O and the combined extracts were concentrated. Enantiomeric excesses were determined by chiral SFC analysis (Chiralpak OD, 0.3% MeOH, 0.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{r\text{-major}}$, 37.0 min, $t_{r\text{-minor}}$ 41.5 min).

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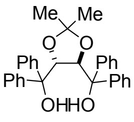
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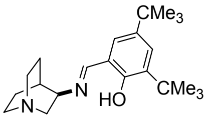
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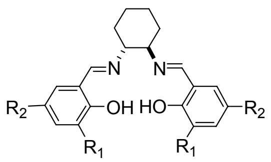
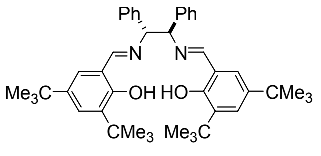

15 $R_1 = R_2 = CMe_3$
16 $R_1 = R_2 = H$
17 R_1=Me; R_2 = H
18 R_1 = OMe; R_2 = H
19 R_1 = H; R_2 = Cl
20 $R_1 = R_2 = CMe_3$;
$R_1' = R_2' = H$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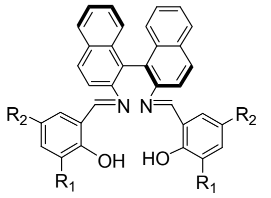
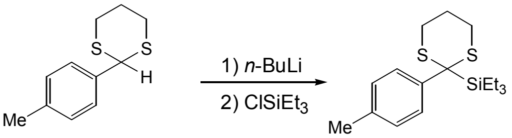
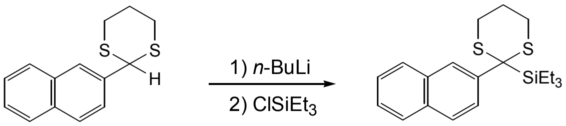

22 R_1=R_2=H
23 R_1=R_2=CMe_3

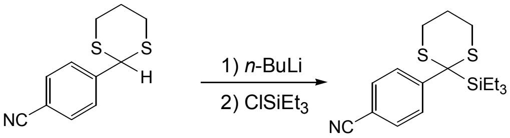
General Procedure (A) for the preparation of silyldithianes.[4, 5] To a dry 100 mL round-bottom flask with a magnetic stir bar was added 7.5 mmol of dithiane. THF (35 mL) was added *via* syringe. The resulting solution stirred under N_2 at –78 °C for 30 min, then *n*-butyllithium (2.5 M in hexanes, 8.3 mmol, 1.1 equiv) was added dropwise to the solution *via* syringe. The reaction was stirred at –78 °C for 2 h and 8.3 mmol triethylsilyl chloride (1.1 equiv) was added dropwise *via* syringe at the same temperature. After 30 min, the reaction was warmed to 25 °C for 30 min and then quenched with 40 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted with three 30 mL portions of Et_2O. The organic extracts were combined, dried ($MgSO_4$), filtered, and the solvent was removed with a rotary evaporator. The crude product was purified by flash chromatography, if necessary, eluting with the indicated solvent system to afford the pure silyldithiane.



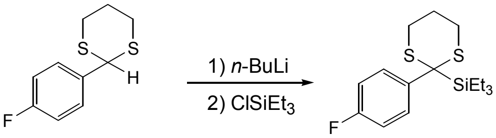
2-(4-Methyl)phenyl-2-triethylsilyl-1,3-dithiane. The title compound was prepared according to General Procedure **A** using 8.96 g (42.6 mmol) of dithiane, 29.3 mL of *n*-BuLi (1.6 M in hexanes, 46.8 mmol), and 7.9 mL (46.8 mmol) of TESCl to yield 13.83 g (100%) of the silyl dithiane as a clear oil that was used without further purification. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 6.0 Hz, 2H), 2.83-2.74 (m, 2H), 2.41-2.32 (m, 2H), 2.35 (s, 3H), 2.02 (dtt, *J* = 13.6, 12.8, 2.4 Hz, 1H), 1.86 (m, 1H), 0.92 (t, *J* = 8.4 Hz, 9H), 0.71-0.64 (m, 6H); TLC (95:5 hexanes-EtOAc) R_f 0.27.



2-Naphthyl-2-triethylsilyl-1,3-dithiane. The title compound was prepared according to General Procedure **A** using 2.0 g (8.1 mmol) of dithiane, 5.6 mL of *n*-BuLi (1.6 M in hexanes, 8.9 mmol), and 1.4 mL (8.5 mmol) of $ClSiEt_3$ to yield 2.9 g (100%) of the silyl dithiane as a clear oil that was used without further purification. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.0 Hz, 1 H), 8.08 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.86-7.75 (m, 3H), 7.48-7.40 (m, 2H), 2.77 (ddd, *J* = 13.6, 13.6, 2.8 Hz, 2H), 2.39 (ddd, *J* = 13.6, 4.0, 4.0 Hz, 2H), 2.02 (dtt, *J* = 13.6, 13.2, 2.8 Hz, 1H), 1.91 (dtt, *J* = 13.2, 4.0, 2.8 Hz), 0.90 (t, *J* = 4.0 Hz, 9H), 0.68 (q, *J* = 4.0 Hz, 6H); TLC (5:95 EtOAc-petroleum ether) R_f 0.56.

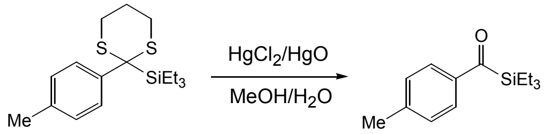


2-(4-Cyano)phenyl-2-triethylsilyl-1,3-dithiane. The title compound was prepared according to General Procedure **A** using 4.19 g (19.1 mmol) of dithiane, 13.2 mL of *n*-BuLi (1.6 M in hexanes, 21.0 mmol), and 3.5 mL (21.01 mmol) of TESCl to yield 4.39 g (69%) of the silyl dithiane as a white solid after flash chromatography with 39:1 Hexanes-EtOAc. Analytical data for title compound: **IR** (Nujol, cm^{-1}) 2933, 2228, 1600, 1492, 1463, 1377, 1274, 1241, 1010, 917; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 2.66 (ddd, *J* = 14.7, 14.7, 2.7, 2H), 2.42 (ddd, *J* = 14.1, 3.6, 3.6 Hz, 2H), 2.04 (dtt, *J* = 13.5, 12.9, 3.0, 1H), 1.95-1.85 (m, 1H), 0.92 (t, *J* = 8.1 Hz, 9H), 0.68 (q, *J* = 7.2 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.5, 132.3, 130.6, 119.3, 109.3, 48.7, 25.6, 25.1, 8.0, 1.9; TLC (95:5 hexanes-EtOAc) R_f 0.28. **Anal.** Calcd for $C_{17}H_{25}NS_2Si$: C, 60.84; H, 7.51; N, 4.17. Found: C, 60.83; H, 7.56; N, 4.15.

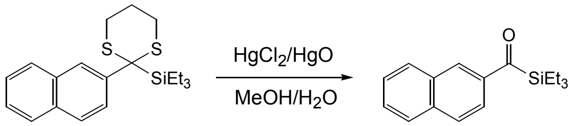


2-(4-Fluoro)phenyl-2-triethylsilyl-1,3-dithiane. The title compound was prepared according to General Procedure **A** using 1.32 g (6.1 mmol) of dithiane, 4.30 mL of *n*-BuLi (1.6 M in hexanes, 6.8 mmol), and 1.2 mL (6.8 mmol) of TESCl to yield 1.32 g (98%) of the silyl dithiane as a clear oil that was used without further purification. Analytical data for title compound: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94-7.85 (m, 2H), 7.10-7.00 (m, 2H), 2.74 (ddd, *J* = 14.1, 14.1, 2.7 Hz, 2H), 2.39 (ddd, *J* = 14.1, 3.9, 3.9 Hz, 2H), 2.03 (dtt, *J* = 13.2, 13.2, 3.3 Hz, 1H), 1.94-1.84 (m, 1H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.68 (q, *J* = 7.2 Hz, 6H); TLC (95:5 hexanes-EtOAc) R_f 0.61.

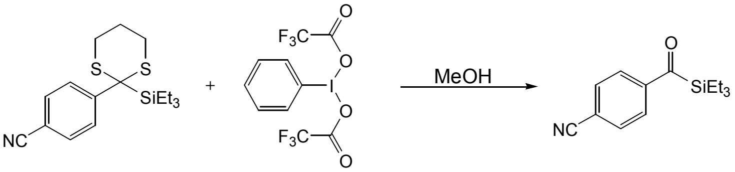
General procedure (B) for the preparation of acylsilanes (2).[6] A 250 mL round-bottom flask with a magnetic stir bar was charged with 5 mmol of silyldithiane, 10 mmol mercuric chloride, 10 mmol of mercuric oxide, and 30 mL of a methanol/water solution (9:1). The reaction mixture was heated to the indicated temperature for the given amount of time. After cooling to 25 °C, the solids were removed by filtration. The filtrate was extracted three times with pentane. The organic extracts were combined, dried ($MgSO_4$), and the solvent was evaporated to afford oily material that was purified by flash chromatography using the indicated eluent.



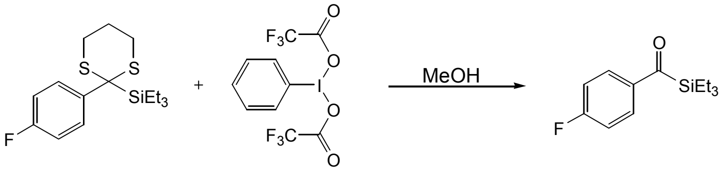
4-Methylbenzoyl triethylsilane. The title compound was prepared according to General Procedure **B**, using 14.7 g (45.3 mmol) of the silyl dithiane, 30.7 g (113.3 mmol) of mercuric chloride, and 24.5 g (113.3 mmol) of mercuric oxide and was stirred for 48 h at room temperature. The product was purified by flash chromatography with a linear gradient of 99:1 to 95:5 hexanes-EtOAc to afford 8.30 g (83%, 2 steps) of the product as a clear yellow oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 2955, 2876, 1593, 1459, 1415, 1218, 1171, 1077; **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 2.39 (s, 3H), 1.03-0.96 (m, 9H), 0.94-0.91 (m, 6H); **^{13}C NMR** (75 MHz, CDCl$_3$) δ 235.1, 143.5, 140.5, 129.5, 127.5, 21.8, 7.6, 4.0; TLC (95:5 hexanes:EtOAc) R_f 0.43. **Anal.** Calcd for $C_{14}H_{22}OSi$: C, 71.73; H, 9.46. Found: C, 71.99; H, 9.69.



2-Naphthoyl triethylsilane. The title compound was prepared according to General Procedure **B**, using 2.9 g (8.1 mmol) of the silyl dithiane, 5.5 g (20.3 mmol) of mercuric chloride, and 4.4 g (20.3 mmol) of mercuric oxide and was stirred for 12 h at 50 °C. The crude product was purified by flash chromatography with a linear gradient of 100% petroleum ether to 90:10 Et$_2$O-petroleum ether to afford 1.8 g (82 %, 2 steps) of the product as a clear yellow oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3058, 2956, 2910, 2875, 1713, 1593, 1350, 1271, 1018; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.31 (s, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.82-7.88 (m, 3H), 7.50-7.60 (m, 2H), 0.92-1.04 (m, 15H); **^{13}C NMR** (75 MHz, CDCl$_3$) δ 235.8, 140.2, 135.7, 133.0, 130.5, 129.8, 128.8, 128.5, 128.1, 126.9, 122.4, 7.7, 4.1; TLC (5:95 EtOAc-petroleum ether) R_f 0.50. **Anal.** Calcd for $C_{17}H_{22}OSi$: C: 75.50; H: 8.20. Found: C: 75.63; H: 8.29.

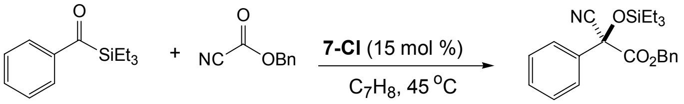


4-Cyanobenzoyl triethylsilane. To a 25-mL round bottom flask purged with Ar and equipped with a magnetic stir bar was added bis(trifluoroacetoxy)iodobenzene (5.23 g, 12.1 mmol, 2.0 equiv) and MeOH (5.3 mL). To the solution 2-(4-cyano)phenyl-2-triethylsilyl-1,3-dithiane (2.05 g, 6.07 mmol, 1.0 equiv) was added slowly with stirring The solution became warm and after 2.5 h the solvent was removed and the crude product was purified by flash chromatography (1:1 hexanes-methylene chloride) to yield 0.52 g (35%) of the product as a yellow solid. Analytical data for title compound: **IR** (thin film, cm^{-1}) 2957, 2876, 2231, 1618, 1598, 1464, 1401, 1291, 1202, 1168, 1015; **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.84 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 1.00-0.87 (m, 15H); **^{13}C NMR** (75 MHz, CDCl$_3$) δ 235.9, 144.6, 132.9, 127.4, 118.25, 115.9, 7.5, 3.6; TLC (95:5 hexanes-EtOAc) R$_f$ 0.38. **Anal.** Calcd for $C_{14}H_{19}NOSi$: C, 68.52; H, 7.80; N, 5.71. Found: C, 68.51; H, 7.89; N, 5.66.



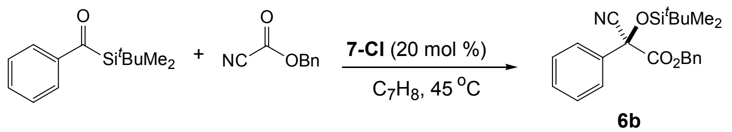
4-Fluorobenzoyl triethylsilane. To a 25-mL round bottom flask purged with Ar and equipped with a magnetic stir bar was added bis(trifluoroacetoxy)iodobenzene (4.12 g, 9.59 mmol, 2.0 equiv) and MeOH (4.0 mL). To the solution 2-(4-fluoro)phenyl-2-triethylsilyl-1,3-dithiane (1.58 g, 4.80 mmol, 1.0 equiv) was added slowly with stirring. The solution became warm and after 2.5 h the solvent was removed and the crude product was purified by gradient flash chromatography (99:1 to 97:3 hexanes-EtOAc) to yield 0.71 g (51%, 2 steps) of the product as a clear yellow oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 2957, 2877, 1615, 1584, 1501, 1225, 1204, 1010; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89-7.80 (m, 2H), 7.20-7.10 (m, 2H), 1.03-0.96 (m, 9H), 0.94-0.85 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 234.0, 167.3, 163.9, 139.3, 139.2, 130.0, 129.8, 116.1, 115.8, 7.6, 3.9; TLC (95:5 hexanes-EtOAc) R$_f$ 0.53. **Anal.** Calcd for $C_{13}H_{19}FOSi$: C, 65.50; H, 8.03. Found: C, 65.68; H, 8.03.

General procedure (C) for the enantioselective reaction of acylsilanes with cyanoformates in the presence of 7-Cl. A flame-dried Schlenk tube equipped with a magnetic stir bar was charged with aluminum complex **7-Cl** (19.4 mg, 0.033 mmol, 0.15 equiv) under Ar. Acylsilane (60 mg, 0.22 mmol, 1.0 equiv), cyanoformate (71.5 mg, 0.44 mmol, 2.0 equiv), and C_7H_8 (4.4 mL, 0.05 M) were all added to the Schlenk tube under Ar and the tube was sealed and heated to 45 °C. After 72 h, the flask was cooled to 25 °C, the solvent was removed *in vacuo* and the crude product was purified by flash chromatography using the indicated eluent.



