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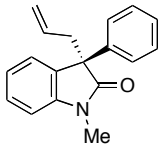
Palladium-Catalyzed Asymmetric Allylation of Prochiral Nucleophiles: Synthesis of 3-Allyl-3-Aryl Oxindoles.

Barry M. Trost* and Mathias U. Frederiksen

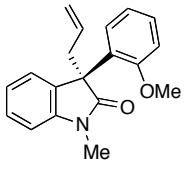
Department of Chemistry, Stanford University, Stanford, California 94305-5080



A

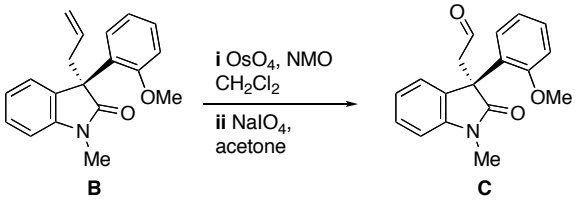
General procedure for the Pd-catalyzed AAA of 3-aryl oxindoles. The preparation of 3-allyl-1-methyl-3-phenyl-1,3-dihydro-indol-2-one (**A**) is representative. A test-tube was charged with *N*-methyl-3-phenyl oxindole (22.3 mg, 0.1 mmol), which was dissolved in dry degassed toluene (0.33 mL). Freshly distilled *t*-BuOH (38 μL, 0.4 mmol) was added and the resultant solution was stirred at –78ºC. Meanwhile in a separate test-tube, allyl palladium dimer [$(\eta^3$-$C_3H_5PdCl)_2$] (7.3 mg, 20 μmol) and anthracenyl ligand **7** (32 mg, 40 μmol) were dissolved in dry degassed toluene (2.64 mL). This solution was stirred at ambient temperature (15 min). Freshly distilled allyl acetate (95 mL, 0.87 mmol) was added and the resultant lime green suspension was stirred (5 min), whereupon 0.33 mL of this solution was withdrawn in a gas-tight syringe and added to the oxindole solution at –78ºC. The reaction mixture was placed at 4ºC overnight. The reaction was quenched by the addition of methanol (0.5 mL). The volatiles were removed and the residue was chromatographed on silica (10% EtOAc / hexane), which gave pure oxindole **A** as a colourless oil [24 mg, 93 μmol, 93%, 81% *ee* by Chiral HPLC, OJ-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 8.32 min, t_B (minor) = 27.02 min]: R_f = 0.5 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 3056, 2924, 2854, 1714, 1613, 1470, 1253, 1079, 921; ^{1}H NMR (500 MHz, d_6-PhH): δ = 7.54 – 7.52 (m, 2 H), 7.11 – 7.06 (m, 2 H), 7.06 – 7.01 (m, 3 H), 6.90 – 6.87 (m, 1 H), 6.33 (d, *J* = 7.5, 1 H), 5.51 – 5.42 (m, 1 H), 5.00 – 4.96 (m, 1 H), 4.81 – 4.79 (m, 1 H), 3.10 – 3.05 (m, 1 H), 2.94 – 2.90 (m, 1 H), 2.64 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.2, 144.4, 140.3, 133.0, 131.7, 128.6,

128.2, 127.5, 127.2, 125.4, 122.1, 118.9, 108.1, 56.3, 42.6, 25.7; Anal calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.28; H, 6.70; N, 5.40.



B

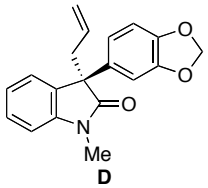
(*S*)-3-allyl-3-(2-methoxyphenyl)-1-methylindolin-2-one (A). 1-Methyl-3-(2-methoxyphenyl)oxindole (25 mg, 0.1 mmol) was used to give oxindole **B** as a colourless oil, which proved inseparable from the starting material (27 mg mass recovery). This mixture was therefore converted to the corresponding aldehyde by oxidative cleavage (*vide infra*): [97 % *ee* by chiral HPLC, OD-H-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 8.35 min, t_B (minor) = 12.24 min]: IR (film) υ_{max}/cm^{-1}: 2920, 1713, 1611, 1493, 1468, 1373, 1346, 1250, 1123, 1086, 1020; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.0, 1H), 7.14 – 6.97 (m, 2H), 6.93 – 6.90 (m, 1H), 6.77 – 6.72 (m, 1H), 6.44 (d, *J* = 8.0, 1H), 6.37 (d, *J* = 7.0, 1H), 5.57 – 5.49 (m, 1H), 5.02 (d, *J* = 15.5, 1H), 4.85 (d, *J* = 10.0, 1H), 3.07 (dd, *J* = 13.0, 12.7, 1H), 2.96 (s, 3H), 2.85 (dd, *J* = 13.0, 12.7, 1H), 2.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 179.5, 157.4, 144.6, 133.5, 132.0, 129.9, 128.9, 127.8, 122.8, 122.3, 121.2, 119.3, 112.5, 107.3, 56.2, 54.0, 40.8, 26.4; MS (EI) (M^+) 293; HRMS calcd for $C_{19}H_{19}NO_2$: 293.1416; found 293.1404.



