Enantioselective Synthesis of Trifluoromethyl-substituted Cyclopropanes.

Justin R. Denton, Dinesh Sukuaran, and Huw M. L. Davies*

**Department of chemistry, University at Buffalo, The state University of New York, Buffalo, NY*

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Supporting Information

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General: Reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated. Analytical thin layer chromatography was performed on Whatman silica gel plates using UV light unless stated otherwise. Flash column chromatography was carried out using E. Merck silica 60. ^1H NMR spectra were recorded on a Varian Nuclear Magnetic Resonance spectrometer at 300, 400, or 500 MHz. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δH 0.00 for the residual protons in TMS), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets), coupling constant (J/Hz), and integration. ^{13}C spectra were recorded at 75.45 or 125 MHz and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δC 77.0 for CDCl_3 . ^{19}F NMR spectra were recorded on a Varian Nuclear Magnetic Resonance spectrometer at 375 MHz, with an internal reference of TMS. Infrared spectra were obtained on a Nicolet Impact 420 FT-IR spectrometer. Mass spectra were recorded on a Hewlett-Packard GC-MS system using 70 eV electron impact (EI) ionization or carried out by LC-MS (ESI). High-resolution mass spectra were obtained from the Mass Spectrometry Facility at the University at Buffalo, The State University of New York. Elemental analyses were determined by Atlantic Microlab, Inc., Norcross, GA. Melting points are uncorrected and optical rotations were measured at the sodium D line (589 nm) and reported as follows: $[\alpha]_{\text{D}}^{25}$, concentration (c in g/100 mL), and solvent (CHCl_3). Enantiomeric excess was determined by high performance liquid chromatography (HPLC) using Chiralcel OJ chiral analytical column (UV detection at 230 nm) unless otherwise stated. All moisture sensitive reactions were performed using glassware flame dried under vacuum and purged with argon prior to use. Solvents used in rhodium carbenoid transformations were degassed with argon for 10-15 min. prior to use. $\text{Rh}_2(\text{S-PTTL})_4$ was synthesized from the literature procedure¹ and used without additional purification. $\text{Rh}_2(\text{S-DOSP})_4$ and $\text{Rh}_2(\text{S-PTAD})_4$ are both commercially available from STREM®.

9

1-Phenyl-2,2,2-trifluorodiazoethane (9):

The diazo compound (9) was synthesized *via* a modified literature procedure.² KOH (11.6 mmol, 0.650 g) was dissolved in MeOH (15 mL) by stirring at room temperature. 4-Methyl-*N*'-(2,2,2-trifluoro-1-phenylethylidene)benzenesulfonylhydrazide (11) (5.8 mmol, 2.00 g) was added in one portion and the contents were heated to reflux for ~1 h and then cooled by addition of water (15 mL). The aqueous layer was then extracted with dichloromethane (DCM), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The orange residue was further purified by flash chromatography (silica gel, pentane) to give 9 (0.442g, ~40% yield with trace amounts of pentane). ^1H NMR (400 MHz, CDCl_3) δ

¹ Tsutsui, H.; Abe, T.; Nakamura, S.; Anada, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2005**, 53, 1366.

² Shepard, R. A.; Wentworth, S. E. *J. Org. Chem.* **1967**, 32, 3197.

7.42-7.38 (m, 2H), 7.22-7.18 (m, 1H), 7.10 (d, $J = 8.4$ Hz, 2H). The ^1H NMR data were consistent with the published values.¹

11

4-Methyl-*N'*-(2,2,2-trifluoro-1-phenylethylidene)benzenesulfonohydrazide (**11**):

2,2,2-Trifluoroacetophenone (2.60 mmol, 0.448 g) was added to ethanol (5 mL) at room temperature and *p*-toluenesulfon hydrazide (2.20 mmol, 0.410 g) was added in one portion. The contents were then stirred for ~10 min. and 2 drops of acetic acid were added. A condenser was then attached and the contents were heated to reflux. After ~8 h at reflux, the contents were cooled to room temperature with stirring and then the hydrazone was precipitated by adding distilled water (~10 mL). The white solid was collected by vacuum filtration and was recrystallized from boiling absolute ethanol to give **11** (0.612 g, yield 82 %). ^1H NMR (400 MHz, CDCl_3) δ 7.92 (s, 1H), 7.82 (d, $J = 7.6$ Hz, 2H), 7.55-7.53 (m, 3H), 7.37 (d, $J = 7.2$ Hz, 2H), 7.26-7.24 (m, 2H), 2.48 (s, 3H). The ^1H NMR data were consistent with the published values¹.

