Catalytic Stereoselective Synthesis of Cyclopentanones from Donor-Acceptor Cyclopropanes and in situ-generated Ketenes

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Experimental

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General Information:

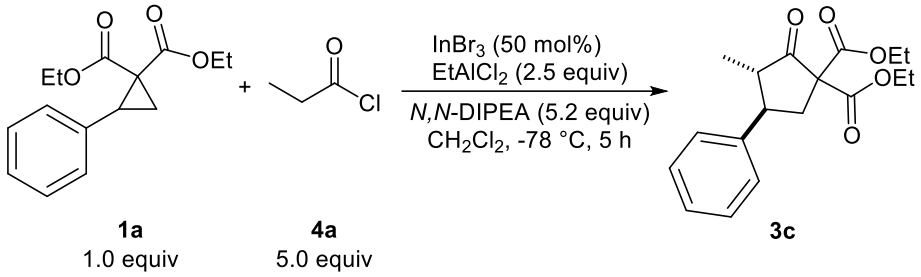
THF was freshly distilled from benzophenone ketyl radical under nitrogen prior to use, while Hünig's base (diisopropylethylamine) was distilled from calcium hydride.[1] Most anhydrous solvents (dichloromethane and diethyl ether) were obtained by passing through activated alumina columns on a solvent purification system or distilled from calcium hydride. All chemicals were purchased from Sigma Aldrich (Merck Life Sciences) or Fisher Scientific and used as received from the supplier without further purification unless otherwise mentioned. All racemic and enantioenriched donor acceptor cyclopropanes **1a**-**1n** were synthesised according to reported literature procedures.[2] Ketenes were generated in situ from commercially available acyl chlorides.

NMR spectra were recorded on a Bruker DPX Avance 200 spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C), on a Bruker 600 MHz spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C). NMR chemical shifts were reported relative to TMS (0 ppm) or $CHCl_3$ (7.26 ppm) for ^{1}H and to $CDCl_3$ (77.23 ppm) for ^{13}C spectra. High resolution mass spectra were recorded at Trinity College Dublin using APCI or ESI. Low resolution mass spectra were recorded on a GC-MS Hewlett Packard HP 6890 GC instrument with a 5973 mass selective detector. IR spectra were recorded on a Bio Rad FTS-175C spectrometer. Optical rotations were measured on a Rudolph DigiPol 781 TDV automatic polarimeter.

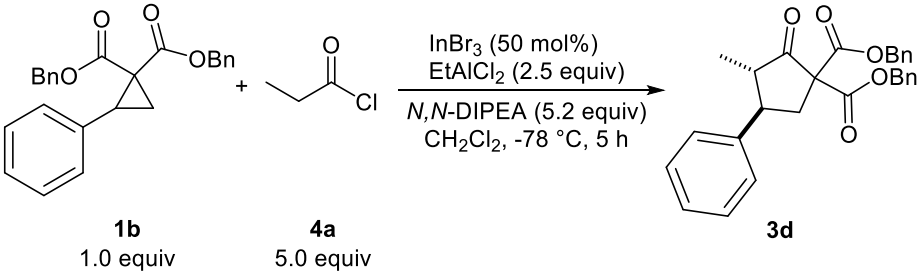
Chiral high-performance liquid chromatography analysis (HPLC) was performed using a Chiralpak AD-H column (Daicel chemical Ind., Ltd.) on an Agilent 1200 series instrument attached with a Variable Wavelength Detector with HPLC-grade isopropanol and hexanes as the eluting solvents. Enantiomeric excesses were determined at λ = 250 nm (details given for each compound).

General procedure for catalytic synthesis of cyclopentanones from in situ-generated ketenes:

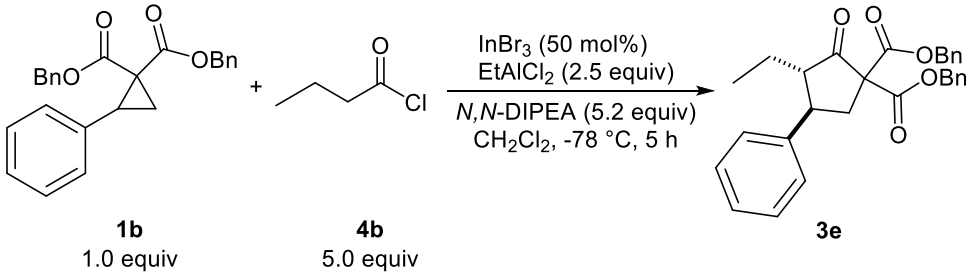
To a stirring suspension of indium bromide (0.07-0.11 mmol, 0.3-0.5 equiv) in dichloromethane (7 mL) at −78 °C, the appropriate acid chloride **4** (1.13 mmol, 5.0 equiv) was added. *i*-Pr_2NEt (1.18 mmol, 5.2 equiv) was added to the suspension over 15-20 min. To the stirring reaction mixture, a solution of cyclopropane **1** (0.23 mmol, 1.0 equiv) in dichloromethane (2 mL) was added over a period of 1 h via syringe pump. During half addition of the cyclopropane solution, ethyl aluminium dichloride solution (1.0 M in hexanes, 0.57 mmol, 2.5 equiv) was added. The reaction was stirred at −78 °C for another 4 h and then quenched by addition of a mixture of methanol-triethylamine (2:1, 1.0 mL). Then the reaction mixture was poured into cold 10% hydrochloric acid solution (20 ml) and extracted with dichloromethane (25 mL × 2). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was stirred in a mixture of silica gel (5 g) and dichloromethane (10 mL) for 2 h at 50 °C. The crude mixture was filtered and washed with copious amounts of dichloromethane. The combined filtrate was evaporated under reduced pressure to obtain the crude product. Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product (major isomer was the *trans*-isomer). Where purity was not ≥95% at this stage, gradient silica gel flash column chromatographic purification using a mixture of ethyl acetate and hexanes (0-10% EtOAc/hexane) was performed to afford the desired product **3** with high purity.



Diethyl 3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate (3c): Diethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (120 mg, 0.46 mmol) converted to **3c**, isolated as a colorless gum (115 mg, 79%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 9:1 (by crude ^{1}H NMR analysis); IR (thin film) 2983, 1725, 1497, 1366, 1255, 1188, 1018, 939, 761, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.37-7.35 (m, 2H), 7.29-7.26 (m, 3H), 4.30-4.25 (m, 4H), 2.93-2.88 (m, 2H), 2.60-2.58 (m, 1H), 2.48-2.45 (m, 1H), 1.31-1.28 (m, 6H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.8, 167.2, 167.0, 140.7, 129.0, 127.4, 127.3, 68.2, 62.6, 62.5, 51.5, 47.3, 39.0, 14.1, 12.9; $(M + H)^+$ HRMS m/z calcd for $(C_{18}H_{23}O_5)^+$: 319.1545; found: 319.1544.

