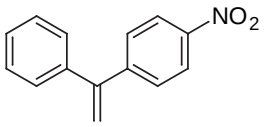
Stereoselectivity of Methyl Aryl-diazoacetate Cyclopropanations of 1,1-Diarylethylene. Asymmetric Synthesis of a Cyclopropyl Analog of Tamoxifen

Huw M. L. Davies,* Tadamichi Nagashima and James Klino III

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14260

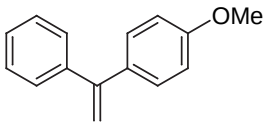
hdavies@acsu.buffalo.edu

Supporting Information

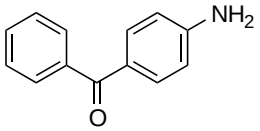


1-(4-Nitrophenyl)-1-phenylethylene. To a solution of methyltriphenylphosphonium bromide (7.25 g, 20.3 mmol) in THF (30 mL) was added BuLi (2.5 M in hexanes, 6.2 mL, 16 mmol) at 0 °C. After 25 min, 4-nitrobenzophenone (3.35 g, 14.7 mmol) was added as solid in one portion. After 2 h, H_2O (50 mL) was added, and the mixture was stirred for 3 h. After the separation of two layers, the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 3 % H_2O_2 (1 × 100 mL), 0.5 N NaOH (1 × 100 mL), and brine (1 × 100 mL), and were dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, pentane/Et_2O = 60/1–20/1) to give the product (2.78 g, 12.3 mmol, 84 % yield): IR (film) 1595, 1515, 1346, 911, 860, 779, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 2 H), 7.50 (d, J = 8.7 Hz, 2 H), 7.40–7.25 (m, 5 H), 5.63 (s, 1 H), 5.59 (s, 1 H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 148.38, 148.04, 147.30, 140.12, 129.00, 128.53, 128.36, 128.15, 123.56, 117.28; MS (EI) *m/z* 225, 178; HRMS (EI) *m/z* calcd for $C_{14}H_{11}NO_2$ 225.0790, found 225.0801.

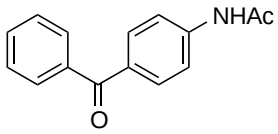


1-(4-Methoxyphenyl)-1-phenylethylene. To a solution of methyltriphenylphosphonium bromide (17.4 g, 48.8 mmol) in THF (100 mL) was added BuLi (2.5 M in hexanes, 18 mL, 45 mmol) at 0 °C. After 2 h, 4-methoxybenzophenone (8.71 g, 41.0 mmol) in THF (20 mL) was added dropwise. After 2 h, the cooling bath was removed, and the mixture was stirred for 4 h at 23 °C. H_2O (150 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The combined ether layers were washed with H_2O (1 × 100 mL) and brine (1 × 100 mL), and were dried over $MgSO_4$. After the removal of the solvent by a rotavap, pentane–Et_2O(50/1, 100 mL) was added, and the mixture was passed through a SiO_2 pad. The SiO_2 pad was washed with pentane-Et_2O (50/1). The filtrate was concentrated to give white powder, and the product was purified by recrystallization from MeOH–H_2O (9/1, 150 mL) to give the product (6.38 g, 30.3 mmol, 74% yield): IR (film) 1606, 1508, 1249, 1028, 901, 842, 785, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 7 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.40 (d, *J* = 1.2 Hz, 1 H), 5.36 (d, *J* = 0.8 Hz, 1 H), 3.83 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.35, 149.53, 141.84, 134.00, 129.43, 128.36, 128.17, 127.69, 113.55, 113.00, 55.30; MS (EI) *m/z* 210, 195, 167; HRMS (EI) *m/z* calcd for $C_{15}H_{14}O$ 210.1045, found 210.1058.

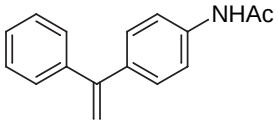


4-Aminobenzophenone. To a solution of 4-nitrobenzophenone (2.23 g, 9.81 mmol) in AcOH (30 mL) and EtOH (30 mL) was added Fe powder (5.8 g, 0.10 mol). The mixture was refluxed for 2 h, and was poured into H_2O (500 mL), and Na_2CO_3 was added until no bubble was formed. The mixture was extracted with EtOAc (1 × 200 mL, and then 2 × 100 mL). The combined organic layers were washed with H_2O (2 × 100 mL) and brine (1 × 100 mL), and were dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 2/1 to 3/2) to give the title compound (1.77 g, 8.97 mmol, 91% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.8 Hz, 4 H), 7.54 (t, *J* = 7.6 Hz, 1

H), 7.45 (t, *J* = 7.6 Hz, 2 H), 6.68 (d, *J* = 8.4 Hz, 2 H), 4.16 (br s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.47, 151.41, 138.83, 132.91, 131.37, 129.42, 128.04, 126.82, 113.51.

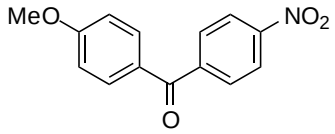


4-Acetamidobenzophenone. To a solution of 4-aminobenzophenone (0.974 g, 4.94 mmol) in benzene (10 mL) and CH_2Cl_2 (5 mL) was added Ac_2O (1.2 mL, 13 mmol) at 23 °C. After 13 h, H_2O (2 mL) was added, and the mixture was stirred for 15 min, and then most of the solvent was removed under a reduced pressure (ca. 20 mmHg). To the residue was added H_2O (50 mL), and the mixture was vigorously stirred for 0.5 h. The precipitate was collected by filtration, and was dissolved in EtOAc, and was dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 1/1) to give the title compound (0.872 g, 3.84 mmol, 78% yield): IR (film) 3326, 1672, 1640, 1593, 1525, 1314, 1281, 855, 743, 699, 657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2 H), 7.77 (d, *J* = 7.2 Hz, 2 H), 7.64 (d, *J* = 8.8 Hz, 2 H), 7.61–7.55 (m, 2 H), 7.48 (t, *J* = 7.2 Hz, 2 H), 2.23 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.23, 169.38, 142.45, 137.76, 132.71, 132.42, 131.62, 129.88, 128.36, 118.94, 24.63; MS (EI) *m/z* 239, 197, 120; HRMS (EI) *m/z* calcd for $C_{15}H_{13}NO_2$ 239.0946, found 239.0948.

