Palladium catalysed aryl enol ether synthesis from vinyl triflates

Michael C. Willis,[a]* Dawn Taylor[a] and Adam T. Gillmore[b]

[a]Department of Chemistry, University of Bath, Bath, BA2 7AY, UK. Fax: (44) 01225 386231; Tel: (44) 01225 386568; E-mail: m.c.willis@bath.ac.uk

[b]Chemical Research and Development Department, Pfizer Global Research and Development, Sandwich, Kent, CT13 9NJ.

Supplementary Information

General Experimental

^{1}H NMR spectra were recorded on JEOL 400 EX or Bruker AM-300 spectrometers at 400 MHz and 300 MHz respectively. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) or TMS (δ_H = 0 ppm) were used as internal references. Coupling constants were measured in Hz. ^{13}C spectra were recorded in $CDCl_3$, unless otherwise stated, at 100 MHz or 75 MHz on JEOL 400 EX and Bruker AM-300 spectrometers respectively, using the resonance of $CDCl_3$ (δ_C = t, 77 ppm) as the internal reference. Infra red spectra were recorded in the range of 4000-600 cm^{-1} on a Perkin Elmer FT 1000 spectrometer with internal calibration. Mass spectra were carried out at the University of Wales Swansea (Finnigan MAT 900 XLT instrument).

Analytical thin layer chromatography was carried out using glass backed plates coated with Merck Kieselgel 60 GF_{254} or aluminium backed plates coated with Merck G/UV_{254}. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, vanillin or cerium ammonium molybdate followed by heating. Flash chromatography was carried out using either Merck 60 H silica or Merck Florisil®. Samples were pre-absorbed on silica or used as saturated solutions in an appropriate solvent.

All the reactions were performed under a positive pressure of nitrogen or argon in oven or flame dried apparatus.

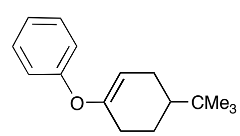
All vinyl triflate substrates were prepared by treating the corresponding ketones with trifluoromethanesulfonic anhydride and anhydrous sodium carbonate; all gave spectroscopic data identical to that reported in the literature.[1,2,3]

General procedure for the palladium catalysed preparation of aryl vinyl ethers

Palladium dibenzylideneacetone [$Pd_2(dba)_3$] (0.021 mmol, 0.019 g), bis-*tert*-butylbiphenylphosphine (0.063 mmol, 0.018 g) and sodium *tert*-butoxide (1.223 mmol, 0.1176 g) were added to a flask containing phenol (1.049 mmol, 0.099 g). The flask was purged with nitrogen and the mixture taken up in dry toluene (5 mL) prior to the addition of triflate (0.699 mmol). The reaction mixture was allowed to stir at 100 ºC for between 19-24 hours, after which time the reaction was cooled to room temperature, diluted with hexane (30 mL), filtered through celite and reduced *in vacuo*. The product was purified by flash column chromatography: neutral alumina; petrol:ethyl acetate to yield the products as oils in moderate to excellent yields (see Table 2).

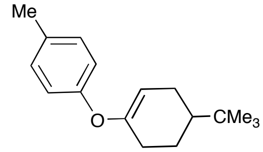
Data for new compounds:

(4-*t*-butyl-cyclohex-1-enyloxy)-benzene (table 2, entry 1)



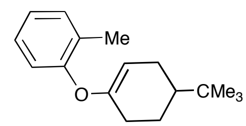
Colourless oil (95% conv., 85% yield, 0.136 g). ν_{max} (NaCl)/cm^{-1} 1679, 1226 and 1150; δ_H (300 MHz, $CDCl_3$) 0.83 (9H, s), 1.21-1.33 (2H, m), 1.79-1.89 (2H, m), 1.95-2.21 (3H, m), 4.97 (1H, app. dt, *J* 6, 3), 6.86-7.01 (3H, m), 7.16-7.28 (2H, m); δ_C (100 MHz, $CDCl_3$) 22.4, 23.2, 25.5, 25.6, 25.9, 42.2, 105.2, 116.6, 120.5, 127.4, 156.7, 157.7; *m/z* (EI) 230 (22%, M), 173 (17%), 94 (83%); (ES+) [M^+] calc. 230.1671, measured 230.1675.