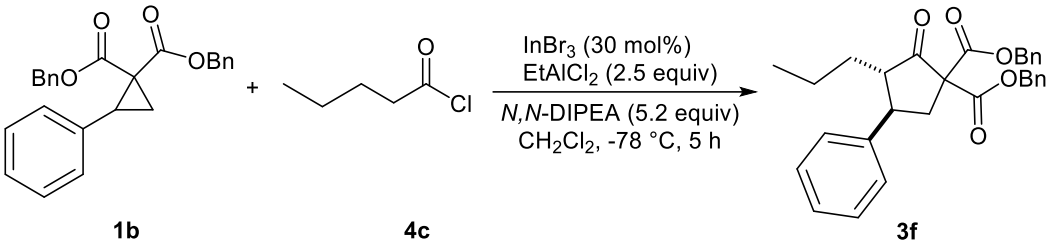


Dibenzyl 3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate (3d): Dibenzyl 2-phenylcyclopropane-1,1-dicarboxylate **1b** (120 mg, 0.31 mmol) converted to **3d**, isolated as a colorless gum (123 mg, 90%). R_f = 0.4 (EtOAc/hexanes 1:9); dr = 33:1 (by crude ^{1}H NMR analysis); IR (thin film) 3031, 2932, 1766, 1730, 1497, 1454, 1374, 1257, 1175, 959, 738, 696 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.35-7.24 (m, 13H), 7.19 (d, *J* = 7.3 Hz, 2H), 5.27-5.17 (m, 4H), 2.91 (dd, *J* = 6.0, 13.3 Hz, 1H), 2.86-2.81 (m, 1H), 2.58 (*app* t, *J* = 12.8 Hz, 1H), 2.48-2.43 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.4, 166.9, 166.7, 140.5, 135.2, 135.1, 129.0, 128.7, 128.7, 128.6, 128.5, 128.2, 128.1, 127.5, 127.3, 68.3, 68.1, 68.0, 51.5, 47.3, 39.0, 12.8; $(M + H)^+$ HRMS m/z calcd for $(C_{28}H_{27}O_5)^+$: 443.1858; found: 443.1852.



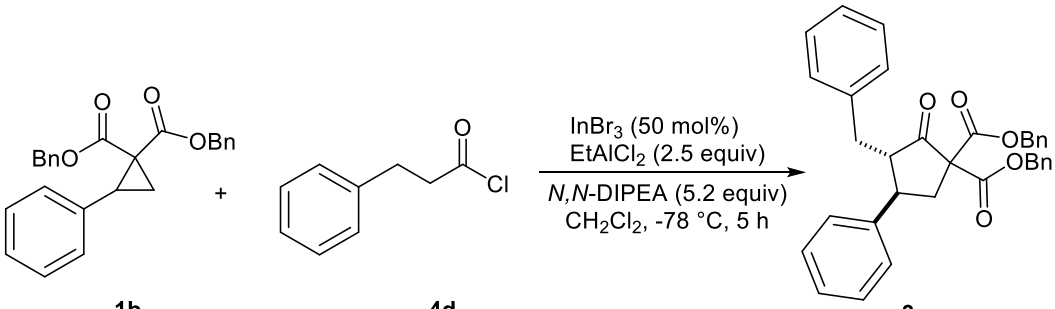
Dibenzyl 3-ethyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate (3e): Dibenzyl 2-phenylcyclopropane-1,1-dicarboxylate **1b** (60 mg, 0.16 mmol) converted to **3e**, isolated as a colorless oil (63 mg, 88%). R_f = 0.45

(EtOAc/hexanes 1:9); dr = 4:1 (by crude ^{1}H NMR analysis); IR (thin film) 3031, 2963, 1766, 1734, 1497, 1455, 1375, 1260, 1173, 988, 750, 697 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.33-7.24 (m, 13H), 7.20-7.19 (m, 2H), 5.24-5.16 (m, 4H), 3.04-2.99 (m, 1H) 2.90 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.53 (*app* t, *J* = 13.0 Hz, 1H), 2.47-2.44 (m, 1H), 1.62-1.49 (m, 2H), 0.73 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.1, 167.0, 166.5, 141.2, 135.2, 135.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.4, 128.1, 127.4, 127.3, 68.7, 68.1, 68.0, 57.2, 44.5, 39.4, 21.0, 10.8; $(M + H)^+$ HRMS m/z calcd for $(C_{29}H_{29}O_5)^+$: 457.2015; found: 457.2011.



1b 1.0 equiv **4c** 5.0 equiv **3f**

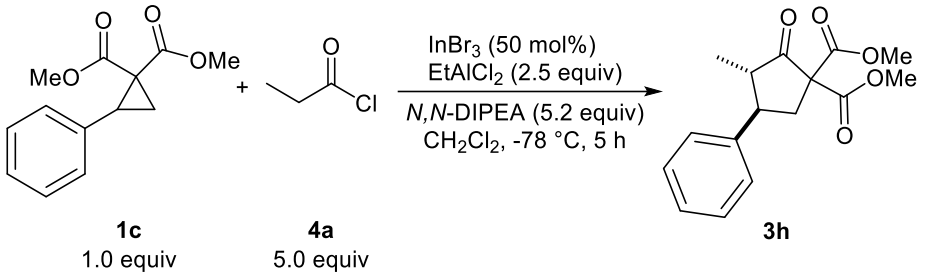
Dibenzyl 2-oxo-4-phenyl-3-propylcyclopentane-1,1-dicarboxylate (3f): Dibenzyl 2-phenylcyclopropane-1,1-dicarboxylate **1b** (60 mg, 0.16 mmol) converted to **3f**, isolated as a colorless gum (68 mg, 93%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 17:1 (by crude ^{1}H NMR analysis); IR (thin film) 3031, 2957, 1764, 1724, 1497, 1454, 1376, 1259, 1171, 973, 737, 696 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.38-7.35 (m, 12H), 7.32-7.29 (m, 1H), 7.27-7.25 (m, 2H), 5.32-5.21 (m, 4H), 3.07-3.01 (m, 1H), 2.96 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.61-2.59 (m, 1H), 2.57-2.53 (m, 1H), 1.62-1.56 (m, 1H), 1.52-1.47 (m, 1H), 1.31-1.25 (m, 1H), 1.14-1.11 (m, 1H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.4, 167.0, 166.6, 141.2, 135.2, 135.1, 129.0, 128.7, 128.7, 128.6, 128.4, 128.4, 128.0, 127.4, 127.3, 68.7, 68.1, 68.0, 55.7, 45.3, 39.6, 30.8, 19.8, 14.2; $(M + H)^+$ HRMS m/z calcd for $(C_{30}H_{31}O_5)^+$: 471.2171; found: 471.2174.