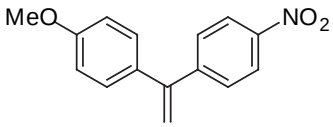


1-(4-Acetamidophenyl)-1-phenylethylene. To a suspension of methyltriphenylphosphonium bromide (1.02 g, 2.86 mmol) in THF (20 mL) was added BuLi (2.5 M in hexanes, 1.0 mL, 2.5 mmol) at 0 °C. After 2 h, 4-acetamidobenzophenone (0.234 g, 0.978 mmol) was added in one portion, and then the cooling bath was removed. After 15 h, H_2O (50 mL) and EtOAc (10 mL) were added, and the mixture was stirred for 1 min. The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with a mixture of H_2O (20 mL) and brine (5 mL) (1 ×), and brine (1 × 20 mL), and were dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 1/1) to give the title compound(0.220 g, 0.927 mmol, 95 % yield): IR (film) 3298, 1667, 904, 843, 778, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2 H), 7.33 (s, 5 H), 7.30 (d, *J*

= 8.8 Hz, 2 H), 7.26 (Br s, 1 H), 5.43 (d, *J* = 0.8 Hz, 1 H), 5.41 (s, 1 H), 2.19 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.90, 149.32, 141.38, 137.57, 137.41, 128.76, 128.26, 128.16, 127.74, 119.78, 113.83, 24.50; MS (EI) *m/z* 237, 195, 180; HRMS (EI) *m/z* calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1165; Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.77; H, 6.38; N, 5.81.

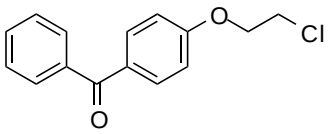


4-Methoxy-4'-nitrobenzophenone. To a mixture of anisole (30 mL, 0.28 mol) and 4-nitrobenzoyl chloride (9.3 g, 50 mmol) in CH_2Cl_2 (60 mL) was added $AlCl_3$ (7.6 g, 57 mmol) at 0 °C. After 1 h, the cooling bath was removed, and the mixture was stirred at 23 °C for 15 h. The mixture was poured into ice–water (200 mL), and the mixture was stirred for 15 min. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4. Most of the solvent (CH_2Cl_2) was removed by a rotavap, and then hexanes (100 mL) was added. The precipitate was collected by filtration, and it was purified by recrystallization from hexanes (200 mL)–$CHCl_3$(110 mL) to give the title compound (11 g, 44 mmol, 88% yield): IR (film) 1641, 1591, 1513, 1319, 1264, 1020, 851, 739, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.5 Hz, 2 H), 7.86 (d, *J* = 9.0 Hz, 2 H), 7.79 (d, *J* = 9.0 Hz, 2 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 3.89 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.41, 163.98, 149.47, 143.77, 132.63, 130.31, 128.89, 123.46, 113.97, 55.64; MS (EI) *m/z* 257, 135; HRMS (EI) *m/z* calcd for $C_{14}H_{11}NO_4$ 257.0688, found 257.0674.

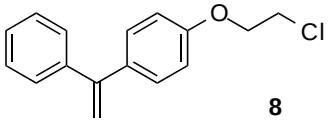


1-(4-Methoxyphenyl)-1-(4-nitrophenyl)ethylene. To a suspension of methyltriphenylphosphonium bromide (0.949 g, 2.66 mmol) in THF (20 mL) was added BuLi (2.5 M in hexanes, 1.0 mL, 2.5 mmol) at 0 °C. After 44 min, a suspension of 4-methoxy-4'-nitrobenzophenone (0.512 g, 1.99 mmol) in THF (1 mL) was added in one portion. After 2.5 h, the cooling bath was removed, and the mixture was stirred at 23 °C for 2.5 d. H_2O (25 mL) was added, and after 5.5 h, the mixture was extracted with Et_2O (3 × 10 mL). The combined ether layers were washed with H_2O (1 × 10 mL) and brine (1 × 10 mL), and were dried over $MgSO_4$. The crude product was purified by flash

chromatography (SiO_2, pentane/Et_2O = 10/1) to give the title compound (0.276 g, 1.08 mmol, 54 % yield): IR (film) 1512, 1345, 1249, 861, 837, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.0 Hz, 2 H), 7.49 (d, *J* = 8.5 Hz, 2 H), 7.22 (d, *J* = 9.0 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 5.56 (s, 1 H), 5.48 (s, 1 H), 3.84 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.75, 148.46, 147.87, 147.26, 132.56, 129.33, 129.04, 123.51, 115.85, 113.86, 55.36; MS (EI) *m/z* 255, 165; HRMS (EI) *m/z* calcd for $C_{15}H_{13}NO_3$ 255.0895, found 255.0918.



4-(2-Chloroethoxy)benzophenone. To a solution of 4-hydroxybenzophenone (8.98 g, 45.3 mmol), PPh_3 (13.4 g, 51.5 mmol) and 2-chloroethanol (3.5 mL, 52 mmol) in THF (150 mL) was added DEAD (8.74 g, 50.2 mmol) at 0 °C. After 3 h, the cooling bath was removed, and the mixture was stirred at 23 °C for 16 h. H_2O (20 mL) was added, and after 7 min, the mixture was poured into H_2O (250 mL). The mixture was extracted with Et_2O (4 × 50 mL). The combined ether layers were washed with 3 % aqueous H_2O_2 (1 × 100 mL), 1 N NaOH (2 × 100 mL), and brine (1 × 100 mL), and were dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc = 10/1), and then recrystallization from hexanes–$CHCl_3$(v/v = 10/1) to give the title compound (8.65 g, 33.2 mmol, 74 % yield): IR (film) 1649, 1600, 1250, 1034, 844, 740, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.0 Hz, 2 H), 7.74 (d, *J* = 7.0 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 4.29 (t, *J* = 6.0 Hz, 2 H), 3.38 (t, *J* = 6.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.35, 161.67, 138.04, 132.51, 131.97, 130.68, 129.68, 128.19, 114.10, 68.04, 41.69; MS (EI) *m/z* 260, 183; HRMS (EI) *m/z* calcd for $C_{15}H_{13}ClO_2$ 260.0604, found 260.0618; Anal. Calcd for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 68.99; H, 5.10.



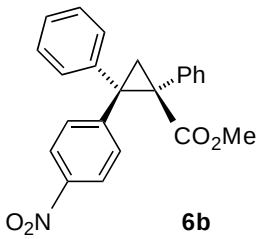
8

1-[4-(2-Chloroethoxy)phenyl]-1-phenylethylene (8). To a suspension of methyltriphenylphosphonium bromide (1.04 g, 2.91 mmol) in THF (25 mL) was added BuLi (2.5 M in hexanes, 1.0 mL, 2.5 mmol) at 0 °C. After 1 h, 4-(2-chloroethoxy)benzophenone (0.554 g, 2.12 mmol) in THF (1 mL) was added, and the cooling bath was removed. After being stirred at 23 °C for 1 h, H_2O (30 mL) and Et_2O (10

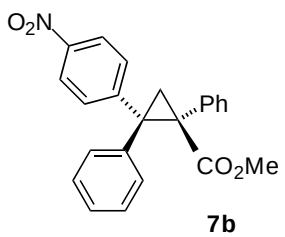
mL) were added, and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with H_2O (1 × 30 mL) and brine (1 × 30 mL), and were dried over $MgSO_4$. The crude product was purified by flash chromatography (SiO_2, Hexanes/Et_2O = 5/1) to give **8** (0.538 g, 2.08 mmol, 98 % yield): IR (film) 1607, 1508, 1244, 900, 836, 783, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 5 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 9.2 Hz, 2 H), 5.40 (d, *J* = 1.6 Hz, 1 H), 5.37 (d, *J* = 1.2 Hz, 1 H), 4.25 (t, *J* = 6.4 Hz, 2 H), 3.83 (t, *J* = 6.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.94, 149.40, 141.71, 134.79, 129.55, 128.33, 128.19, 127.74, 114.36, 113.29, 68.10, 41.97; MS (EI) *m/z* 258, 195, 181, 165, 152; HRMS (EI) *m/z* calcd for $C_{16}H_{15}ClO$ 258.0811, found 258.0798; Anal. Calcd for $C_{16}H_{15}ClO$: C, 74.27; H, 5.84. Found: C, 74.15; H, 5.90.