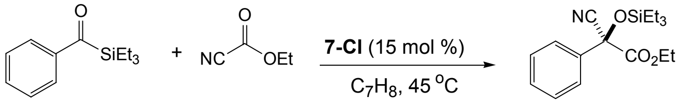
6a
83% yield, 79% ee

(*S*)-(+)-Benzyl 2–cyano–2–phenyl-2–triethylsiloxyacetate (6a). The title compound was prepared according to General Procedure **C** using 60 mg (0.27 mmol) of acylsilane, 87.8 mg (0.54 mmol) of benzyl cyanoformate, 23.8 mg (0.04 mmol) of **7-Cl**, and 5.4 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 petroleum ether-EtOAc to afford 85.3 mg (83%) of **6a** as a colorless oil in 79% ee as determined by chiral SFC analysis (Chiralpak OD, 0.3% MeOH, 0.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-major}}$ 37.0 min, $t_{\text{r-minor}}$ 41.5 min). Analytical data for title compound: $[\alpha]_D^{25}$ +4.2 (c = 1.97, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3067, 3035, 2958, 2878, 2245, 1766, 1588, 1451, 1241, 1152, 1003, 835; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2H), 7.38-7.35 (m, 3H), 7.29-7.26 (m, 3H), 7.19-7.17 (m, 2H), 5.17 (s, 2H), 0.93 (t, J = 7.6 Hz, 9H), 0.70 (q, J = 7.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 134.5, 129.9, 128.9, 128.8, 128.7, 128.2, 125.7, 118.3, 75.1, 68.9, 6.8, 5.4; TLC (95:5 hexanes/EtOAc) R$_f$ 0.35; **Anal.** Calcd for $C_{22}H_{27}NO_3Si$: C, 69.25; H, 7.13; N, 3.67. Found: C, 69.37; H, 7.28; N, 3.60.



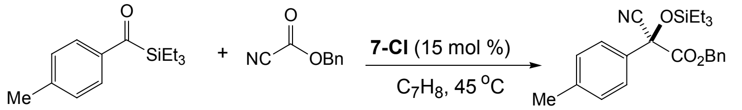
6b
81% yield, 64% ee

(*S*)-(+)-Benzyl 2–cyano-2–phenyl-2–*tert*-butyldimethylsiloxyacetate (6b). The title compound was prepared according to General Procedure **C** using 60 mg (0.27 mmol) of acylsilane, 87 mg (0.54 mmol) of benzyl cyanoformate, 31.7 mg (0.054 mmol) of **7-Cl**, and 5.4 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 petroleum ether-EtOAc to afford 82 mg (81%) of **6b** as a colorless oil in 64% ee as determined by chiral SFC analysis (Chiralpak OD, 0.3% MeOH, 0.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-major}}$ 27.6 min, $t_{\text{r-minor}}$ 29.9 min). Analytical data for title compound: $[\alpha]_D^{25}$ +2.8 (c = 1.52, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3067, 3036, 2957, 2930, 2858, 2241, 1767, 1588, 1472, 1258, 1148; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67-7.61 (m, 2H), 7.40-7.34 (m, 3H), 7.31-7.25 (m, 3H), 7.20-7.16 (m, 2H), 5.18 (s, 2H), 0.94 (s, 9H), 0.22 (s, 3H), 0.14(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 136.9, 134.6, 129.9, 129.0, 128.9, 128.8, 128.3, 125.8, 118.2, 75.8, 69.0, 25.8, 25.8, 18.6, -3.9, -4.2; TLC (95:5 hexanes/EtOAc) R_f 0.35. Attempts to obtain acceptable combustion analysis were not successful. See previous communication for a ^{1}H NMR spectrum.[3]



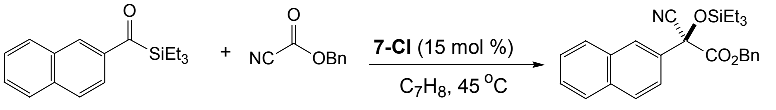
6c
93% yield, 77% ee

(*S*)-(-)-Ethyl 2–cyano-2–phenyl–2–triethylsiloxyacetate (6c). The title compound was prepared according to General Procedure **C** using 60 mg (0.27 mmol) of acylsilane, 53.5 mg (0.54 mmol) of ethyl cyanoformate, 23.8 mg (0.04 mmol) of **7-Cl**, and 10.8 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 petroleum ether-EtOAc to afford 80.2 mg (93%) of **6c** as a colorless oil in 77% ee as determined by chiral SFC analysis after reduction of the nitrile and coupling with (*S*)-mandelic acid. Analytical data for title compound: $[\alpha]_D^{25}$ -4.4 (c = 1.06, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3067, 2959, 2878, 2242, 1764, 1746, 1451, 1240, 1193, 1153, 1013, 734, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72-7.62 (m, 2H), 7.46-7.36 (m, 3H), 4.26-4.13 (ABX, J_{AB} = 10.8 Hz, J_{AX} = 6.8 Hz, 2H), 1.24 (t, J = 6.8 Hz, 3H), 0.99 (t, J = 7.6 Hz, 9H), 0.76 (q, J = 7.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 136.8, 129.6, 128.7, 125.4, 118.2, 74.8, 63.4, 13.8, 6.6, 5.2; TLC (20:1 hexanes/EtOAc) R_f 0.33; **Anal.** Calcd for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.89; N, 4.38. Found: C, 64.09; H, 7.98; N, 4.41.



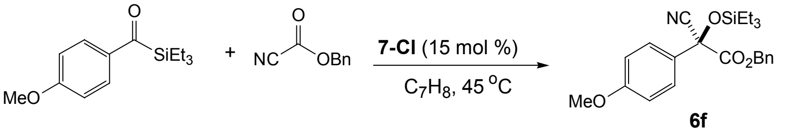
6d
86% yield, 80% ee

(*S*)-(+)-Benzyl 2–cyano–2–(4–methyl)phenyl-2–triethylsiloxyacetate (6d). The title compound was prepared according to General Procedure **C** using 60 mg (0.26 mmol) of acylsilane, 82.4 mg (0.51 mmol) of benzyl cyanoformate, 22.3 mg (0.04 mmol) of **7-Cl**, and 5.1 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 petroleum ether-EtOAc to afford 88.4 mg (86 %) of **6d** as a colorless oil in 80% ee as determined by chiral SFC analysis (Chiralpak OD, 0.3% MeOH, 0.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-major}}$ 42.2 min, $t_{\text{r-minor}}$ 48.0 min). Analytical data for title compound: $[\alpha]_D^{25}$ 0.76 (c = 2.29, CH_2Cl_2); **IR** (thin film, cm^{-1}) 2957, 2878, 2242, 1766, 1509, 1457, 1262, 1153, 1010; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 9 Hz, 2H), 7.32-7.29 (m, 3H), 7.24-7.15 (m, 4H), 5.18 (s, 1H), 5.17 (s, 1H), 2.36 (s, 3H), 0.94 (t, *J* = 8.1 Hz, 9H), 0.74-0.65 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2, 140.0, 134.6, 134.0, 129.6, 128.7, 128.2, 125.6, 118.4, 21.4, 6.8, 5.5; TLC (95:5 hexanes-EtOAc) R_f 0.33; **Anal.** Calcd for $C_{23}H_{29}NO_3Si$: C, 69.84; H, 7.39; N, 3.54. Found: C, 69.91; H, 7.43; N, 3.57.



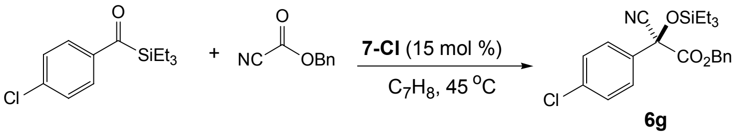
6e
91% yield, 62% ee

(*S*)-(-)-Benzyl 2–cyano–2–naphthyl-2–triethylsiloxyacetate (6e). The title compound was prepared according to General Procedure **C** using 60 mg (0.22 mmol) of acylsilane, 71.5 mg (0.44 mmol) of benzyl cyanoformate, 19.4 mg (0.033 mmol) of **7-Cl**, and 5.4 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 petroleum ether-EtOAc to afford 86.2 mg (91%) of **6e** as a colorless oil in 62% ee as determined by chiral SFC analysis (Chiralpak AD, 1.0% MeOH, 1.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-minor}}$ 37.8 min, $t_{\text{r-major}}$ 43.4 min). Analytical data for title compound: $[\alpha]_D^{25}$ –4.58 (c = 2.59, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3064, 3035, 2956, 2877, 2243, 1767, 1508, 1456, 1414, 1375, 1260, 1227, 1171, 1142; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10-8.13 (m, 1H), 7.79-7.86 (m, 3H), 7.63-7.68 (m, 1H), 7.48-7.53 (m, 2H), 7.13-7.23 (m, 5H), 5.16 (s, 1H), 5.15 (s, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.68-0.75 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.0 134.5, 134.0, 133.9, 132.9, 129.0, 128.8, 128.7, 128.6, 128.2, 127.9, 127.4, 126.9, 125.6, 122.7, 118.3, 75.4, 69.0, 6.8, 5.5; TLC (95:5 hexanes/EtOAc) R_f 0.41; **Anal.** Calcd for $C_{26}H_{29}NO_3Si$: C, 72.35; H, 6.77; N, 3.25. Found: C, 72.26; H, 6.85; N, 3.09.



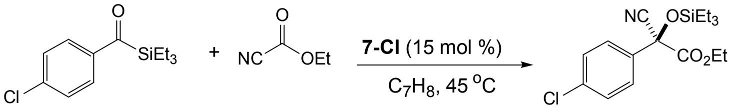
6f
84% yield, 82% ee

(*S*)-(-)-Benzyl 2–cyano–2–(4–methoxy)phenyl-2–triethylsiloxyacetate (6f). The title compound was prepared according to General Procedure **C** using 60 mg (0.24 mmol) of acylsilane, 77.2 mg (0.48 mmol) of benzyl cyanoformate, 21.2 mg (0.04 mmol) of **7-Cl**, and 2.4 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography (gradient from 97.5:2.5 petroleum ether-MeO^{t}Bu to 95:5 petroleum ether-MeO^{t}Bu) to afford 82.6 mg (84%) of **6f** as a colorless oil in 82% ee as determined by chiral SFC analysis (Chiralpak OD, 0.5% MeOH, 0.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-major}}$ 59.4 min, $t_{\text{r-minor}}$ 68.6 min). Analytical data for title compound: $[\alpha]_D^{25}$ –0.77 (c = 2.48, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3035, 2956, 2877, 2838, 2242, 1767, 1585, 1458, 1417, 1377, 1255; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.27-7.29 (m, 3H), 7.19-7.20 (m, 2H), 6.85 (dd, *J* = 6.8, 2.0 Hz, 2H), 5.16 (s, 2H), 3.79 (s, 3H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.70-0.64 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 160.8, 134.6, 128.8, 128.6, 128.4, 128.1, 118.4, 114.3, 74.9, 55.5, 6.8, 5.4; TLC (95:5 petroleum ether-MeO^{t}Bu) R_f 0.22; Attempts to obtain acceptable combustion analysis were not successful. See Appendix B for ^{1}H NMR spectrum.



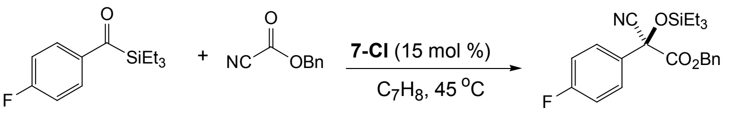
6g
91% yield, 64% ee

(*S*)-(+)-Benzyl 2–cyano–2–(4–chloro)phenyl-2–triethylsiloxyacetate (6g). The title compound was prepared according to General Procedure **C** using 60 mg (0.24 mmol) of acylsilane, 76.1 mg (0.47 mmol) of benzyl cyanoformate, 21.2 mg (0.036 mmol) of **7-Cl**, and 4.8 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 petroleum ether-EtOAc to afford 90.4 mg (91%) of **6g** as a colorless oil in 64% ee as determined by chiral SFC analysis after reduction of the nitrile and protecting as the *N*-BOC amide. Analytical data for title compound: $[\alpha]_D^{25}$ +2.8 (c = 1.04, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3035, 2958, 2877, 2242, 1767, 1593, 1489, 1456, 1402, 1377, 1240, 1191; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.57 (m, 2H), 7.36-7.31 (m, 5H), 7.23-7.21 (m, 2H), 5.19 (s, 2H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.75-0.69 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 136.1, 135.4, 134.3, 129.2, 129.0, 128.8, 128.4, 127.1, 117.9, 74.6, 69.2, 6.8, 5.4; TLC (95:5 petroleum ether-EtOAc) R_f 0.47; **Anal.** Calcd for $C_{22}H_{26}ClNO_3Si$: C, 63.52; H, 6.30; N, 3.37. Found: C, 63.65; H, 6.42; N, 3.50.



6h
88% yield, 61% ee

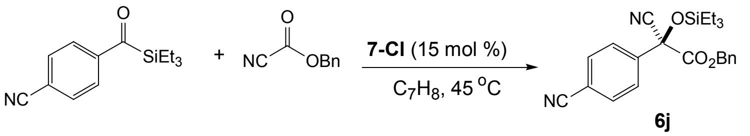
(*S*)-(-)-Ethyl 2–cyano–2–(4–chloro)phenyl-2–triethylsiloxyacetate (6h). The title compound was prepared according to General Procedure **C** using 60 mg (0.24 mmol) of acylsilane, 46.6 mg (0.47 mmol) of ethyl cyanoformate, 21.2 mg (0.036 mmol) of **7-Cl**, and 4.8 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 petroleum ether-EtOAc to afford 74.7 mg (88%) of **6h** as a colorless oil in 61% ee as determined by chiral SFC analysis after reduction of the nitrile and coupling to (*S*)-mandelic acid. Analytical data for title compound: $[\alpha]_D^{25}$ –3.9 (c = 3.63, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3153, 3125, 2959, 2879, 2244, 1771, 1751, 1463, 1232, 1158, 1141, 1018, 747; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.7 Hz, 2.1 Hz, 2H), 7.39 (dd, *J* = 8.7 Hz, 2.1 Hz, 2H), 4.23 (ABX, J_{AB} = 10.8 Hz, J_{AX} = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 8.1 Hz, 9H), 0.77 (q, *J* = 8.1 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 135.8, 135.4, 128.9, 126.9, 117.9, 74.3, 63.6, 13.8, 6.6, 5.2; TLC (30:1 hexanes-EtOAc) R_f 0.2; **Anal.** Calcd for $C_{17}H_{24}ClNO_3Si$: C, 57.69; H, 6.84; N, 3.96. Found: C, 57.93; H, 6.95; N, 4.01.



6i

85% yield, 78% ee

(*S*)-(+)-Benzyl 2–cyano–2–(4–fluoro)phenyl-2–triethylsiloxyacetate (6i). The title compound was prepared according to General Procedure **C** using 60 mg (0.25 mmol) of acylsilane, 81.5 mg (0.5 mmol) of benzyl cyanoformate, 22.3 mg (0.038 mmol) of **7-Cl**, and 5.1 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 hexanes-EtOAc to afford 85.3 mg (85%) of **6i** as a colorless oil in 78% ee as determined by chiral SFC analysis after reduction of the nitrile and protecting as the *N*-BOC amide. Analytical data for title compound: $[\alpha]_D^{25}$ +4.98 (c = 4.3, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3069, 3036, 2959, 2879, 2243, 1766, 1605, 1507, 1457, 1412, 1377, 1230, 1190, 1156; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65-7.58 (m, 2H), 7.33-7.30 (m, 3H), 7.23-7.19 (m, 2H), 7.08-7.02 (m, 2H), 5.19 (s, 2H), 1.00-0.92 (m, 9H), 0.76-0.68 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.9, 165.3, 162.0, 134.4, 132.7, 132.6, 128.9, 128.8, 128.4, 127.8, 127.7, 118.1, 116.1, 115.8, 74.6, 69.1, 6.8, 5.4; TLC (95:5 Hexanes-EtOAc) R$_f$ 0.36; **Anal.** Calcd for $C_{22}H_{26}FNO_3Si$: C, 66.14; H, 6.56; N, 3.51. Found: C, 66.43; H, 6.70; N, 3.62.