1b 1.0 equiv **4d** 5.0 equiv **3g**

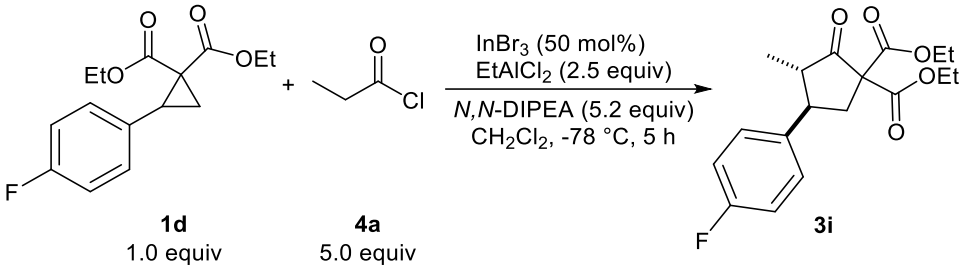
Dibenzyl 3-benzyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate (3g): Dibenzyl 2-phenylcyclopropane-1,1-dicarboxylate **1b** (60 mg, 0.16 mmol) converted to **3g**, isolated as a colorless gum (59 mg, 74%). R_f = 0.6 (EtOAc/hexanes 1:9); dr 7:1 (by crude ^{1}H NMR analysis); IR (thin film) 3030, 2915, 2847, 1768, 1736, 1496, 1454, 1374, 1264, 1167, 993, 736, 697 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.36-7.21 (m, 13H), 7.13-7.12 (m, 2H), 7.09-7.08 (m, 3H), 6.95-6.91 (m, 2H), 5.18 (dd, *J* = 12.3, 10.7 Hz, 2H), 5.07 (dd, *J* = 12.3, 7.0 Hz, 2H), 2.98-2.97 (m, 1H), 2.96 (d, *J* = 4.6 Hz, 1H), 2.91-2.89 (m, 1H), 2.88-2.86 (m, 1H), 2.81 (dd, *J* = 8.0, 5.9 Hz, 1H), 2.46 (dd, *J* = 13.4, 12.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 205.4,

167.0, 165.9, 140.6, 138.0, 135.2, 135.2, 129.8, 128.9, 128.7, 128.7, 128.5, 128.5, 128.2, 128.2, 128.1, 127.5, 127.3, 126.4, 68.5, 68.0, 68.0, 57.3, 44.2, 39.8, 33.5; $(M + H)^+$ HRMS m/z calcd for $(C_{31}H_{34}O_5)^+$: 519.2171; found: 519.2166.



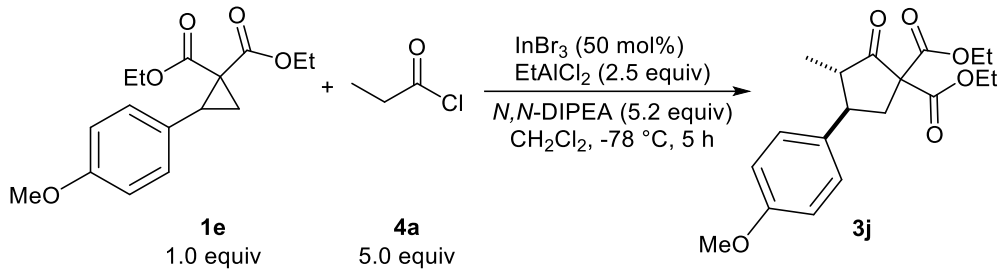
1c 1.0 equiv **4a** 5.0 equiv **3h**

Dimethyl 3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate (3h): Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1c** (60 mg, 0.26 mmol) converted to **3h**, isolated as a colorless gum (48 mg, 65%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 3:1 (by crude ^{1}H NMR analysis); IR (thin film) 2954, 1766, 1726, 1497, 1454, 1375, 1253, 1176, 974, 762, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 7.37 (t, *J* = 7.6 Hz, 2H), 7.31-7.26 (m, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 2.97-2.93 (m, 1H), 2.89 (dd, *J* = 12.2, 6.2 Hz, 1H), 2.59 (*app* t, *J* = 12.5 Hz, 1H), 2.53-2.47 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 206.6, 167.7, 167.4, 140.5, 129.1, 127.5, 127.3, 68.0. 53.6, 53.5, 51.6, 47.4, 39.1, 12.9; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{19}O_5)^+$: 291.1232; found: 291.1233.