B **C**

(*S*)-2-(3-(2-methoxyphenyl)-1-methyl-2-oxoindolin-3-yl)acetaldehyde (C). Oxindole **B** was subjected to standard oxidative cleavage. Thus the impure product mixture was dissolved in dichloromethane (0.5 mL). NMO (22 mg, 0.70 mmol) was added followed by osmium tetraoxide (50 μL, 4% solution in water). The reaction mixture was stirred vigorously at ambient temperature (2 h), whereupon the reaction was quenched with saturated aqueous Na_2SO_3 solution. The layers were separated and the aqueous phase was

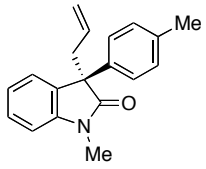
further extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to reveal the diol as white solid, which was dissolved in acetone (1 mL) and water (0.5 mL). Solid sodium periodate (80 mg, 0.81 mmol) was added and the reaction was stirred at room temperature until deemed complete by TLC (3 h). The reaction was poured into water (10 mL) and diethyl ether (10 mL). The layers were separated and the aqueous phase was further extracted with diethyl ether (3 x 10 mL), washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed (50% EtOAc / hexane) to reveal the aldehyde **C** as an amorphous solid (21 mg, 72 mmol, 72 % over 2 steps): $[\alpha]_D^{24} = 41.4^o$ (*c* 0.44 $CHCl_3$); R_f = 0.15 (50% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2922, 2852, 1716, 1611, 1493, 1471, 1373, 1349. 1256, 1131, 1091, 1025, 751; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.73 (t, *J* = 2.3, 1 H), 7.40 (d, *J* = 7.7, 1 H), 7.31 – 7.26 (m, 3 H), 7.04 – 6.99 (m, 2 H), 6.90 (d, *J* = 7.8, 1 H), 6.85 (d, *J* = 7.7, 1 H), 3.57 (s, 3 H), 3.67 (s, 3 H), 3.34 – 3.30 (m, 1 H), 3.11 – 3.07 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 200.7, 178.1, 157.4, 143.8, 132.5, 129.5, 128.5, 127.9, 123.5, 123.0, 121.4, 112.7, 108.1, 56.1, 51.8, 48.5, 29.9, 26.8; MS (EI) (M^+) 295; HRMS calcd for $C_{18}H_{17}NO_3$: 295.1208; found 295.1202.



D

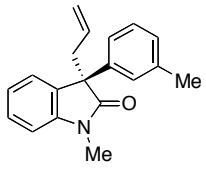
(*R*)-3-allyl-3-(benzo[*d*][1,3]dioxol-5-yl)-1-methylindolin-2-one (D). 3-(1,3-Benzodioxol-5-yl)-1-methyloxindole (27 mg, 0.1 mmol) was used to give oxindole **D** was obtained as a colourless oil [21 mg, 68 μmol, 68%, 79 % *ee* by chiral HPLC, OJ-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (minor) = 9.94 min, t_B (major) = 20.80 min]: $[\alpha]_D^{24} = 125.7^o$ (*c* 1 $CHCl_3$); R_f = 0.2 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2921, 1715, 1610, 1489, 1436, 1373, 1240, 1039; ^1H NMR (400 MHz, d_6-PhH): δ = 7.24 (d, *J* = 2.0, 1H), 7.04 – 6.99 (m, 2H), 6.89 – 6.84 (m, 2H), 6.55 (d, *J* = 8.0, 1H), 6.31 (d, *J* = 7.5, 1H), 5.49 – 5.41 (m, 1H), 5.23 (dd, *J* = 8.5, 2H), 4.98 (m, 1H), 4.81 – 4.79 (m, 1H), 2.99 – 2.95 (m, 1H), 2.88 – 2.83 (m, 1H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, d_6-PhH) δ = 177.3, 148.3, 147.3, 144.3, 134.1, 132.9, 131.8, 125.3, 122.1,

120.8, 118.9, 108.4, 108.4, 108.1, 108.0, 100.7, 55.9, 44.7, 25.7, ; MS (EI) (M^+) 307; HRMS calcd for $C_{19}H_{17}NO_3$: 307.1208; found 307.1196.



E

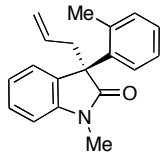
(*R*)-3-allyl-1-methyl-3-*p*-tolylindolin-2-one (E). 1-Methyl-3-(*p*-tolyl)oxindole (20 mg, 84 μmol) was used to give oxindole **E** as a colourless oil [17 mg, 63 μmol, 75%, 80 % *ee* by chiral HPLC, OD-H-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 6.72 min, t_B (minor) = 9.40 min]: $[\alpha]_D^{24}$ = -125.1° (*c* 1, $CHCl_3$); R_f = 0.3 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2918, 1714, 1610, 1491, 1468, 1371, 1341, 1124, 1089, 742; ^1H NMR (500 MHz, d_6-PhH): δ = 7.47 – 7.45 (m, 2H), 7.07 – 7.02 (m, 2H), 6.96 – 6.94 (d, *J* = 8.6, 2H), 6.91 – 6.87 (m, 1H), 6.34 (d, *J* = 8.0, 1H), 5.54 – 5.46 (m, 1H), 5.00 (d, *J* = 17.0, 1H), 4.81 (d, *J* = 10.0, 1H), 3.11 – 3.07 (m, 1H), 2.98 – 2.94 (m, 1H), 2.66 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, d_6-PhH) δ =177.4, 144.4, 137.8, 136.8, 133.2, 132.0, 129.2, 128.2, 127.4, 125, 4, 122.1, 118.9, 108.1, 56.1, 42.6, 30.1, 25.7, 20.8; MS (EI) (M^+) 277; HRMS calcd for $C_{19}H_{19}NO$: 277.1455; found 277.1467.



