# Synthesis of Highly Enantioenriched All Carbon Quaternary Centers; Conjugate Additions of Chiral Organolithium Nucleophiles to α,α-Dinitrile β,β-Disubstituted Olefins

## Supporting Information

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### General Procedures

All reactions involving air sensitive compounds were carried out under a nitrogen atmosphere in oven or flame-dried glassware which was cooled under nitrogen. All reagents were used as received, unless other wise noted. Solvents were distilled immediately prior to use; diethyl ether and THF were distilled from Na/benzophenone ketyl under nitrogen, and toluene and methylene chloride were distilled over $CaH_2$ under nitrogen. TMEDA and 1.6 M *n*-BuLi were bought from Aldrich. The base *n*-BuLi was titrated according to the method of Suffert.[1] (–)-Sparteine was distilled over $CaH_2$. (Aldrich)

Standard workup of reactions involved extraction from diethyl ether and water, addition of brine if necessary, drying of the organic layer by $MgSO_4$, and concentration under vacuum.

Flash chromatography was performed on silica gel (230-400 mesh). Preparative HPLC was performed on a Dynamax 60-A 8 μm silica column (Rainin Instrument Co., Woburn, MA 01801, 25 cm x 21.4 mm i.d.) coupled to a Rainin HPXL solvent delivery pump system, attached to a Rheodyne 7125 Syringe Loading Sample Injector and a Knauer UV detector (254 nm). Thin layer chromatography (TLC) was performed on Merck silica plates (0.25 mm) with QF-254 indicator. Visualization was accomplished by UV, basic $KMnO_4$, and CAM.

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed at the University of Illinois Microanalytical Service Laboratory. $^{1}H$ and $^{13}C$ NMR spectra were recorded at the University of Illinois VOICE NMR Laboratory on a Unity 400 or 500 Spectrometer. Chemical shifts are reported in ppm relative to reference solvent ($CDCl_3$, acetone-$d_6$, or DMSO-$d_6$). All mass spectra data was obtained at the University of Illinois Mass Spectrometry Laboratory.

Analysis of enantiomeric ratios were carried out using a racemic standard followed by the enantioenriched product. Analytical chiral stationary phase (CSP) HPLC was performed on a 5 μm Rexchrom Reversible, covalent Pirkle (S,S)-Whelk-O column (Regis Chemical Co., Morton Grove, IL 60053, 25 cm x 4.6 mm i.d.) or a Chiralpak AD (Daicel, 25 cm x 4.6 mm i.d.) using isopropanol and hexane mixtures with a Rainin HPXL pump system attached to a Rheodyne pump, a Dynamax variable wavelength detector (254 nm), and a Macintosh computer equipped with a Dynamax MacIntegrator. When indicated, analytical supercritical fluid chromatography (SFC) was performed on a Berger Instruments SFC with built-in photometric detector (λ=220 nm) using Daicel Chiralpak columns. In almost every case, complete baseline separation is observed, and enantiomeric ratios are rounded down to the nearest whole number.

**Representative Lithiation of *N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-benzyl amine (1) and Electrophilic Substitution: Preparation of (*1R,2S*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3,3-Dicyano-2-ethyl-1,2-diphenylpropane-1-amine (4).** A solution of **1** (169 mg, 0.54 mmol) and (–)-sparteine (0.136 ml, 0.59 mmol) in toluene (6 ml) was cooled to –78 °C. *n*-BuLi (0.40 ml, 1.50 M, 0.59 mmol) was added and the solution was stirred for 1 h. A solution of 2-(1-Phenyl-propylidene)-malononitrile (147 mg, 0.81 mmol) in toluene (3 ml) was added over 1 h via syringe pump and stirred for 1 h. The reaction was quenched with methanol at –78 °C, and after warming to ambient temperature, standard workup and chromatography of the resultant oil (1:6 ethyl acetate: pet. ether) afforded **4** (236 mg, 89%) as a 95:5 mixture of diastereomers. **4**: $^{1}H$ NMR (acetone-$d_6$, 500 MHz) δ 1.18 (bt, 3H, $CH_3$), 1.48 (m, 11H, $CH_2$, $(CH_3)_3$), 2.69 (m, 2H, CHPh, CHCN), 3.73 (s, 3H, $OCH_3$), 6.60-7.60 (m, 14H, CH-

Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 9.30 ($CH_3$), 10.61 ($CH_2$), 27.72 (($CH_3$)$_3$), 29.24 (CH), 54.97 ($OCH_3$), 80.94 (C), 113.35 (CH-Ar), 114.68 (CN), 128.03 (CH-Ar), 128.15 (CH-Ar), 128.45 (CH-Ar), 128.71 (CH-Ar), 131.72 (CH-Ar), 138.22 (C-Ar), 158.71 (C=O). Anal. Cald. for $C_{31}H_{33}N_3O_3$: C, 75.13; H, 6.71; N, 8.48. Found: C, 75.17; H, 6.75; N, 8.67. The enantiomeric ratio of **4** was determined to be 99:1 by CSP HPLC ((*S*,*S*)-Whelk-O column, 2.5% *i*-PrOH/hexane, 0.75 ml/min). The major enantiomer had a retention time of 18.56 min and the minor enantiomer had a retention time of 24.24 min.

**(*1R*,*2R*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3,3-Dicyano-2-ethyl-2-methyl-1-phenylpropane-1-amine (5).** The amine **5** was obtained with 2-*sec*-Butylidene-malononitrile as the electrophile, following the procedure used for the preparation of **4**. The product was purified by chromatography (1:10 ethyl acetate: pet. ether) and preparative HPLC (5% ethyl acetate/hexane) to afford **5** (60%) as a 78:22 mixture of diastereomers. **5**: $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, *J*=7.86, 3H, $CH_3$), 1.37 (s, 9H, ($CH_3$)$_3$), 1.44 (s, 3H, $CH_3$), 1.86 (m, 1H, $CH_2$), 2.02 (m, 1H, $CH_2$), 3.79 (s, 3H, $OCH_3$), 4.64 (m, 1H, CHPh), 5.92 (m, 1H, CHCN), 6.70-7.50 (m, 9H, CH-Ar). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 8.53 ($CH_3$), 20.86 ($CH_2$), 28.13 (($CH_3$)$_3$), 30.11 ($CH_3$), 30.72 (CH), 44.97 (C), 55.28 ($OCH_3$), 71.69 (CH), 80.10 (C), 112.04 (CN), 113.49 (CN), 113.74 (CH-Ar), 128.74 (CH-Ar), 128.98 (CH-Ar), 130.06 (CH-Ar), 136.66 (C-Ar), 157.67 (C-Ar), 158.23 (C=O) HRMS ($M^+$) Cald. for $C_{26}H_{31}N_3O_3$: 443.2365; Found: 443.2364. The enantiomeric ratio of **5** was determined to be 98:2 by CSP HPLC ((*S*,*S*)-Whelk-O column, 3% *i*-PrOH/hexane, 1 ml/min). The major enantiomer had a retention time of 26.37 min and the minor enantiomer had a retention time of 23.87 min.

**(*1R*,*2R*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3,3-Dicyano-2-*n*-propyl-2-ethyl-1-phenylpropane-1-amine (6).** The amine **6** was obtained with 2-(1-Methyl-butylidene)-malononitrile as the electrophile, following the procedure used for the preparation of **4**. The product was purified by chromatography (1:10 ethyl acetate: pet. ether) and preparative HPLC (5% ethyl acetate/hexane) to afford **6** (94%) as an 87:13 mixture of diastereomers. **6**: $^1$H NMR (acetone-$d_6$, 400 MHz) δ 1.14 (t, *J*=7.63, 3H,

$CH_3$), 1.38 (s, 9H, $(CH_3)_3$), 1.44 (s, 3H, $CH_3$), 2.05 (m, 2H, $CH_2$), 3.78 (s, 3H, $OCH_3$), 5.02 (m, 1H, CHPh), 5.72 (m, 1H, CHCN), 6.80-7.40 (m, 9H, CH-Ar). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 14.43 ($CH_3$), 17.32 ($CH_3$), 21.41 ($CH_2$), 28.17 ($(CH_3)_3$), 31.03 ($CH_2$), 39.76 (CH), 44.81 (C), 55.26 ($OCH_3$), 71.90 (CH), 81.07 (C), 112.00 (CN), 113.48 (CN), 113.73 (CH-Ar), 128.75 (CH-Ar), 128.97 (CH-Ar), 130.05 (CH-Ar), 136.59 (C-Ar), 157.03 (C-Ar), 158.21 (C=O). HRMS ($M^+$) Cald. for $C_{27}H_{33}N_3O_3$: 447.2521; Found: 447.2515. The enantiomeric ratio of **6** was determined to be 98:2 by CSP HPLC ((*S*,*S*)-Whelk-O column, 1.5% *i*-PrOH/hexane, 1 ml/min). The major enantiomer had a retention time of 24.07 min and the minor enantiomer had a retention time of 18.56 min.