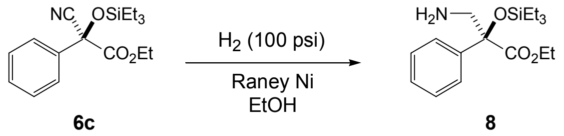


6j

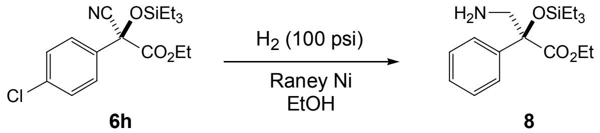
70% yield, 64% ee

(*S*)-(+)-Benzyl 2–cyano–2–(4–cyano)phenyl-2–triethylsiloxyacetate (6j). The title compound was prepared according to General Procedure **C** using 60 mg (0.25 mmol) of acylsilane, 78.9 mg (0.5 mmol) of benzyl cyanoformate, 21.6 mg (0.037 mmol) of **7-Cl**, and 4.9 mL of C_7H_8. After 72 h at 45 °C, the crude product was purified by flash chromatography with 95:5 hexanes-EtOAc to afford 69.7 mg (70%) of **6j** as a colorless oil in 64% ee as determined by chiral SFC analysis (Chiralpak OD, 0.40 % MeOH, 2.00 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-major}}$ 39.8 min, $t_{\text{r-minor}}$ 32.8 min). Analytical data for title compound: $[\alpha]_D^{25}$ +6.40 (c = 3.2, CH_2Cl_2); **IR** (thin film, cm^{-1}) 2961, 2878, 2232, 1767, 1457, 1241, 1156, 1018, 854; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 7.68-7.65 (m, 2H), 7.34-7.30 (m, 3H), 7.23-7.18 (m, 2H), 5.20 (s, 1H), 5.19 (s, 1H), 0.99-0.90 (m, 9H), 0.80-0.072 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.2, 141.6, 134.0, 132.7, 129.2, 128.9, 126.5, 118.2, 117.5, 115.0, 77.5, 69.6, 6.8, 5.4; TLC (95:5 hexanes-EtOAc) R$_f$ 0.17; **Anal.** Calcd for $C_{23}H_{26}N_2O_3Si$: C, 67.95; H, 6.45; N, 6.89. Found: C, 67.97; H, 6.50; N, 6.98.

General procedure (D) for the reduction of nitriles (6) to amines via H_2/Raney Ni. Nitrile **6** (0.19 mmol) was added to a 20-mL vial equipped with a magnetic stir bar. Raney Ni (0.4 mL of a 50% dispersion in H_2O) was added followed by 95 % EtOH (4 mL). The vial was placed in a hydrogenation apparatus, purged with H_2 three times and charged to the indicated pressure. After the given amount of time the vessel was vented and the reaction was filtered through a bed a celite, and rinsed with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography using the indicated solvent system to afford the pure amine.

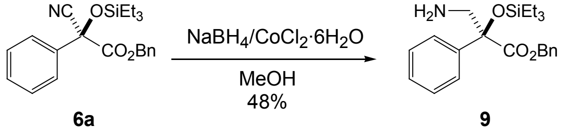


(*S*)-(+)-3-Amino-2-phenyl-2-triethylsilyloxypropionic acid ethyl ester (8). The title compound was prepared according to General Procedure **D** using 62 mg (0.19 mmol) of **6c**, 0.4 mL of Raney Ni dispersion, and 100 psi of H_2. Workup following General Procedure **D** afforded the crude product which was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 45.2 mg (72%) of **8** as a colorless oil. Analytical data for title compound: $[\alpha]_D^{25}$ +26.4 (c = 1.75, CH_2Cl_2, 77% ee); **IR** (thin film, cm^{-1}) 3394, 3059, 2960, 2875, 1720, 1601, 1448, 1367, 1265, 1016; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H), 7.44-7.23 (m, 3H), 4.25 (ABX, J_{AB} = 10.8 Hz, J_{AX} = 7.2 Hz, 1H), 4.17 (ABX, J_{AB} = 10.8 Hz, J_{AX} = 7.2 Hz, 1H), 3.15-3.08 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.8 Hz, 9H), 0.67-0.48 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.3, 141.1, 128.6, 128.5, 128.4, 127.9, 126.0, 125.9, 125.8, 77.4, 61.7, 52.7, 14.3, 7.5, 6.7; TLC (5:20:80 Et_3N-EtOAc-petroleum ether) R_f 0.40; **Anal.** Calcd for $C_{17}H_{29}NO_3Si$: C, 63.02; H, 9.04; N, 4.33. Found: C, 62.83; H, 8.94; N, 4.34.

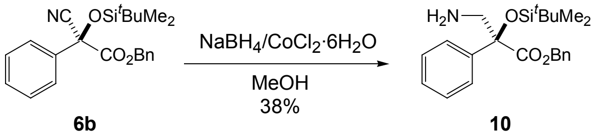


(*S*)-(+)-3-Amino-2-phenyl-2-triethylsilyloxypropionic acid ethyl ester (8). The title compound was prepared according to General Procedure **D** using 96.5 mg (0.27 mmol) of nitrile **6h**, 0.4 mL of Raney Ni dispersion, and 100 psi of H_2. Work up following General Procedure **D** afforded the crude product which was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 45.2 mg (72%) of **8** (the C-Cl bond was unexpectedly hydrogenated) as a colorless oil. Analytical data for title compound matched the data reported above for **8**: $[\alpha]_D^{25}$ +20.5 (c = 1.3, CH_2Cl_2, 61% ee).

General procedure (E) for the reduction of nitriles (6) to amines with $CoCl_2$/$NaBH_4$.[7] A 20-mL round bottom flask equipped with a stir bar was charged with $CoCl_2 \bullet 6H_2O$ (0.76 mmol), the nitrile (0.19 mmol) dissolved in MeOH (1 mL), and an additional 2 mL of MeOH. This solution was chilled to 0 °C and $NaBH_4$ (6.63 mmol) was carefully added in portions (evolution of H_2!) to give a black suspension. Once H_2 evolution had ceased, the reaction was warmed to 25 °C and stirred for an additional 30 min. The indicated aqueous workup was applied (x μL H_2O followed by addition of x μL of a 15% (w/w) NaOH solution, followed by an additional 3x μL H_2O, where x = total amount of $NaBH_4$ added in mg), the resultant mixture was filtered through a cotton plug, and the filtrate was dried ($MgSO_4$). Concentration *in vacuo* gave the crude product which was purified by flash chromatography.

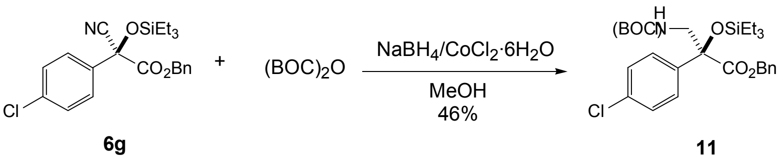


(*S*)-(+)-3-Amino-2-phenyl-2-triethylsilyloxypropionic acid benzyl ester (9). The title compound was prepared according to General Procedure **E** using 80.7 mg (0.21 mmol) of the nitrile, 201 mg of $CoCl_2•6H_2O$ (0.85 mmol), 280 mg (7.35 mmol) $NaBH_4$, and 4 mL of MeOH. Workup following General Procedure **E** (280 μL H_2O followed by addition of 280 μL of a 15% (w/w) NaOH solution, followed by an additional 840 μL H_2O) afforded the crude product which was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 38.9 mg (48%) of **9** as a colorless oil. Analytical data for title compound: $[\alpha]_D^{25}$ +26.4 (c = 1.75, CH_2Cl_2, 79% ee); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 2H), 7.35-7.23 (m, 8H), 5.25 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 3.20-3.12 (m, 2H), 0.89 (t, *J* = 7.6 Hz, 9H), 0.64-0.49 (m, 6H); TLC (5:20:80 Et_3N-EtOAc-petroleum ether) R_f 0.27.



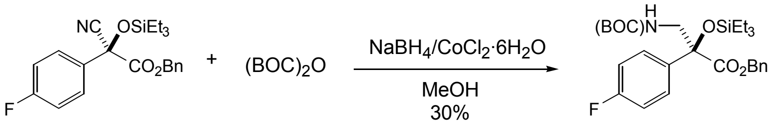
(*S*)-(+)-3-Amino-2-phenyl-2-*tert*-butyldimethylsilyloxypropionic acid benzyl ester (10). The title compound was prepared according to General Procedure **E** using 71.0 mg (0.19 mmol) of nitrile **6b**, 181 mg of $CoCl_2•6H_2O$ (0.76 mmol), 250 mg (6.63 mmol) $NaBH_4$, and 4 mL of MeOH. Workup following General Procedure **E** (250 μL H_2O followed by addition of 250 μL of a 15% (w/w) NaOH solution, followed by an additional 750 μL H_2O) afforded the crude product which was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 27.7 mg (38%) of amine **10** as a colorless oil. Analytical data for title compound: $[\alpha]_D^{25}$ +21.4 (c = 1.32, CH_2Cl_2, 64% ee); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.33 (m, 2H), 7.31-7.20 (m, 8H), 5.23 (d, *J* = 12.0 Hz, 1H), 5.06 (d, *J* = 12.0 Hz, 1H), 3.25 (br s, 2H), 1.41 (br s, 2H), 0.92 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.9, 140.7, 135.4, 128.7, 128.6, 128.5, 128.2, 128.1, 126.0, 77.4, 67.3, 51.6, 26.3, 19.1, -2.7, -3.1; TLC (5:20:80 Et_3N-EtOAc-petroleum ether) R_f 0.27.

General procedure (F) for the reduction of nitriles (6) to *N*-BOC protected amines with $(BOC)_2O/CoCl_2/NaBH_4$. A 20-mL round bottom flask equipped with a stir bar was charged with $CoCl_2•6H_2O$ (0.76 mmol), the nitrile (0.19 mmol) dissolved in MeOH (1 mL), *tert*-butoxycarbonyl anhydride ($(BOC)_2O$, 0.38 mmol), and an additional 2 mL of MeOH. This solution was chilled to 0 °C and $NaBH_4$ (6.63 mmol) was carefully added in portions (evolution of H_2!) to give a black suspension. Once H_2 evolution had ceased, the reaction was warmed to 25 °C and stirred for an additional 30 min. The indicated aqueous workup was applied (x μL H_2O followed by addition of x μL of a 15% (w/w) NaOH solution, followed by an additional 3x μL H_2O, where x = total amount of $NaBH_4$ added in mg). The resultant mixture was filtered through a cotton plug and the filtrate was dried ($MgSO_4$). Concentration *in vacuo* gave the crude product which was purified by flash chromatography.



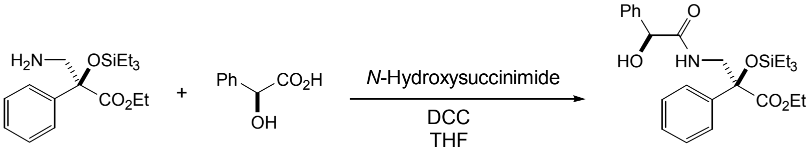
(*S*)-(+)-3-*tert*-Butoxycarbonylamino-2-(4-chlorophenyl)-2-triethylsilyloxypropionic acid benzyl ester (11). The title compound was prepared according to General Procedure **F** using 58.6 mg (0.14 mmol) of nitrile **6g**, 133 mg of $CoCl_2•6H_2O$ (0.56 mmol), 186 mg (4.9 mmol)

$NaBH_4$, and 4 mL of MeOH. Workup following General Procedure **F** (185 μL H_2O followed by addition of 185 μL of a 15% (w/w) NaOH solution, followed by an additional 555 μL H_2O) afforded the crude product which was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 33.4 mg (46%) of **11** as a colorless oil in 64% ee as determined by chiral SFC analysis (Whelk-O 1, 1.0 % MeOH, 1.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-major}}$ 26.8 min, $t_{\text{r-minor}}$ 29.1 min). Analytical data for title compound: $[\alpha]_D^{25}$ +17.0 (c = 1.98, CH_2Cl_2, 64% ee); **IR** (thin film, cm^{-1}) 3456, 2956, 2875, 1747, 1726, 1595, 1495, 1456, 1392, 1367, 1232, 1163 **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 9H), 5.24-5.12 (m, 2H), 4.69-4.61 (m, 1H), 3.79-3.63 (m, 2H), 1.34 (s, 9H), 0.92 (t, *J* = 8.1 Hz, 9H), 0.67-0.51 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2, 155.8, 138.7, 134.2, 128.8, 128.7, 128.5, 128.4, 127.5, 81.1, 79.5, 67.8, 49.4, 28.5, 7.3, 6.5; TLC (5:95 EtOAc-petroleum ether) R_f 0.27.



6i

(*S*)-3-*tert*-Butoxycarbonylamino-2-(4-fluorophenyl)-2-triethylsilyloxypropionic acid benzyl ester. The title compound was prepared according to General Procedure **F** using 41.7 mg (0.11 mmol) of nitrile **6i**, 100 mg of $CoCl_2$•$6H_2O$ (0.42 mmol), 139 mg (3.7 mmol) $NaBH_4$, and 4 mL of MeOH. Workup following General Procedure **F** (185 μL H_2O followed by addition of 185 μL of a 15% (w/w) NaOH solution, followed by an additional 555 μL H_2O) afforded the crude product which was purified by flash chromatography (95:5 Hexanes-EtOAc) to yield 28.2 mg (30%) of the title compound as a colorless oil in 78% ee as determined by chiral SFC analysis (Whelk-O 1, 1.0 % MeOH, 1.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-major}}$ 19.7 min, $t_{\text{r-minor}}$ 21.6 min). Analytical data: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.26 (m, 7H), 6.97 (t, *J* = 8.7 Hz, 2H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 4.71-4.62 (m, 1H), 3.80 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.67 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.33 (s, 9H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.69-0.50 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4, 164.3, 161.0, 155.8, 135.9, 135.0, 128.8, 128.7, 127.9, 127.8, 115.4, 115.1, 81.1, 79.5, 67.8, 49.5, 28.6, 7.3, 6.5; TLC (95:5 Hexanes-EtOAc) R_f 0.17.

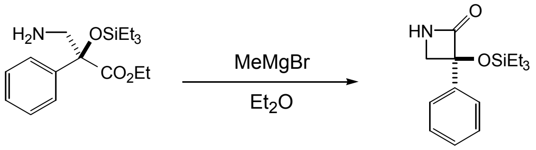


8

(*2S*)-Phenyl-3-((*2S*)-hydroxy-2-phenyl acetylamino)-2-triethylsilyloxypropionic acid ethyl ester. To a 25-mL round bottom flask equipped with a magnetic stir bar was added (*S*)-mandelic acid (5.2 mg, 0.034 mmol, 1.1 equiv), *N*-hydroxysuccinimide (3.9 mg, 0.034, 1.1 equiv), and dicyclohexylcarbodiimide (7.0 mg, 0.034 mmol, 1.1 equiv). The flask was fitted with a septum, purged with Ar, and THF (1 mL) was added with stirring. After 30 min, a white precipitate formed, after which amine **8** (10 mg, 0.031 mmol, 1.0 equiv), dissolved in THF (2 mL) was added via cannula. After 1 h, the solvent was removed by rotary evaporator and the crude product was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 12.6 mg (89%) of the pure product as a white solid in 77% de as determined by chiral SFC analysis (Chiralpak OD, 5.0 % MeOH, 1.5 mL/min, 150 psi, 40 °C, 240 nm, $t_{\text{r-major}}$ 23.7 min,

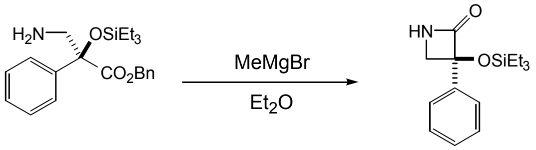
$t_{\text{r-minor}}$ 26.6 min). Analytical data for title compound (1:1 mixture of diastereomers derived from the racemate): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.17 (m, 16H), 7.10-7.02 (m, 2H), 6.50-6.39 (m, 2H), 4.83 (d, *J* = 3.0 Hz, 1H), 4.80 (d, *J* = 3.0 Hz, 1H), 4.24-3.98 (m, 4H), 3.94-3.66 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 0.98-0.84 (m, 18H), 0.68-0.49 (m, 12H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.3, 172.2, 172.0, 172.0, 139.8, 139.8, 139.4, 139.3, 128.9, 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 127.0, 126.9, 125.8, 125.7, 81.3, 81.0, 74.2, 74.1, 62.1, 62.0, 48.5, 48.2, 14.1, 14.0, 7.3, 7.3, 6.5, 6.4; TLC (5:20:80 Et_3N-EtOAc-petroleum ether) R_f 0.19.

General procedure (G) for the cyclization of primary amines to β-lactams. To a solution of the amine (0.061 mmol) in Et_2O (2 mL) under Ar was added MeMgBr (0.18 mmol) at 0 °C with stirring. After 15 min, the solution was warmed to 23 °C and stirring was maintained for 12 h, after which it was quenched by the addition of saturated NH_4Cl (aq) solution. The layers were separated and the water layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude β-lactam which was purified by flash chromatography using the indicated eluent.