F

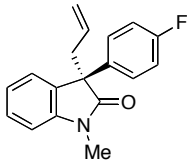
(*R*)-3-allyl-1-methyl-3-*m*-tolylindolin-2-one (F). 1-Methyl-3-(*m*-tolyl)oxindole (19 mg, 80 μmol) was used to give oxindole **F** was obtained as a colourless oil [18 mg, 66 μmol, 96%, 77 % *ee* by chiral HPLC, OD-H-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 6.85 min, t_B (minor) = 17.01 min]: $[\alpha]_D^{24}$ = -128.8° (*c* 1.0, $CHCl_3$); R_f = 0.3 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2918, 1714, 1610, 1491, 1468, 1371, 1341, 1124, 1089, 742; ^1H NMR (500 MHz, d_6-PhH): δ = 7.46 (s, 1H), 7.33 (d, *J* = 3.0, 1H), 7.07 – 7.02 (m, 3H), 6.90-6.87 (m, 2H), 6.34 (d, *J* = 8.0, 1H), 5.53 – 5.45 (m, 1H),

5.05 (d, J = 17.0, 1H), 4.81 (d, J = 11.0, 1H), 3.13 – 3.09 (m, 1H), 2.98 – 2.94 (m, 1H); ^{13}C NMR (125 MHz, d_6-PhH) δ = 177.4, 144.4, 140.3, 138.1, 133.1, 131.9, 128.6, 125.4, 124.6, 122.1, 118.9, 108.1, 56.3, 42.6, 30.1, 25.7, 21.4; MS (EI) (M^+) 277; HRMS calcd for $C_{19}H_{19}NO$: 277.1467; found 277.1466.



G

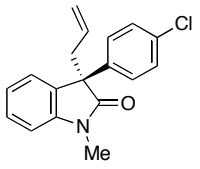
(*R*)-3-allyl-1-methyl-3-*o*-tolylindolin-2-one (G). 1-Methyl-3-(*o*-tolyl)oxindole (23 mg, 0.1 mmol) was used to give oxindole **G** as white needles [19 mg, 68 μmol, 69 %, 70 % *ee* by chiral HPLC, OD-H-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 6.72 min, t_B (minor) = 9.40 min]: mp 138°C (hexane); $[\alpha]_D^{24}$ = +7.40° (*c* 0.15 $CHCl_3$); R_f = 0.3 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2918, 1714, 1612, 1493, 1470, 1372, 1343, 1124, 1084, 748; ^{1}H NMR (400 MHz, d_6-PhH): δ = 7.50 (d, J = 10, 1H), 7.18 [m (partially concealed under solvent peak), 1H] 7.07 (t, J = 7.5, 1H), 6.99 (dd, J = 8.0, 7.5, 1H), 6.89 (d, J = 7.5, 1H), 6.73 (dd, J = 8.0, 7.0, 1H), 6.58 (d, J = 7.5, 1H), 6.34 (d, J = 8.0, 1H), 5.46 – 5.37 (m, 1H), 4.98 (d, J = 17, 1H), 4.83 (d, J = 10.5, 1H), 3.11 (dd, J = 12.3, 12.0, 1H), 2.84 (dd, J = 12.5, 10.0, 1H), 2.82 (s, 3H), 1.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.5, 144.5, 138.8, 137.4, 132.8, 132.2, 132.2, 126.1, 123.5, 122.6, 119.1, 107.4, 65.7, 56.2, 42.7, 30.1, 25.5, 19.5; MS (EI) (M^+) 277; HRMS calcd for $C_{19}H_{19}NO$: 277.1467; found 277.1453.



H

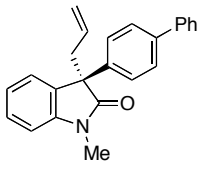
(*R*)-3-allyl-3-(4-fluorophenyl)-1-methylindolin-2-one (H). 1-Methyl-3-(*p*-fluorophenyl)oxindole (25 mg, 0.1 mmol) was used to give oxindole **H** was obtained as a colourless oil [21 mg, 73 μmol, 73%, 75 % *ee* by chiral HPLC, OD-H-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 5.37 min, t_B (minor) = 5.90 min]:

$[\alpha]_D^{24}$ = -196.7° (*c* 1, $CHCl_3$); R_f = 0.3 (20% EtOAc / hexane); R_f = 0.3 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 3076, 2918, 1715, 1612, 1508, 1471, 1372, 1348, 1233, 1163, 1090, 1023, 754; ^1H NMR (500 MHz, d_6-PhH): δ =7.24 – 7.32 (m, 2H), 7.05 – 7.02 (m, 1H), 6.94 (d, *J* = 7.5, 1H), 6.89 – 6.86 (m, 1H), 6.79 – 7.75 (m, 2H), 6.32 (d, *J* = 7.5, 1H), 5.44 – 5.36 (m, 1H), 4.96 (d, *J* = 15.0, 1H), 4.80 (d, *J* = 11.0, 1H), 2.96 – 2.92 (m, 1H), 2.82 – 2.78 (m, 1H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, d_6-PhH) δ =177.1, 163.4, 161.4, 144.3, 135.9, 132.7, 131.4, 129.3, 129.2, 125.3, 122.2, 119.1, 115.4, 115.2, 108.2, 55.6, 42.9, 25.7; MS (EI) (M^+) 281; HRMS calcd for $C_{18}H_{16}FNO$: 281.1207; found 281.1216.