**Representative Lithiation of *N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-phenyl-(*E*)-2-propene-1-amine (7) and Electrophilic Substitution: Preparation of (*3S,4S*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5,5-dicyano-4-ethyl-3,4-diphenyl-(*Z*)-1-pentene-1-amine (10).** A solution of **7** (142 mg, 0.42 mmol) and (–)-sparteine (0.106 ml, 0.46 mmol) in toluene (6 ml) was cooled to –78 °C. *n*-BuLi (0.307 ml, 1.50 M, 0.46 mmol) was added and the solution was stirred for 1 h. A solution of 2-(1-Phenyl-propylidene)-malononitrile (115 mg, 0.63 mmol) in toluene (3 ml) was added over 1 h via syringe pump and stirred for 1 h. The reaction was quenched with methanol at –78 °C, and after warming to ambient temperature, standard workup, chromatography (1:6 ethyl acetate: pet. ether), and preparatory HPLC (10% ethyl acetate/hexane) afforded **10** (187 mg, 86%) as an 80:20 mixture of diastereomers. **10a**: $^1$H NMR (acetone-$d_6$, 500 MHz) δ 1.10 (t, *J*=7.50, 3H, $CH_3$), 1.41 (s, 9H, $(CH_3)_3$), 2.07 (m, 1H, $CH_2$), 2.61 (m, 1H, $CH_2$), 3.56 (d, *J*=10.72, 1H, CHPh), 3.78 (s, 3H, $OCH_3$), 4.67 (s, 1H, CHCN), 5.03 (m, 1H, CH-Ar) 6.19 (m, 2H, CH-Ar), 6.75-7.40 (m, 11H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 8.98 ($CH_3$), 27.64 ($(CH_3)_3$), 29.28 ($CH_2$), 50.39 (CH), 52.71 (CH) 55.08 ($OCH_3$), 80.87 (C), 113.52 (CN), 113.93 (CN), 114.37 (CH-Ar), 127.47 (CH-Ar), 127.59 (CH-Ar), 128.03 (CH-Ar), 128.09 (CH-Ar), 128.45 (CH-Ar), 129.23 (CH-Ar), 129.76 (CH-Ar), 130.88 (CH-Ar), 134.13 (C-Ar), 135.07 (C-Ar), 137.23 (C-Ar), 153.34 (C=O). HRMS ($M^+$) Cald. for $C_{33}H_{35}N_3O_3$: 521.2678; Found: 521.2676. The enantiomeric ratio of **10a** was determined to be 95:5 by CSP HPLC (Chiralpak AD column, 1.5% *i*-PrOH/hexane,

1.0 ml/min). The major enantiomer had a retention time of 15.11 min and the minor enantiomer had a retention time of 13.14 min. **10b**: $^{1}$H NMR (acetone-$d_6$, 500 MHz) δ 1.03 (t, *J*=7.50, 3H, $CH_3$), 1.46 (s, 9H, $(CH_3)_3$), 1.98 (m, 2H, $CH_2$), 3.64 (d, *J*=11.57, 1H, CHPh), 3.77 (s, 3H, $OCH_3$), 5.18 (dd, *J*=11.36, 8.57. 1H, CH-Ar), 5.45 (s, 1H, CHCN) 5.98 (d, *J*=7.29 1H, CH-Ar), 6.68-7.40 (m, 12H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 8.78 ($CH_3$), 27.71 ($(CH_3)_3$), 28.30 ($CH_2$), 29.74 (CH), 50.38 (CH), 52.50 (C) 55.09 ($OCH_3$), 81.08 (C), 113.52 (CN), 113.89 (CN), 113.96 (CH-Ar), 127.19 (CH-Ar), 127.63 (CH-Ar), 128.17 (CH-Ar), 128.20 (CH-Ar), 129.24 (CH-Ar), 129.67 (CH-Ar), 132.06 (CH-Ar), 134.65 (C-Ar), 135.42 (C-Ar), 136.60 (C-Ar), 157.92 (C=O). HRMS ($M^+$) Cald. for $C_{33}H_{35}N_3O_3$: 521.2678; Found: 521.2682. The enantiomeric ratio of **10b** was determined to be 87:13 by CSP HPLC (Chiralpak AD column, 1.5% *i*-PrOH/hexane, 1.0 ml/min). The major enantiomer had a retention time of 9.74 min and the minor enantiomer had a retention time of 13.10 min.