General Procedure for =N-NH₂ hydrazone formation:

The following procedure is typical for all of the NH₂ hydrazone formation reactions. Trifluoromethyl ketone (1.05 mmol) was added to absolute ethanol (~5 mL) and stirred at room temperature. Anhydrous hydrazine (1.00 mmol) was then slowly added drop wise and stirred for ~5 min. Acetic acid (~2 drops) was then added and a condenser was then attached. The contents were then refluxed overnight (~12 hr). Contents were then cooled to room temperature. At room temperature water (10 mL) was added and the solution was extracted with diethyl ether (3 X 10 mL). The organic layers were combined, dried over MgSO_4 , filtered, and then concentrated at reduced pressure. The crude hydrazone was then purified by column chromatography (silica gel, diethyl ether) at a fast rate to reduce product decomposition.

12

1-(2,2,2-Trifluoro-1-phenylethylidene)hydrazine (**12**):

Reaction was performed using 0.17 mL (5.47 mmol) of hydrazine. The crude hydrazone was purified by column chromatography (silica gel, diethyl ether, $R_f = 0.67$) to give **12** (1.023 g, 94% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.49 (m, 3H), 7.38 (d, $J = 7.2$ Hz, 2H), 5.85 (bs, 2H). The ^1H NMR data were consistent with the published values¹.

13a

1-(2,2,2-Trifluoro-1-*p*-tolylethyldene)hydrazine (13a):

The reaction was performed using 0.080 mL (2.53 mmol) of hydrazine. The crude hydrazone was purified by column chromatography (silica gel, diethyl ether, R_f = 0.65) to give **13a** (0.496 g, 91% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H), 5.84 (bs, 2H), 2.41(s, 3H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 140.5, 135.6 (q, J_{CCF} = 34.4 Hz), 130.2, 128.5, 123.8, 121.3 (q, J_{CF} = 272.5 Hz), 21.3; ^{19}F NMR (400 MHz, CDCl_3) δ -67.13; FTIR(neat): 1604, 1512, 1105, 975, 735; GCMS: 202 m/z; Anal. calcd. for $\text{C}_8\text{H}_7\text{F}_3\text{N}_2$: C, 53.47; H, 4.49; N, 13.86. Found: C, 53.23; H, 4.49; N, 13.57.

13b

1-(2,2,2-Trifluoro-1-(4-fluorophenyl)ethyldene)hydrazine (13b):

The reaction was performed using 0.08 mL (2.53 mmol) of hydrazine. The crude hydrazone was purified by column chromatography (silica gel, diethyl ether, R_f = 0.71) to give **13b** (0.472 g, 90% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.36 (m, 2H), 7.26-7.20 (m, 2H), 5.85 (bs, 2H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 163.6 (d, J_{CF} = 250.8 Hz), 134.2 (q, J_{CCF} = 34.4 Hz), 131.0 (d, J_{CCCF} = 8.6 Hz), 122.7 (d, J_{CCCF} = 3.4 Hz), 121.1 (q, J_{CF} = 272.0 Hz), 116.8 (d, J_{CCF} = 21.7 Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -67.20, -109.32 (q, J = 3.0 Hz); FTIR(neat): 1603, 1509, 1109, 841; GCMS: 206 m/z; Anal. calcd. for $\text{C}_8\text{H}_6\text{F}_4\text{N}_2$: C, 46.61; H, 2.93; N, 13.59. Found: C, 46.90; H, 2.95; N, 13.45.

13c

1-(1-(4-Bromophenyl)-2,2,2-trifluoroethyldene)hydrazine (13c):

The reaction was performed using 0.250 mL (7.96 mmol) of hydrazine. The crude hydrazone was purified by column chromatography (silica gel, diethyl ether, R_f = 0.70) to give **13c** (1.935 g, 91% yield with trace impurities). ^1H NMR (400 MHz, CDCl_3) δ 7.67 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 5.87 (s, 2H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 134.0 (q, J_{CCF} = 34.9 Hz), 132.9, 130.4, 125.6, 124.8, 121.0 (q, J_{CF} = 272.6 Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -67.01; FTIR(neat): 1604, 1488, 1106, 827; GCMS: 265.9 m/z ($\text{Br}^{79}\text{M}+100\%$), 267.9 m/z ($\text{Br}^{81}\text{M}+98.64\%$); HRMS (EI) m/z calcd. for $\text{C}_8\text{H}_6\text{F}_3\text{N}_2\text{Br}$: 265.9662. Found: 265.9669.

General Procedure for oxidation and cyclopropanation:

The following procedure is typical for all of the diazo compound formation reactions. Trifluoromethyl hydrazone (1 mmol) was added to α,α,α -trifluorotoluene (TFT, 5 mL). The contents were degassed by bubbling argon through the solution for 5 min. MgSO_4 (equal mass as hydrazone) was added and then the contents were placed in an ice bath for ~10 min. At 0°C , MnO_2 (5.0 mmol) was added in one portion and the contents were allowed to stir overnight gradually warming to room temperature (~12 h). The orange/black colored solution was then filtered through SiO_2 and MgSO_4 (2:1 ratio by mass) and washed with a pentane and TFT mixture (4:1 ratio by volume) until the filtrate was colorless. The orange filtrate was then degassed by bubbling argon through the solution for 5 min and used without further purification in the following carbenoid reaction.