Rh_2(DOSP)$_4$ Catalyzed Cyclopropanation: Typical Procedure and Products Data

Typical Procedure for Rh_2(*S*-DOSP)$_4$ Catalyzed Cyclopropanation of 1,1-Diarylethylenes and Methyl Aryldiazoacetates. To a solution of Rh_2(*S*-DOSP)$_4$ (7.1 mg, 3.7×10^{-3} mmol) and 1-(4-nitrophenyl)-1-phenylethylene (0.135 g, 0.599 mmol) in pentane (3 mL) was added methyl phenyldiazoacetate (45.5 mg, 0.258 mmol) in pentane (5 mL) dropwise over the period of 15 min at 23 °C. After 2.5 h, the solvent was removed by a rotavap, and the diastereomer ratio was determined by ^1H NMR of the crude mixture. The remaining 1-(4-nitrophenyl)-1-phenylethylene and Rh_2(*S*-DOSP)$_4$ were removed by flash chromatography (SiO_2, pentane/Et_2O = 10/1–5/1). The amount of the products were determined to be 0.232 mmol (90% yield) by ^1H NMR using DMAP (19.6 mg, 0.160 mmol) as an internal standard. To remove DMAP, the mixture was dissolved in Et_2O and was washed with 1 N HCl (2 × 15 mL) and brine (1 × 15 mL). The two diastereomers were separated by preparative TLC. The enantiomeric excess of the products were determined by chiral HPLC analysis.



6b



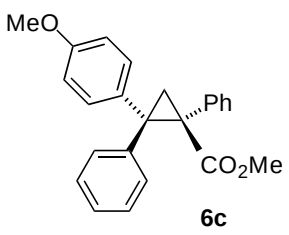
7b

Methyl (*1S,2S*)-1,2-diphenyl-2-(4-nitrophenyl)cyclopropane-1-carboxylate (6b) and **methyl (*1S,2R*)-1,2-diphenyl-2-(4-nitrophenyl)cyclopropane-1-**

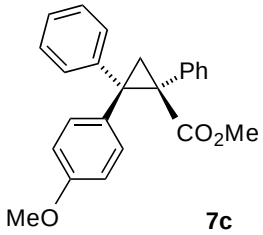
carboxylate (7b) were prepared from 1-(4-nitrophenyl)-1-phenylethylene (0.135 g, 0.599 mmol) and methyl phenyldiazoacetate **3** (45.5 mg, 0.258 mmol). The combined yield = 90 %; the diastereomer ratio **6b** : **7b** = 55 : 45. The two diastereomers were separated by preparative TLC (SiO_2, pentane/EtOAc = 5/1, 8/1, and then 10/1).

Methyl (*1S,2S*)-1,2-Diphenyl-2-(4-nitrophenyl)cyclopropane-1-carboxylate (6b). 95% ee ((R,R)-Whelk-O column, 30% ^{i}PrOH in hexanes); $[\alpha]^{24}_{D}$ = 273 ° (c = 0.65, $CHCl_3$); IR (film) 1722, 1519, 1348, 1224, 862, 748, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.0 Hz, 2 H), 7.67 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 7.0 Hz, 2 H), 7.18–7.10 (m, 3 H), 7.04–6.95 (m, 5 H), 3.43 (s, 2 H), 2.69 (d, *J* = 5.5 Hz, 1 H), 2.52 (d, *J* = 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.07, 149.71, 146.81, 138.03, 134.75, 131.69, 130.82, 128.81, 127.99, 127.68, 127.33, 126.84, 123.73, 52.60, 44.41, 43.19, 23.13; MS (EI) *m/z* 373, 341, 314, 296, 266, 236; HRMS (EI) *m/z* calcd for $C_{23}H_{19}NO_4$ 373.1314, found 373.1307.

Methyl (*1S,2R*)-1,2-Diphenyl-2-(4-nitrophenyl)cyclopropane-1-carboxylate (7b). 91% ee ((R,R)-Whelk-O column, 30% ^{i}PrOH in hexanes); $[\alpha]^{24}_{D}$ = 218 ° (c = 0.47, $CHCl_3$); IR (film) 1724, 1517, 1345, 1218, 860, 747, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2 H), 7.49 (d, *J* = 7.0 Hz, 2 H), 7.38 (t, *J* = 7.5 Hz, 2 H), 7.34–7.29 (m, 3 H), 7.20–7.13 (m, 3 H), 7.07 (3, *J* = 8.5 Hz, 2 H), 3.39 (s, 3 H), 2.80 (d, *J* = 6.0 Hz, 1 H), 2.47 (d, *J* = 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.62, 147.57, 145.93, 140.40, 134.66, 131.77, 130.13, 129.44, 128.77, 127.97, 127.72, 127.62, 122.71, 52.51, 44.06, 43.79, 23.61; MS (EI) *m/z* 373, 341, 314, 296, 266, 236; HRMS (EI) *m/z* calcd for $C_{23}H_{19}NO_4$ 373.1314, found 373.1334.



6c

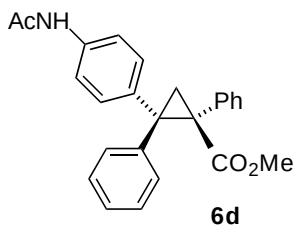


7c

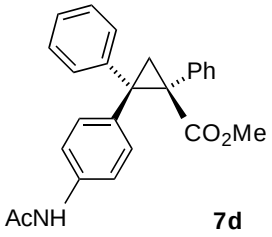
Methyl (*1S,2R*)-1,2-diphenyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (6c) and **methyl (*1S,2S*)-1,2-diphenyl-2-(4-methoxyphenyl)-cyclopropane-1-carboxylate (7c)** were prepared by the addition of a solution of methyl phenyldiazoacetate **3** (43.7 mg, 0.248 mmol) in pentane (2 mL) to a mixture of 1-(4-methoxyphenyl)-1-phenylethylene (0.119 g, 0.566 mmol) and Rh_2(*S*-DOSP)$_4$ (4.6 mg, 2.4×10^{-3} mmol) in pentane (20 mL). The combined yield = 84 %; the diastereomer ratio **6c** : **7c** = 87 : 13. The two diastereomers were separated by preparative TLC (SiO_2, pentane/Et_2O = 15/1).