**(*3S,4S*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5,5-dicyano-4-ethyl-4-methyl-3-phenyl-(*Z*)-1-pentene-1-amine (11).** The amine **11** was obtained with 2-*sec*-Butylidene-malononitrile as the electrophile, following the procedure used for the preparation of **10**. The product was purified by chromatography (1:10 ethyl acetate: pet. ether) and preparative HPLC (7% ethyl acetate/hexane) to afford **11** (96%) as a 59:41 mixture of diastereomers. **11a**: $^{1}$H NMR (acetone-$d_6$, 500 MHz) δ 0.89 (t, *J*=7.07, 3H, $CH_3$), 1.11 (s, 3H, $CH_3$), 1.43 (m, 11H, $CH_2$, $(CH_3)_3$), 3.58 (d, *J*=11.58, 1H, CHPh), 3.78 (s, 3H, $OCH_3$), 4.46 (s, 1H, CHCN), 5.58 (t, *J*=11.15 1H, CH-Ar), 6.65-7.20 (m, 10H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 8.02 ($CH_3$), 18.76 ($CH_3$), 20.92 ($CH_2$), 27.65 ($(CH_3)_3$), 30.80 (CHPh), 44.33 (C), 44.12 (C), 47.81 (CHCN) 55.05 ($OCH_3$), 80.78 (C), 113.18 (CN), 113.44 (CN), 113.95 (CH-Ar), 127.06 (CH-Ar), 127.70 (CH-Ar), 128.02 (CH-Ar), 129.48 (CH-Ar), 130.60 (CH-Ar), 131.34 (CH-Ar), 135.25 (C-Ar), 138.02 (C-Ar), 153.34 (C-Ar), 157.97 (C=O). HRMS ($M^+$) Cald. for $C_{28}H_{33}N_3O_3$: 459.2522; Found: 459.2523. The enantiomeric ratio of **11a** was determined to be 95:5 by CSP HPLC (Chiralpak AD column, 1.5% *i*-PrOH/hexane, 1.0 ml/min). The major enantiomer had a retention time of 19.55 min and the minor enantiomer had a retention time of 23.22 min. **11b**: $^{1}$H NMR (acetone-$d_6$, 500 MHz) δ 1.00 (t, *J*=7.50, 3H, $CH_3$), 1.09 (s, 3H,

$CH_3$), 1.42 (m, 11H, $CH_2$, $(CH_3)_3$), 3.53 (d, *J*=11.34, 1H, CHPh), 3.77 (s, 3H, $OCH_3$), 4.09 (s, 1H, CHCN), 5.56 (m, 1H, CH-Ar), 6.65-7.20 (m, 10H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 8.18 ($CH_3$), 19.06 ($CH_3$), 27.65 (($CH_3)_3$), 31.18 (CHPh), 44.25 (C), 47.88 (CHCN) 55.04 ($OCH_3$), 80.71 (C), 113.00 (CN), 113.19 (CN), 114.03 (CH-Ar), 116.18 (CH-Ar), 127.22 (CH-Ar), 127.95 (CH-Ar), 128.57 (CH-Ar), 129.56 (CH-Ar), 130.58 (CH-Ar), 135.00 (C-Ar), 138.05 (C-Ar), 153.32 (C-Ar), 157.99 (C=O). HRMS ($M^+$) Cald. for $C_{28}H_{33}N_3O_3$: 459.2522; Found: 459.2516. The enantiomeric ratio of **11b** was determined to be 94:6 by CSP HPLC (Chiralpak AD column, 1.5% *i*-PrOH/hexane, 1.0 ml/min). The major enantiomer had a retention time of 16.43 min and the minor enantiomer had a retention time of 20.65 min.