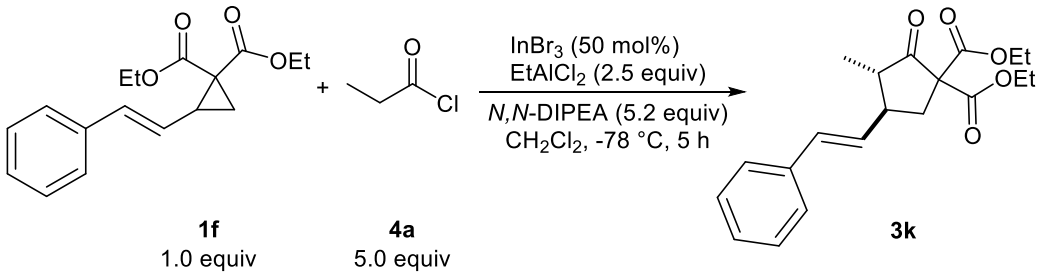


1d 1.0 equiv **4a** 5.0 equiv **3i**

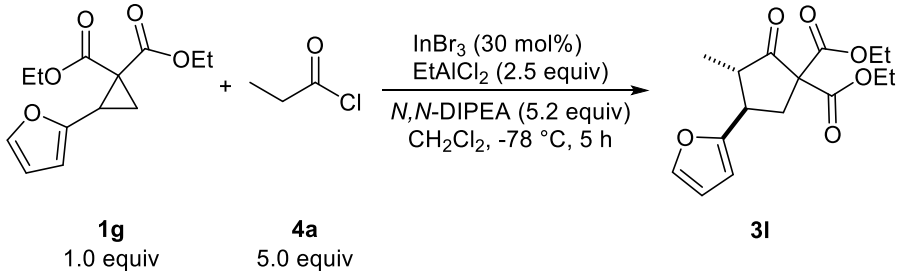
Diethyl 4-(4-fluorophenyl)-3-methyl-2-oxocyclopentane-1,1-dicarboxylate (3i): diethyl 2-(4-fluorophenyl)cyclopropane-1,1-dicarboxylate **1d** (60 mg, 0.21 mmol) converted to **3i**, isolated as a solidifying-colorless gum (57 mg, 79%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 31:1 (by crude ^{1}H NMR analysis); IR (thin film) 2981, 1767, 1733, 1511, 1454, 1367, 1257, 1187, 1015, 939, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 7.25-7.22 (m, 2H), 7.07-7.04 (m, 2H), 4.31-4.25 (m, 4H), 2.92-2.86 (m, 2H), 2.56-2.51 (m, 1H), 2.42-2.39 (m, 1H), 1.32-1.28 (m, 6H), 1.10 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): δ 206.4, 167.2, 166.9, 162.1 (d, *J* = 240 Hz, 1C), 136.4 (d, *J* = 2.9 Hz, 1C), 128.8 (d, *J* = 7.8 Hz, 1C), 115.9 (d, *J* = 21.0 Hz, 1C), 68.2, 62.7, 62.6, 51.6, 46.7, 39.1, 14.1, 12.9; $(M + H)^+$ HRMS m/z calcd for $(C_{18}H_{22}FO_5)^+$: 337.1451; found: 337.1447.



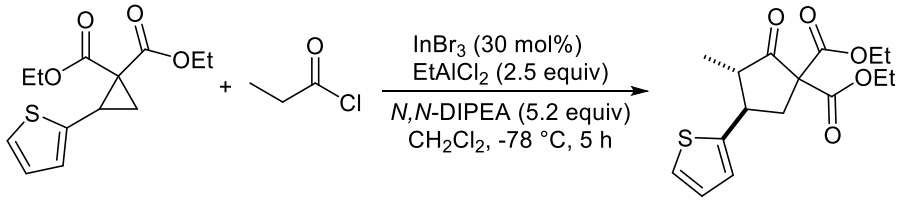
Diethyl 4-(4-methoxyphenyl)-3-methyl-2-oxocyclopentane-1,1-dicarboxylate (3j): Diethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate **1e** (60 mg, 0.21 mmol) converted to **3j**, isolated as a colorless gum (58 mg, 81%). R_f = 0.4 (EtOAc/hexanes 1:9); dr = 26:1 (by crude ^{1}H NMR analysis); IR (thin film) 2979, 1764, 1720, 1513, 1455, 1367, 1245, 1178, 1031, 938, 831 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 7.19-7.17 (m, 2H), 6.91-6.89 (m, 2H), 4.30-4.25 (m, 4H), 3.81 (s, 3H), 2.91-2.87 (m, 1H), 2.83 (dd, *J* = 12.2, 6.2 Hz, 1H), 2.53 (*app* t, *J* = 12.5 Hz, 1H), 2.42-2.39 (m, 1H), 1.32-1.28 (m, 6H), 1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): δ 206.9, 167.3, 167.0, 158.9, 132.7, 128.2, 114.4, 68.3, 62.6, 62.5, 55.4, 51.6, 46.6, 39.2, 14.1, 12.9; $(M - H)^-$ HRMS m/z calcd for $(C_{19}H_{23}O_6)^-$: 347.1495; found: 347.1494.



Diethyl 3-methyl-2-oxo-4-((*E*)-styryl)cyclopentane-1,1-dicarboxylate (3k): diethyl (E)-2-styrylcyclopropane-1,1-dicarboxylate **1f** (100 mg, 0.35 mmol) converted to **3k**, isolated as a colorless gum (83 mg, 70%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 5:1 (by crude ^{1}H NMR analysis); IR (thin film) 2979, 1765, 1722, 1449, 1366, 1250, 1185, 1015, 967, 858, 750, 694 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 7.37 (d, *J* = 7.4 Hz, 2H), 7.35-7.29 (m, 2H), 7.27-7.23 (m, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.10 (dd, *J* = 15.7, 8.1 Hz, 1H), 4.29-4.24 (m, 4H), 2.82 (dd, *J* = 13.3, 6.1 Hz, 1H), 2.55-2.51 (m, 1H), 2.38 (*app* t, *J* = 12.3 Hz, 1H), 2.22-2.19 (m, 1H), 1.31-1.28 (m, 6H), 1.17 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): δ 206.9, 167.2, 167.0, 136.8, 132.1, 130.1, 128.8, 127.8, 126.3, 67.8, 62.6, 62.5, 50.2, 45.4, 37.5, 14.1, 12.8; $(M + H)^+$ HRMS m/z calcd for $(C_{20}H_{25}O_5)^+$: 345.1702; found: 345.1699.

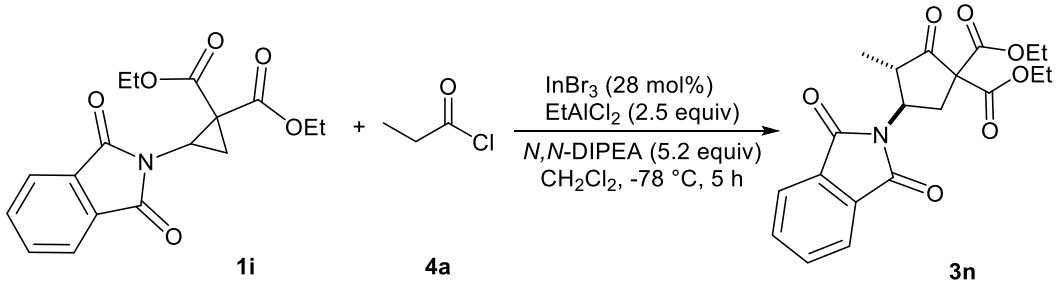


Diethyl 4-(furan-2-yl)-3-methyl-2-oxocyclopentane-1,1-dicarboxylate (3l): Diethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate **1g** (100 mg, 0.40 mmol) converted to **3l**, isolated as a colorless gum (101 mg, 83%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 13:1 (by crude ^{1}H NMR analysis); IR (thin film) 2981, 1766, 1727, 1454, 1256, 1189, 1013, 938, 740 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 7.37 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.33 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.15 (*app* d, *J* = 3.0 Hz, 1H), 4.29-4.23 (m, 4H), 3.06-3.01 (m, 1H), 2.92 (dd, J = 13.2, 6.0 Hz, 1H), 2.65 (dd, *J* = 13.2, 12.0 Hz, 1H), 2.56-2.50 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 206.4, 166.9, 166.9, 154.4, 142.1, 110.4, 106.0, 67.9, 62.7, 62.5, 49.4, 40.6, 36.2, 14.1, 13.5; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{20}O_6)^+$: 308.1260; found: 309.1333.