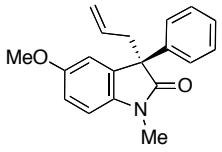
I

(*R*)-3-allyl-3-(4-chlorophenyl)-1-methylindolin-2-one (I). 1- Methyl-3-(*p*-chlorophenyl)oxindole (26 mg, 0.1 mmol) was used to give oxindole **I** as an amorphous solid [24 mg, 81 μmol, 81%, 70 % *ee* by chiral HPLC, OD-H-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 5.36 min, t_B (minor) = 6.10 min]: $[\alpha]_D^{24}$ = -107.1° (*c* 0.39 $CHCl_3$); R_f = 0.3 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 3076, 2922, 1714, 1609, 1492, 1469, 1369, 1347, 1252, 1093, 1012, 749; ^1H NMR (500 MHz, d_6-PhH): δ = 7.29 – 7.27 (m, 2H), 7.08 – 7.02 (m, 3H), 6.89 – 6.86 (m, 2H), 6.32 (d, *J* = 8.0, 1H), 5.44 – 5.35 (m, 1H), 4.96 (d, *J* = 16.5, 1H), 4.81 (d, *J* = 15.0, 1H), 2.95 – 2.90 (m, 1H), 2.81 – 2.77 (m, 1H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, d_6-PhH) δ =176.8, 144.3, 138.7, 133.5, 132.6, 131.1, 128.9, 128.7, 125.3, 122.2, 119.2, 108.2, 55.8, 42.6, 30.1, 25.7; MS (EI) (M^+) 297; HRMS calcd for $C_{18}H_{16}ClNO$: 297.0920; found 297.0926.



J

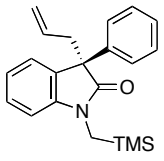
(*R*)-3-allyl-3-(4-biphenyl)-1-methylindolin-2-one (J). 1-Methyl-3-(*p*-biphenyl)oxindole (5 mg, 15 μmol) was used to give oxindole **J** as a yellow oil [5 mg, 13.5 μmol, 90%, 73 % *ee* by chiral HPLC, OD-H-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 6.94 min, t_B (minor) = 8.53 min]: $[\alpha]_D^{24}$ = -42.4° (*c* 0.5 $CHCl_3$); R_f = 0.25 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2924, 2853, 1714, 1610, 1469, 1372, 1346, 1258, 1090, 1022, 753; ^{1}H NMR (500 MHz, d_6-PhH): δ = 7.60 – 7.56 (m, 2H), 7.43 – 7.41 (m, 4H), 7.19 – 7.16 (m, 2H), 7.11 – 7.04 (m, 3H), 6.93 – 6.90 (m, 1H), 6.34 (d, *J* = 8.0, 1H), 5.55 – 5.47 (m, 1H), 5.15 (d, *J* = 15.0, 1H), 4.87 (d, *J* = 10.0, 1H), 3.14 – 3.10 (m, 1H), 2.99 – 2.96 (m, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.2, 144.4, 141.1, 140.5, 139.3, 133.0, 131.7, 128.9, 127.4, 127.3, 127.2, 125.4, 122.2, 119.0, 108.2, 56.2, 42.7, 30.1, 25.7; MS (EI) (M^+) 339; HRMS calcd for $C_{24}H_{21}NO$: 339.1623; found 339.1637.



K

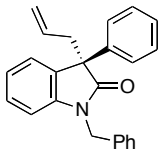
3-Allyl-5-methoxy-1-methyl-3-phenyl-1,3-dihydro-indol-2-one (K). 5-Methoxy-1-methyl-3-phenyl-oxindole (15 mg, 60 μmol) was used to give oxindole **K** [15 mg, 50 μmol, 83%, 74 % *ee* by chiral HPLC, OJ-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 35.39 min, t_B (minor) = 42.27 min] was obtained as a yellow oil: $[\alpha]_D^{24}$ = +1.6° (*c* 0.66, $CHCl_3$); R_f = 0.5 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 3061, 2937, 2835, 1715, 1600, 1504, 1359, 1288, 1232, 1158, 1035; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.36 (m, 2 H), 7.31 – 7.29 (m, 2 H), 7.26 – 7.23 (m, 1 H), 6.87 – 6.85 (m, 2 H), 6.80 (d, *J* = 8.0, 1 H), 5.44 – 5.36 (m, 1 H), 5.07 – 5.03 (1 H), 4.95 – 4.92 (m, 1 H), 3.80 (s, 3 H), 3.18 (s, 3 H), 3.07 (d, *J* = 6.4, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.9, 56.1, 139.7, 137.7, 133.3, 132.6, 128.8, 127.6, 127.3, 119.5, 112.9,

112.6, 108.7, 57.1, 56.1, 42.1, 26.7; MS (EI) (M^+) 293; HRMS calcd for $C_{19}H_{19}NO_2$: 293.1416; found 293.1410



L

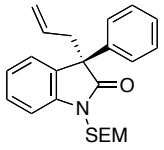
(*R*)-3-allyl-3-phenyl-1-((trimethylsilyl)methyl)indolin-2-one (L). 3-Phenyl-1-[(trimethylsilyl)methyl] oxindole (28 mg, 95 μmol) was used to give oxindole **L** [24 mg, 72 μmol, 76%) was obtained as a yellow oil: $[\alpha]_D^{24}$ = -6.0° (*c* 4.4, $CHCl_3$); R_f = 0.5 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 3057, 2955, 2922, 2851, 1706, 1610, 1488, 1465, 1352, 1250, 1162, 846; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 – 7.23 (m, 7 H), 7.09 – 7.06 (m, 1 H), 6.83 (d, *J* = 7.8, 1 H), 5.46 – 5.37 (m, 1 H), 5.07 – 5.03 (1 H), 4.93 – 4.90 (m, 1H), 3.80 (s, 3 H), 3.19 (s, 3 H), 3.07 (d, *J* = 7.7, 2 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.5, 144.6, 140.2, 132.9, 132.4, 130.6, 128.7, 128.3, 127.5, 127.3, 125.3, 122.2, 119.4, 108.8, 56.3, 42.1, 31.8, 29.9, -1.12; MS (EI) (M^+) 335; HRMS calcd for $C_{21}H_{25}NOSi$: 335.1705; found 335.1709. NOTE: due to difficult separation on chiral phase HPLC, the *N*-TMSM oxindole was converted to the corresponding *N*-Me oxindole **A** by protodesilylation with TBAF. Thus, oxindole **L** (9 mg, 27 μmol) was dissolved in anhydrous THF (0.2 mL) and cooled to 0°C. TBAF (30 μL, 30 μmol, 1 M in THF) was added and the reaction mixture was stirred at ambient temperature until complete conversion was reached as judged by TLC. 3-Allyl-1-methyl-3-phenyl-1,3-dihydro-indol-2-one **A** was isolated identical in all respects to previously isolated material [7.1 mg, 27 μmol, 100%, 80% *ee* by Chiral HPLC, OJ-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 8.32 min, t_B (minor) = 27.02 min].