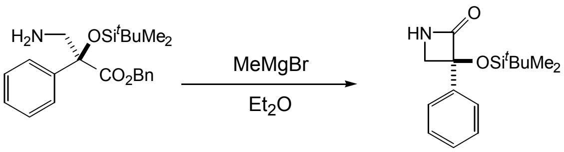
8

(*S*)-(-)-3-Phenyl-3-triethylsilyloxyazetidin-2-one. The title compound was prepared according to General Procedure **G** using 45 mg (0.14 mmol) of amine **8**, 92 µL of MeMgBr (3.0 M in Et_2O, 0.28 mmol), and 1.4 mL Et_2O. Workup following General Procedure **G** afforded the crude product which was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 19.2 mg (50%) of the title compound as a colorless oil. Analytical data: $[\alpha]_D^{25}$ -11.3 (c = 0.96, CH_2Cl_2, 63% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.38-7.24 (m, 3H), 6.02 (br s, 1H), 3.57 (d, *J* = 5.4 Hz, 1H), 3.52 (d, *J* = 5.4 Hz, 1H), 0.88 (t, *J* = 7.8 Hz, 9H), 0.70-0.50 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.1, 139.9, 128.7, 128.4, 125.8, 89.2, 55.2, 6.9, 5.8; TLC (5:20:80 Et_3N-EtOAc-petroleum ether) R_f 0.31.



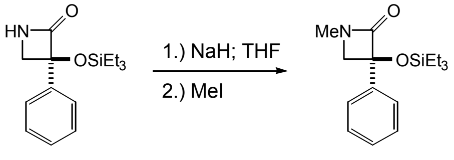
9

(*S*)-(-)-3-Phenyl-3-triethylsilyloxyazetidin-2-one. The title compound was prepared according to General Procedure **G** using 23.7 mg (0.061 mmol) of amine **9**, 61 µL of MeMgBr (3.0 M in Et_2O, 0.18 mmol), and 2 mL Et_2O. Workup following General Procedure **G** afforded the crude product which was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 11.3 mg (67%) of the title compound as a colorless oil. Analytical data matched that for the previous compound: $[\alpha]_D^{25}$ –20.0 (c = 0.46, CH_2Cl_2, 78% ee).



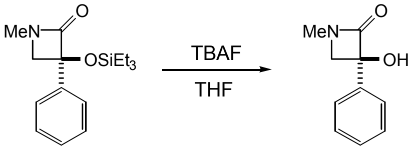
10

(*S*)-(-)-3-(tert-Butyldimethylsilyloxy)-3-phenylazetidin-2-one. The title compound was prepared according to General Procedure **G** using 18.1 mg (0.047 mmol) of amine **10**, 47 μL of MeMgBr (3.0 M in Et_2O, 0.14 mmol), and 2 mL Et_2O. Workup following General Procedure **G** afforded the crude product which was purified by flash chromatography (5:20:80 Et_3N-EtOAc-petroleum ether) to yield 7.3 mg (56%) of the title compound as a colorless oil. Analytical data: $[\alpha]_D^{25}$ –10.6 (c = 0.37, CH_2Cl_2, 64% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51-7.46 (m, 2H), 7.39-7.27 (m, 3H), 5.97 (br s, 1H), 3.56 (d, *J* = 5.4 Hz, 1H), 3.52 (d, *J* = 5.4 Hz), 0.90 (s, 9H), 0.10 (s, 3H), -0.01 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.0 139.8, 128.7, 128.4, 125.9, 89.3, 55.2, 25.9, 18.4, -3.4, -3.5; TLC (5:20:80 Et_3N-EtOAc-petroleum ether) R_f 0.31.



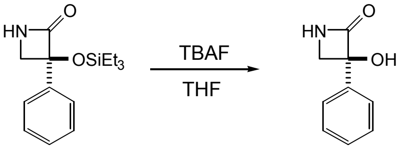
14

(*S*)-1-Methyl-3-phenyl-3-triethylsilyloxyazetidin-2-one. To a suspension of NaH (50% dispersion in mineral oil, 5.0 mg, 0.10 mmol; previously washed under Ar with hexane) in THF (1 mL) was added β-lactam **14** (19.2 mg, 0.069 mmol) in THF (1.5 mL) via cannula at 0 °C. After stirring for 30 min, the reaction was cooled to -78 °C and 6 μL of MeI (14.2 mg, 0.10 mmol) was added by syringe. TLC indicated that the reaction was complete after 3 h. The reaction was discontinued by addition of a saturated NH_4Cl (aq) solution. The organic and aqueous layers were separated, the aqueous layer was extracted with Et_2O (3 x 5 mL), the organic layers were combined and dried ($MgSO_4$). Concentration of the organic layer *in vacuo* gave 20.1 mg (100%) of the product as a colorless oil which was used without further purification. Analytical data for the title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49-7.42 (m, 2H), 7.35-7.23 (m, 3H), 3.49 (d, *J* = 5.2 Hz, 1H), 3.46 (d, *J* = 5.2 Hz, 1H), 2.91 (s, 3H), 0.86 (t, *J* = 8.0 Hz, 9H), 0.68-0.51 (m, 6H); TLC (5:20:80 Et_3N-EtOAc-petroleum ether) R_f 0.46.

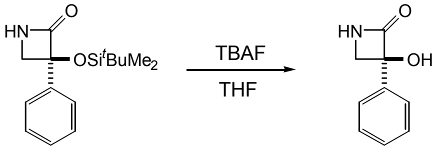


(*S*)-(-)-1-Methyl-3-phenyl-3-hydroxyazetidin-2-one. To a solution of (*S*)-1-Methyl-3-phenyl-3-triethylsilyloxyazetidin-2-one (20.1 mg, 0.069) in THF (2 mL) was added 69 μL of tetrabutylammonium fluoride (1.0 M in THF, 0.069 mmol) at 0 °C. After stirring for 30 min, the solvent was removed and the crude product was purified by flash chromatography (100% Et_2O) to give 8.5 mg (70% for 2 steps) of the free alcohol which matched the analytical data previously reported in the literature.[8] **Literature**: $[\alpha]_D^{25}$ –99.7 (c = 0.34, $CHCl_3$, 99% ee) **This work**: $[\alpha]_D^{25}$ –54.2 (c = 0.18, $CHCl_3$, 63% ee); therefore, the absolute configuration is **(*S*)**. Analytical data for title compound: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49-7.41 (m, 2H), 7.36-7.25

(m, 3H), 5.17 (br s, 1H), 3.58 (d, *J* = 5.4 Hz, 1H), 3.48 (d, *J* = 5.4 Hz, 1H), 2.87 (s, 3H); ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 170.3, 138.6, 128.6, 128.4, 125.5, 86.2, 59.3, 28.5; TLC (Et$_2$O) R$_f$ 0.23.

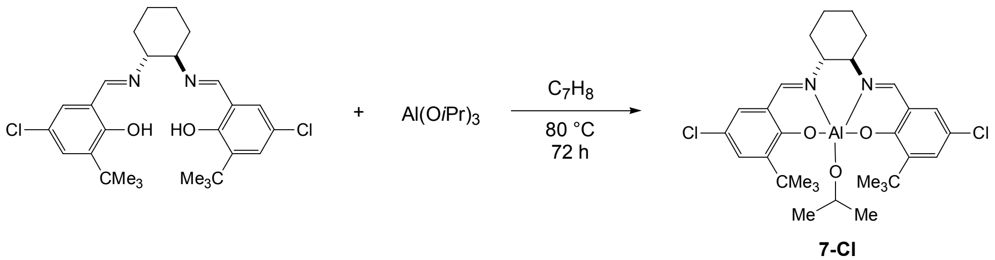


(*S*)-(-)-3-Phenyl-3-hydroxyazetidin-2-one. To a solution of (*S*)-(-)-3-Phenyl-3-triethylsilyloxyazetidin-2-one (11.3 mg, 0.041) in THF (2 mL) was added 45 μL of tetrabutylammonium fluoride (1.0 M in THF, 0.045 mmol) at 0 °C. After stirring for 30 min, the solvent was removed and the crude product was purified by flash chromatography (100% Et$_2$O) to give 5.0 mg (75%) of the title compound. Analytical data: $[\alpha]_D^{25}$ –57.4 (c = 0.25, CHCl$_3$, 80% ee); ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.51-7.42 (m, 2H), 7.40-7.28 (m, 3H), 6.26 (br s, 1H), 3.90 (br s, 1H), 3.64 (d, *J* = 5.6 Hz, 1H), 3.54 (d, *J* = 5.6 Hz, 1H); ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 170.9, 138.4, 129.0, 128.9, 125.6, 87.6, 53.9; TLC (Et$_2$O) R$_f$ 0.21.



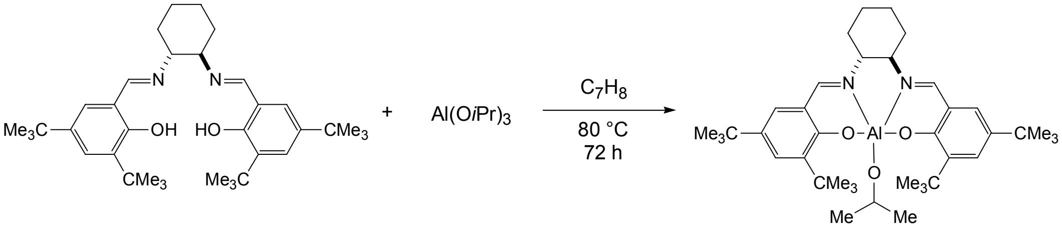
(*S*)-(-)-3-Phenyl-3-hydroxyazetidin-2-one. To a solution of (*S*)-(-)-3-(tert-butyldimethylsilyloxy)-3-phenylazetidin-2-one (7.3 mg, 0.026) in THF (1 mL) was added 29 μL of tetrabutylammonium fluoride (1.0 M in THF, 0.029 mmol) at 0 °C. After stirring for 3 h, the solvent was removed and the crude product was purified by flash chromatography (100% Et$_2$O) to give 3.8 mg (90%) of the free alcohol which matched the data for the previous compound. $[\alpha]_D^{25}$ –33.4 (c = 0.19, CHCl$_3$, 64% ee).

General procedure (H) for the preparation of catalysts 7-X.[9] To a flamed-dried Schlenk tube equipped with a magnetic stir bar was added, in a dry box, the salen ligand (1.49 mmol, 1.0 equiv), Al(O*i*Pr)$_3$ (1.49 mmol, 1.0 equiv), and the indicated amount of C$_7$H$_8$. The tube was sealed and heated to 80 °C and was maintained at that temperature with stirring for 72 h. After 72 h, the green solution was transferred back to a glove box and the toluene was removed under reduced pressure. The residual solid was washed with pentane three times and the solid was again dried under reduced pressure to give the pure **7-X**.



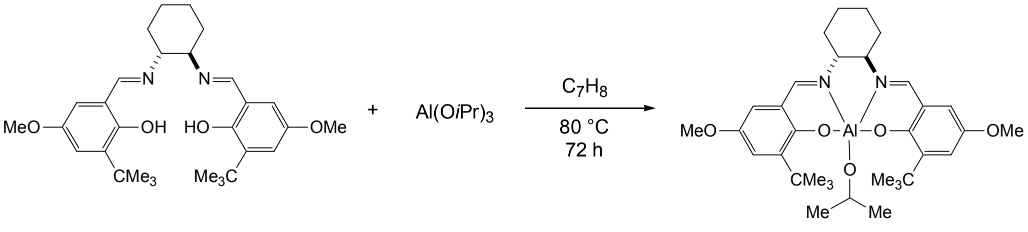
7-Cl

(*R*,*R*)-7-Cl. The catalyst was prepared according to General Procedure **H** using 900 mg (1.79 mmol) of salen ligand, 365 mg (1.79 mmol) of Al(O*i*Pr)$_3$, and 6 mL of toluene to give 910 mg (87%) of **7-Cl** as a yellow powder. Analytical data for title compound: ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 8.27 (s, 1H), 8.05 (s, 1H), 7.33 (d, *J* = 2.8 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.08 (d, *J* = 2.8 Hz, 1H), 3.90-3.87 (m, 1H), 3.62 (sept, *J* = 6.0 Hz, 1H), 3.12-3.11 (m, 1H), 2.56-2.52 (m, 1H), 2.37-2.34 (m, 1H), 2.08-2.05 (m, 2H), 1.50 (s, 18H), 1.47 (s, 18H), 1.45-1.40 (m, 4H), 0.83 (d, *J* = 6.0 Hz), 0.79 (d, *J* = 6.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.8, 164.8, 163.2, 161.4, 144.1, 143.9, 130.6, 130.5, 130.2, 130.1, 120.9, 120.5, 120.1, 119.9, 63.2, 62.9, 62.7, 35.9, 35.8, 29.9, 29.8, 29.7, 29.6, 27.6, 27.5, 27.4, 27.3. A ^{1}H NMR spectrum of **7-Cl** is attached in Appendix B.



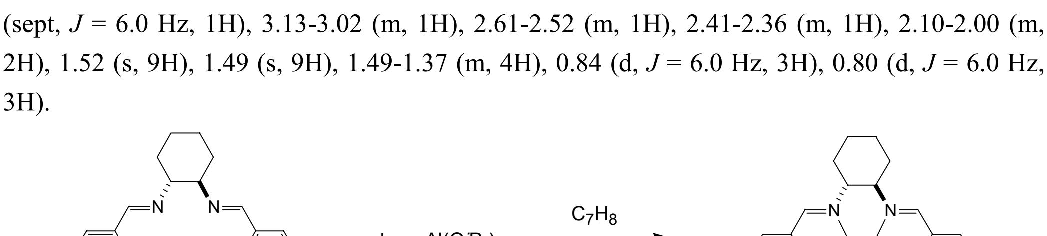
7-CMe$_3$

(*R*,*R*)-7-CMe$_3$. The catalyst was prepared according to General Procedure **H** using 750 mg (1.44 mmol) of salen ligand, 295 mg (1.44 mmol) of Al(O*i*Pr)$_3$, and 5 mL of toluene to give 864 mg (95%) of **7-CMe$_3$** that match the previously reported spectroscopic data.[9] Analytical data for title compound: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.15 (s, 1H), 7.49 (d, *J* = 2.7 Hz, 1H), 7.47 (d, *J* = 2.7 Hz, 1H), 7.05 (d, *J* = 2.7 Hz, 1H), 6.98 (d, *J* = 2.7 Hz, 1H), 3.97-3.87 (m, 1H), 3.71 (sept, *J* = 5.7 Hz, 1H), 3.10-3.00 (m, 1H), 2.65-2.57 (m, 1H), 2.46-2.39 (m, 1H), 2.11-2.02 (m, 2H), 1.55 (s, 9H), 1.52 (s, 9H), 1.52-1.47 (m, 4H), 1.30 (s, 9H), 1.29 (s, 9H), 0.89 (d, *J* = 5.7 Hz, 3H), 0.85 (d, *J* = 5.7 Hz, 3H).



7-OMe

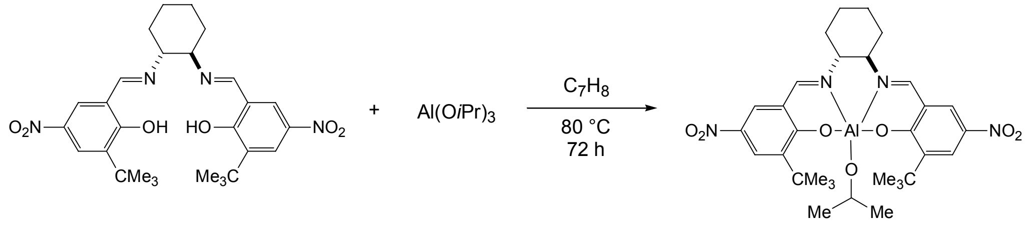
(*R*,*R*)-7-OMe. The catalyst was prepared according to General Procedure **H** using 700 mg (1.42 mmol) of salen ligand, 289 mg (1.42 mmol) of Al(O*i*Pr)$_3$, and 5 mL of toluene to give 764 mg (93%) of **7-OMe** as a yellow powder. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.09 (s, 1H), 7.11 (d, *J* = 3.3 Hz, 1H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.53 (d, *J* = 3.0 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 3.94-3.83 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.68 (sept, *J* = 6.0 Hz, 1H), 3.13-3.02 (m, 1H), 2.61-2.52 (m, 1H), 2.41-2.36 (m, 1H), 2.10-2.00 (m, 2H), 1.52 (s, 9H), 1.49 (s, 9H), 1.49-1.37 (m, 4H), 0.84 (d, *J* = 6.0 Hz, 3H), 0.80 (d, *J* = 6.0 Hz, 3H).