1-(4-*t*-butyl-cyclohex-1-enyloxy)-4-methyl-benzene (table 2, entry 2)



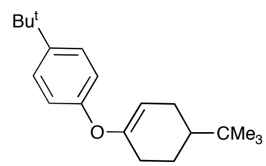
Pale amber oil (100% conv., 83% yield, 0.135 g). ν_{max} (NaCl)/cm^{-1} 1678, 1220 and 1100; δ_H (300 MHz, $CDCl_3$) 0.81 (9H, s), 1.15-1.34 (2H, m), 1.68-1.89 (2H, m), 2.00-2.18 (3H, m), 2.24 (3H, s), 4.87 (1H, app. dt, *J* 6, 3), 6.80 (2H, app. d, *J* 8), 7.02 (2H, app. d, *J* 8); δ_C (100 MHz, $CDCl_3$) 24.6, 25.4, 26.8, 27.8, 28.2, 44.4, 54.1, 105.8, 119.2, 130.1, 138.0, 146.6, 148.0; *m/z* (CI+, NH_3) 245 (100%, M+H), 229, 187, 172, 108; (ES+) [M^+H] calc. 245.1900, measured 245.1894.

1-(4-*t*-butyl-cyclohex-1-enyloxy)-2-methyl-benzene (table 2, entry 3)



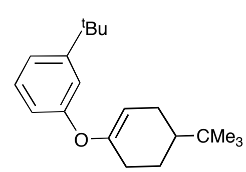
Colourless oil (60% conv., 34% yield, 0.110 g). ν_{max} (NaCl)/cm^{-1} 1679, 1250 and 1125; δ_H (300 MHz, $CDCl_3$) 0.82 (9H, s), 1.03-1.27 (2H, m), 1.48 (3H, s), 1.66-2.02 (2H, m), 2.08-2.27 (3H, m), 4.62 (1H, app. dt, *J* 6, 2), 6.86 (1H, d, *J*, 9), 6.92 (1H, app. t, *J*, 8), 7.03-7.15 (2H, m); δ_C (100 MHz, $CDCl_3$) 16.5, 24.6, 25.3, 27.8, 28.3, 32.6, 44.5, 103.3, 119.7, 123.4, 126.9, 129.9, 131.2, 153.6, 154.1; *m/z* (CI+, NH_3) 263 (M^+NH_4), 246 (M^+H), 245 (M), 187; (ES+) [M^+H] calc. 245.1900, measured 245.1899.

1-*t*-Buty-4-(4-*t*-butyl-cyclohex-1-enyloxy)-benzene (table 2, entry 4)



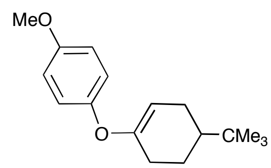
Amber oil (100% conv., 98% yield, 0.201 g). ν_{max} (NaCl)/cm-^{1} 1678, 1231 and 1190; δ_H (300 MHz, $CDCl_3$) 0.82 (9H, s), 1.23 (9H, s), 0.97-1.16 (2H, m), 1.65-1.90 (2H, m), 1.91-2.28 (3H, m), 4.93 (1H, app. dt, *J* 5, 3), 6.83 (2H, app. d, *J* 9), 7.23 (2H, app. d, *J* 9); δ_C (100 MHz, $CDCl_3$) 24.5, 25.3, 27.7, 28.0, 31.8, 32.5, 34.5, 44.3, 106.5, 118.2, 126.2, 145.2, 153.1, 153.9; *m/z* (ES) 286 (5%, M^+), 229, 150, 135; (ES+) [M^+H] calc. 287.2361, measured 287.2369.