M

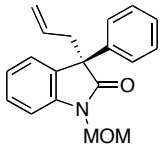
(*R*)-3-allyl-1-benzyl-3-phenylindolin-2-one (M). 1-Benzyl-3-phenyloxindole (6 mg, 20 μmol) was used to give *N*-benzyl oxindole **M** as a colourless oil [5 mg, 15 μmol, 75%,

70% *ee* by Chiral HPLC, OJ-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (major) = 13.60 min, t_B (minor) = 26.58 min]: $[\alpha]_D^{24}$ = -14.0° (*c* 4.4, $CHCl_3$); R_f = 0.5 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 3059, 2956, 1699, 1611, 1488, 1465, 1353, 1251, 1163, 847; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 – 7.39 (m, 2 H), 7.34 – 7.18 (m, 9 H), 7.21 – 7.18 (m, 1 H), 7.09 – 7.06 (m, 1 H), 6.67 (d, *J* = 7.9, 1 H), 5.43 – 5.38 (m, 1 H), 5.11 – 5.07 (m, 1 H), 4.99 – 4.93 (m, 2 H), 4.84 (d, *J* = 15.5 1 H), 3.16 – 3.05 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 178.3, 143.2, 140.0, 136.1, 132.7, 132.0, 128.9, 128.8, 128.4, 127.8, 127.6, 127.3, 125.4, 122.8, 119.7, 109.6, 56.7, 44.2, 42.2; MS (EI) (M^+) 339; HRMS calcd for $C_{24}H_{21}NO$: 339.1623; found 339.1626.



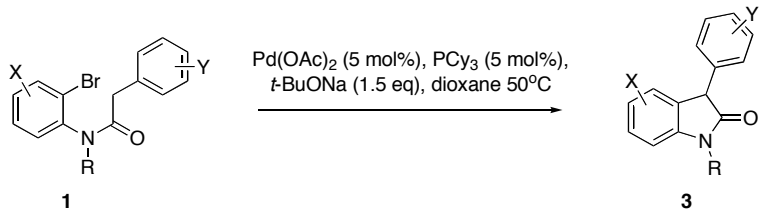
N

(*R*)-3-allyl-3-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-2-one (N). 3-Phenyl-1-[(2-(trimethylsilyl)ethoxy)methyl]oxindole (36 mg, 0.11 mmol) was used to give oxindole **N** as a colourless oil [32 mg, 86 μmol, 81%, 68% *ee* by Chiral HPLC, OD-H-column, 99/1 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (minor) = 8.96 min, t_B (major) = 11.20 min]: $[\alpha]_D^{24}$ = -54.03° (*c* 1.1, $CHCl_3$); R_f = 0.5 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2952, 1723, 1613, 1488, 1468, 1341, 1249, 1078, 920, 860, 836, 754; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 – 7.30 (m, 7 H), 7.23 – 7.19 (m, 2 H), 5.52 – 5.44 (m, 1 H), 5.22 (q, *J* = 16.4, 11.1, 2 H), 5.15 – 5.11 (m, 1 H), 5.01 – 4.99 (m, 1 H), 3.62– 3.52 (m, 1 H), 3.20 – 3.08 (m, 2 H), 0.95 (t, *J* = 8.3, 2 H), - 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 178.7, 142.5, 139.9, 132.7, 131.5, 128.9, 128.6, 127.7, 127.2, 125.4, 123.2, 119.6, 110.2, 69.8, 66.2, 57.1, 42.2, 18.0, -1.2; MS (EI) (M^+) 379; HRMS calcd for $C_{23}H_{29}NO_2Si$: 379.1968; found 379.1973.



O

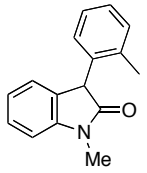
(*R*)-3-allyl-1-(methoxymethyl)-3-phenylindolin-2-one (O). 1-(Methoxymethyl)-3-phenylindolin-2-one (29 mg, 0.12 mmol) was used to give oxindole **O** as a colourless oil [32 mg, 110 μmol, 96%, 66% *ee* by Chiral HPLC, OD-H-column, 90/10 heptane / *i*-PrOH, flow rate 1 mL/min, t_A (minor) = 5.64 min, t_B (major) = 6.79 min]: $[\alpha]_D^{24}$ = -57.72° (*c* 1.1, $CHCl_3$); R_f = 0.5 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2936, 1722, 1612, 1488, 1462, 1343, 1237, 1094, 1017, 915; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 – 7.39 (m, 2 H), 7.38 – 7.25 (m, 7 H), 7.17 – 7.14 (m, 1 H), 7.10 (d, *J* = 7.9, 1 H), 5.45 – 5.37 (m, 1 H), 5.15 – 5.06 (m, 3 H), 4.96 – 4.93 (m, 1 H), 4.84 (d, *J* = 15.5 1 H), 3.28 (s, 3 H), 3.13 – 3.02 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 178.8, 143.4, 139.8, 132.6, 131.4, 128.9, 128.7, 127.7, 127.2, 125.5, 123.3, 119.8, 109.9, 71.8, 57.2, 56.6, 42.2; MS (EI) (M^+) 293; HRMS calcd for $C_{19}H_{19}NO_2$: 293.1416; found 293.1429.