**(*3S,4S*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5,5-dicyano-4-propyl-4-methyl-3-phenyl-(*Z*)-1-pentene-1-amine (12).** The amine **12** was obtained with 2-(1-Methyl-butylidene)-malononitrile as the electrophile, following the procedure used for the preparation of **10**. The product was purified by chromatography (1:6 ethyl acetate: pet. ether) and preparative HPLC (7% ethyl acetate/hexane) to afford **12** (89%) as a 55:45 mixture of diastereomers. **12a**: $^1$H NMR (acetone-$d_6$, 500 MHz) δ 0.94 (t, *J*=7.08, 3H, $CH_3$), 1.10 (s, 3H, $CH_3$), 1.42 (s, 9H, $(CH_3)_3$), 1.59 (m, 4H, $CH_2$), 3.54 (d, *J*=11.23, 1H, CHPh), 3.77 (s, 3H, $OCH_3$), 4.05 (s, 1H, CHCN), 5.57 (t, *J*=10.04 1H, CH-Ar), 6.65-7.20 (m, 10H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 14.44 ($CH_3$), 17.25 ($CH_2$), 19.60 ($CH_3$), 27.65 (($CH_3)_3$), 31.59 (CHPh), 39.04 ($CH_2$), 44.12 (C), 47.83 (CHCN) 55.04 ($OCH_3$), 80.71 (C), 113.06 (CN), 113.17 (CN), 114.03 (CH-Ar), 127.24 (CH-Ar), 127.96 (CH-Ar), 127.97 (CH-Ar), 129.51 (CH-Ar), 130.60 (CH-Ar), 135.04 (C-Ar), 137.97 (C-Ar), 153.32 (C-Ar), 157.95 (C=O). HRMS ($M^+$) Cald. for $C_{29}H_{35}N_3O_3$: 473.2678; Found: 473.2679. The enantiomeric ratio of **12a** was determined to be 88:12 by CSP SFC (Chiralpak OJ column, 3% MeOH, 3.0 ml/min). The major enantiomer had a retention time of 3.28 min and the minor enantiomer had a retention time of 2.10 min. **12b**: $^1$H NMR (acetone-$d_6$, 500 MHz) δ 0.81 (t, *J*=6.59, 3H, $CH_3$), 1.11 (s, 3H, $CH_3$), 1.30 (m, 4H, $CH_2$), 1.42 (s, 9H, $(CH_3)_3$), 3.57 (d, *J*=11.72, 1H, CHPh), 3.77 (s, 3H, $OCH_3$), 4.44 (s, 1H, CHCN), 5.57 (m, 1H, CH-Ar) 6.65-7.20 (m, 10H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 14.02 ($CH_3$), 17.10 ($CH_2$), 19.32 ($CH_3$), 27.66 (($CH_3)_3$), 31.25

(CHPh), 39.35 ($CH_2$), 44.21 (C), 47.27 (CHCN) 55.05 ($OCH_3$), 80.79 (C), 113.21 (CN), 113.43 (CN), 113.93 (CH-Ar), 127.08 (CH-Ar), 127.72 (CH-Ar), 127.99 (CH-Ar), 129.39 (CH-Ar), 131.36 (CH-Ar), 135.22 (C-Ar), 138.04 (C-Ar), 153.32 (C-Ar), 157.93 (C=O). Anal. Cald. for $C_{29}H_{35}N_3O_3$: C, 73.54; H, 7.45; N, 8.87. Found: C, 73.46; H, 7.75; N, 8.98. The enantiomeric ratio of **12b** was determined to be 90:10 by CSP SFC (Chiralpak OJ column, 3% MeOH, 3.0 ml/min). The major enantiomer had a retention time of 2.70 min and the minor enantiomer had a retention time of 2.16 min.