1-*t*-Buty-3-(4-*t*-butyl-cyclohex-1-enyloxy)-benzene (table 2, entry 5)



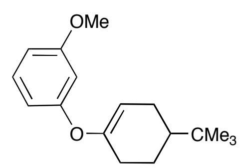
Amber oil (100% conv., 86% yield, 0.108 g). ν_{max} (NaCl)/cm^{-1} 1678, 1271 and 1100; δ_H (300 MHz, $CDCl_3$) 0.84 (9H, s), 1.25 (9H, s), 1.35-1.36 (2H, m), 1.73-1.93 (2H, m), 1.94-2.09 (1H, m), 2.10-2.28 (2H, m), 4.95 (1H, app. dt, *J* 6, 2), 6.73 (1H, ddd, *J* 8, 2, 1), 6.95 (1H, t, *J* 2), 7.00 (1H, ddd, *J* 8, 2, 1), 7.16 (1H, t, *J* 8); δ_C (100 MHz, $CDCl_3$) 24.7, 25.5, 27.9, 28.2, 31.8, 32.7, 35.2, 44.5, 106.6, 115.5, 116.5, 119.7, 120.7, 128.9, 153.0, 156.1; *m/z* (CI+, NH_3) 287 (100%, M^+H), 271, 229, 154, 135; (ES+) [M^+H] calc. 287.2369, measured 287.2366.

1-(4-*t*-butyl-cyclohex-1-enyloxy)-4-methoxy-benzene (table 2, entry 6)



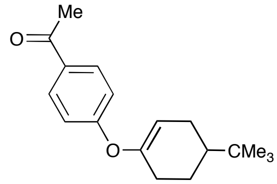
Amber oil (98% conv., 46% yield, 0.083 g). ν_{max} (NaCl)/cm^{-1} 1678, 1296 and 1130, 2850; δ_H (300 MHz, $CDCl_3$) 0.89 (9H, s), 1.21-1.38 (2H, m), 1.78-1.99 (2H, m), 2.01-2.30 (3H, m, CH), 3.79 (3H, s), 4.79 (1H, app. dt, *J* 6, 3), 6.82 (2H, app. d, *J* 8), 6.95 (2H, app. d, *J* 8); δ_C (100 MHz, $CDCl_3$) 24.6, 25.3, 27.8, 28.3, 32.6, 44.5, 56.0, 103.8, 114.7, 121.0, 149.6, 154.6, 155.5; *m/z* (EI) 260 (12%, M), 203, 124, 109; (EI) [M^+] calc. 260.1771, measured 260.1770.

1-(4-*t*-butyl-cyclohex-1-enyloxy)-3-methoxy-benzene (table 2, entry 7)



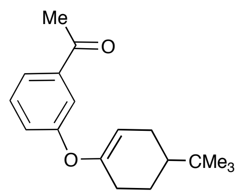
Amber oil (100% conv., 37% yield, 0.066 g). ν_{max} (NaCl)/cm^{-1} 2875, 1680, 1263 and 1040; δ_H (300 MHz, $CDCl_3$) 0.83 (9H, s), 1.00-1.15 (2H, m), 1.70-1.90 (2H, m), 1.95-2.27 (3H, m), 3.72 (3H, s), 5.04 (1H, app. dt, *J* 6, 2), 6.47 (1H, t, *J* 2), 6.51 (2H, app. dd, *J* 8, 2), 7.12 (1H, t, *J* 9); δ_C (100 MHz, $CDCl_3$) 24.6, 25.4, 27.8, 31.9, 32.6, 44.4, 55.7, 104.7, 108.1, 108.3, 110.9, 130.0, 157.0, 159.0, 163.0; *m/z* (EI) 261 (M^+H), 260, 203, 124; (ES+) [M^+H] calc. 261.1849, measured 261.1848.