The following procedure is typical for the intermolecular cyclopropanation reactions. Catalyst (2 mol %) and alkene (5.0 mmol) were added to TFT (5 mL) at room temperature. A syringe pump was then used to add the diazo compound solution (~1 mmol, described above) over 3 h to the catalyst solution. After the addition, the reaction was allowed to stir for 1 h at room temperature. The contents were then concentrated at reduced pressure and put under high vacuum. The diastereomeric excess was then determined by ^1H NMR on the crude residue. The crude residue was further purified by column chromatography (silica gel) to give the pure cyclopropane. The enantiomeric excess of the purified product was then determined by chiral HPLC.

10a

((1*R*,2*S*)-1-(Trifluoromethylcyclopropane-1,2-diyl)dibenzene (10a):

The reaction was performed using 0.038 g (0.202 mmol) of the hydrazone **12**. The crude residue was purified by column chromatography (silica gel, pentane, R_f = 0.24) to give **10a** (0.037 g, 71% yield). Mp = $68\text{--}69^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.20–7.08 (m, 8H), 6.77 (dd, J = 3.6 Hz, J = 6.8 Hz, 2H), 2.85 (dd, J = 6.8 Hz, J = 9.6 Hz, 1H), 1.89 (dd, J = 5.8 Hz, J = 9.4 Hz, 1H), 1.70–1.67 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 135.6, 132.5, 131.5, 128.1, 127.94, 127.88, 127.82, 126.5, 125.9 (q, J_{CF} = 274.3 Hz), 35.8 (q, J_{CCF} = 32.6 Hz), 25.6 (d, J_{CCCF} = 2.3 Hz), 14.6 (d, J_{CCCF} = 2.3 Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -69.74; FTIR (neat): 1498, 1320, 1281, 1135, 695, 652; GCMS: 262 m/z; HRMS (EI) m/z calcd. for $\text{C}_{16}\text{H}_{13}\text{F}_3$: 262.0964. Found: 262.0955; Anal. calcd. for $\text{C}_{16}\text{H}_{13}\text{F}_3$: C, 73.27; H, 5.00. Found: C, 72.99; H, 4.81; HPLC analysis: >99 % ee (chiralcel OJ, 1 % *i*Pr-OH in hexane, 0.8 mL/min λ = 230 nm, t_R = 6.42 min, major; t_R = 7.61 min, minor), $[\alpha]_D^{25}$ = +113.0° (c 1.00, CHCl_3).

10b

1-((1R,2S)-2-(4-Methylphenyl)-1-(trifluoromethyl)cyclopropyl)benzene (10b):

The reaction was performed using 0.011 g (0.058 mmole) of the hydrazone **12**. The crude residue was purified by column chromatography (silica gel, pentane, R_f = 0.24) to give **10b** (0.012 g, 72% yield). Mp = 70–71 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.24–7.14 (m, 5H), 6.90 (d, J = 8.0 Hz, 2H), 6.66 (d, J = 8.0 Hz, 2H), 2.81 (dd, J = 7.0 Hz, J = 9.4 Hz, 1H), 2.23 (s, 3H), 1.87 (dd, J = 5.8 Hz, J = 9.4 Hz, 1H), 1.66–1.63 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 136.0, 132.5, 131.7, 128.5, 128.1, 127.9, 127.8, 124.1, 35.6 (q, J_{CCF} = 32.6 Hz), 25.3 (d, J_{CCCF} = 2.3 Hz), 20.9, 14.7; ^{19}F NMR (400 MHz, CDCl_3) δ -69.73; FTIR (neat): 1519, 1380, 1133, 699, 652; GCMS: 276 m/z; Anal. calcd. for $\text{C}_{17}\text{H}_{15}\text{F}_3$: C, 73.90; H, 5.47. Found: C, 73.62; H, 5.47; HPLC analysis: 90 % ee (chiralcel OJ, 1 % *i*Pr-OH in hexane, 1.0 mL/min λ = 230 nm, t_R = 4.9 min, major; t_R = 6.1 min, minor), $[\alpha]_D^{25}$ = +57.2 (c 0.50, CHCl_3)

10c

1-((1R,2S)-2-(4-Methoxyphenyl)-1-(trifluoromethyl)cyclopropyl)benzene (10c):

The reaction was performed using 0.039 g (0.207 mmol) of the hydrazone **12**. The crude residue was purified by column chromatography (silica gel, diethyl ether / pentane 1:25 ratio by volume, R_f = 0.50) to give **10c** (0.047 g, 78% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.12–7.13 (m, 5H), 6.70–6.62 (m, 4H), 3.71 (s, 3H), 2.80 (dd, J = 7.2 Hz, J = 9.6 Hz, 1H), 1.86 (dd, J = 5.6 Hz, J = 9.6 Hz, 1H), 1.62–1.59 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 158.2, 132.5, 131.7, 128.8, 128.0, 127.9, 127.5, 125.9 (q, J_{CF} = 274.3 Hz), 113.3, 55.0, 35.3 (q, J_{CCF} = 32.7 Hz), 25.0 (d, J_{CCCF} = 2.9 Hz), 14.6 (d, J_{CCCF} = 2.3 Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -69.63; FTIR (neat): 3032, 2810, 1517, 1131, 699, 652; GCMS: 292 m/z; Anal. calcd. for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{O}$: C, 69.85; H, 5.17. Found: C, 69.74; H, 5.03; HPLC analysis: 88 % ee (chiralcel OJ, 1 % *i*Pr-OH in hexane, 0.8 mL/min λ = 230 nm, t_R = 8.6 min, major; t_R = 11.4 min, minor), $[\alpha]_D^{25}$ = +105.4 (c 4.50, CHCl_3).