**(*3S,4S*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5,5-dicyano-4-(triisopropylsilyl)-methanol-4-methyl-3-phenyl-(*Z*)-1-pentene-1-amine (17).** The amine **17** was obtained with 2-(1-Triisopropysilyl-hydroxy-ethylidene)-malononitrile as the electrophile, following the procedure used for the preparation of **10**. The product was purified by chromatography (1:8 ethyl acetate: pet. ether) and preparative HPLC (5% ethyl acetate/hexane) to afford **17** (70%) as a 95:5 mixture of diastereomers. **17**: $^1$H NMR (acetone-$d_6$, 500 MHz) δ 1.15 (m, 21H, $(CH(CH_3)_2)_3$, 1.40 (s, 9H, $(CH_3)_3$), 3.42 (d, *J*=11.23, 1H, CHPh), 3.75 (m, 2H, $CH_2$), 3.78 (s, 3H, $OCH_3$), 4.18 (s, 1H, CHCN), 5.57 (dd, *J*=11.23, 9.26, 1H, CH-Ar), 6.70-7.25 (m, 10H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 12.07 ($CH_3$), 16.46 (CH), 17.83 ($CH_3$), 27.65 ($(CH_3)_3$), 29.51 (CHPh), 45.82 (CHCN), 46.81 (C), 55.08 ($OCH_3$), 67.22 ($CH_2$), 55.08 ($OCH_3$), 80.81 (C), 112.62 (CN), 112.95 (CN), 114.24 (CH-Ar), 127.52 (CH-Ar), 128.16 (CH-Ar), 129.49 (CH-Ar), 130.47 (CH-Ar), 134.86 (C-Ar), 137.48 (C-Ar), 153.31 (C-Ar), 158.14 (C=O). HRMS ($M^+$ +1) Cald. for $C_{36}H_{51}N_3O_4Si$: 618.3727; Found: 618.3730. The enantiomeric ratio of **17** was determined to be 97:3 by CSP SFC (Chiralpak OD column, 5% MeOH, 3.0 ml/min). The major enantiomer had a retention time of 3.81 min and the minor enantiomer had a retention time of 3.34 min.

**(*3S,4S*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5,5-dicyano-4-methyl-4-phenyl-3-(2-*tert*-butyl)-phenyl-(*Z*)-1-pentene-1-amine (18).** The amine **18** was obtained with *N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-(2-*tert*-butyl)-phenyl-(*E*)-2-propene-1-amine (**13**) as the starting material amine and 2-(1-Phenyl-ethylidene)-malononitrile as the electrophile, following the procedure used for the preparation of **10**. The product was

purified by chromatography (1:15 ethyl acetate: pet. ether) to afford **18** (62%) as a 99:1 mixture of diastereomers. **18**: $^{1}$H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 9H, $(CH_3)_3$), 1.40 (s, 3H, $CH_3$), 1.57 (s, 9H, $(CH_3)_3$), 3.77 (s, 3H, $OCH_3$), 4.83 (d, *J*=10.0, 1H, CH), 5.50 (dd, *J*=10.0, 8.5, 1H, CH), 5.61 (bs, 1H, CH), 6.09 (dd, *J*=8.5, 1.5, 1H, CH), 6.65 (d, *J*=9.0, 1H, CH), 6.76 (dt, *J*=7.5, 1.0 1H, CH-Ar), 6.81 (d, *J*=9.5, 2H, CH-Ar), 7.06 (dt, *J*=7.0, 1.5, 1H, CH-Ar), 7.30 (dd, *J*=8.0, 1.5, 1H, CH-Ar), 7.34 (d, *J*=9.0, 3H, CH-Ar), 7.41 (m, 4H, CH-Ar). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 21.37 ($CH_3$), 28.16 ($CH_3$), 32.47 ($CH_3$), 34.28 (C), 35.93 (C), 43.95 (CH), 50.78 (CHCN), 55.44 ($OCH_3$), 82.84 (C), 112.48 (CN), 113.78 (CH-Ar) 114.37 (CN), 124.83 (CH-Ar), 126.16 (CH-Ar), 126.95 (CH-Ar), 127.23 (CH-Ar), 128.29 (CH-Ar), 128.49 (CH-Ar), 129.86 (CH-Ar), 129.96 (CH-Ar), 133.05 (C-Ar), 135.72 (C-Ar), 136.99 (C-Ar), 138.22 (C-Ar), 148.69 (C-Ar), 157.39 (C=O). The enantiomeric ratio of **18** was determined to be 97:3 by CSP HPLC (Chiralpak-AD column, 3% *i*-PrOH, 1.0 ml/min). The major enantiomer had a retention time of 5.73 min and the minor enantiomer had a retention time of 6.65 min.

