ELECTRONIC SUPPORTING INFORMATION

Diaryl Ether Synthesis in Supercritical Carbon Dioxide in Batch and Continuous Flow Mode

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General experimental methods

***Caution!* All high pressure scCO$_2$ reactions should be carried out with adequate containment and with extreme caution.**

^{1}H NMR spectra were recorded on a Bruker DPX-400 (400 MHz) and DRX-500 (500 MHz) at ambient temperature, using the chemical shift of a residual protic solvent (CHCl$_3$ at δ 7.28 ppm or DMSO at δ 2.50 ppm) as an internal reference. All shifts are quoted in parts per million (ppm) relative to CHCl$_3$ or DMSO and coupling constants *J* are measured in Hz. The multiplicity of the signal is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), dm (doublet of multiplets) and br (broad).

In cases where product purity was measured by quantitative ^{1}H-NMR technique, spectra were recorded with a set of modified acquisition parameters (number of scans, 12; data points, 64000; spectrum width, 17 ppm; pulse, 45 deg; pulse delay, 30 seconds; window function, 0.2 Hz) in the presence of an internal standard (maleic acid in DMSO-d_6 or 2,3,5,6-tetrachloronitrobenzene in CDCl$_3$).[23, 24]

^{13}C NMR spectra were recorded on a Bruker DPX-400 (101 MHz), Bruker DRX-500 (126 MHz) with cryoprobe and Bruker Avance 700 (176 MHz) spectrometer using the central resonance of the triplet of CDCl$_3$ at δ 77.0 ppm as an internal reference.

Infrared spectra were recorded on a Nicolet 510 series FT-IR or PerkinElmer Spectrum One series FT-IR spectrometer using KBr pellet, thin film on NaCl window or neat sample on top of a diamond sampling tip. Melting points were determined using an Electrothermal IA 9010 or Büchi 510 melting point apparatus. Microanalyses were carried out by the Department of Chemistry (University of Cambridge, UK) or Chemical & Micro Analytical Services Pty. Ltd. (Australia). Mass spectra were recorded by the EPSRC Swansea Mass Spectrometry Service (UK), the School of Chemistry (University of Melbourne, Australia) or CSIRO (Australia).

Gas chromatograms were recorded by a Hewlett-Packard GC (5890 series) equipped with a capillary column (BP-5, SGE). Helium was used as the carrier gas and a programmed oven temperature profile was used to control sample elution. In cases where reaction yields were estimated by gas chromatography, the sample was injected with a known amount of internal standard (mesitylene). From the peak areas of the sample and internal standard in the chromatogram, the yield was calculated using a pre-acquired calibration curve.

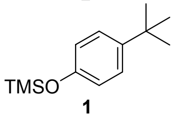
Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) silica. Analytical and preparative thin layer chromatography (TLC) was done on pre-coated 0.2 mm thick Merck Kieselgel 60 F$_{254}$ silica gel plates and visualized by absorption of UV light and cerium (IV) sulfate or permanganate dip.

All CO$_2$ batch-mode reactions were performed in a 10 cm^3 Hastelloy reaction vessel. When adding reagents into the 10 cm^3 reaction vessel, liquid compounds were measured in volume and delivered with an Effendorf precision microliter pipette. CO$_2$ was passed through an Oxisorb™ catalyst to remove traces of oxygen and was delivered to the reaction vessel in a safety-glass cabinet using a Pickel PM101 N$_2$-driven CO$_2$ pump at the desired pressure. The reactor was heated to the desired temperature using thermocouple-controlled heating tape. The reactions were stirred with a magnetic stirrer bar. The pressure of the system was measured by a pressure transducer (A105, RDP Electronics) and displayed on a digital display (E308, RDP Electronics). The internal temperature was measured by an Industrial Mineral Isolated Thermocouple (Type K, RS Electronics) and displayed on a temperature indicator (T200, RS Electronics). The reaction products were collected by allowing the reactor vessel to cool to ambient temperature and slowly venting the CO_2 vapor into a flask containing an appropriate solvent.

Heptane (HPLC grade, Aldrich) and chlorobenzene were used as received. Carbon dioxide (purity, 99.999% min.) was purchased from Messer or Air Liquide. The Merrifield peptide synthesis resin (1.24 mmol Cl/g, 200-400 mesh, Aldrich), Bu_4NBr (Aldrich), Bu_3P (Fluka), 2-*tert*-butylphenol (Aldrich), 4-*tert*-butylphenol (Aldrich), Cs_2CO_3 (Aldrich), CsF (Aldrich), 2,4-difluoronitrobenzene (Lancaster), ethyl 4-fluorobenzoate (Aldrich), 4-fluorobenzaldehyde (Aldrich), 4-fluorobenzonitrile (Lancaster), 4-fluorobenzophenone (Avocado), 1-fluoro-4-nitrobenzene (Aldrich), 1,1,1,3,3,3-hexamethyldisilazane (Aldrich), 4-hydroxybenzotrifluoride (Fluorochem), mesitylene (Aldrich), 4-methoxyphenol (Aldrich), *p*-thiocresol (Lancaster), TMSCl (Aldrich) and 2,4,6-trifluorobenzonitrile (Fluorochem) were used without further purification.