10d

1-((1R,2S)-2-(4-Chlorophenyl)-1-(trifluoromethyl)cyclopropyl)benzene (10d):

The reaction was performed using 0.011 g (0.058 mmol) of the hydrazone **12**. The crude residue was purified by column chromatography (silica gel, pentane, R_f = 0.26) to give

10d (0.011 g, 64% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.23-7.11 (m, 5H), 7.07-7.05 (m, 2H), 6.70-6.68 (m, 2H), 2.81 (dd, $J = 7.2$ Hz, $J = 9.6$ Hz, 1H), 1.91 (dd, $J = 6.2$ Hz, $J = 9.8$ Hz, 1H), 1.66-1.63 (m, 1H); ^{13}C NMR (75.35 MHz, CDCl_3) δ 134.3, 132.4, 132.3, 131.1, 129.1, 128.3, 128.1, 128.0, 125.7 (q, $J_{\text{CF}} = 274.3$ Hz), 35.9 (q, $J_{\text{CCF}} = 32.7$ Hz), 25.0 (d, $J_{\text{CCCF}} = 2.3$ Hz), 14.8; ^{19}F NMR (400 MHz, CDCl_3) δ -69.84; FTIR(neat): 3032, 1497, 1134, 699, 653; GCMS: 296 m/z; HRMS (ES) m/z calcd. for $\text{C}_{16}\text{H}_{12}\text{ClF}_3$: 296.0574. Found: 296.0574; HPLC analysis: 90 % ee (chiralcel OJ, 1 % *i*Pr-OH in hexane, 1.0 mL/min $\lambda = 230$ nm, $t_{\text{R}} = 6.1$ min, major; $t_{\text{R}} = 8.4$ min, minor), $[\alpha]_{\text{D}}^{25} = +55.5$ (*c* 0.80, CHCl_3).

10e

1-((1R,2S)-2-(4-(Trifluoromethyl)phenyl)-1-(trifluoromethyl)cyclopropyl)benzene (10e):

The reaction was performed using 0.025 g (0.133 mmol) of the hydrazone **12**. The crude residue was purified by column chromatography (silica gel, pentane, $R_f = 0.45$) to give **10e** (0.027 g, 61% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 8.0$ Hz, 2H), 7.25-7.11 (m, 5H), 6.86 (d, $J = 8.0$ Hz, 2H), 2.88 (dd, $J = 7.2$ Hz, $J = 9.2$ Hz, 1H), 1.97 (dd, $J = 6.0$ Hz, 1H), 1.74-1.71 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 140.1, 132.4, 130.8, 128.4, 128.2, 128.1, 125.7 (q, $J_{\text{CF}} = 274.3$ Hz), 124.7 (q, $J_{\text{CCF}} = 4.0$ Hz), 124.0 (q, $J_{\text{CF}} = 280$ Hz), 36.4 (q, $J_{\text{CCF}} = 32.7$ Hz), 25.3 (d, $J_{\text{CCCF}} = 2.3$ Hz), 15.2; ^{19}F NMR (400 MHz, CDCl_3) δ -62.49, -70.05; FTIR(neat): 3032, 1620, 1323, 1070, 700, 655; GCMS: 330 m/z; HRMS (EI) m/z calcd. for $\text{C}_{17}\text{H}_{12}\text{F}_6$: 330.0839. Found: 330.0840; HPLC analysis: >94 % ee (chiralcel OJ, 0 % *i*Pr-OH in hexane, 1.0 mL/min $\lambda = 230$ nm, $t_{\text{R}} = 10.9$ min, major; $t_{\text{R}} = 16.5$ min, minor), $[\alpha]_{\text{D}}^{25} = +109.1$ (*c* 1.10, CHCl_3).