7-NMe$_2$

(*R*,*R*)-7-NMe$_2$. The catalyst was prepared according to General Procedure **H** using 65 mg (0.125 mmol) of salen ligand, 25.5 mg (0.125 mmol) of Al(O*i*Pr)$_3$, and 1 mL of toluene to give

51.7 mg (68%) of **7-NMe$_2$** as an orange powder. Analytical data for title compound: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.31 (s, 1H), 8.09 (s, 1H), 7.17 (d, *J* = 3.2 Hz, 1H), 7.13 (d, *J* = 3.2 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 6.43 (d, *J* = 3.2 Hz, 1H), 3.92-3.83 (m, 1H), 3.66 (sept, *J* = 6.0 Hz, 1H), 3.10-3.01 (m, 1H), 2.79 (s, 6H), 2.77 (s, 6H), 2.58-2.52 (m, 1H), 2.39-2.33 (m, 1H), 2.08-2.00 (m, 2H), 1.54 (s, 9H), 1.50 (s, 9H), 1.50-1.35 (m, 4H), 0.83 (d, *J* = 6.0 Hz, 3H), 0.81 (d, *J* = 6.0 Hz, 3H).

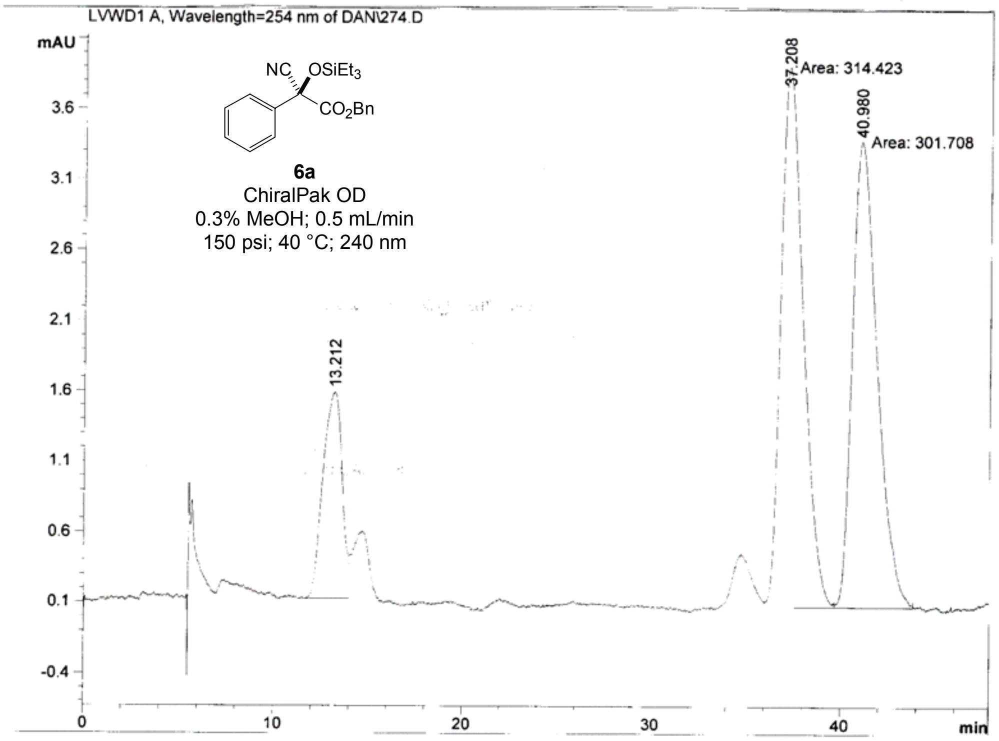


7-NO$_2$

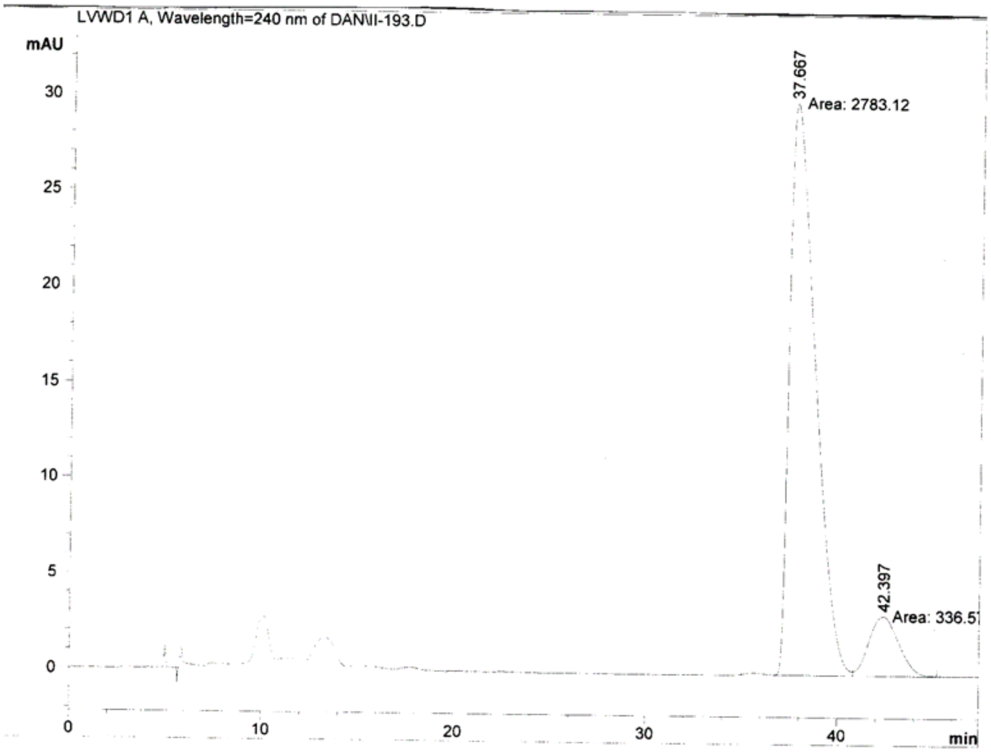
(*R*,*R*)-7-NO$_2$. The catalyst was prepared according to General Procedure **H** using 300 mg (0.57 mmol) of salen ligand, 117 mg (0.57 mmol) of Al(O*i*Pr)$_3$, and 3 mL of toluene to give 295 mg (85%) of **7-NO$_2$** as a yellow powder. Analytical data for title compound: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.47 (s, 1H), 8.33 (d, *J* = 2.8 Hz, 1H), 8.31 (d, *J* = 2.8 Hz, 1H), 8.25 (s, 1H), 8.20 (d, *J* = 2.8 Hz, 1H), 8.19 (d, *J* = 2.8 Hz, 1H), 3.99-3.90 (m, 1H), 3.60 (sept, *J* = 6.0 Hz, 1H), 3.25-3.16 (m, 1H), 2.65-2.59 (m, 1H), 2.47-2.40 (m, 1H), 2.17-2.11 (m, 2H), 1.54 (s, 9H), 1.51 (s, 9H), 1.50-1.40 (m, 4H), 0.83 (d, *J* = 6.0 Hz, 3H), 0.80 (d, *J* = 6.0 Hz, 3H).

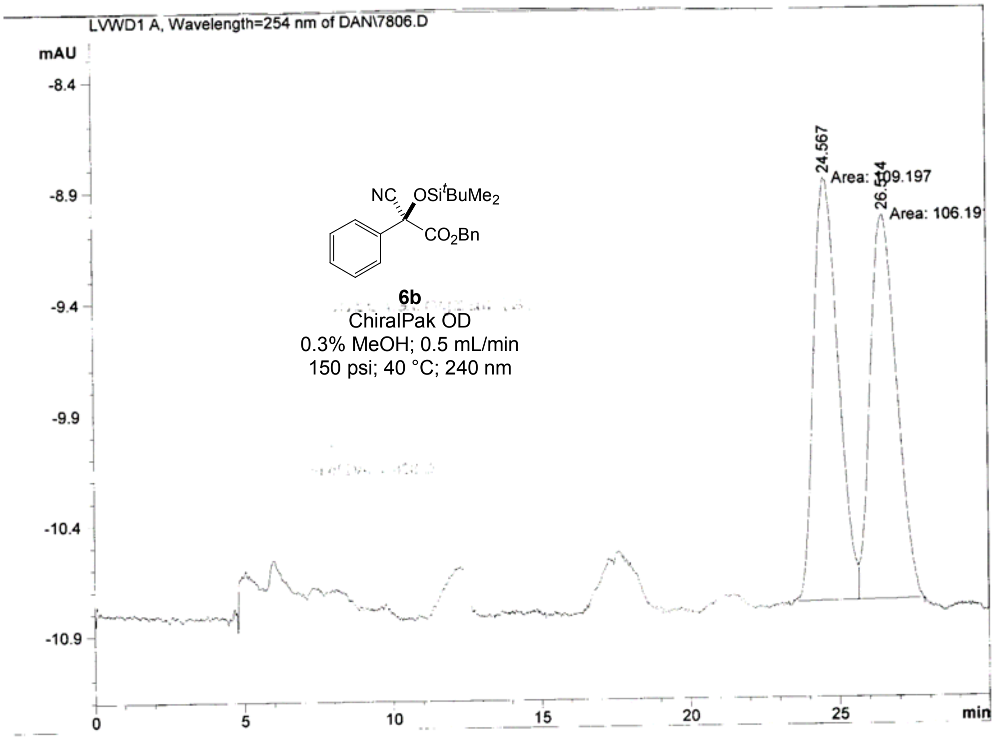
Reaction of 7-Cl with NCC(O)OBn in CDCl$_3$ using Cp$_2$Fe as internal standard. In a dry box 12.0 mg (0.0205 mmol) of **7-Cl** and 1.9 mg of Cp$_2$Fe (0.0102 mmol) were added to a vial and dissolved in CDCl$_3$ (0.5 mL). This solution was transferred to an NMR tube and the tube was fitted with a septa. Figure 1 (Appendix C) depicts an initial ^{1}H NMR spectrum that was acquired (the resonance at 4.13 ppm corresponds to the Cp$_2$Fe). Benzyl cyanoformate (6 μL, 0.041 mmol) was then added via syringe. A ^{1}H NMR spectra was acquired (resonance at 5.30 ppm is the benzyl cyanoformate; resonance at 5.12 ppm is isopropyl benzyl carbonate; resonance at 1.35 ppm is isopropyl cyanoformate; resonance at 5.15 ppm is dibenzylcarbonate) after 30 min, depicted in Figure 2 (Appendix C). A second ^{1}H NMR spectrum was acquired at 120 min, depicted in Figure 3 (Appendix C). This spectrum shows complete consumption of **7-Cl**. The calculated yields of isopropyl benzyl carbonate and isopropyl cyanoformate are 47% and 42%, respectively.

Appendix A – CSP-SFC Traces

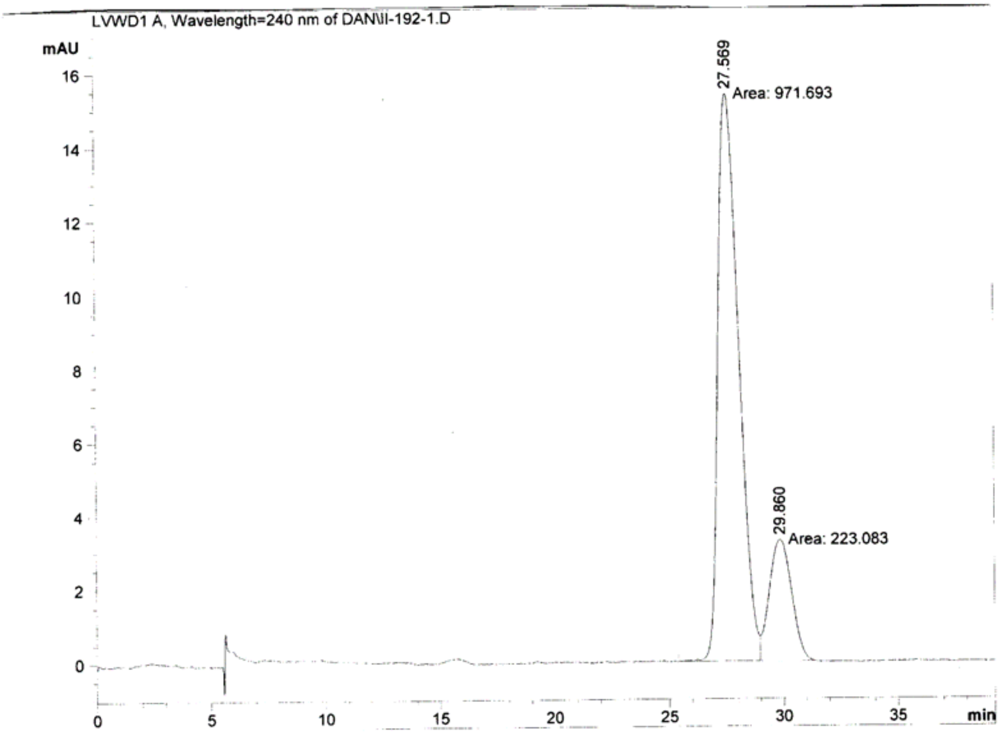


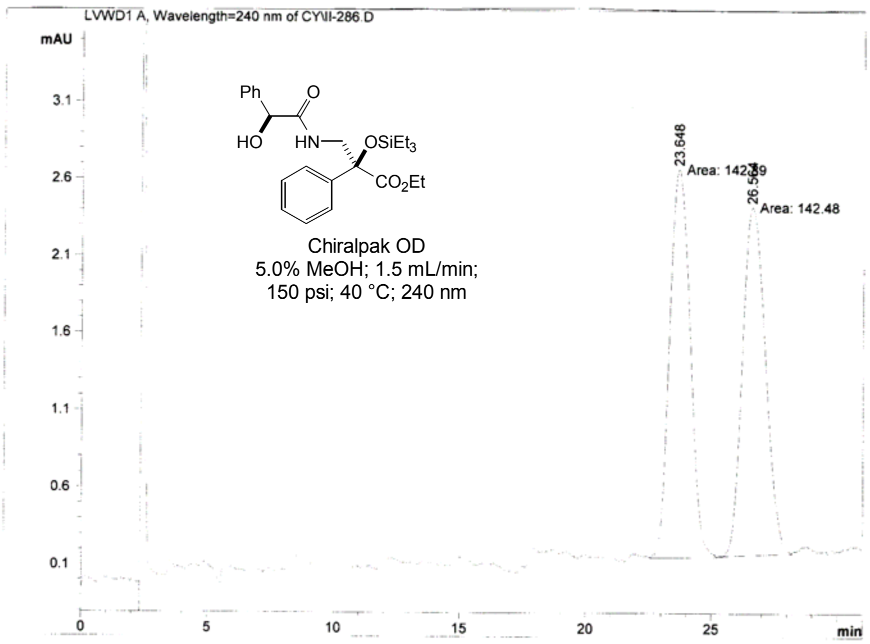
6a
ChiralPak OD
0.3% MeOH; 0.5 mL/min
150 psi; 40 °C; 240 nm