Methyl (*1S,2R*)-1,2-diphenyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (6c). 99% ee (Chiracel OD column, 2.5% ^{i}PrOH in hexanes); $[\alpha]^{24}_{D}$ = 251 ° (c = 1.12, $CHCl_3$); IR (film) 1723, 1512, 1250, 1219, 1141, 1027, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 2 H), 7.36–7.30 (m, 4 H), 7.24 (t, *J* = 7.0 Hz, 1 H), 7.18–7.09 (m, 3 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 6.52 (d, *J* = 8.5 Hz, 2 H), 3.63 (s, 3 H), 3.35 (s, 3 H), 2.67 (d, *J* = 5.5 Hz, 1 H), 2.36 (d, *J* = 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.53, 157.75, 142.37, 135.89, 131.99, 131.86 129.89, 129.80, 128.36, 127.55, 126.96, 126.88, 113.00, 55.05, 52.16, 44.04, 43.07, 23.02; MS (EI) *m/z* 358, 326, 299, 221; HRMS (EI) *m/z* calcd for $C_{24}H_{22}O_3$ 158.1569, found 358.1562.

Methyl (*1S,2S*)-1,2-diphenyl-2-(4-methoxyphenyl)-cyclopropane-1-carboxylate (7c). 96% ee (Chiracel OD column, 4% ^{i}PrOH in hexanes); $[\alpha]^{24}_{D}$ = 323 ° (c = 0.14, $CHCl_3$); IR (film) 1724, 1513, 1247, 1218, 738, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.16–7.08 (m, 3 H), 7.02–6.92 (m, 5 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 3.80 (s, 3 H), 3.40 (s, 3 H), 2.65 (d, *J* = 5.6 Hz, 1 H), 2.39 (d, *J* = 5.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.48, 158.45, 140.07, 135.80, 134.13, 132.00, 131.09, 128.64, 127.55, 127.51, 126.97, 126.01, 113.74, 55.23, 52.31, 43.56, 43.41, 23.02; MS (EI) *m/z* 358, 326, 299, 221, 191; HRMS (EI) *m/z* calcd for $C_{24}H_{22}O_3$ 158.1569, found 358.1586.



6d



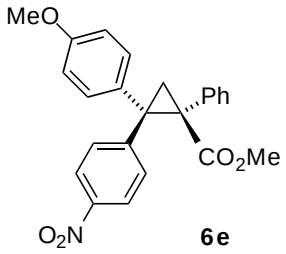
7d

Methyl (*1S,2R*)-1,2-diphenyl-2-(4-acetamidophenyl)cyclopropane-1-carboxylate (6d) and **methyl (*1S,2S*)-1,2-diphenyl-2-(4-acetamidophenyl)cyclopropane-1-carboxylate (7d)** were prepared by the addition of a solution of methyl phenyldiazoacetate **3** (44.1 mg, 0.250 mmol) in pentane (5 mL) to a mixture of 1-(4-acetamidophenyl)-1-phenylethylene (0.135 g, 0.569 mmol) and Rh_2(*S*-DOSP)$_4$ (6.1 mg, 3.2×10^{-3} mmol) in pentane (2 mL)–CH_2Cl_2 (3 mL). The combined yield = 75 %; the diastereomer ratio **6d** : **7d** = 76 : 24. The two diastereomers were separated by preparative TLC (SiO_2, pentane/EtOAc = 2/1).

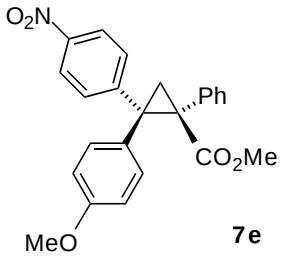
Methyl (*1S,2R*)-1,2-Diphenyl-2-(4-acetamidophenyl)cyclopropane-1-carboxylate (6d). 92% ee (Chiracel OD column, 20% ^{i}PrOH in hexanes); $[\alpha]^{24}_{D}$ = 227 ° (c = 0.93, $CHCl_3$); IR (film) 3308, 1722, 1671, 1532, 1220, 737, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 2 H), 7.35–7.30 (m, 4 H), 7.24 (t, *J* = 7.5 Hz, 1 H),

7.17–7.08 (m, 5 H), 6.94 (br s, 1 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 3.35 (s, 3 H), 2.68 (d, *J* = 5.5 Hz, 1 H), 2.37 (d, *J* = 5.5 Hz, 1 H), 2.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.47, 168.26, 141.89, 136.04, 135.58, 135.40, 131.92, 129.89, 129.23, 128.37, 127.58, 127.05, 126.98, 118.78, 52.25, 44.12, 43.18, 24.46, 22.99; MS (EI) *m/z* 385, 353, 325, 311, 283, 206, 191; HRMS (EI) *m/z* calcd for $C_{25}H_{23}NO_3$ 385.1678, found 385.1685.

Methyl (*1S,2S*)-1,2-Diphenyl-2-(4-acetamidophenyl)cyclopropane-1-carboxylate (7d). 88% ee (Chiracel OD column, 40% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = 240 ° (c = 0.27, $CHCl_3$); IR (film) 3309, 1722, 1669, 1531, 1315, 1220, 733, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.31 (d, *J* = 7.0 Hz, 2 H), 7.19 (br s, 1 H), 7.16–7.08 (m, 3 H), 7.00–6.92 (m, 5 H), 3.40 (s, 3 H), 2.65 (d, *J* = 5.5 Hz, 1 H), 2.41 (d, *J* = 5.5 Hz, 1 H), 2.17 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.48, 168.31, 139.52, 137.82, 136.79, 135.57, 131.96, 130.59, 128.67, 127.59, 127.53, 127.03, 126.15, 119.61, 52.43, 43.85, 43.34, 24.70, 22.98; MS (EI) *m/z* 385, 353, 325, 311, 283, 206, 191; HRMS (EI) *m/z* calcd for $C_{25}H_{23}NO_3$ 385.1678, found 385.1666.



6e



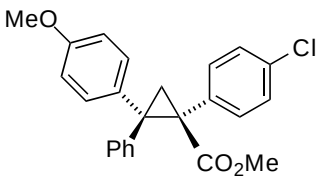
7e

Methyl (*1S,2R*)-2-(4-methoxyphenyl)-2-(4-nitrophenyl)-1-phenylcyclopropane-1-carboxylate (6e) and **methyl (*1S,2S*)-2-(4-methoxyphenyl)-2-(4-nitrophenyl)-1-phenylcyclopropane-1-carboxylate (7e)** were prepared by the addition of a solution of methyl phenyldiazoacetate **5** (46.0 mg, 0.261 mmol) in pentane (10 mL) to a mixture of 1-(4-methoxyphenyl)-1-(4-nitrophenyl)ethylene **4e** (0.135 g, 0.529 mmol) and Rh_2(*S*-DOSP)$_4$ (4.8 mg, 2.5 × 10^{-3} mmol) in CH_2Cl_2 (1.5 mL). The combined yield = 80 %; the diastereomer ratio **6e** : **7e** = 88 : 12. The two diastereo-mers were separated by preparative TLC (SiO_2, pentane/Et_2O = 10/1).