**(*3R,4S*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5,5-dicyano-4-methyl-4-phenyl-3-cyclohexyl-(*Z*)-1-pentene-1-amine (19).** The amine **19** was obtained with *N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-cyclohexyl-(*E*)-2-propene-1-amine (**14**) as the starting material amine and 2-(1-Phenyl-ethylidene)-malononitrile as the electrophile, following the procedure used for the preparation of **10**. The product was purified by chromatography (1:6 ethyl acetate: pet. ether) and preparatory HPLC (10% ethyl acetate/hexane) to afford **19** (61%) as a 65:35 mixture of diastereomers. **19**: $^{1}$H NMR (acetone-$d_6$, 500 MHz) δ 1.18-1.38 (m, 16H, $CH_2$, $(CH_3)_3$), 1.65-1.90 (m, 5H, $CH_2$), 2.15 (bs, 1H, $CH_2$), 3.75 (s, 3H, $OCH_3$), 4.71 (bs, 1H, CH), 5.86 (s, 2H, CHCN, CH-Ar), 6.10 (m, 3H, CH-Ar), 6.72 (m, 2H, CH-Ar), 7.45-7.66 (m, 5H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ 18.56 ($CH_3$), 25.97 ($CH_2$), 25.99 ($CH_2$), 26.13 ($CH_2$), 27.69 ($CH_3$), 32.25 ($CH_2$), 32.33 ($CH_2$), 40.76 (CH), 48.92 (C), 54.97 ($OCH_3$), 79.55 (C), 112.82 (CN), 113.15 (CN), 113.49 (CH-Ar), 122.13 (CH-Ar), 128.01 (CH-Ar), 128.53 (CH-Ar), 131.04 (CH-Ar), 138.84 (C-Ar), 143.92 (CH-Ar), 158.88 (C=O). HRMS ($M^+$) Cald. for $C_{32}H_{39}N_3O_3$: 514.3069; Found: 514.3070. The enantiomeric ratio of **19** was determined to be 96:4 by CSP HPLC (Chiralpak AD column, 10% *i*-PrOH, 0.8 ml/min). The major

enantiomer had a retention time of 5.33 min and the minor enantiomer had a retention time of 7.12 min.

**(*3R,4R*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-5,5-dicyano-4-methyl-4-phenyl-3-trimethylsilyl-(*Z*)-1-pentene-1-amine (20).** The amine **20** was obtained with *N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-trimethylsilyl-(*E*)-2-propene-1-amine (**15**) as the starting material amine and 2-(1-Phenyl-ethylidene)-malononitrile as the electrophile, following the procedure used for the preparation of **10**. The product was purified by chromatography (1:6 ethyl acetate: pet. ether) to afford **20** (66%) as a 90:10 mixture of diastereomers. **20**: $^{1}$H NMR (acetone-$d_6$, 400 MHz) δ 0.16 (s, 9H, $(CH_3)_3$), 1.18 (m, 12H, , $CH_3$, $(CH_3)_3$), 3.75 (s, 3H, $OCH_3$), 4.80 (m, 1H, CH), 5.82 (s, 1H, CHCN), 6.40 (m, 3H, CH-Ar), 6.72 (m, 2H, CH-Ar), 7.40-7.70 (m, 5H, CH-Ar). $^{13}$C NMR (acetone-$d_6$, 125 MHz) δ -2.12 ($CH_3$), 18.36 ($CH_3$), 27.67 ($CH_3$), 36.09 (CHSi), 48.74 (C), 54.96 (CHCN), 54.99 ($OCH_3$), 80.88 (C), 112.86 (CN), 113.13 (CN), 113.48 (CH-Ar), 128.02 (CH-Ar), 128.59 (CH-Ar), 129.82 (CH-Ar), 131.04 (CH-Ar), 138.51 (CH-Ar), 138.73 (C-Ar), 140.09 (CH-Ar), 158.89 (C=O). HRMS ($M^+$ + 1) Cald. for $C_{29}H_{37}N_3O_3Si$: 504.2682; Found: 504.2684. The enantiomeric ratio of **20** was determined to be 96:4 by CSP SFC (Whelk-O column, 3% MeOH, 2.5 ml/min). The major enantiomer had a retention time of 9.68 min and the minor enantiomer had a retention time of 9.00 min.