1h 1.0 equiv **4a** 5.0 equiv **3m**

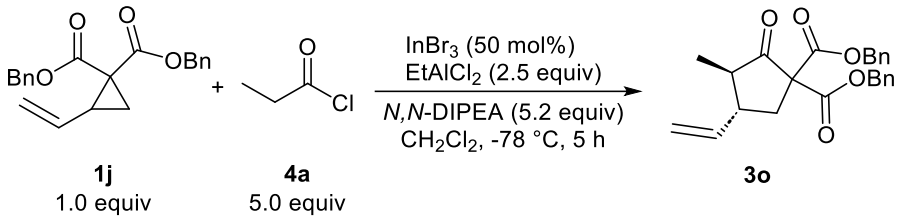
Diethyl 3-methyl-2-oxo-4-(thiophen-2-yl)cyclopentane-1,1-dicarboxylate (3m): Diethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate **1h** (100 mg, 0.37 mmol) converted to **3m**, isolated as a yellow gum (89 mg, 74%). R_f = 0.5 (EtOAc/hexanes 2:8); dr = 37:1 (by crude ^{1}H NMR analysis); IR (thin film) 2980, 1768, 1732, 1445, 1366, 1257, 1189, 1017, 938, 734 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): *δ* 7.23 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.00-6.98 (m, 1H), 6.94-6.93 (m, 1H), 4.30-4.25 (m, 4H), 3.23-3.18 (m, 1H), 3.03 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.62-2.58 (m, 1H), 2.46-2.40 (m, 1H), 1.32-1.28 (m, 6H), 1.21 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): δ 206.1, 166.9, 166.8, 144.8, 127.2, 124.4, 124.0, 68.3, 62.7, 62.6, 52.5, 42.6, 39.8, 14.1, 14.1, 13.3; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{21}O_5S)^+$: 325.1110; found: 325.1106.



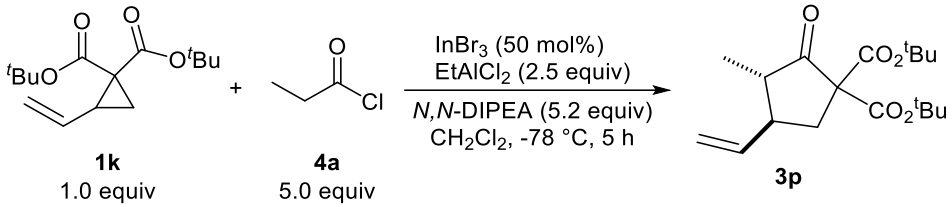
1i 1.0 equiv **4a** 5.0 equiv **3n**

Diethyl 4-(1,3-dioxoisoindolin-2-yl)-3-methyl-2-oxocyclopentane-1,1-dicarboxylate (3n): Diethyl 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate **1i** (62 mg, 0.19 mmol) converted to **3n**, isolated as a colorless gum (29 mg, 42%). R_f = 0.5 (EtOAc/hexanes 1.5:8.5); dr = 9:1 (by crude ^{1}H NMR analysis); IR (thin film) 2985, 2934, 1772, 1712, 1466, 1382, 1258, 1195, 1112, 939, 721, 630 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): *δ* 7.88-7.86 (m, 2H), 7.77-7.75 (m, 2H), 4.55-4.54 (m, 1H), 4.32-4.27 (m, 4H), 3.43-3.40 (m, 1H), 3.32-3.26 (m, 1H), 2.84-2.81 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 203.5, 168.2, 166.6, 166.2, 134.5, 131.7, 123.7, 67.9, 62.9,

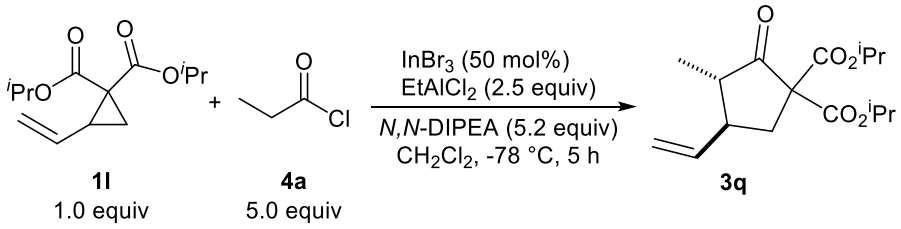
62.7, 51.9, 45.7, 33.3, 14.1, 12.4; $(M + Na)^+$ HRMS m/z calcd for $(C_{20}H_{21}NNaO_7)^+$: 410.1216; found: 410.1218.



Dibenzyl 3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate (3o): dibenzyl 2-vinylcyclopropane-1,1-dicarboxylate **1j** (60 mg, 0.18 mmol) converted to **3o**, isolated as a colorless gum (57 mg, 81%). R_f = 0.4 (EtOAc/hexanes 1:9); dr = 17:1 (by crude ^{1}H NMR analysis); IR (thin film) 2968, 1767, 1733, 1498, 1454, 1374, 1258, 1186, 950, 737, 696 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.33-7.30 (m, 6H), 7.29-7.26 (m, 4H), 5.72-5.67 (m, 1H), 5.21-5.17 (m, 4H), 5.16-5.11 (m, 2H), 2.76-2.74 (m, 1H), 2.35-2.31 (m, 1H), 2.30-2.26 (m, 1H), 2.12-2.07 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.6, 166.9, 166.7, 138.4, 135.2, 135.1, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 117.0, 68.1, 68.0, 67.8, 49.8, 45.8, 37.2, 12.6; $(M + H)^+$ HRMS m/z calcd for $(C_{24}H_{25}O_5)^+$: 393.1702; found: 393.1694.

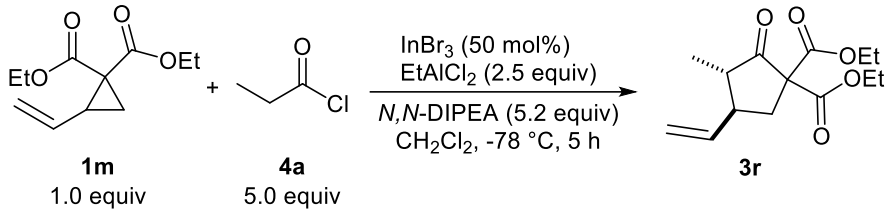


Di-tert-butyl 3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate (3p): Di-tert-butyl 2-vinylcyclopropane-1,1-dicarboxylate **1k** (60 mg, 0.22 mmol) converted to **3p**, isolated as a colorless gum (41 mg, 56%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 3:1 (by crude ^{1}H NMR analysis); IR (thin film) 2978, 1728, 1457, 1368, 1249, 1166, 1138, 1014, 847 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 5.77-5.71 (m, 1H), 5.18-5.12 (m, 2H), 2.64 (dd, J = 13.1, 5.9 Hz, 1H), 2.34-2.28 (m, 1H), 2.21 (*app* t, J = 13.0 Hz, 1H), 2.06-2.02 (m, 1H), 1.49-1.45 (m, 18H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 207.6, 166.5, 166.3, 139.0, 116.5, 83.0, 82.8, 69.5, 49.7, 45.8, 37.1, 28.0, 28.0, 13.0; $(M + H)^+$ HRMS m/z calcd for $(C_{18}H_{28}NaO_5)^+$: 347.1834; found: 347.1830.