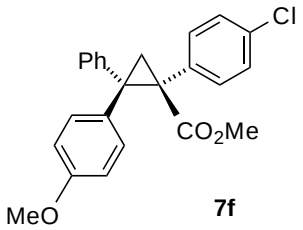
Methyl (*1S,2R*)-2-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1-phenylcyclopropane-1-carboxylate (6e). 93% ee (Chiracel OD column, 8% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = 267 ° (c = 1.34, $CHCl_3$); IR (film) 1721, 1602, 1514, 1348, 1250, 1225, 855, 730, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 2 H), 7.64 (d, *J* = 9.0 Hz, 2 H), 7.32 (d, *J* = 7.0 Hz, 2 H), 7.20–7.11 (m, 3 H), 6.88 (d, *J* = 9.5 Hz, 2 H),

6.55 (d, *J* = 9.0 Hz, 2 H), 3.64 (s, 3 H), 3.42 (s, 3 H), 2.67 (d, *J* = 6.0 Hz, 1 H), 2.45 (d, *J* = 6.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.16, 158.18, 150.08, 146.68, 134.93, 131.70, 130.62, 130.12, 129.93, 127.69, 127.29, 123.72, 113.38, 55.09, 52.53, 44.02, 43.07, 23.28; MS (EI) *m/z* 403, 386, 371, 344, 266; HRMS (EI) *m/z* calcd for $C_{24}H_{21}NO_5$ 403.1420, found 403.1413.

Methyl (*1S,2S*)-2-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1-phenylcyclopropane-1-carboxylate (7e). 74% ee (Chiracel OD column, 10% ^{i}PrOH in hexanes); IR (film) 1724, 1602, 1513, 1346, 1247, 1217, 1031, 860, 732, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 7.35–7.27 (m, 2 H), 7.19–7.12 (m, 3 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 3.82 (s, 3 H), 3.43 (s, 3 H), 2.77 (d, *J* = 5.6 Hz, 1 H), 2.44 (d, *J* = 5.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.67, 158.93, 148.04, 145.85, 134.76, 132.35, 131.82, 131.23, 129.33, 127.97, 127.61, 122.68, 114.13, 55.33, 52.61, 44.31, 42.93, 23.82; MS (EI) *m/z* 403, 386, 371, 344, 266; HRMS (EI) *m/z* calcd for $C_{24}H_{21}NO_5$ 403.1420, found 403.1423.



6f



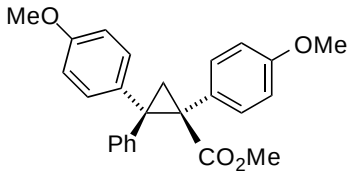
7f

Methyl (*1S,2R*)-1-(4-chlorophenyl)-2-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (6f) and **methyl (*1S,2S*)-1-(4-chlorophenyl)-2-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (7f)** were prepared by the addition of a solution of methyl (4-chlorophenyl)diazoacetate (53.6 mg, 0.254 mmol) in pentane (5 mL) to a mixture of 1-(4-methoxyphenyl)-1-phenylethylene (0.114 g, 0.542 mmol) and Rh_2(*S*-DOSP)$_4$ (6.7 mg, 3.5×10^{-3} mmol) in pentane (3 mL). The combined yield = 94 %; the diastereomer ratio **6f** : **7f** = 89 : 11. The two diastereomers were separated by preparative TLC (SiO_2, pentane/Et_2O = 10/1).

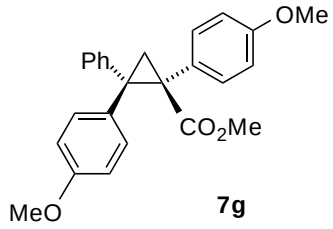
Methyl (*1S,2R*)-1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (6f). 99% ee (Chiracel OD column, 2% ^{i}PrOH in hexanes); IR (film) 1724, 1513, 1250, 1219, 1141, 837, 788, 753, 727, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 2 H), 7.33 (t, *J* = 7.2 Hz, 2 H), 7.29–7.22 (m, 3 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.56 (d, *J* = 8.8 Hz, 2 H), 3.67 (s, 3 H), 3.36 (s, 3 H), 2.68 (d, *J* = 5.2 Hz, 1 H), 2.35 (d, *J* = 5.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.13, 134.58, 133.26, 132.88, 131.44, 129.76, 128.42, 127.80,

126.99, 113.22, 55.14, 52.28, 44.34, 42.37, 22.99; MS (EI) *m/z* 392, 360, 333, 298, 225, 121; HRMS (EI) *m/z* calcd for $C_{24}H_{21}ClO_3$ 392.1179, found 392.1158.

Methyl (*1S,2S*)-1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (7f). 95% ee (Chiracel OD column, 4% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = 265 ° (c = 0.16, $CHCl_3$); IR (film) 1724, 1513, 1247, 1217, 1092, 835, 773, 744, 721, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 7.04–6.92 (m, 5 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 3.80 (s, 3 H), 3.39 (s, 3 H), 2.65 (d, *J* = 5.6 Hz, 1 H), 2.36 (d, *J* = 5.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.14, 158.49, 139.67, 134.47, 133.86, 133.26, 132.90, 130.96, 128.57, 127.79, 127.75, 126.30, 113.79, 55.27, 52.42, 43.84, 42.69, 22.99; MS (EI) *m/z* 392, 360, 333; HRMS (EI) *m/z* calcd for $C_{24}H_{21}ClO_3$ 392.1179, found 392.1187.



6g

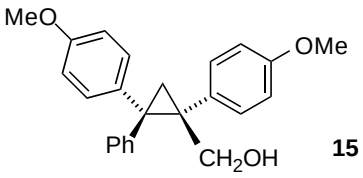


7g

Methyl (*1S,2R*)-1,2-bis(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (6g) and **methyl (*1S,2S*)-1,2-bis(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (7g)** were prepared by the addition of a solution of methyl (4-methoxyphenyl)diazoacetate (53.5 mg, 0.259 mmol) in pentane (5 mL) to a mixture of 1-(4-methoxyphenyl)-1-phenylethylene (0.143 g, 0.680 mmol) and Rh_2(*S*-DOSP)$_4$ (4.4 mg, 2.3×10^{-3} mmol) in pentane (3 mL). The combined yield = 84 %; the diastereomer ratio **6g** : **7g** = 90 : 10. The two diastereomers were separated by preparative TLC (SiO_2, pentane/Et_2O = 10/1).