1 **3**

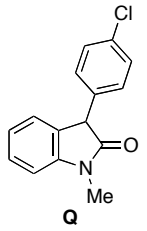
General procedure for the synthesis of oxindoles from 2-bromoanilides substrates using Hartwig's procedure. $Pd(OAc)_2$ (11.2 mg, 0.0500 mmol), PCy_3 (14.0 mg, 0.0500 mmol) and *t*-BuOH (144 mg, 1.50 mmol) were combined in a small test-tube. The tube was sealed with a septum and removed form the glovebox. Anhydrous 1,4-dioxane (8 mL) was added, and the resulting mixture was allowed to stir for 1 min, at which time the 2-bromoanilide (**1**) (1 mmol) in dioxane (2 mL) was added and the test-tube was placed in an oil bath at 50°C and stirred overnight. The reaction was poured into 20 mL of saturated aqueous NH_4Cl and extracted with Et_2O (3 x 20 mL). The combined ether extracts were washed with brine (60 mL), dried over $MgSO_4$, and filtered. The solvent

was removed under vacuum, and the resulting crude product was purified by flash chromatography on silica gel (15% EtOAc / hexane).



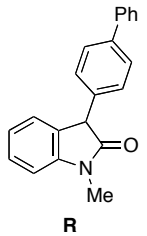
P

1-Methyl-3-(*o*-tolyl)oxindole (P). Isolated in 55% yield as a white solid [mp 130-133 °C (hexane), lit 131-132ºC) identical to previously described material:[1] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (m, 1H), 7.17-6.93 (m, 6H), 6.82 (d, *J* = 7.8 Hz, 1H), 4.76 (br s, 1H), 3.19 (s, 3H), 2.29 (br s, 3H); ^{13}C NMR (125 MHz, CDCl3): δ = 176.58, 144.77, 137.60, 135.81, 131.40, 129.61, 128.64, 128.08, 126.74, 124.98, 123.15, 108.48, 50.64, 26.84, 20.17.



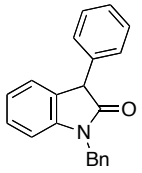
Q

1- Methyl-3-(*p*-chlorophenyl)oxindole (Q). Isolated in 38% yield as a off-white solid identical to previously isolated material:[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (t, *J* = 10, 1H), 7.29 (m, 3H), 7.14 (d, *J* = 8.5, 2H), 7.07 (t, *J* = 7.5, 1H), 6.90 (d, *J* = 10, 1H), 4.57 (s, 1H), 3.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.8, 144.7, 135.3, 133.8, 130.1, 129.3, 129.0, 128.5, 125.3, 123.1, 108.6, 51.6.



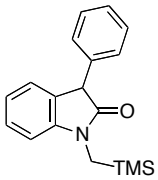
R

1-Methyl-3-(*p*-biphenyl)oxindole (R). Isolated in 50% yield as a colourless oil: $R_f = 0.2$ (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 2919, 2850, 1711, 1611, 1490, 1469, 1371, 1346, 1261, 1125, 1086.



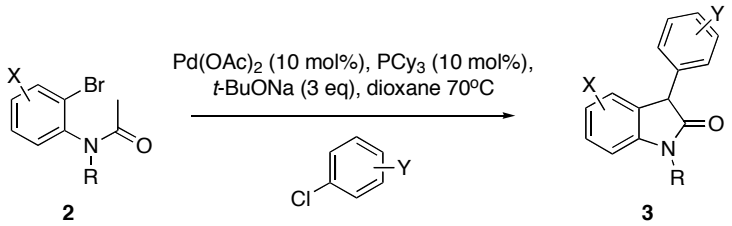
S

1-Benzyl-3-(phenyl)oxindole (S). Isolated as a colourless solid (75%): [mp 115-116 °C (hexane)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 – 7.15 (m, 12H), 7.03 – 6.99 (m, 1H), 6.78 (d, *J* = 9.2 Hz, 1H), 5.01 – 4.99 (m, 1H), 4.91 – 4.88 (m, 1H), 4.70 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.37, 143.83, 137.0, 136.17, 129.22, 129.18, 129.07, 128.73, 128.59, 127.92, 127.89, 127.63, 125.40, 123.04, 109.48, 52.33, 44.21; (film) υ_{max}/cm^{-1}: 3060, 3030, 2922, 1714, 1612, 1488, 1466, 1348, 1201, 1182, 1162, 751; MS (EI) (M^+) 299; HRMS calcd for $C_{21}H_{17}NO$: 299.1310; found 299.1325.

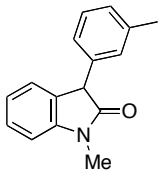


T

1-(Trimethylsilyl)methyl-3-(phenyl)oxindole (T). Isolated as a colourless oil (61%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 – 7.26 (m, 4H), 7.20 – 7.13 (m, 3H), 7.05 – 7.00 (m, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 4.58 (s, 1H), 3.35 – 3.31 (m, 1H), 3.19 – 3.15 (m, 1H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.59, 145.16, 137.24, 129.58, 129.08, 128.65, 128.42, 127.69, 125.15, 122.52, 108.77, 52.11, 31.79, -1.13; (film) υ_{max}/cm^{-1}: 3059, 2955, 2897, 1709, 1611, 1488, 1466, 1351, 1249, 1178, 1155, 1094, 852, 749, 695; MS (EI) (M^+) 299; HRMS calcd for $C_{18}H_{21}NOSi$: 295.1392; found 295.1400.