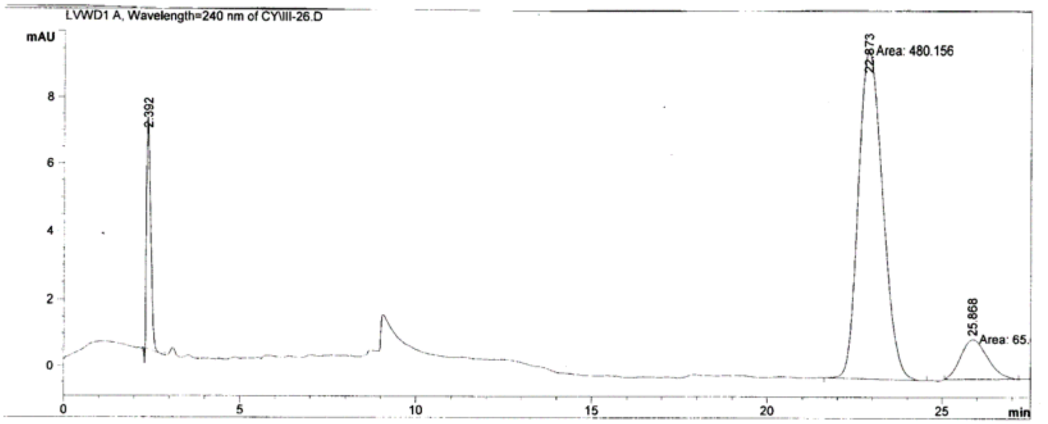


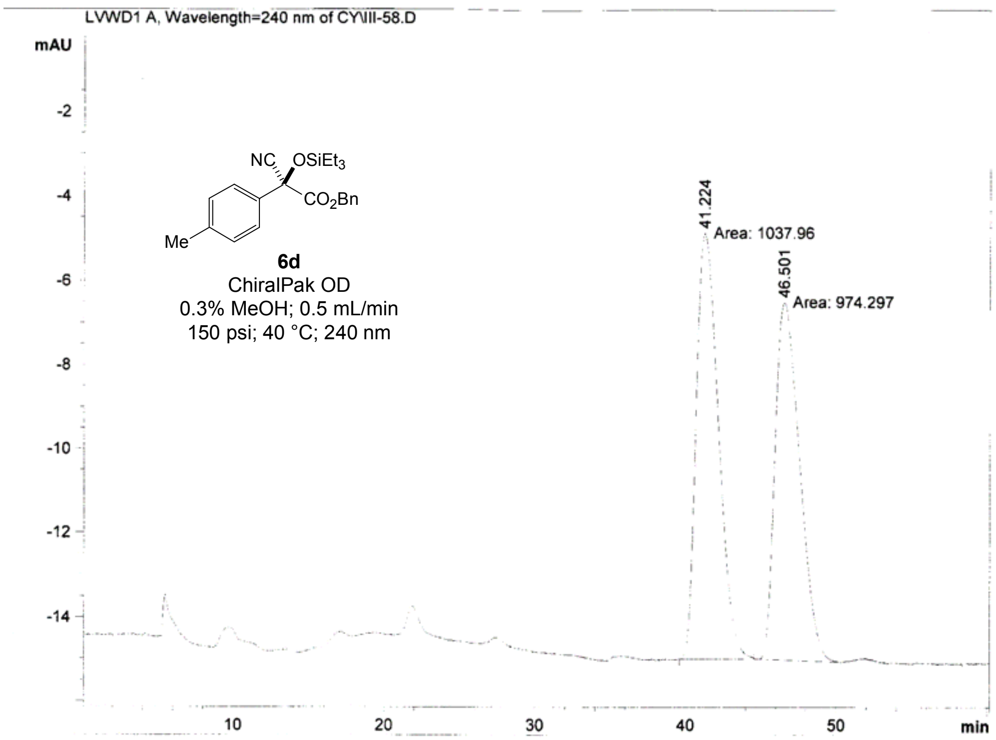
6b
ChiralPak OD
0.3% MeOH; 0.5 mL/min
150 psi; 40 °C; 240 nm





Chiralpak OD
5.0% MeOH; 1.5 mL/min;
150 psi; 40 °C; 240 nm



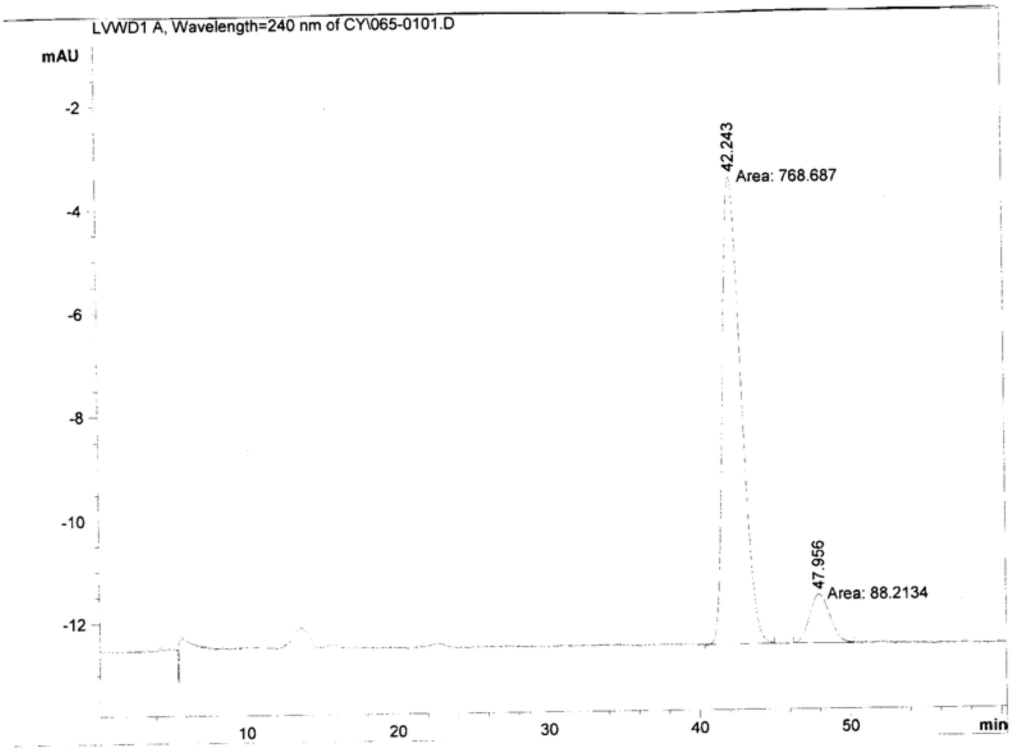


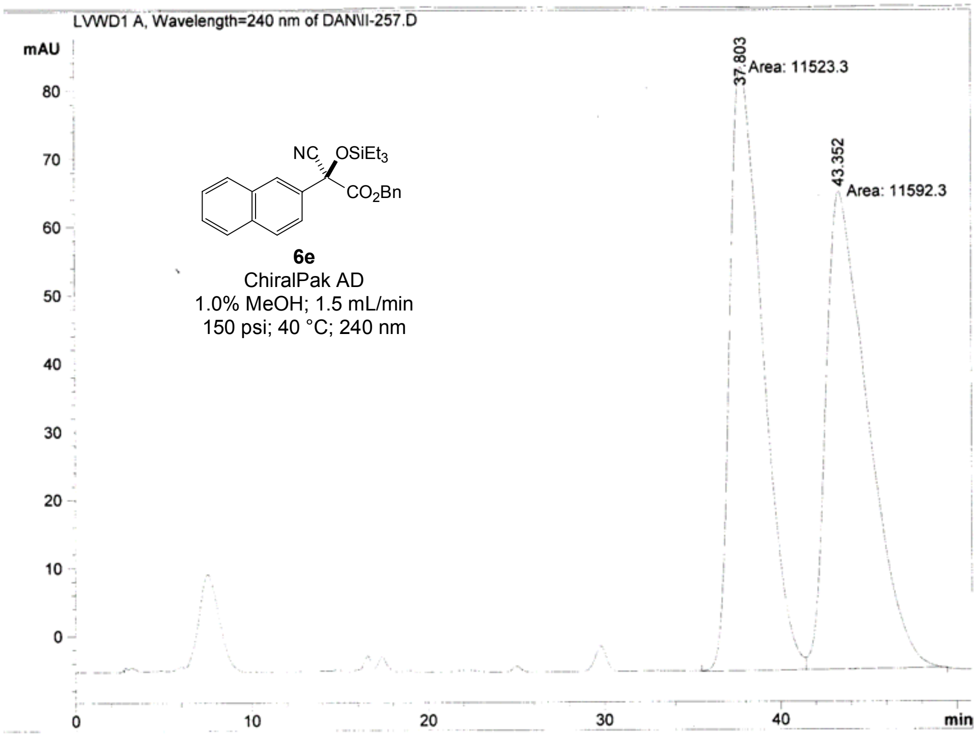
6d

ChiralPak OD

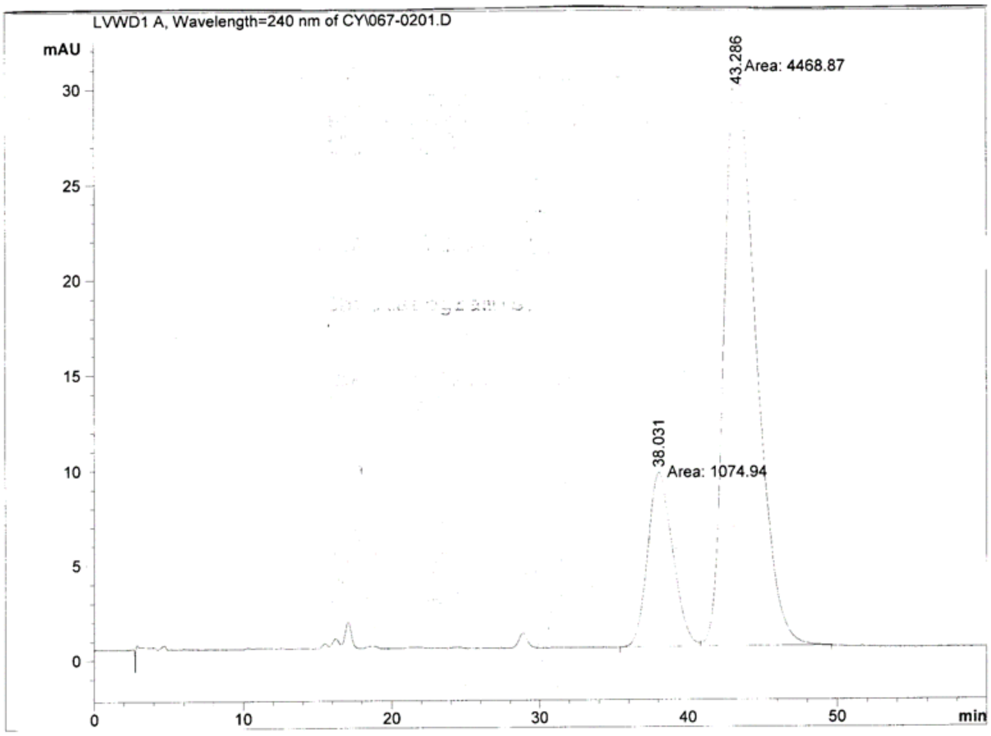
0.3% MeOH; 0.5 mL/min

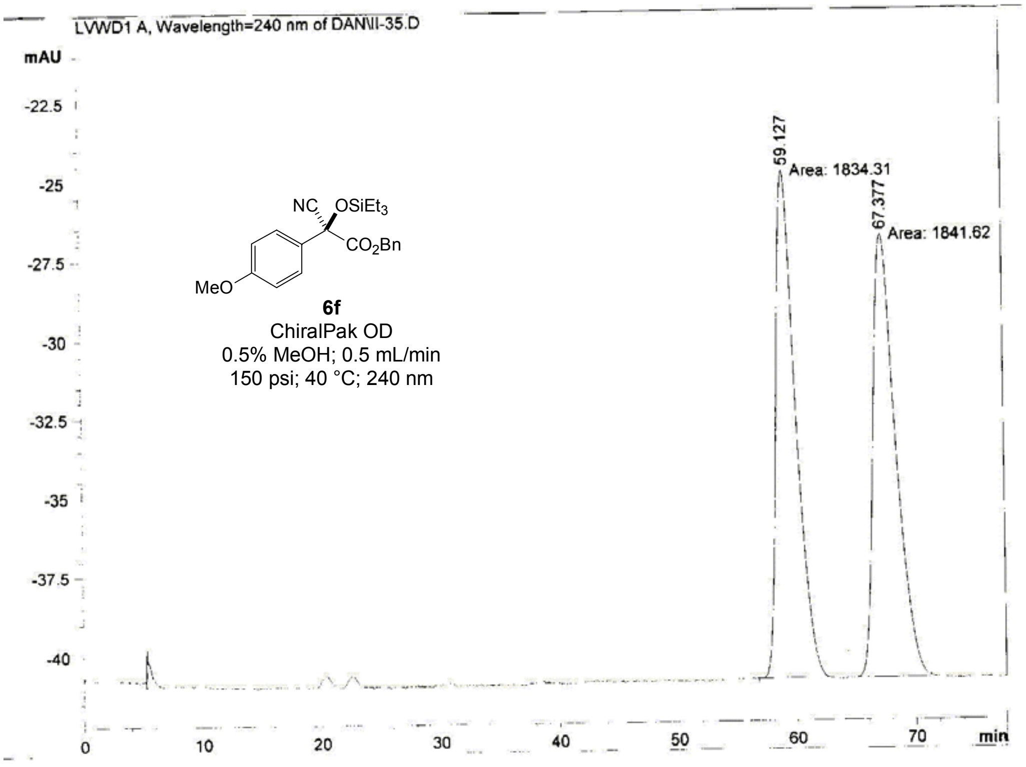
150 psi; 40 °C; 240 nm



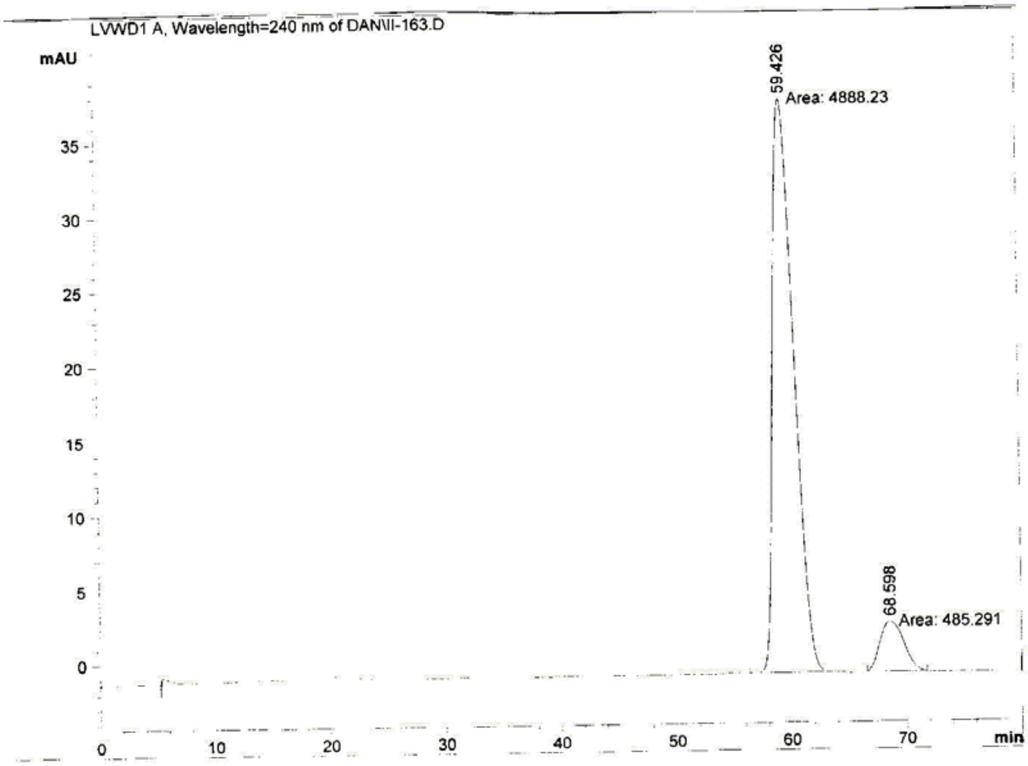


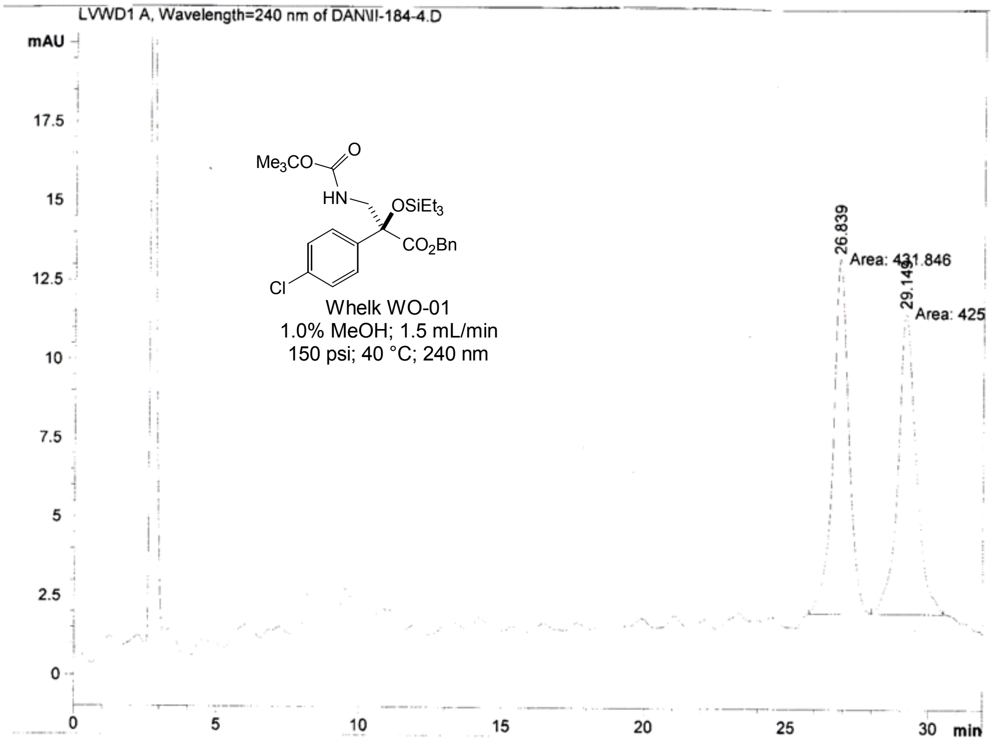
6e
ChiralPak AD
1.0% MeOH; 1.5 mL/min
150 psi; 40 °C; 240 nm