10f

1-((1R,2S)-2-Naphthyl-1-(trifluoromethyl)cyclopropyl)benzene (10f):

The reaction was performed using 0.024 g (0.128 mmol) of the hydrazone **12**. The crude residue was purified by column chromatography (silica gel, pentane, $R_f = 0.19$) to give **5f** (0.028 g, 75% yield). Mp= 81-82°C; ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.68 (m, 1H), 7.61-7.59 (m, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.40-7.34 (m, 2H), 7.31 (s, 1H), 7.18-7.08 (m, 5H), 6.81 (dd, $J = 1.6$ Hz, $J = 8.4$ Hz, 1H), 2.99 (dd, $J = 7.2$ Hz, $J = 9.6$ Hz, 1H), 1.95 (dd, $J = 6.4$ Hz, $J = 9.6$ Hz, 1H), 1.82-1.78 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 133.3, 133.0, 132.1, 131.4, 132.4, 128.2, 128.0, 127.5, 127.4, 127.3, 126.9, 126.0, 125.91 (q, $J_{\text{CF}} = 274.3$ Hz), 125.90, 125.5, 35.9 (q, $J_{\text{CCF}} = 32.1$ Hz), 25.8 (q, $J_{\text{CCCF}} = 2.3$ Hz), 14.9 (q, $J_{\text{CCCF}} = 2.3$ Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -69.71; FTIR(neat): 3059, 1601, 1347, 1294, 1135, 1126, 699; GCMS: 312 m/z; Anal. calcd. for $\text{C}_{20}\text{H}_{15}\text{F}_3$: C, 76.91; H,

4.84. Found: C, 76.55; H, 4.72; HPLC analysis: 89 % ee (chiralcel OJ, 1 % *i*Pr-OH in hexane, 0.8 mL/min λ = 230 nm, t_R = 7.9 min, major; t_R = 15.3 min, minor), $[\alpha]_D^{25}$ =+84.6 (*c* 2.30, CHCl₃).

10g

1-(1-(Trifluoromethyl)-2-octylcyclopropyl)benzene (10g):

To a flame dried round bottom flask equipped with stir bar under argon, 1-decene (5 mmole, 0.200 g, 5 eq.), TFT (10 mL), and catalyst Rh₂(OAc)₄ (2 mol %, 9 mg) were added and degassed by argon. A syringe pump was then used to add diazo compound **9** (1 mmole, 0.186 g in TFT and pentane 1:1 by volume, 10mL) over 3 hr to the catalyst solution. After the addition, reaction was allowed to stir for 1 h. Contents were concentrated *in vacuo* and then put under high vacuum. This residue was further purified by chromatography (silica gel, pentane, R_f = 0.61) to give **10g** (0.104 g, 20% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.30 (m, 5H), 1.55-1.21 (m, 15H), 0.88-0.85 (m, 4H), 0.53-0.49 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) (δ 77.00ppm) δ 133.2, 131.9, 128.2, 128.1, 126.4 (q, J_{CF} = 273.5 Hz), 32.3 (q, J_{CCF} = 32.3 Hz), 31.8, 29.9, 29.5, 29.3, 29.2, 29.1, 22.6, 20.9 (q, J_{CCCF} = 2.3 Hz), 15.0 (q, J_{CCCF} = 2.8 Hz), 14.1; ¹⁹F NMR (400 MHz, CDCl₃) δ -71.89; FTIR(neat): 2927, 2856, 1303, 1151, 1134, 700, 659; GCMS: 298 m/z; Anal. calcd. for C₁₈H₂₅F₃: C, 72.45; H, 8.44. Found: C, 72.57; H, 8.46. Diastereomeric Excess and Enantiomeric Excess were not determined.

14a

1-Methyl-4-((1*R*,2*S*)-2-phenyl-1-(trifluoromethyl)cyclopropyl)benzene (14a):

The reaction was performed using 0.023 g (0.114 mmol) of the hydrazone **13a**. The crude residue was purified by column chromatography (silica gel, pentane, R_f = 0.23) to give **14a** (0.023 g, 75% yield). Mp=67-68°C; ¹H NMR (400 MHz, CDCl₃) δ 7.10-7.08 (m, 3H), 7.02(d, J = 8 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.80-6.78 (m, 2H), 2.81 (dd, J = 7.2 Hz, J = 9.6 Hz, 1H), 2.25 (s, 3H), 1.85 (dd, J = 5.8 Hz, J = 9.4 Hz, 1H), 1.65-1.63 (m, 1H); ¹³C NMR (75.45 MHz, CDCl₃) δ 137.9, 135.8, 132.3, 128.7, 128.4, 128.0, 127.8, 126.0 (q, J_{CF} = 273.7 Hz), 126.4, 35.4 (q, J_{CCF} = 32.6 Hz), 25.6 (d, J_{CCCF} = 2.3 Hz), 21.1, 14.7 (d, J_{CCCF} = 2.3 Hz); ¹⁹F NMR (400 MHz, CDCl₃) δ -69.78; FTIR(neat): 3031, 1518, 1133, 910, 811, 695; GCMS: 276 m/z; Anal. calcd. for C₁₇H₁₅F₃: C, 73.90; H, 5.47. Found: C, 74.00; H, 5.54; HPLC analysis: 99 % ee (chiralcel OJ, 0.5 % *i*Pr-OH in hexane, 1.0 mL/min λ = 230 nm, t_R = 4.5 min, major; t_R = 5.7 min, minor), $[\alpha]_D^{25}$ =+124.4 (*c* 1.00, CHCl₃).