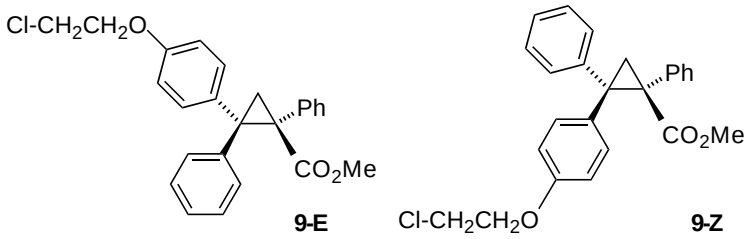
Methyl (*1S,2R*)-1,2-Bis(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (6g). 98 % ee (The enantiomeric excess of this compound was determined by its derivative **15**; see below); $[\alpha]^{24}_D$ = 253 ° (c = 0.67, $CHCl_3$); IR (film) 1724, 1514, 1249, 1032, 837, 789, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.0 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 7.26–7.21 (m, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 6.69 (d, *J* = 8.5 Hz, 2 H), 6.54 (d, *J* = 9.0 Hz, 2 H), 3.73 (s, 3 H), 3.65 (s, 3 H), 3.34 (s, 3 H), 2.64 (d, *J* = 5.5 Hz, 1 H), 2.30 (d, *J* = 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.79, 158.32, 157.65, 124.41, 132.92, 131.94, 129.85, 129.79, 128.29, 127.93, 126.79, 112.99, 112.96, 55.08, 55.03, 52.12, 44.03, 42.34, 23.15; MS (EI) *m/z* 388, 356, 329, 280, 221; HRMS (EI) *m/z* calcd for $C_{25}H_{24}O_4$ 388.1675, found 388.1657.

Methyl (*1S,2S*)-1,2-Bis(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (7g). 94 % ee (Chiracel OD column, 4% ^{i}PrOH in hexanes); $[\alpha]^{24}_{D}$ = 280 ° (c = 0.088, $CHCl_3$); IR (film) 1724, 1513, 1247, 1035, 835, 742, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 9.0 Hz, 2 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 7.03–6.92 (m, 3 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 6.67 (d, *J* = 8.5 Hz, 2 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.39 (s, 3 H), 2.62 (d, *J* = 5.5 Hz, 1 H), 2.33 (d, *J* = 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.80, 158.39, 158.37, 140.17, 134.20, 132.99, 131.10, 128.67, 127.88, 127.59, 125.98, 113.71, 112.97, 55.26, 55.15, 52.32, 43.55, 42.75, 23.25; MS (EI) *m/z* 388, 356, 329, 280, 221; HRMS (EI) *m/z* calcd for $C_{25}H_{24}O_4$ 388.1675, found 388.1650.



15

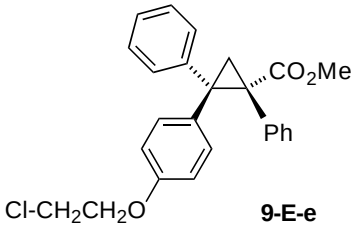
(*1S,2R*)-1,2-Bis(4-methoxyphenyl)-2-phenyl-1-(hydroxymethyl)cyclopropane (15). To a solution of methyl (*1S,2R*)-1,2-bis(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate **6g** (54.7 mg, 0.141 mmol) in THF (5 mL) was added $LiAlH_4$ (1.0 M in THF, 0.30 mL, 0.30 mmol) at –78 °C. The temperature was raised gradually to 0 °C over the period of 3 h. H_2O (1 mL) was added dropwise, and then Et_2O (15 mL) and 1 N HCl (20 mL) were added. The mixture was stirred until the white precipitate dissolved, and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with 1 N HCl (1 × 10 mL) and brine (1 × 10 mL), and were dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, pentane/Et_2O = 2/1) to give **15** (39.0 mg, 77% yield): 98% ee (Chiracel OD column, 30% ^{i}PrOH in hexanes); $[\alpha]^{24}_{D}$ = 118 ° (c = 0.78, $CHCl_3$); IR (film) 3440, 1513, 1247, 1180, 1035, 831, 788, 757, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2 H), 7.33 (t, *J* = 7.6 Hz, 2 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.19 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 6.53 (d, *J* = 8.8 Hz, 2 H), 3.91 (br d, *J* = 11.6 Hz, 1 H), 3.75 (s, 3 H), 3.64 (s, 3 H), 3.33 (br d, *J* = 11.2 Hz, 1 H), 2.07 (d, *J* = 5.2 Hz, 1 H), 1.72 (d, *J* = 5.2 Hz, 1 H), 1.30 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.10, 157.26, 143.06, 134.48, 131.20, 130.79, 130.11, 130.04, 128.60, 126.57, 113.62, 113.01, 69.54, 55.18, 55.05, 41.84, 39.42, 22.33; MS (EI) *m/z* 342 $[M - H_2O]^+$, 329, 311, 211; HRMS (EI) *m/z* calcd for $C_{24}H_{22}O_2$ $[M - H_2O]^+$ 342.1620, found 342.1624.



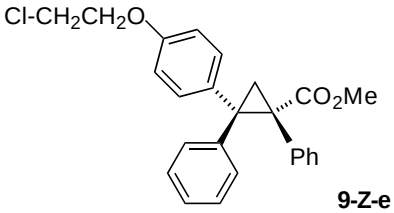
Methyl (*1S,2R*)-2-[4-(2-chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate (9-E) and **methyl (*1S,2S*)-2-[4-(2-chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate (9-Z)** were prepared by the addition of a solution of methyl phenyldiazoacetate **3** (0.271 g, 1.54 mmol) in pentane (1 mL) to a mixture of 1-[4-(2-chloroethoxy)phenyl]-1-phenylethylene **8** (0.779 g, 3.01 mmol) and Rh_2(*S*-DOSP)$_4$ (21 mg, 1.1×10^{-2} mmol) in pentane (40 mL). The combined yield = 93 %; the diastereomer ratio **9-E** : **9-Z** = 87 : 13. The two diastereomers were separated by preparative TLC (SiO_2, pentane/Et_2O = 15/1).

Methyl (*1S,2R*)-2-[4-(2-Chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate (9-E). 98% ee (Chiracel OD column, 8% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = 226 ° (c = 1.22, $CHCl_3$); IR (film) 1721, 1511, 1245, 1220, 834, 742, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (2 H, d, *J* = 7.2 Hz), 7.38–7.30 (4 H, m), 7.24 (1 H, t, *J* = 7.6 Hz), 7.19–7.09 (3 H, m), 6.89 (2 H, d, *J* = 8.4 Hz), 6.54 (2 H, d, *J* = 8.8 Hz), 4.04 (2 H, t, *J* = 5.6 Hz), 3.68 (2 H, t, *J* = 5.6 Hz), 3.35 (3 H, s), 2.68 (1 H, d, *J* = 5.6 Hz), 2.36 (1 H, d, *J* = 5.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.35, 156.25, 142.17, 135.72, 132.62, 131.89, 129.85, 129.80, 128.32, 127.51, 126.94, 126.86, 113.76, 67.74, 52.13, 43.95, 43.04, 41.79, 22.95; MS (EI) *m/z* 406, 374, 347, 283, 191; HRMS (EI) *m/z* calcd for $C_{25}H_{23}ClO_3$ 406.1336, found 406.1313.