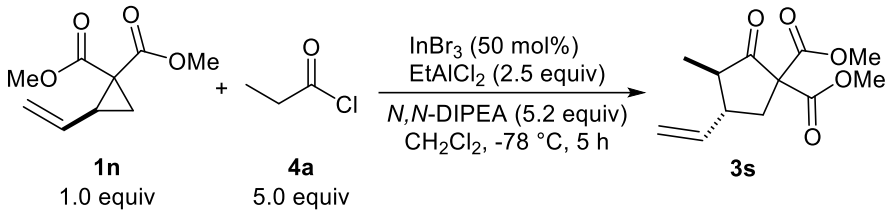


Diisopropyl 3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate (3q): Diisopropyl 2-vinylcyclopropane-1,1-dicarboxylate **1l** (100 mg, 0.42 mmol) converted to **3q**, isolated as a colorless gum (82 mg, 68%). R_f = 0.4 (EtOAc/hexanes 1:9); dr = 6:1 (by crude ^{1}H NMR analysis); IR (thin film) 2981, 1766, 1719, 1454, 1375, 1265, 1194, 1101, 946, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 5.77-5.71 (m, 1H), 5.18-5.12 (m, 2H), 5.09-5.05 (m, 2H), 2.70 (dd, J = 13.2, 5.9 Hz, 1H), 2.35-2.33 (m, 1H), 2.25

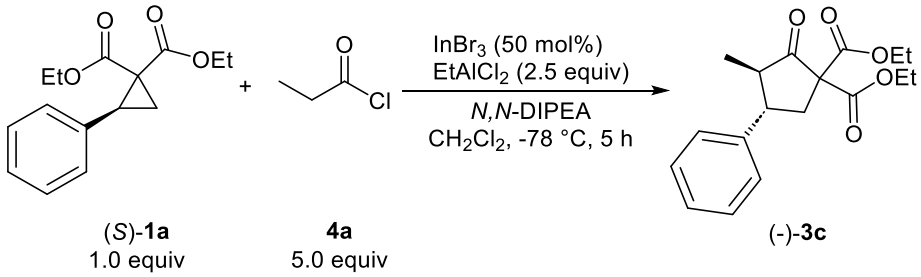
(*app* t, *J* = 13.1 Hz, 1H), 2.09-2.06 (m, 1H), 1.29-1.22 (m, 12H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 207.1, 166.8, 166.7, 138.8, 116.7, 70.2, 70.1, 68.0, 49.7, 45.8, 37.0, 21.7, 21.6, 21.6, 21.6, 12.8; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{25}O_5)^+$: 297.1702; found: 297.1697.



Diethyl 3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate (3r): Diethyl 2-vinylcyclopropane-1,1-dicarboxylate **1m** (100 mg, 0.47 mmol) converted to **3r**, isolated as a colorless oil (89 mg, 71%). R_f = 0.4 (EtOAc/hexanes 0.8:9.2); dr = 4:1 (by crude ^{1}H NMR analysis); IR (thin film) 2981, 1767, 1733, 1454, 1366, 1256, 1191, 938, 860 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 5.76-5.71 (m, 1H), 5.19-5.13 (m, 2H), 4.27-4.22 (m, 4H), 2.74 (dd, *J* = 13.2, 5.8 Hz, 1H), 2.39-2.32 (m, 1H), 2.27 (dd, *J* = 13.0, 12.3 Hz, 1H), 2.12-2.07 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 207.1, 167.2, 167.0, 138.6, 116.9, 67.8, 62.5, 62.5, 49.8, 45.8, 37.1, 14.1, 12.7; $(M + H)^+$ HRMS m/z calcd for $(C_{14}H_{21}O_5)^+$: 269.1389; found: 269.1390.

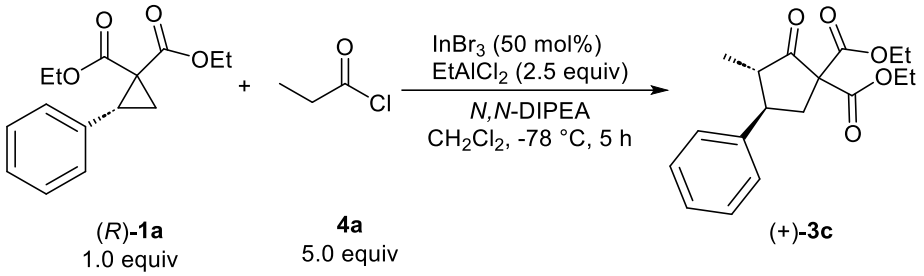


Dimethyl 3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate (3s): Dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **1n** (60 mg, 0.33 mmol) converted to **3s**, isolated as a colorless gum (44 mg, 56%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 14:1 (by crude ^{1}H NMR analysis); IR (thin film) 2955, 1765, 1726, 1434, 1253, 1200, 1141, 979 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 5.76-5.70 (m, 1H), 5.20-5.14 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.77 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.37-2.33 (m, 1H), 2.29-2.25 (m, 1H), 2.14-2.10 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 206.9, 167.7, 167.4, 138.4, 117.0, 67.6, 53.5, 53.5, 49.8, 45.8, 37.2, 12.7; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{15}O_5)^+$: 239.0919; found: 239.0913.

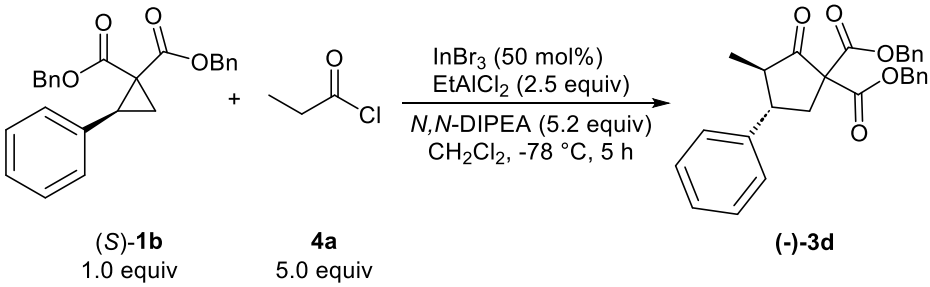


Diethyl (3*R*,4*S*)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate ((–)-3c): Diethyl (*S*)-2-phenylcyclopropane-1,1-dicarboxylate **1a** converted to (–)-**3c**, isolated as a colorless gum (77 mg, 77%).