1-[4-(4-*t*-butyl-cyclohex-1-enyloxy)-phenyl]-ethanone (table 2, entry 9)



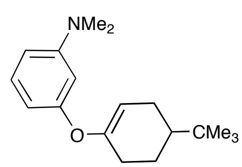
Colourless oil (90% conv., 46% yield, 0.087 g). ν_{max} (NaCl)/cm^{-1} 1676, 1267 and 1127; δ_H (300 MHz, $CDCl_3$) 0.85 (9H, s), 1.16-1.41 (2H, m), 1.71-1.93 (2H, m), 1.96-2.30 (3H, m), 2.49 (3H, s), 5.22 (1H, app. dt, *J* 6, 2), 6.93 (2H, app. d, *J* 9), 7.86 (2H, app. d, *J* 9); δ_C (100 MHz, $CDCl_3$) 24.6, 25.6, 27.7, 27.8, 28.6, 32.7, 44.3, 111.4, 117.1, 130.6, 130.6, 131.4, 151.4, 161.2, 196.0; *m/z* (CI+, NH_3), 290 (M^+NH_4), 273, 219, 216, 173, 154, 137; (EI) [M^+] calc. 272.1771, measured 272.1768.

1-[3-(4-*t*-butyl-cyclohex-1-enyloxy)-phenyl]-ethanone (table 2, entry 10)



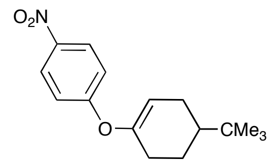
Yellow oil (90% conv., 60% yield, 0.113 g). ν_{max} (NaCl)/cm^{-1} 1688, 1260 and 1110; δ_H (300 MHz, $CDCl_3$) 0.83 (9H, s), 1.22-1.40 (2H, m), 1.72-1.91 (2H, m), 1.94-2.26 (3H, m), 2.52 (3H, s), 4.99 (1H, app. dt, *J* 6, 2), 7.12 (1H, ddd, *J* 8, 2, 1), 7.32 (1H, app. t, *J* 8), 7.48 (1H, m), 7.55 (1H, app. d, *J* 8); δ_C (100 MHz, $CDCl_3$) 24.6, 25.5, 27.69, 27.85, 28.03, 32.7, 44.4, 108.2, 118.2, 122.7, 123.5, 129.7, 138.7, 152.7, 156.8, 196.0; *m/z* (CI+, NH_3) 290 (M^+NH_4), 273; (ES+) [M^+H] calc. 273.1849, measured 273.1851.

[3-(4-*t*-butyl-cyclohex-1-enyloxy)-phenyl]-dimethylamine (table 2, entry 12)



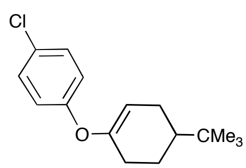
Amber oil (90%conv., 45% yield, 0.875 g). ν_{max}(NaCl)/cm^{-1} 2815, 1679, 1232 and 1148; δ_H (300 MHz, $CDCl_3$) 0.82 (9H, s), 1.15-1.33 (2H, m), 1.71-1.92 (2H, m), 1.94-2.33 (3H, m, CH), 2.86 (6H, s), 4.99 (1H, app. dt, *J* 6, 3), 6.25-6.32 (2H, m), 6.38 (1H, app. d, *J* 9), 7.07 (1H, app. t, *J* 8); δ_C (100 MHz, $CDCl_3$) 24.6, 25.4, 27.8, 28.1, 32.6, 41.0, 44.4, 103.6, 106.8, 107.3, 129.7, 142.5, 152.5, 157.5; *m/z* (CI+, NH_3) 299 (M^+NH_4), 274 (M^+H), 216, 154, 137; (EI) [M^+] calc. 273.2087, measured 273.2086.