Methyl (*1S,2S*)-2-[4-(2-Chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate (9-Z). 95% ee (Chiracel OD column, 4% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = 245 ° (c = 0.50, $CHCl_3$); IR (film) 1722, 1511, 1242, 1219, 740, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 6.4 Hz, 2 H), 7.18–7.06 (m, 3 H), 7.02–6.91 (m, 5 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 4.22 (t, *J* = 6.0 Hz, 2 H), 3.81 (t, *J* = 5.6 Hz, 2 H), 3.40 (s, 3 H), 2.65 (d, *J* = 5.6 Hz, 1 H), 2.40 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.42, 157.05, 139.89, 135.69, 134.93, 131.97, 131.20, 128.62, 127.57, 127.51, 127.51, 126.99, 126.07, 114.50, 68.00, 52.37, 43.57, 43.40, 42.01, 23.06; MS (EI) *m/z* 406, 374, 347, 283, 191; HRMS (EI) *m/z* calcd for $C_{25}H_{23}ClO_3$ 406.1336, found 406.1308.



9-E-e



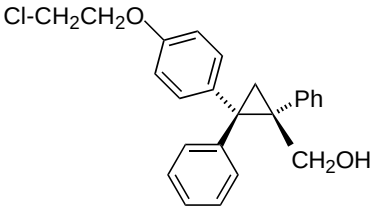
9-Z-e

Methyl (*1R,2S*)-2-[4-(2-chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate (9-E-e) and **methyl (*1R,2R*)-2-[4-(2-chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate (9-Z-e)** were prepared by the same procedure described for **9-E** and **9-Z** except using Rh_2(*R*-DOSP)$_4$. The combined yield = 92 %; the diastereomer ratio **9-E-e** : **9-Z-e** = 87 : 13.

Methyl (*1R,2S*)-2-[4-(2-Chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate (9-E-e). 98% ee (Chiracel OD column, 8% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = –228 ° (c = 1.02, $CHCl_3$).

methyl (*1R,2R*)-2-[4-(2-Chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate (9-Z-e). 93% ee (Chiracel OD column, 4% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = –241 ° (c = 0.40, $CHCl_3$).

Preparation of a Cyclopropyl Tamoxifen Analog 2

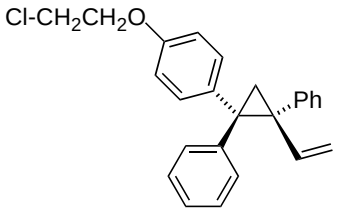


10

(*1S,2R*)-2-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-1-(hydroxymethyl)-cyclopropane (10). To a solution of methyl (*1S,2R*)-2-[4-(2-chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate **9-E** (98.1% ee, 0.353 g, 0.867 mmol) in THF (15 mL) was added $LiAlH_4$ (1.0 M in THF, 1.1 mL, 1.1 mmol) at –78 °C. After 20 min, the temperature was raised to 0 °C. After 1 h, H_2O (1 mL) was added dropwise, and 5 min later, 1N HCl (10 mL) was added. After 5 min, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 N HCl (1 × 10 mL), saturated. aqueous $NaHCO_3$ (1 × 10 mL), and brine (1 × 10 mL), and were dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, pentane/Et_2O = 2/1) to give the alcohol **10** (0.304 g, 0.802 mmol, 93% yield): 98.6% ee (Chiracel OD column, 40% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = 101 ° (c = 1.24, $CHCl_3$); IR (film) 3415, 1510, 1242, 1042, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.0 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz,

2 H), 7.30–7.18 (m, 5 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 6.52 (d, *J* = 9.0 Hz, 2 H), 4.03 (d, *J* = 6.5 Hz, 2 H), 3.97 (d, *J* = 11.5 Hz, 1 H), 3.68 (d, *J* = 6.5 Hz, 2 H), 3.36 (d, *J* = 11.5 Hz, 1 H), 2.13 (d, *J* = 5.5 Hz, 1 H), 1.75 (d, *J* = 5.5 Hz, 1 H), 1.55 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.87, 142.79, 138.77, 135.13, 130.18, 130.13, 129.98, 128.62, 128.16, 126.66, 126.54, 113.80, 69.37, 67.77, 41.87, 41.85, 40.07, 22.12; MS (EI) *m/z* 378, 360, 347; HRMS (EI) *m/z* calcd for $C_{24}H_{23}ClO_2$ 378.1387, found 378.1384.

(*1R,2S*)-2-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-1-(hydroxymethyl)-cyclopropane (10-e) was prepared from methyl (*1R,2S*)-2-[4-(2-chloroethoxy)phenyl]-1,2-diphenylcyclopropane-1-carboxylate **9-E-e** (98.0% ee, 0.353 g, 0.867 mmol) by the same procedure described above. Yield = 94%; 98.0% ee (Chiracel OD column, 40% ^{i}PrOH in hexanes); $[\alpha]^{24}_D$ = –101 ° (c = 1.15, $CHCl_3$).

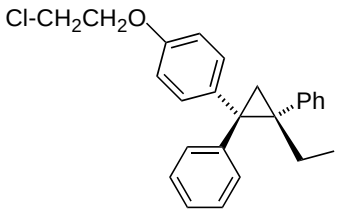


11

(*1R,2S*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-2-vinylcyclopropane (11). Oxalyl chloride (2.0 M in CH_2Cl_2, 0.7 mL, 1.4 mmol) was added to CH_2Cl_2 (25 mL) at –78 °C. DMSO (0.12 mL, 0.13 g, 1.7 mmol) was added, and after 0.5 h, (*1S,2R*)-2-[4-(2-chloroethoxy)phenyl]-1,2-diphenyl-1-(hydroxymethyl)-cyclopropane **10** (98% ee, 0.261 g, 0.689 mmol) in CH_2Cl_2 (1 mL) was added. After 0.7 h, the mixture was warmed to –45 ℃ (acetonitrile–dry ice bath). After 1h, Et_3N (0.51 mL, 3.7 mmol) was added. After 10 min, the mixture was warmed to 0 ℃ (ice–water bath). After 2h, saturated aqueous NH_4Cl (50 mL) was added, and 10 min later, then H_2O (10 mL) was added. The mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl (1 × 25 mL) and brine (1 × 25 mL), and were dried over $MgSO_4$. The solvent was removed by a rotavap. The crude product in THF (1 mL) was added at 0 °C to a solution of a Wittig reagent that was prepared from $Ph_3(Me)PBr$ (0.86 g, 2.4 mmol) and BuLi (2.5 M in hexanes, 0.65 mL, 1.6 mmol) in THF (15 mL) at 0 ℃ for 2 h. After 0.5 h, H_2O (50 mL) and Et_2O (30 mL) was added. After the separation, the aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined ether layers were washed with brine (1 × 50 mL), and were dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2, pentane/Et_2O = 20/1) to give **11** (0.227 g, 0.605 mmol, 88% yield): $[\alpha]^{24}_D$ = 260 ° (c = 0.92, $CHCl_3$); IR (film) 1511, 1243, 1039, 907,