R_f = 0.5 (EtOAc/hexanes 1:9); dr = 28:1 (by crude ^{1}H NMR analysis); HPLC analysis: 99% ee [Daicel Chiralcel AD-H column; 1.0 mL/min; solvent system: 3% isopropanol in hexane; retention times: 10.7 min (minor), 15.4 min (major)]; $[\alpha]_D^{24}$ = -27 (c = 0.1, CH_2Cl_2); IR (thin film) 2979, 1765, 1722, 1497, 1454, 1366, 1251, 1187, 1018, 938, 760, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.38-7.36 (m, 2H), 7.30-7.27 (m, 3H), 4.31-4.25 (m, 4H), 2.94-2.92 (m, 1H), 2.91-2.88 (m, 1H), 2.61-2.56 (m, 1H), 2.49-2.46 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H) 1.11 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.8, 167.3, 167.0, 140.7, 129.0, 127.5, 127.3, 68.3, 62.6, 62.5, 51.5, 47.4, 39.0, 14.1, 13.0; $(M + H)^+$ HRMS m/z calcd for $(C_{18}H_{23}O_5)^+$: 319.1545; found: 319.1541.

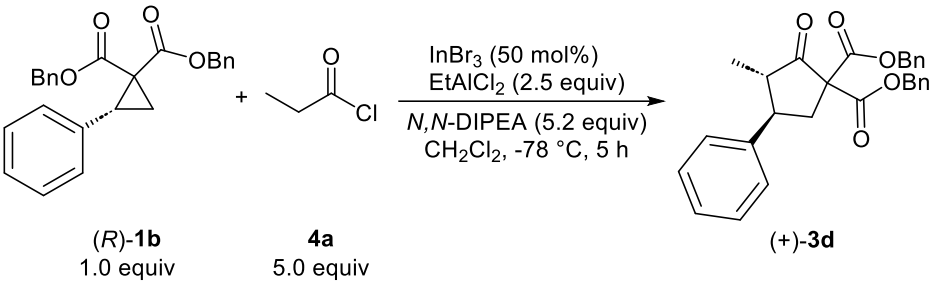


Diethyl (3*S*,4*R*)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate ((+)-3c): Diethyl (*R*)-2-phenylcyclopropane-1,1-dicarboxylate **1a** (60 mg, 0.23 mmol) converted to (+)-**3c**, isolated as a colorless gum (56 mg, 78%). R_f = 0.5 (EtOAc/hexanes 1:9); dr = 11:1 (by crude ^{1}H NMR analysis); HPLC analysis: >99% ee [Daicel Chiralcel AD-H column; 1.0 mL/min; solvent system: 3% isopropanol in hexane; retention time: 10.3 min (major); $[\alpha]_D^{24}$ = +27 (c = 0.06, CH_2Cl_2); IR (thin film) 2980, 1730, 1496, 1454, 1368, 1255, 1188, 1029, 939, 763, 701 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.38-7.36 (m, 2H), 7.30-7.26 (m, 3H), 4.31-4.25 (m, 4H), 2.94-2.89 (m, 2H), 2.61-2.56 (m, 1H), 2.50-2.45 (m, 1H), 1.32-1.29 (m, 6H), 1.11 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.8, 167.3, 167.0, 140.7, 129.0, 127.5, 127.3, 68.3, 62.6, 62.5, 51.5, 47.4, 39.0, 14.1, 12.9; $(M + H)^+$ HRMS m/z calcd for $(C_{18}H_{23}O_5)^+$: 319.1545; found: 319.1544.

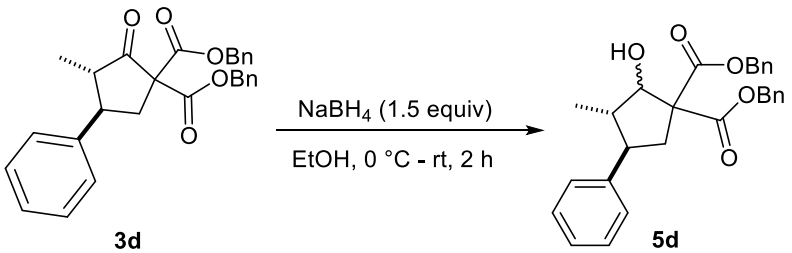


Dibenzyl (3*R*,4*S*)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate ((–)-3d)): Dibenzyl (*S*)-2-phenylcyclopropane-1,1-dicarboxylate **1b** (55 mg, 0.14 mmol) converted to (–)-**3d**, isolated as a colorless gum (55 mg, 87%). R_f = 0.4 (EtOAc/hexanes 1:9); dr = 25:1 (by crude ^{1}H NMR analysis); HPLC analysis: 98% ee [Daicel Chiralcel AD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexane; retention times: 14.7 min (minor), 26.5 min (major)]; $[\alpha]_D^{24}$ = -41 (c = 0.07, CH_2Cl_2); IR (thin film) 3031, 2929, 1766, 1731, 1497, 1454, 1375, 1260, 1176, 960, 748, 697 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.35-7.29 (m, 12H), 7.29-7.27 (m, 1H), 7.29-7.19 (m, 2H), 5.26-5.19 (m, 4H), 2.92 (dd, *J* = 13.3, 6.2 Hz, 1H), 2.87-

2.82 (m, 1H), 2.59 (dd, *J* = 13.1, 12.6, Hz, 1H), 2.49-2.43 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.4, 167.0, 166.7, 140.6, 135.2, 135.1, 129.0, 128.7, 128.7, 128.6, 128.5, 128.3, 128.1, 127.5, 127.3, 68.3, 68.2, 68.0, 51.5, 47.3, 39.0, 12.8; $(M + H)^+$ HRMS m/z calcd for $(C_{28}H_{27}O_5)^+$: 443.1858; found: 443.1853.