14b

1-Fluoro-4-((1*R*,2*S*)-2-phenyl-1-(trifluoromethyl)cyclopropyl)benzene (14b):

The reaction was performed using 0.024 g (0.116 mmol) of the hydrazone **13b**. The crude residue was purified by column chromatography (silica gel, pentane, R_f = 0.30) to give **14b** (0.026 g, 78% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.11-7.08 (m, 5H), 6.85 (m, 2H), 6.76 (dd, J = 3.2 Hz, J = 6.8 Hz, 2H), 2.84 (dd, J = 6.8 Hz, J = 9.6 Hz, 1H), 1.88 (dd, J = 5.8 Hz, J = 9.4 Hz, 1H), 1.65 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 162.5 (d, J_{CF} = 247.9 Hz), 135.3, 134.3, 134.2, 128.0, 127.9, 126.6, 125.8 (q, J_{CF} = 274.8 Hz), 115.0 (d, J_{CCF} = 21.8 Hz), 35.0 (q, J_{CCF} = 32.6 Hz), 25.7 (d, J_{CCCF} = 2.3 Hz), 14.6 (d, J_{CCCF} = 2.3 Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -69.82, -113.09; FTIR(neat): 2918, 1513, 1302, 1133, 909, 728; GCMS: 280 m/z; Anal. calcd. for $\text{C}_{16}\text{H}_{12}\text{F}_4$: C, 68.57; H, 4.31. Found: C, 68.64; H, 4.33; HPLC analysis: 97 % ee (chiralcel OJ, 1.0 % *i*Pr-OH in hexane, 1.0 mL/min λ = 230 nm, t_R = 4.8 min, major; t_R = 7.4 min, minor), $[\alpha]_D^{25}$ = +99.8 (*c* 1.05, CHCl_3).

14c

1-Bromo-4-((1*R*,2*S*)-2-phenyl-1-(trifluoromethyl)cyclopropyl)benzene (14c):

The reaction was performed using 0.105 g (0.393 mmol) of the hydrazone **13c**. The crude residue was purified by column chromatography (silica gel, pentane, R_f = 0.26) to give **14c** (0.103 g, 77% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, J = 8.4 Hz, 2H), 7.12-7.10 (m, 3H), 7.00 (d, J = 8.4 Hz, 2H), 6.79-6.77 (m, 2H), 2.85 (dd, J = 7.2 Hz, J = 9.6 Hz, 1H), 1.87 (dd, J = 6.0 Hz, J = 9.6 Hz, 1H), 1.66-1.63 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 135.0, 134.1, 131.2, 130.7, 128.0, 127.9, 126.7, 125.6 (q, J_{CF} = 274.2 Hz), 122.6, 35.2 (q, J_{CCF} = 32.7 Hz), 25.6 (d, J_{CCCF} = 2.3 Hz), 14.5 (d, J_{CCCF} = 2.3 Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -69.71; FTIR(neat): 3033, 1396, 1133, 975, 696; GCMS: 340 m/z, 342 m/z; Anal. calcd. for $\text{C}_{16}\text{H}_{12}\text{BrF}_3$: C, 56.33; H, 3.55. Found: C, 56.34; H, 3.45; HPLC analysis: 98 % ee (chiralcel OJ, 1.0 % *i*Pr-OH in hexane, 1.0 mL/min λ = 230 nm, t_R = 4.8 min, major; t_R = 6.5 min, minor), $[\alpha]_D^{25}$ = +123.8 (*c* 2.30, CHCl_3).

15a

4,4'-(1*R*,2*S*)-1-(Trifluoromethyl)cyclopropane-1,2-diylbis(bromobenzene) (15a):

The reaction was performed using 0.029 g (0.109 mmol) of the hydrazone **13c**. The crude residue was purified by column chromatography (silica gel, pentane, R_f = 0.32) to give **15a** (0.036 g, 78 % yield). ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, J = 8.4 Hz, 2H), 7.13-7.11 (m, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.80-6.77 (m, 2H), 2.85 (dd, J = 7.2 Hz, J = 9.6 Hz, 1H), 1.88 (dd, J = 6.0 Hz, 9.6 Hz, 1H), 1.70-1.63 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 134.3, 134.0, 131.5, 131.2, 130.2, 129.5, 125.4 (q, J_{CF} = 274.9 Hz), 122.9, 120.7, 35.4 (q, J_{CCF} = 32.7 Hz), 25.1, 14.8; ^{19}F NMR (400 MHz, CDCl_3) δ -69.86; FTIR(neat): 1593, 1491, 1292, 1137, 1011, 724, 668; HRMS (EI) m/z calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{Br}_2$: 417.9174. Found: 417.9175; HPLC analysis: >99 % ee (chiralcel OJ, 1.0 % *i*Pr-OH in hexane, 1.0 mL/min λ = 230 nm, t_R = 7.3 min, major; t_R = 11.7 min, minor), $[\alpha]_D^{25}$ = +117.0 (c 8.10, CHCl_3).