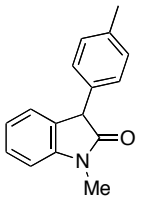


General procedure for the synthesis of oxindoles from *N*-(2-bromophenyl)-*N*-methylacetamide and aryl chlorides. $Pd(OAc)_2$ (25 mg, 0.100 mmol), PCy_3 (30.0 mg, 0.100 mmol), and *t*-BuONa (288 mg, 3.00 mmol) were combined in a test-tube in the glovebox, and the reaction vessel was sealed with a septum and removed form the drybox. Freshly degassed dry 1,4-dioxane (2.0 mL) was added. The resulting mixture was allowed to stir for 1 min, at which time *N*-(2-bromophenyl)-*N*-methylacetamide (235 mg, 1.03 mmol) in dioxane (1 mL) and aryl chloride was added (1.0 mmol) were added, and the flask was placed in an oil bath at 70 °C overnight. The reaction was poured into 10 mL of saturated aqueous ammonium chloride and extracted (3 x 20 mL) with diethyl ether. The combined ether extracts were washed with brine (60 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude product was purified by flash chromatography on silica gel. The product was eluted with 20% ethyl acetate in hexanes.



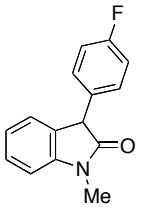
U

1-Methyl-3-(*m*-tolyl)oxindole (U). *m*-Tolyl chloride (127 mg, 1.00 mmol) was used to afford **U** as a off-white gum (76 mg, 0.32 mmol, 32%) after silica gel chromatography: R_f = 0.3 (20% EtOAc / hexane); IR (film) υ_{max}/cm^{-1}: 1715, 1613, 1493, 1470, 1372, 1344, 1255, 1124, 1086; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.05 – 7.02 (m, 3H), 6.97 (d, *J* = 7.5, 2H), 6.88 (dd, *J* = 10, 5, 1H), 6.80 (t, *J* = 7.5, 1H), 6.32 (d, *J* = 7.5, 1H), 4.26 (s, 1H), 2.70 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ =175.0, 145.0, 138.4, 137.4, 129.6, 129.3, 128.8, 128.3, 128.2, 125.9, 125.1, 122.3, 107.9, 51.9, 25.7, 21.2; MS (EI) (M^+) 237; HRMS calcd for $C_{16}H_{15}NO$: 237.1154; found 237.1151.



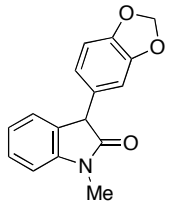
V

1-Methyl-3-(*p*-tolyl)oxindole (V). *p*-Tolyl chloride (127 mg, 1.00 mmol) was used, which gave **U** as a white solid (99 mg, 0.42 mmol, 42%) identical to previously described material:[1] mp 94-95°C (lit 95-96 °C); ^{1}H NMR (500 MHz, d_6-PhH): δ = 7.08 (d, *J* = 8.0, 2H), 7.03 (m, 1H), 6.91 (d, *J* = 8.0, 2H), 6.88 (d, *J* = 7.5, 1H), 6.81 (t, *J* = 8.5, 1H), 6.32 (d, *J* = 8.0, 1H), 4.26 (s, 1H), 2.68 (s, 3H), 2.04 (s, 3H): ^{13}C NMR (125 MHz, d_6-PhH): δ = 175.1, 145.0, 136.9, 134.5, 129.5, 129.3, 128.7, 128.2, 125.1, 122.2, 107.9, 51.6, 25.7, 20.9.



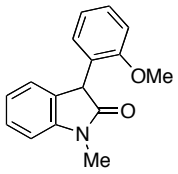
W

1-Methyl-3-(*p*-fluorophenyl)oxindole (W). *p*-Fluorophenyl chloride (110 μL, 1.00 mmol) was used, which gave **W** as a orange solid (110 mg, 0.46 mmol, 46%): R_f = 0.3 (20% EtOAc / hexane); mp 138-139ºC (hexane); IR (film) υ_{max}/cm^{-1}: 1692, 1604, 1510, 1468, 1347, 1224, 1088, 827, 752; ^{1}H NMR (400 MHz, d_6-PhH): δ = 7.04 (dd, *J* = 8.0, 7.0, 1H), 6.95 – 6.91 (m, 2H), 6.83 – 6.78 (m, 2H), 6.74 (dd, *J* = 9.0, 8.5, 2H), 6.31 (d, *J* = 8.0, 1H), 4.13 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (125 MHz, d_6-PhH) δ =174.7, 163.5, 161.5, 144.9, 133.0, 130.4, 125.1, 122.3, 115.7, 115.5, 108.0, 50.9, 25.7; MS (EI) (M^+) 241; HRMS calcd for $C_{15}H_{12}FNO$: 241.0902; found 241.0896



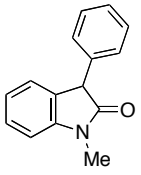
X

3-(1,3-Benzodioxol-5-yl)-1-methyloxindole (X). 5-Chloro-1,3-benzodioxole (120 μL, 1.00 mmol) was used to give oxindole **X** as a white solid (151 mg, 0.56 mmol, 56%):[1] mp 131-132 °C (hexane) lit 131-132ºC (hexane); ^{1}H NMR (500 MHz, d_6-PhH): δ = 7.04 – 7.00 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.81 – 6.78 (m, 1H), 6.70 (s, 1H), 6.55 (s, 2H), 6.32 (d, *J* = 8.0, 1H), 5.27 – 5.25 (m, 2H), 4.13 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (125 MHz, d_6-PhH): δ = 175.0, 148.4, 147.4, 144.9, 131.0, 129.2, 128.3, 125.1, 122.3, 122.1, 109.2, 109.4, 107.9, 100.9, 51.5, 25.7.