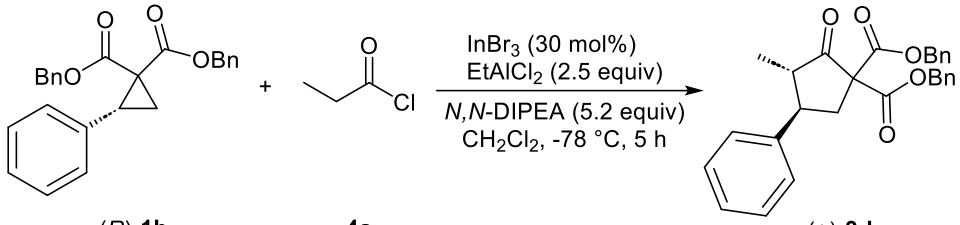
Dibenzyl (3*S*,4*R*)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate ((+)-3d): Dibenzyl (*R*)-2-phenylcyclopropane-1,1-dicarboxylate **1b** (60 mg, 0.16 mmol) converted to (+)-**3d**, isolated as a colorless gum (61 mg, 89%). R_f = 0.4 (EtOAc/hexanes 1:9); dr = 27:1 (by crude ^{1}H NMR analysis); HPLC analysis: 96% ee [Daicel Chiralcel AD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexane; retention times: 14.5 min (major), 25.9 min (minor)]; $[\alpha]_D^{24}$ = +33 (c = 0.1, CH_2Cl_2); IR (thin film) 3031, 2928, 1766, 1723, 1497, 1454, 1375, 1258, 1175, 959, 738, 696 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.34-7.27 (m, 13H), 7.19 (d, *J* = 7.3 Hz, 2H), 5.25-5.17 (m, 4H), 2.91 (dd, *J* = 13.3, 6.2 Hz, 1H), 2.86-2.80 (m, 1H), 2.58 (*app* t, *J* = 12.8 Hz, 1H), 2.47-2.42 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.3, 167.0, 166.7, 140.6, 135.2, 135.1, 129.0, 128.7, 128.7, 128.6, 128.5, 128.3, 128.1, 127.5, 127.3, 68.3, 68.2, 68.0, 51.5, 47.3, 39.0, 12.8; $(M + H)^+$ HRMS m/z calcd for $(C_{28}H_{27}O_5)^+$: 443.1858; found: 443.1852.



Dibenzyl 2-hydroxy-3-methyl-4-phenylcyclopentane-1,1-dicarboxylate (5d): $NaBH_4$ (13 mg, 0.34 mmol) was added in small lots to a stirring solution of cyclopentanone **3d** (100 mg, 0.22 mmol) in ethanol (3 mL) at 0-5 °C. The reaction was then stirred at room temperature for 2h. After this time, cooled water (5 mL) was added to the residue in small lots and the pH of the mixture was adjusted to pH = 7 by addition of 1M HCl (*ca*. 2 mL). The ethanol was evaporated under reduced pressure. The aqueous solution was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with sat. brine solution (20 mL), dried over sodium sulfate, and following filtration, purified through column chromatographic purification (eluting with CH_2Cl_2). Evaporation of the organics afforded **5d** as an off-white oil (68 mg, 68%), with dr = 2:1 (by crude ^{1}H NMR analysis); IR (thin film) 3520, 3030, 2956, 1719, 1496, 1454, 1260, 1174, 696 cm^{-1}; ^{1}H NMR for major diastereomer (600 MHz, $CDCl_3$, TMS): δ 7.33-7.31 (m, 6H), 7.29-7.26 (m, 6H), 7.22-7.19 (m, 3H), 5.22-5.15 (m, 4H), 4.23-4.20 (m, 1H), 2.94 (dd, *J* = 6.2, 3.3 Hz, 1H), 2.65-2.63 (m, 1H), 2.61-2.59

(m, 1H), 2.57-2.53 (m, 1H), 2.21-2.19 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR for major diastereomer (150 MHz, $CDCl_3$): δ 171.8, 171.2, 142.5, 135.5, 135.3, 128.8, 128.7, 128.7, 128.6, 128.5, 128.4, 128.2, 127.8, 126.8, 83.1, 67.6, 67.6, 62.7, 48.0, 47.4, 39.8, 15.4; $(M + Na)^+$ HRMS m/z calcd for $(C_{28}H_{28}NaO_5)^+$: 467.1834; found: 467.1830.

Procedure for large scale synthesis of 3d:



To a stirring suspension of indium bromide (0.28 g, 0.78 mmol) in dichloromethane (70 mL) at -78 °C, propionyl chloride (1.12 mL, 12.9 mmol) was added. *i*-Pr_2NEt (2.34 mL, 13.4 mmol) was added over a period of 15-20 min. To this stirring reaction mixture, a solution of the DA cyclopropane (*R*)-**1b** (1.00 g, 2.6 mmol) in dichloromethane (20 mL) was added over a period of 1 h via syringe pump. During addition of half the cyclopropane solution, the ethyl aluminium dichloride solution (6.47 mL, 1.0 M in hexanes, 6.47 mmol) was added. The reaction was stirred at this temperature for another 4 h and then quenched by addition of a mixture of methanol-triethylamine (2:1, 10 mL). Then the reaction mixture was poured into cold 10% hydrochloric acid solution (200 mL) and extracted with dichloromethane (80 mL × 2). The combined organic layers were washed with water (80 mL), brine (80 mL), dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (50 mL), silica gel (40 g) was added and the mixture stirred for 2 h at 50 °C. Then the reaction mass was filtered, and the residue was washed with dichloromethane (80 mL × 3). The combined filtrate was evaporated under reduced pressure to afford the crude product (1.12 g, 98%), for diastereomeric measurement (dr = 28:1 by ^{1}H NMR). The product was further purified using regular silica gel column chromatographic purification using 10% EtOAc/hexane as eluent to afford **3d** as a colorless gum (1.05 g, 92%). The spectroscopic data obtained agreed with that previously obtained for (+)-**3d** on a small scale (0.16 mmol).

Stereochemistry Determination: The relative stereochemistry of the major isomer of the cyclopentanone **3c** was determined to be *trans* by 2D-NOESY (interaction between 3-Me and 4-H; No interaction between 3-Me and 4-ArH). High stereospecificity was observed in the conversion of cyclopropane (*S*)-**1b** (99% ee) to cyclopentanone (−)-**3d** (98% ee), implying that the [3 + 2]-cycloaddition does not involve an S_N1-type mechanism, as effectively no racemisation occurred, and therefore must involve an S_N2-type mechanism. Consequently, the absolute stereochemistry of (−)-**3d** was assigned to be (3*R*,4*S*) as the reaction involves inversion of stereochemistry at the cyclopropane stereocentre of (*S*)-**1b** through a S_N2-type mechanism (*S*→3*R*). Other examples were assigned stereochemistry by analogy.

References:

1) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th Ed. Butterworth Heinemann, **2002**.

2) (a) Ieki, R.; Kani, Y.; Tsunoi, S.; Shibata, I. *Chem. Eur. J*. **2015**, *21*, 6295. (b) Vermaa, K.; Banerjee, P. *Adv. Synth. Catal*. **2017**, *359*, 3848. (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.*, **2008**, *130*, 8642. (d) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.,* **2008,** *10*, 2541.