15b

1-Bromo-4-((1*R*,2*S*)-2-(4-nitrophenyl)-1-(trifluoromethyl)cyclopropyl)benzene (15b):

The reaction was performed using 0.150 g (0.562 mmol) of the hydrazone **13c**. The crude residue was purified by column chromatography (silica gel, 20:1 v/v pentane / diethyl ether then 2:1 v/v pentane / diethyl ether) to give **15b** (0.162 g, 75 % yield). ^1H NMR (400 MHz, CDCl_3) δ 8.00 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.93 (d, 8.4 Hz, 2H), 2.94 (dd, J = 6.8 Hz, J = 9.2 Hz, 1H), 2.03 (dd, J = 6.4 Hz, J = 9.6 Hz, 1H), 1.77-1.74 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 146.7, 143.2, 133.7, 132.5, 131.9, 131.7, 129.6, 128.5, 125.2 (q, J_{CF} = 257.7 Hz), 123.2, 36.4 (q, J_{CCF} = 33.2 Hz), 25.4, 15.5; ^{19}F NMR (400 MHz, CDCl_3) δ -70.14; FTIR(neat): 1601, 1518, 1343, 1135, 818, 718, 699; Anal. calcd. for $\text{C}_{16}\text{H}_{11}\text{BrF}_3\text{NO}_2$: C, 49.76; H, 2.87; N, 3.63. Found: C, 49.83; H, 2.87; N, 3.61; HPLC analysis: >99 % ee (chiralcel OJ, 2.5 % *i*Pr-OH in hexane, 0.8 mL/min λ = 230 nm, t_R = 18.4 min, major; t_R = 23.8 min, minor), $[\alpha]_D^{25}$ = +172.7 (c 0.30, CHCl_3).

15c

1-Bromo-4-((1*R*,2*S*)-2-naphthyl-1-(trifluoromethyl)cyclopropyl)benzene (15c): The reaction was performed using 0.034 g (0.127 mmol) of the hydrazone **13c**. The crude residue was purified by column chromatography (silica gel, pentane, R_f = 0.21) to give **15c** (0.040 g, 80 % yield). ^1H NMR (400 MHz, CDCl_3) δ 7.73-7.71 (m, 1H), 7.65-7.63 (m, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.43-7.35 (m, 3H), 7.25-7.23 (m, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.8 Hz, 1H), 3.01 (dd, J = 7.2 Hz, J = 9.2 Hz, 1H), 1.96 (dd, J = 5.6 Hz, J = 9.6 Hz, 1H), 1.80-1.77 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 134.0, 133.0, 132.7, 132.2, 131.3, 130.6, 127.6, 127.55, 127.47, 127.40, 126.2, 125.7, 125.6 (q, J_{CF} = 274.3 Hz), 122.6, 35.4 (q, J_{CCF} = 33.2 Hz), 25.9 (d, J_{CCCF} = 2.3 Hz), 14.7 (d, J_{CCCF} = 2.9 Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -69.84; FTIR(neat): 1593, 1490, 1291, 1135, 1012, 814, 748; HRMS (EI) m/z calcd. for $\text{C}_{20}\text{H}_{14}\text{F}_3\text{Br}$: 390.0225. Found: 390.0222; HPLC analysis: 98 % ee (chiralcel OJ, 10.0 % *i*Pr-OH in hexane, 0.8 mL/min λ = 230 nm, t_R = 7.5 min, major; t_R = 17.1 min, minor), $[\alpha]_D^{25}$ = +137.6 (c 2.90, CHCl_3).

15d

(*S*)-2-(4-Bromophenyl)-2-(trifluoromethyl)cyclopropane-1,1-diyl)dibenzene (15d): The reaction was performed using 0.024 g (0.090 mmol) of the hydrazone **13c**. The crude residue was purified by column chromatography (silica gel, 20:1 v/v pentane / diethyl ether, R_f = 0.30) to give **15d** (0.028 g, 75 % yield). ^1H NMR (500 MHz, CDCl_3) δ 7.59 (d, J = 7.0 Hz, 2H), 7.35-7.219 (m, 8H), 7.09 (d, J = 9.0 Hz, 2H), 7.03-7.00 (m, 2H), 6.97-6.94 (m, 1H), 2.37 (dd, J = 1.0 Hz, J = 6.0 Hz, 1H), 2.24 (d, J = 5.5 Hz, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 140.7, 139.6, 133.1, 132.2, 131.1, 129.73, 129.72, 128.7, 128.4, 128.0, 127.1, 126.5, 125.8 (q, J_{CF} = 276.0 Hz), 122.1, 39.6 (q, J_{CCF} = 31.5 Hz), 19.4 (d, J_{CCCF} = 2.3 Hz); ^{19}F NMR (400 MHz, CDCl_3) δ -61.66; FTIR(neat): 1600, 1492, 1334, 1122, 1009, 704, 695; Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{BrF}_3$: C, 63.33; H, 3.86. Found: C, 63.04; H, 3.88; HPLC analysis: 99 % ee (chiralcel OD, 0.5 % *i*Pr-OH in hexane, 1.0 mL/min λ = 230 nm, t_R = 5.4 min, minor; t_R = 7.0 min, major), $[\alpha]_D^{25}$ = +161.3 (c 1.75, CHCl_3).