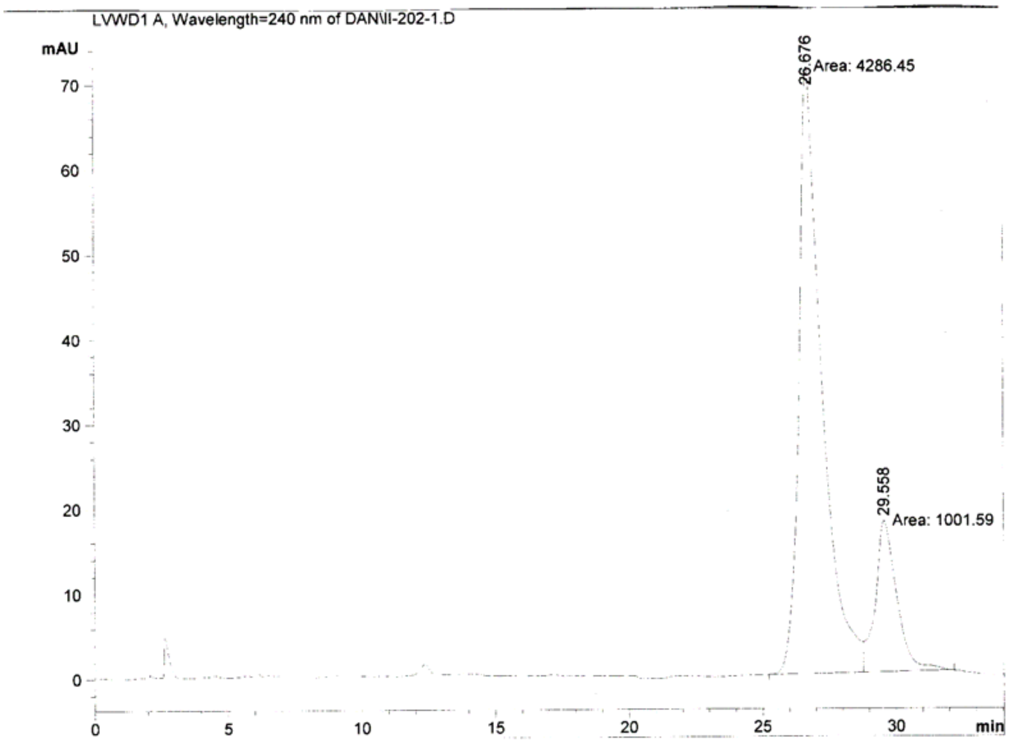


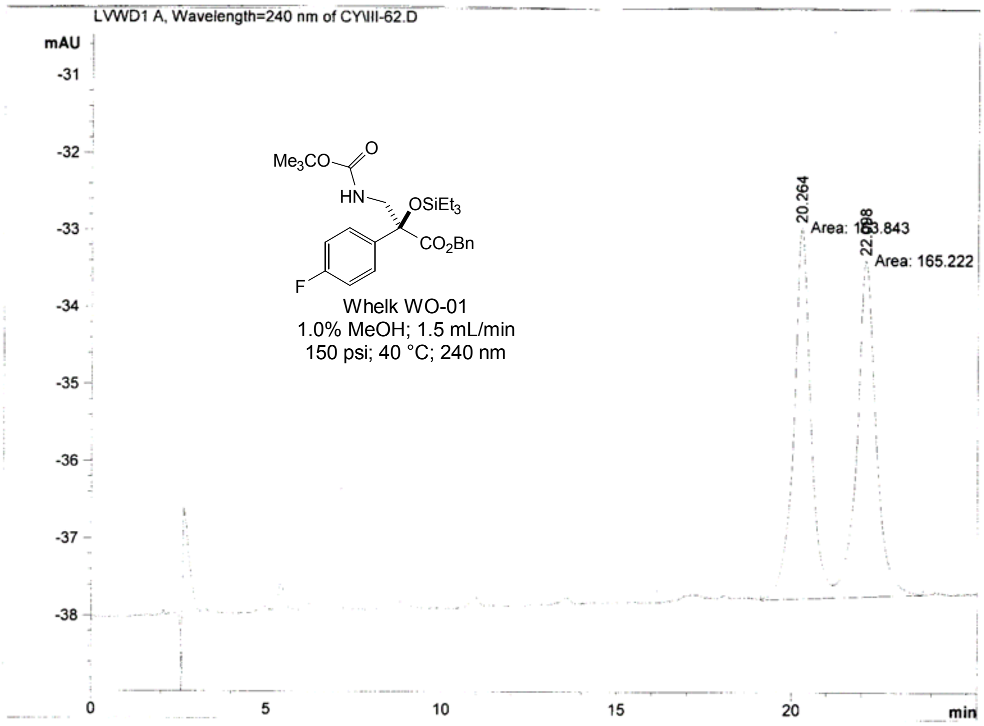
6f
ChiralPak OD
0.5% MeOH; 0.5 mL/min
150 psi; 40 °C; 240 nm



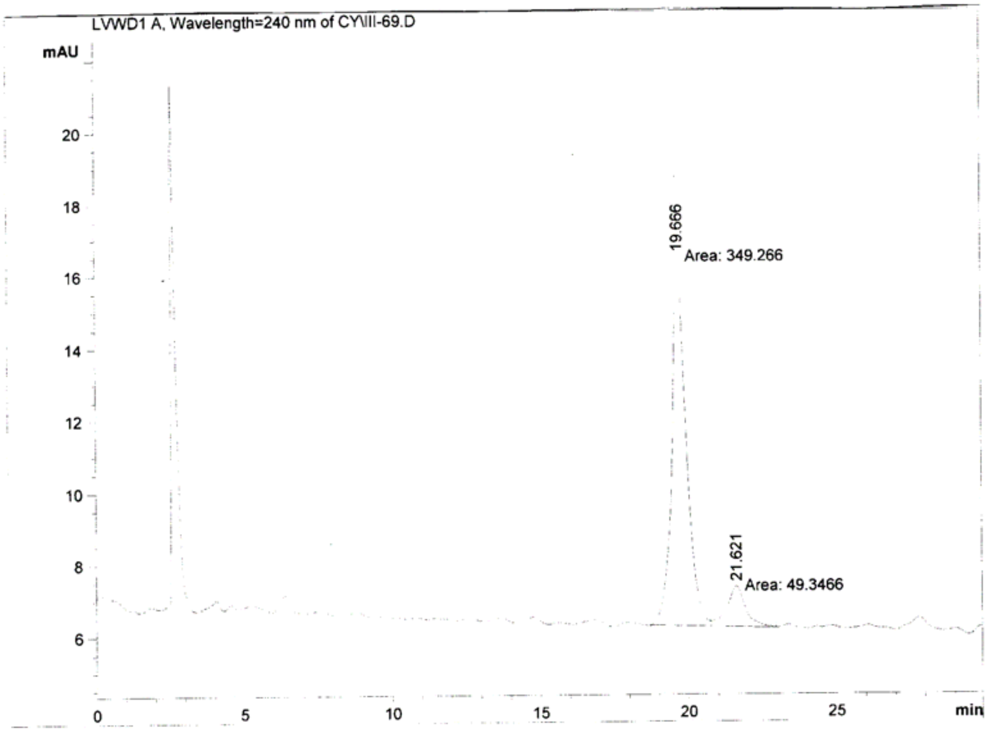


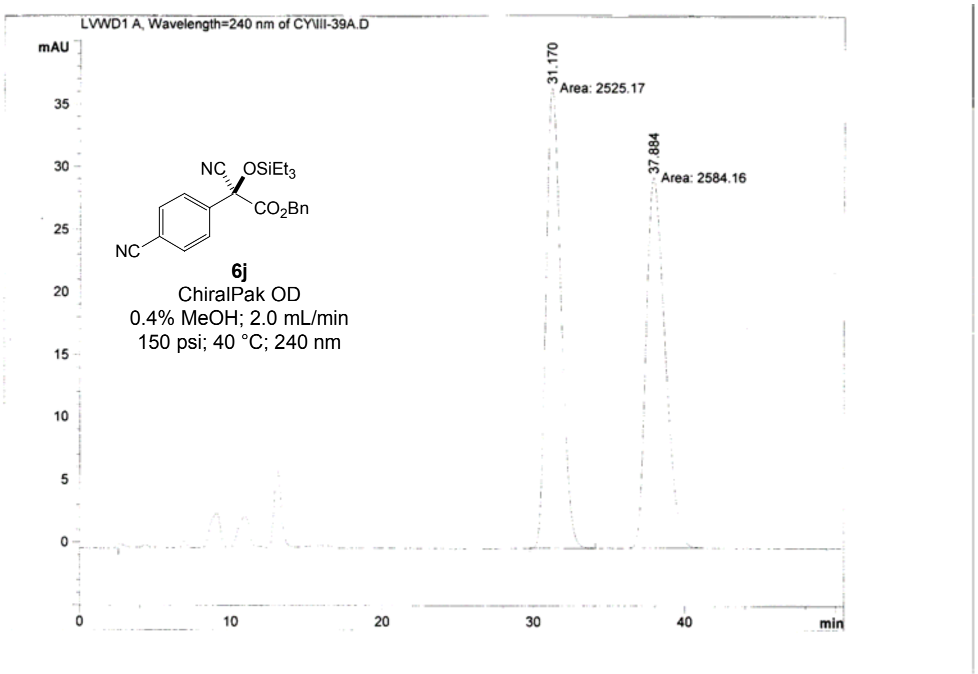
Whelk WO-01
1.0% MeOH; 1.5 mL/min
150 psi; 40 °C; 240 nm



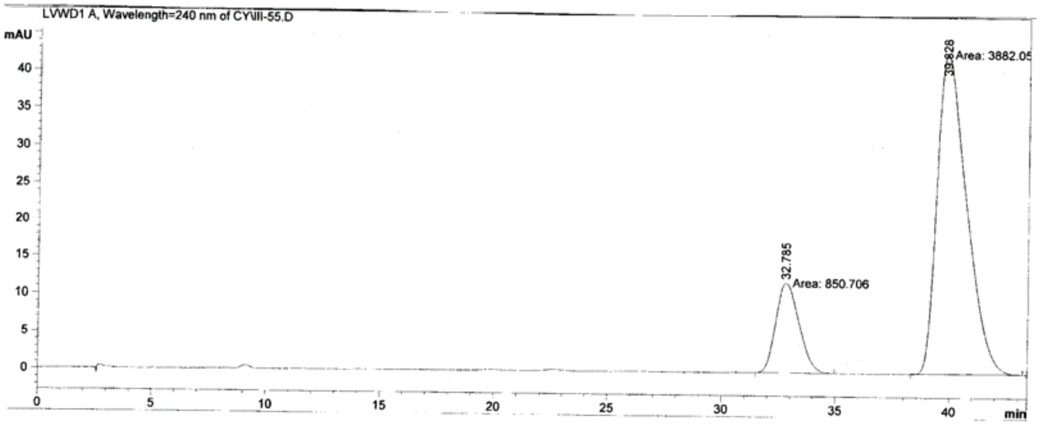


Whelk WO-01
1.0% MeOH; 1.5 mL/min
150 psi; 40 °C; 240 nm

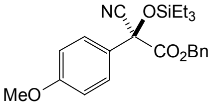




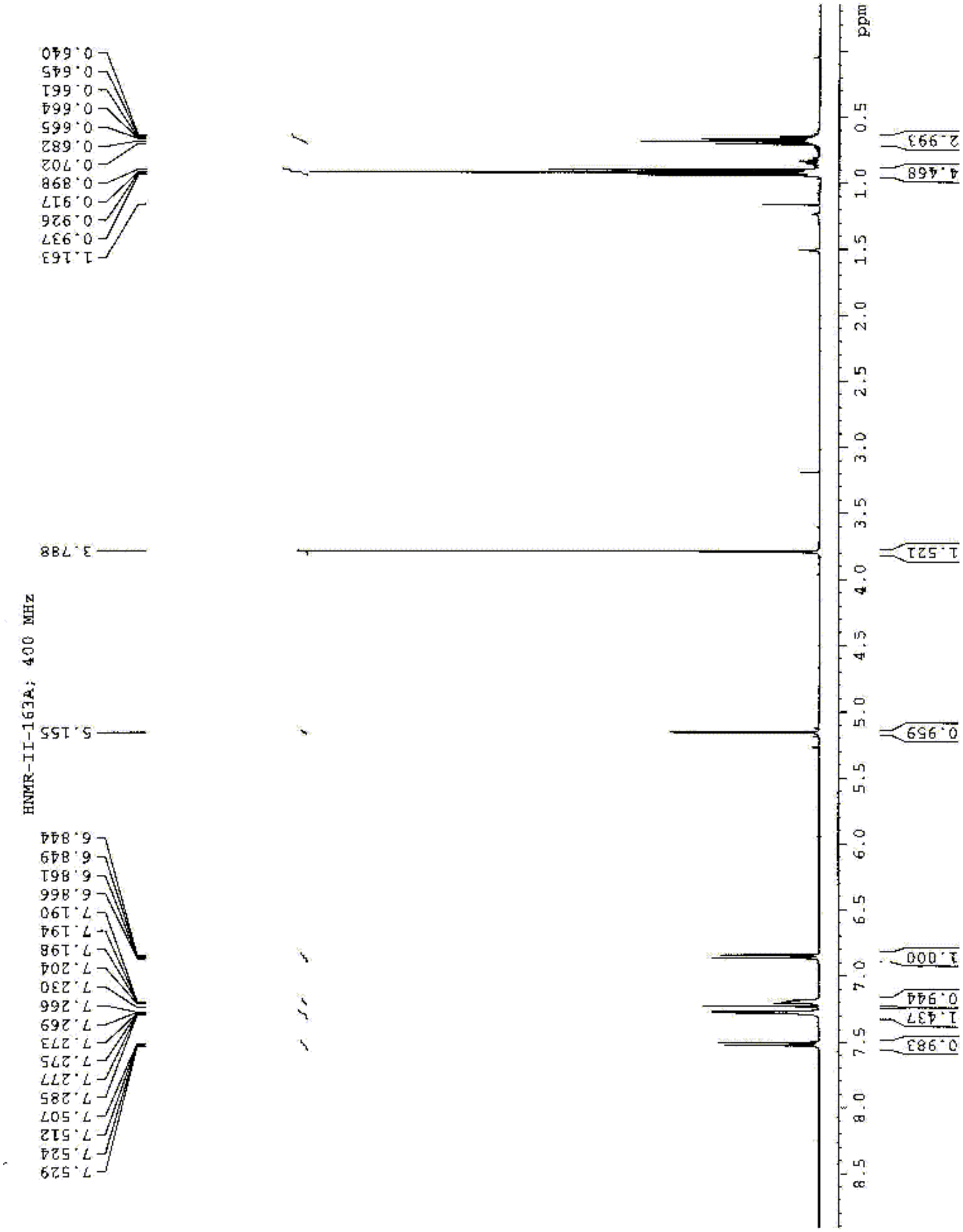
6j
ChiralPak OD
0.4% MeOH; 2.0 mL/min
150 psi; 40 °C; 240 nm