Y

1-Methyl-3-(2-methoxyphenyl)oxindole (Y). 2-Chloroanisole (142 mg, 1.00 mmol) was used, which yielded the known oxindole **Y** (132 mg, 0.40 mmol, 60%) identical to previously isolated material:[1] mp 107°C (hexane), lit 106-107ºC (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.22 (m, 2H), 7.06-6.84, 4.89 (s, 1H), 3.72 (s, 3H), 3.28 (s, 3H).



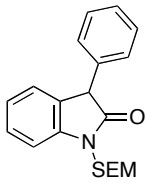
Z

1-Methyl-3-(phenyl)-oxindole (Z). Isolated as a yellow crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 -6.95 (m, 7H), 6.98 (t, *J* = 12.5, 1H), 6.81 (d, *J* = 13.0, 1H), 4.52 (s, 1H), 3.17 (s, 3H).

The *N*-SEM and *N*-MOM protected oxindoles could be prepared by Pd-catalyzed α-arylation, but the yields were not satisfactory. Instead, these substrates were prepared by protection of isatin followed by addition of phenylmagnesium bromide and reduction as described below.

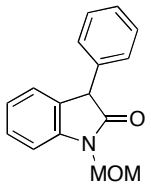
General procedure for protection, alkylation and reduction of isatin. Isatin (500 mg, 3.4 mmol) was dissolved in anhydrous THF, and the resultant solution was cooled to 0ºC, whereupon sodium hydride (60% dispersion in oil, 163 mg, 4.1 mmol) was added in one portion and stirred for 5 minutes. The alkyl chloride (4.1 mmol, MOMCl or SEMCl) was added and the reaction was stirred at ambient temperature overnight. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic portions were dried ($MgSO_4$), filter and concentrated. Column chromatography on silica gel (15% EtOAc / hexane) afforded the pure *N*-alkylated oxindole (610 mg, 3.2 mmol, 94%, for *N*-MOM; 851 mg, 3.1 mmol, 91% for *N*-SEM). The products were dissolved in anhydrous THF (16 mL) and cooled to 0ºC. Phenylmagnesium bromide (1.2 eq, 1M in THF) was added dropwise and the resultant solution was stirred at ambient temperature overnight, whereupon it was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic fractions were dried ($MgSO_4$), filtered, concentrated and chromatographed on silica (20% EtOAc / hexane) to reveal pure the alcohols (560 mg, 2.1 mmol, 65% for *N*-MOM; 476 mg, 1.32 mmol, 42% for *N*-SEM). The alcohols (0.2 mmol) were dissolved in anhydrous CH_2Cl_2 (2 mL), and Huenig's base (0.11 mL, 0.6 mmol). Thionyl chloride (29 μL, 0.24 mmol) was added and the resultant solution was stirred at ambient temperature (15 min), at which point it was poured into saturated aqueous $NaHCO_3$ and extracted three times with diethyl ether. The combined organic fractions were dried ($MgSO_4$), filtered and concentrated. The crude product was dissolved in THF (2 mL) and glacial acetic acid (0.2 mL) and cooled to 0ºC. Zn powder (392 mg, 6 mmol) was added and the reaction mixture was stirred at room temperature (2 h). The reaction mixture was filtered through celite, and the filtrate was diluted with diethyl ether (10 mL) and water (10 mL). The layers were separated and the organic fraction was washed with saturated aqueous $NaHCO_3$,

dried ($MgSO_4$), filtered and concentrated. The crude product was chromatographed on silica (7 % EtOAc / hexane) to reveal the pure oxindoles.



AA

1-[(2-(Trimethylsilyl)ethoxy)methyl]-3-(phenyl)oxindole (AA). Isolated as a colorless oil (62%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 – 7.07 (m, 9H), 5.25 – 5.14 (m, 2H), 4.67 (s, 1H), 3.59 – 3.54 (m, 2H), 0.94 – 0.89 (m, 2H), -0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.64, 143.10, 136.90, 129.19, 128.74, 128.64, 128.61, 127.89, 125.37, 123.41, 110.04, 66.85, 66.28, 52.52, 18.08, -1.22; (film) υ_{max}/cm^{-1}: 3030, 2952, 2894, 1727, 1613, 1489, 1467, 1339, 1248, 1229, 1081, 859, 836, 751, 695; MS (EI) (M^+) 339; HRMS calcd for $C_{20}H_{25}NO_2Si$: 339.1655; found 339.1663.



AB

1-(Methoxymethyl)-3-(phenyl)oxindole (AB). Isolated as a colorless oil (72%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 – 7.08 (m, 9H), 5.21 – 5.13 (m, 2H), 4.70 (s, 1H), 3.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.82, 142.92, 136.78, 129.20, 128.80, 128.64, 128.56, 127.94, 125.47, 123.54, 109.88, 71.75, 56.56, 52.50; (film) υ_{max}/cm^{-1}: 2935, 1723, 1613, 1488, 1467, 1342, 1234, 1118, 1088, 1071, 752; MS (EI) (M^+) 253; HRMS calcd for $C_{20}H_{25}NO_2Si$: 254.1096; found 254.1135.

References

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