¹⁹F{¹H}HOESY analysis

The cyclopropane **14b** was analyzed to find its relative stereochemistry *via* a ¹⁹F{¹H}HOESY NMR experiment.

Figure S1: ¹⁹F{¹H}HOESY of cyclopropane **14b**.

HOESY spectra were recorded using a Bruker AMX-400 spectrometer with a {¹⁹F, ¹H} probe. The spectra were recorded in CDCl₃ at 25°C. A spectral width of 31250 Hz in f₂ dimension (¹⁹F) and 4265 Hz in f₁ dimension (¹H) were used. 128 scans were collected for each of the 128 increments, with a relaxation delay of 2.0 s, using the phase-sensitive TPPI method.³ The spectra were processed using a 2K X 2K matrix, apodized using a cosine-squared function.

³ C. Yu & G. Levy, *J. Am. Chem. Soc.* **1984**, 106, 6533.

X-ray analysis

The cyclopropane **15b** was converted to **16** by the following reactions in order to produce crystalline material which was suitable to grow a crystal for X-ray analysis.

16

1-Bromo-4-((1R,2S)-2-(4-(4-bromophenylamido)phenyl)-1-(trifluoromethyl)cyclopropyl)benzene (**16**):

Cyclopropane **15b** (0.182 g, 0.471 mmol) was dissolved in EtOAc and EtOH (1:1 ratio v/v, 10 mL). $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.460 g, ~5 equiv) was then added in one portion. The contents was brought to reflux and stirred at reflux for 3h. After 3h, the reaction was cooled to room temperature and poured into an ice bath. Sodium bicarbonate was then added until pH of ~8 was obtained, then extracted with EtOAc (3 X 25 mL). The organic layers were combined then washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was then purified *via* column chromatography (silica gel, 1:1 v/v pentane/ Et_2O) to give the cyclopropyl aniline which was subjected to the following step.

The cyclopropyl aniline was dissolved in DCM (10 mL) and stirred at room temperature. Triethyl amine (0.06 mL, 1.10 equiv) was added dropwise, followed by addition of *p*-bromobenzoyl chloride in one portion. The reaction was monitored by TLC for consumption of the cyclopropyl aniline. After consumption was complete (~3 h), sat. NH_4Cl (10 mL) was added. The layers were then separated and the organic layer was washed with sat. NH_4Cl (10 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was further purified by column chromatography (silica gel, pentane, R_f = 0.26) to give **16** (0.138 g, 55 % overall yield). Mp = 200-201°C ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 8.8 Hz, 3H), 7.60 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 2.85 (dd, J = 7.2 Hz, J = 9.6 Hz, 1H), 1.89 (dd, J = 6.4 Hz, J = 9.2 Hz, 1H), 1.65-1.62 (m, 1H); ^{13}C NMR (75.45 MHz, CDCl_3) δ 164.7, 136.4, 134.0, 133.6, 131.9, 131.5, 131.3, 130.6, 128.6, 128.5, 126.6, 125.5 (q, J_{CF} = 274.3 Hz), 122.7, 119.8, 35.2 (q, J_{CCF} = 32.6 Hz), 25.3, 14.6; ^{19}F NMR (400 MHz, CDCl_3) δ -69.81; FTIR(neat): 1648, 1523, 1153, 1131, 815, 699; HRMS (EI) m/z calcd. for $\text{C}_{23}\text{H}_{16}\text{F}_3\text{NOBr}_2$: 536.9545. Found: 536.9554; HPLC analysis: >99 % ee (chiralcel OJ, 10 % *i*Pr-OH in hexane, 0.8mL/min λ = 230 nm, t_R = 33.0 min, major; t_R = 46.4 min, minor), $[\alpha]_D^{25}$ = +130.0 (*c* 1.10, CHCl_3).

Crystalline material of **16** suitable for X-ray analysis was grown as follows: In a 4 mL vial 50 mg of **16** was dissolved in THF (~1 mL). The uncapped vial was then placed inside a larger 20 mL vial which contained 5 mL of pentane. The larger vial was then capped and the pentane vapors were allowed to slowly diffuse into the smaller vial for 5 days at which time crystalline material of **16** suitable for X-ray analysis were obtained.

Figure S2: X-ray structure of compound **16**.⁴

Fig. S2. ORTEP plot and label representation of cyclopropane **16**. Displacement ellipsoids are drawn at the 50 % probability level.

⁴ The X-ray crystallographic data has been submitted to the Cambridge Structure Database: Pitak, M. and Coppens, P. *Private Communication*, **2007**, CCDC 638557.

13a

13b

13c

10a

10b

10c

10d

10e

10f

14a

14b

14c

15d

16