**(*1R,3R,4S*)-Toluene-4-sulfonic-acid-2,2-dicyano-3-methyl-3,4-diphenyl-cyclopentylester (22a).** To a solution of the *cis* enecarbamate **9** (159 mg, 0.306 mmol) in $CHCl_3$ (5 ml), was added HCl (2 ml, 6 M). The reaction was stirred for 12 h, extracted with $CH_2Cl_2$, washed with saturated $NaCO_3$ solution, dried over $MgSO_4$, and concentrated under vacuum. Chromatography of the resultant oil (1:6 ethyl acetate: petroleum ether) afforded **21** (60 mg, 62%) as a 50:50 mixture of diastereomers. To this mixture of diastereomers of **21** (183 mg, 0.578 mmol) in $CH_2Cl_2$ (10 ml), was added $Et_3N$ (0.097 ml, 0.69 mmol), *p*-toluenesulfonyl chloride (133 mg, 0.69 mmol), and 4-dimethylamino pyridine (7 mg, 0.058 mmol). The reaction was stirred for 12 h, extracted with $CH_2Cl_2$, washed with saturated $NaCO_3$ solution, dried over $MgSO_4$, and concentrated under vacuum. Chromatography of the resultant oil (1:8 ethyl acetate:

petroleum ether) afforded **22** (204 mg, 83%) as a 52:48 mixture of diastereomers. The diastereomers were separated by preparatory HPLC (5% ethyl acetate/hexanes) and liquid diffusion of **22a** in $CH_2Cl_2$/heptane afforded the solid suitable for X-ray crystallography, **22a**, as a single diastereomer (73 mg). **22a**: $^1$H NMR ($CDCl_3$, 500 MHz) δ 1.56 (s, 3H, $CH_3$), 2.46 (s, 3H, $CH_3$), 2.73 (m, 1H, $CH_2$), 2.94 (m, 1H, $CH_2$), 4.59 (m, 1H, CHPh), 5.49 (m, 1H, CHO), 7.15-7.93 (m, 14H, CH-Ar). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 20.02 ($CH_3$), 21.98 ($CH_3$), 35.37 ($CH_2$), 46.71 (CHPh), 54.95 (C), 57.24 (C), 80.86 (CHO), 111.43 (CN), 112.99 (CN), 127.33 (CH-Ar), 127.92 (CH-Ar), 128.45 (CH-Ar), 128.78 (CH-Ar), 129.02 (CH-Ar), 129.13 (CH-Ar), 131.51 (CH-Ar), 132.62 (C-Ar), 136.60 (C-Ar), 137.81 (C-Ar), 146.39 (C-Ar).

**(*1R,3R,4S*)-Toluene-4-sulfonic-acid-2,2-dicyano-3-ethyl-3,4-diphenyl-cyclopentylester (23a).** Cyclopentane **23a** was obtained with **10** as the starting material amine, following the procedure used for the preparation of **22**. Chromatography of the resultant oil (1:8 ethyl acetate: petroleum ether) afforded **23** (74%) as a 50:50 mixture of diastereomers. The diastereomers were separated by preparatory HPLC (5% ethyl acetate/hexanes) and vapor diffusion of **23** in $CH_2Cl_2$/pentane afforded the solid suitable for X-ray crystallography, **23a**, as a single diastereomer. mp 136-140 °C. **23a**: $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.24 (t, *J*=7.07, 3H, $CH_3$), 2.06 (m, 1H, $CH_2$), 2.29 (m, 1H, $CH_2$), 2.46 (s, 3H, $CH_3$), 2.69 (m, 1H, $CH_2$), 2.94 (m, 1H, $CH_2$), 4.53 (dd, *J*=10.72, 9.20 1H, CHPh), 5.56 (dd, *J*=9.43, 6.65, 1H, CHO), 7.25-7.94 (m, 14H, CH-Ar). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 10.20 ($CH_3$), 21.98 ($CH_3$), 25.84 ($CH_2$), 36.08 ($CH_2$), 46.57 (CHPh), 55.02 (C), 61.23 (C), 80.50 (CHO), 111.77 (CN), 113.52 (CN), 127.79 (CH-Ar), 128.21 (CH-Ar), 128.37 (CH-Ar), 128.70 (CH-Ar), 128.95 (CH-Ar), 128.97 (CH-Ar), 129.64 (CH-Ar), 130.48 (CH-Ar), 132.76 (C-Ar), 137.05 (C-Ar), 137.34 (C-Ar), 146.30 (C-Ar).

References

(1) Suffert, J. *J. Org. Chem.* **1989**, *54*, 510.