826, 738, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 2 H), 7.35 (t, *J* = 8.0 Hz, 2 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.20–7.14 (m, 4 H), 7.12–7.05 (m, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.51 (d, *J* = 8.8 Hz, 2 H), 5.51 (dd, *J* = 17.2, 10.4 Hz, 1 H), 4.85 (dd, *J* = 10.4, 1.6 Hz, 1 H), 4.51 (dd, *J* = 17.2, 1.6 Hz, 1 H), 4.03 (t, *J* = 6.0 Hz, 2 H), 3.67 (t, *J* = 6.0 Hz, 2 H), 2.42 (d, *J* = 5.2 Hz, 1 H), 1.82 (d, *J* = 5.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.81, 144.41, 142.86, 138.63, 134.96, 131.34, 131.24, 129.84, 128.34, 127.79, 126.48, 126.22, 113.75, 113.11, 67.79, 43.08, 41.86, 41.85, 25.34; MS (EI) *m/z* 374, 283, 269, 205; HRMS (EI) *m/z* calcd for $C_{25}H_{23}ClO$ 374.1437, found 374.1406.

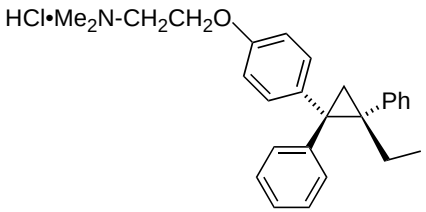
(*1S,2R*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-2-vinylcyclopropane (11-e) was prepared according to the same procedure described above from (*1R,2S*)-2-[4-(2-chloroethoxy)phenyl]-1,2-diphenyl-1-(hydroxymethyl)-cyclopropane **10-e** (98% ee, 0.249 g, 0.657 mmol): Yield = 90%; $[\alpha]^{24}_D$ = –262 ° (c = 0.89, $CHCl_3$).



12

(*1R,2R*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-2-ethylcyclopropane (12). A mixture of (*1R,2S*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-2-vinylcyclopropane **11** (0.109 g, 0.291 mmol) and Rh–Al_2O_3 (5 wt%, 31.0 mg) in EtOAc (15 mL) was stirred vigorously under an H_2 atmosphere (1 atm) for 12 h. The mixture was passed through a filter paper. The product was purified by preparative TLC (pentane/Et_2O = 50/1) to give **12** (76.2 mg, 0.202 mmol, 69% yield) with a trace amount of unidentified impurity: ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.0 Hz, 2 H), 7.32 (t, *J* = 8.0 Hz, 2 H), 7.22–7.12 (m, 5 H), 7.05 (t *J* = 7.0 Hz, 1 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 6.49 (d, *J* = 9.0 Hz, 2 H), 4.01 (t, *J* = 6.0 Hz, 2 H), 3.66 (t, *J* = 6.0 Hz, 2 H), 2.20–2.12 (m, 1 H), 2.10 (dd, *J* = 5.0, 2.0 Hz, 1 H), 1.41 (d, *J* = 5.0 Hz, 1 H), 0.91–0.82 (m, 1 H), 0.73 (t, *J* = 7.0 Hz, 3 H).

(*1S,2S*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-2-ethylcyclopropane (12-e) was prepared according to the same procedure described above from (*1S,2R*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenyl-2-vinylcyclopropane **11-e** (0.106 g, 0.283 mmol): Yield = 65%.



2–HCl salt

(*1R,2R*)-1-[4-(2-(Dimethylamino)ethoxy)phenyl]-1,2-diphenyl-2-ethylcyclopropane hydrochloride salt (2-HCl salt). A mixture of (*1R,2R*)-1-[4-(2-chloroethoxy)-phenyl]-1,2-diphenyl-2-ethylcyclopropane **12** (68.0 mg, 0.180 mmol), Me_2NH (40 wt% in H_2O, 4 mL), and NaI (84 mg, 0.56 mmol) in DMF (8 mL) was stirred at 55 °C for 1 d. After cooling to 23 °C, Et_2O (50 mL) and H_2O (25 mL) were added. After the separation, the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined ether layers were washed with 2% $Na_2S_2O_3$ (1 × 25 mL), H_2O (2 × 25 mL), and brine (1 × 25 mL), and were dried over $MgSO_4$. After the evaporation of the solvent, the crude product **2** was obtained (67.9 mg, 98% yield). The crude product was dissolved in Et_2O (10 mL), and HCl (1 M in Et_2O, 0.5 mL, 0.5 mmol) was added. The solvent was evaporated to give white powder. The HCl salt was purified by recrystallization from EtOAc (6 mL) to give **2-HCl salt** (32.9 mg, 0.0780 mmol, 43% yield): IR (film) 3409, 2455, 1511, 1241, 729, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.0 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.22–7.12 (m, 5 H), 7.07–7.02 (m, 1 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 6.47 (d, *J* = 9.0 Hz, 2 H), 4.24 (t, *J* = 4.5 Hz, 2 H), 3.29 (t, *J* = 4.5 Hz, 2 H), 2.78 (s, 3 H), 2.19–2.11 (m, 1 H), 2.08 (dd, *J* = 5.5, 2.0 Hz, 1 H), 1.41 (d, *J* = 5.0 Hz, 1 H), 0.90–0.81 (m, 1 H), 0.72 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.54, 143.96, 140.67, 137.16, 130.71, 130.25, 129.53, 128.41, 127.82, 126.22, 125.76, 113.54, 62.48, 56.36, 43.53, 42.76, 39.40, 32.04, 22.79, 11.64; MS (FAB^+) *m/z* 386 $(M+H–Cl)^+$; HRMS (FAB^+) *m/z* calcd for $C_{27}H_{33}NO$ $(M+H–Cl)^+$, 386.2484, found 386.2483.

(*1S,2S*)-1-[4-(2-(Dimethylamino)ethoxy)phenyl]-1,2-diphenyl-2-ethylcyclopropane hydrochloride salt (2-HCl-salt-e) was prepared according to the same procedure described above from (*1S,2S*)-1-[4-(2-chloroethoxy)-phenyl]-1,2-diphenyl-2-ethylcyclo-propane **4-e** (64.0 mg, 0.170 mmol): Yield = 39%.