1-(4-*t*-butyl-cyclohex-1-enyloxy)-4-nitro-benzene (table 2, entry 13)



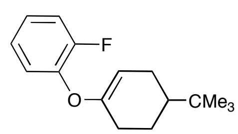
Amber oil (95% conv., 60% yield, 0.115 g). ν_{max} (NaCl)/cm^{-1} 1690, 1590, 1342, 1250 and 1110; δ_H (300 MHz, $CDCl_3$) 0.85 (9H, s), 1.21-1.41 (2H, m), 1.77-1.97 (2H, m), 1.98-2.24 (3H, m), 5.31 (1H, app. dt, *J* 6, 3), 6.96 (2H, app. d, *J* 10), 8.12 (2H, app. d, *J* 10); δ_C (100 MHz, $CDCl_3$) 24.6, 25.6, 27.8, 28.5, 32.7, 44.2, 113.1, 116.9, 126.0, 151.0, 152.0, 162.5; *m/z* (CI+, NH_3) 293 (M^+NH_4), 276, 260, 246, 230, 172, 154; (ES+) [M^+NH_4] calc. 293.1860, measured 293.1860.

1-(4-*t*-butyl-cyclohex-1-enyloxy)-4-chloro-benzene (table 2, entry 14)



Amber oil (75% conv., 50% yield, 0.094 g). ν_{max} (NaCl)/cm^{-1} 1680, 1268 and 1125; δ_H (300 MHz, $CDCl_3$) 0.84 (9H, s), 1.15-1.34 (2H, m), 1.72-1.89 (2H, m), 1.95-2.26 (3H, m), 4.98 (1H, app. dt, *J* 6, 3), 6.85 (2H, app. dt, *J* 8), 7.20 (2H, app. dt, *J* 8); δ_C (100 MHz, $CDCl_3$) 24.6, 25.5, 27.8, 28.0, 31.9, 44.4, 107.7, 120.0, 129.5, 134.5, 152.0, 158.0; *m/z* (CI+, NH_3) 267 (M^+H, ^{37}Cl), 265 (M^+H, ^{35}Cl); (EI) [M^+] (^{35}Cl) calc. 264.1275, measured 264.1278.

1-(4-*t*-butyl-cyclohex-1-enyloxy)-2-fluoro-benzene (table 2, entry 15)



Amber oil (>95% conv., 85% yield, 0.148 g). ν_{max} (NaCl)/cm^{-1} 1683, 1120 and 1260, 1160; δ_H (300 MHz, $CDCl_3$) 0.81 (9H, s), 1.19-1.39 (2H, m), 1.64-1.90 (2H, m), 1.92-2.33 (3H, m), 4.75 (1H, app. dt, *J* 6, 2), 6.91-7.10 (4H, m); δ_C (100 MHz, $CDCl_3$) 24.6, 25.3, 27.9, 28.2, 32.7, 44.4, 104.0, 116.8, 122.1, 124.2, 124.4, 147.0, 153.7; *m/z* (CI+, NH_3) 249 (M^+H); (EI) 249 (M^+H), 248, 191, 112, 95, 93; (ES+) [M^+H] calc. 249.1649, measured 249.1652.

References

1. (a) A. G. Martinez, A. Herrera, E. Teso, A. Garcia, J. Osio, L. Pargada, R. Unanue, L. R. Subramanian and M. Hanack, *J. Heterocycle Chem.*, 1988, **25**, 1237-1241; (b) A. D. Wentworth, P. Wentworth, U. F. Mansoor and K. D. Janda, *Org. Lett.*, 2000, **2**, 477-480.

2. L. Luan, J. S. Song and R. M. Bullock, *J. Org. Chem.*, 1995, **60**, 7170-7176.

3. (a) K. Pal, *Synthesis*, 1995, 1485-1487; (b) G. T. Crisp and M. G. Gebauer, *Tetrahedron*, 1992, **48**, 3541.