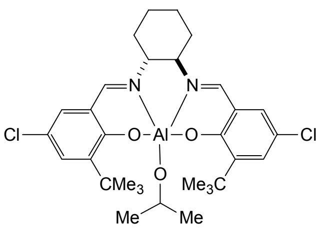


Appendix B - ^{1}H NMR Spectra

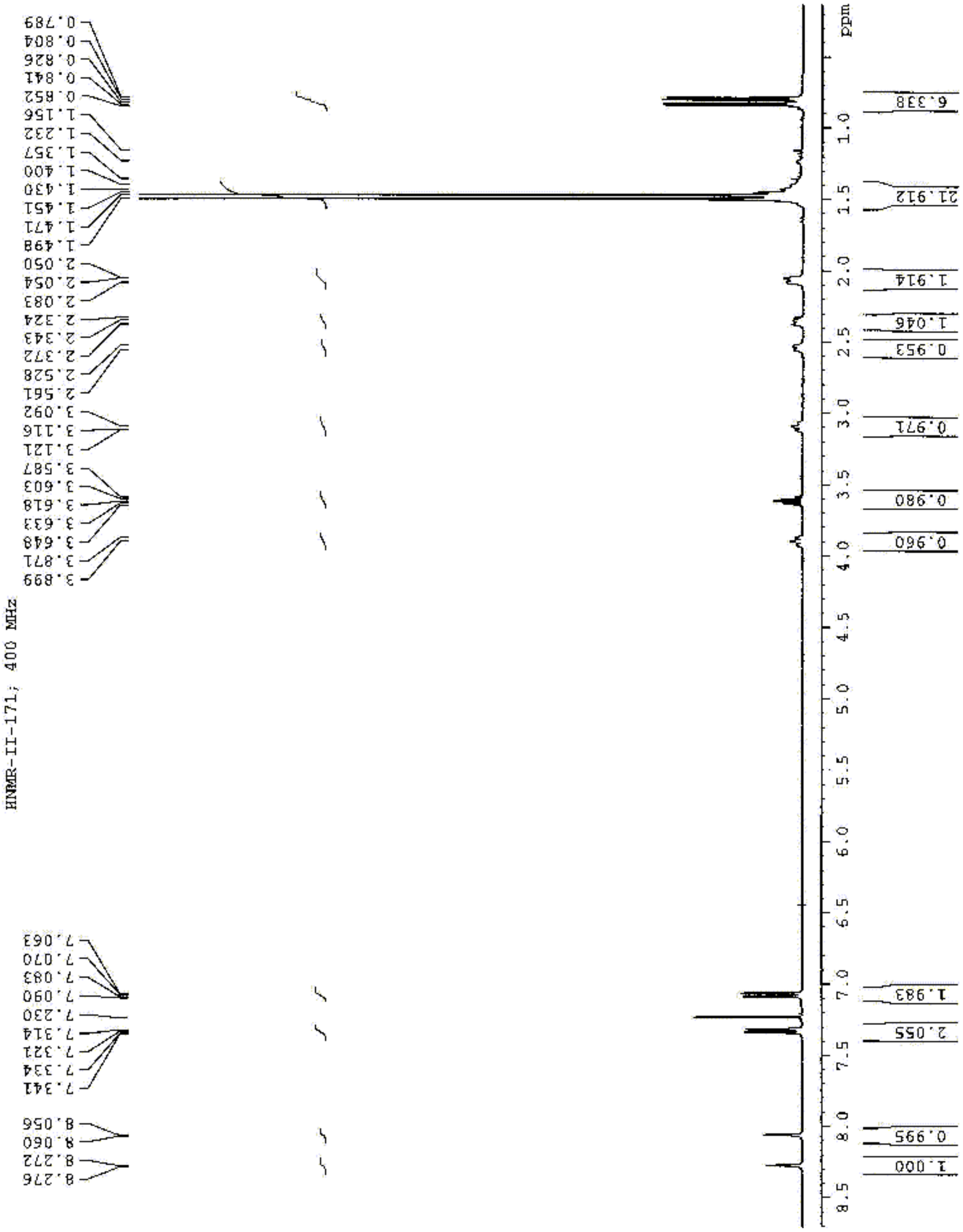


6f



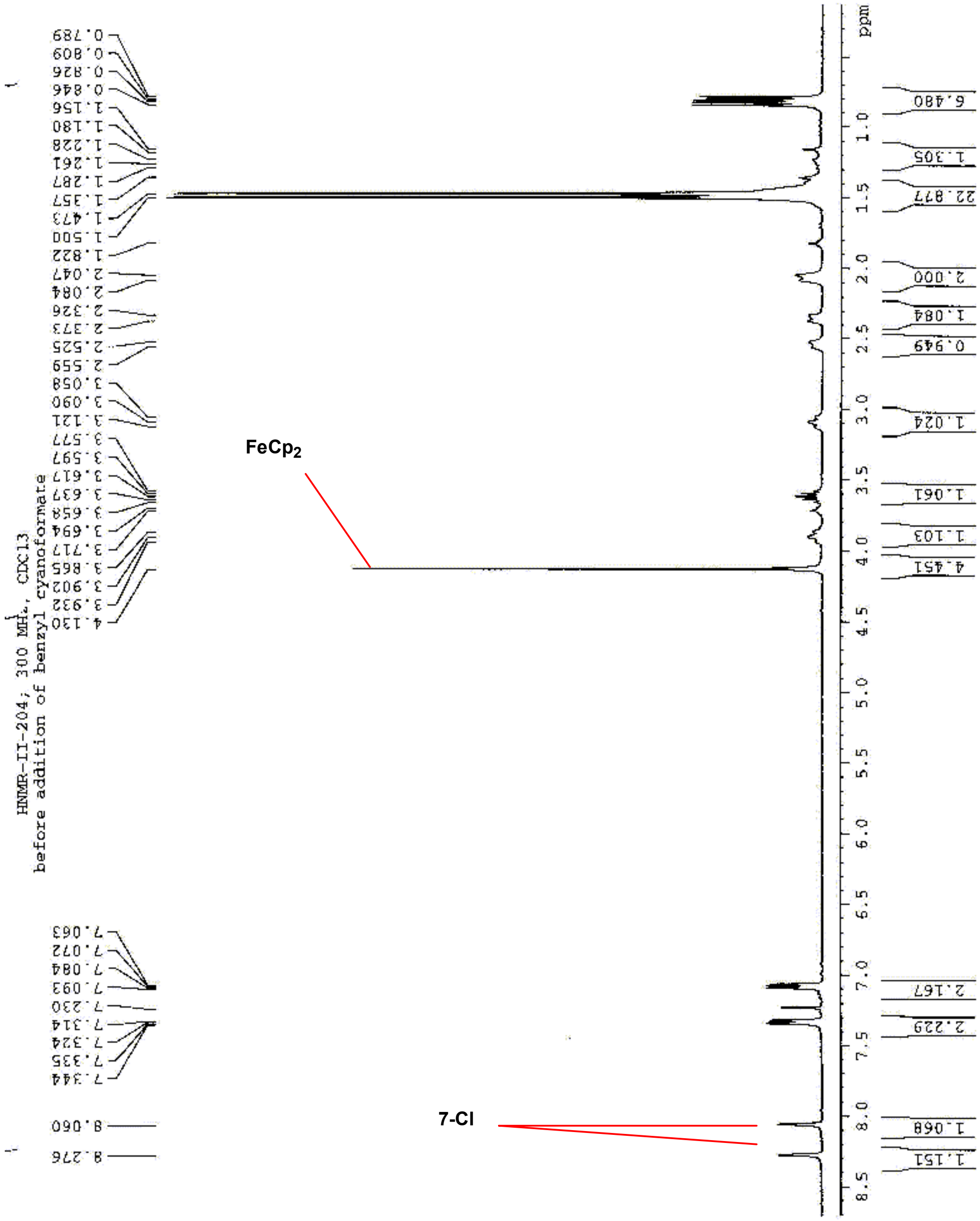

Cl
N
N
O
Al
O
Cl
CMe3
O
Me3C
Me
Me

7-Cl

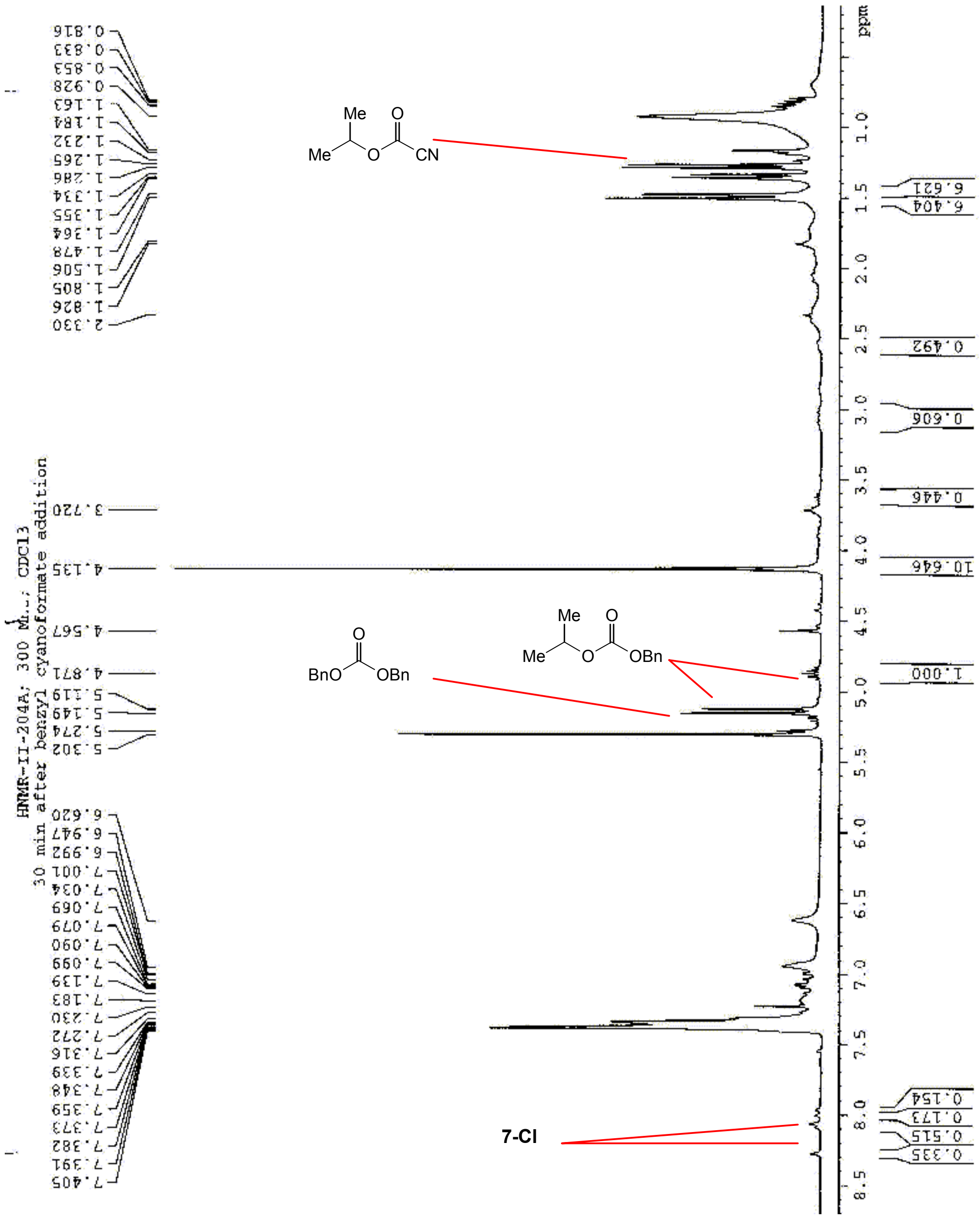

HNMR-II-171; 400 MHz
0.789
0.804
0.826
0.841
0.852
1.156
1.232
1.357
1.400
1.430
1.451
1.471
1.498
2.050
2.054
2.083
2.324
2.343
2.372
2.528
2.561
3.092
3.116
3.121
3.587
3.603
3.618
3.633
3.648
3.871
3.899
7.063
7.070
7.083
7.090
7.230
7.314
7.321
7.334
7.341
8.056
8.060
8.272
8.276
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
6.338
21.912
1.914
1.046
0.953
0.971
0.980
0.960
1.983
2.055
0.995
1.000

Appendix C – Reaction of 7-Cl with BnO_2CCN

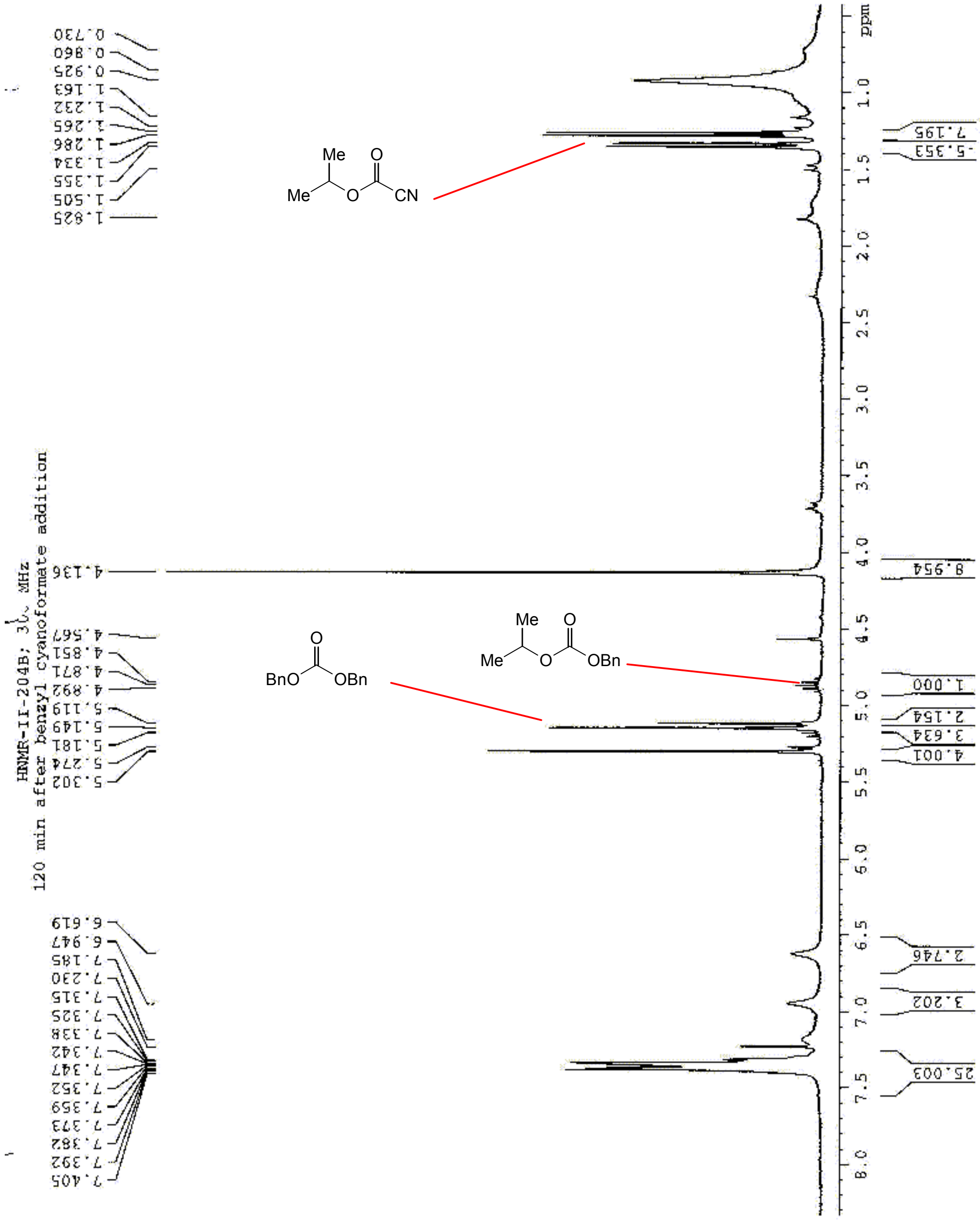
Initial ^1H NMR with Cp_2Fe (Figure 1)



30 min after benzyl cyanoformate addition (Figure 2)



120 min after benzyl cyanoformate addition (Figure 3)



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