Synthetic procedures

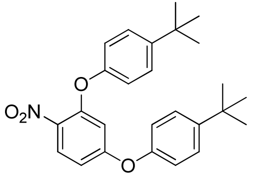
(4-*tert*-Butylphenoxy)trimethylsilane 1[25] (*Representative procedure A*)



1

To a 100 cm^3 round-bottomed flask equipped with a reflux condenser were added 4-*tert*-butylphenol (30.0 g, 200 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (17.7 g, 110 mmol). The suspension was then heated slowly to 130 ºC. During this time, evolution of gaseous NH_3 was observed. After the solution was stirred for 1 h, it was allowed to cool to ambient temperature. Distillation under reduced pressure gave the TMS-protected phenol **1** as a colorless liquid (40.5 g, 91%); bp 53 ºC (0.2 mm Hg) [lit.,[26] 83 ºC (1 mm Hg)]; ν_{max}(film) cm^{-1} 3037, 2960, 2905, 2870, 1607, 1510, 1250, 1178, 916, 841 and 752; δ_H (500 MHz; $CDCl_3$) 0.28 [9 H, s, Si(C*H*$_3$)$_3$], 1.32 [9 H, s, C(C*H*$_3$)$_3$], 6.78 (2 H, d, *J* 8.5, Ar-*H*) and 7.26 (2 H, d, *J* 8.5, Ar-*H*); *m/z* (GC-MS, EI) 222.2 (M^+. $C_{13}H_{22}OSi$ requires 222.1). The ν_{max} data is in agreement with literature values.[27]

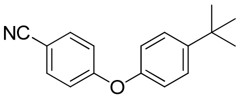
2,4-Bis(4-*tert*-butylphenoxy)-1-nitrobenzene 5 (*Representative procedure B*)



5

To a 10 cm^3 Hastelloy reactor (for $scCO_2$ reaction) were added Bu_4NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 2,4-difluoronitrobenzene **4** (0.159 g, 1.00 mmol) and **1** (0.489 g, 2.20 mmol) at ambient temperature. After purging with N_2 the reactor was sealed, filled to approximately 2/3 full with liquid CO_2, magnetically stirred and heated to 90 °C. At this temperature and internal pressure (23 MPa), a separate liquid phase was observed. After 16 h, the reactor was allowed to cool to ambient temperature. The CO_2 vapor was then released by venting into CH_2Cl_2 (50 cm^3). The reactor was rinsed with another portion of CH_2Cl_2 (20 cm^3). The CH_2Cl_2 solutions were combined and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (1:10 EtOAc-hexane) to give the diaryl ether **5** as pale yellow crystals (0.403 g, 96% yield). A sample was recrystallized from MeOH for chemical analyses; mp 73-74 ºC (from MeOH); R_f 0.45 (1:10 EtOAc-hexane); (Found: C, 74.5; H, 6.8; N, 3.3. $C_{26}H_{29}NO_4$ requires C, 74.4; H, 7.0; N, 3.3%); ν_{max}(solid)/cm^{-1} 2961, 2906, 2869, 1584, 1505, 1478, 1343, 1269, 1212, 1178, 1084, 1014, 985, 835 and 733; δ_H (400 MHz; DMSO-d_6) 1.26 [18 H, s, C(C*H*$_3$)$_3$], 6.45 (1 H, d, *J* 2.5, Ar-*H*), 6.76 (1 H, dd, *J* 2.5 and 9.0, Ar-*H*), 7.02 (2 H, d, *J* 9.0, Ar-*H*), 7.04 (2 H, d, *J* 9.0, Ar-*H*), 7.41 (2 H, d, *J* 9.0, Ar-*H*), 7.42 (2 H, d, *J* 9.0, Ar-*H*) and 8.12 (1 H, d, *J*, 9.0, Ar-*H*); δ_C (126 MHz; $CDCl_3$) 31.4, 31.5, 34.4, 34.5, 108.2, 110.5, 119.0, 119.8, 126.9, 127.0, 128.0, 135.2, 147.8, 148.4, 152.0, 152.8, 153.7 and 163.2; *m/z* (ES) 437.2438 [$(M+NH_4)^+$. $C_{26}H_{33}N_2O_4$: requires *M*, 437.2435], 437 [CI, $(M+NH_4)^+$, 100%], 420 (19), 390 (69), 242 (8) and 135 (6).

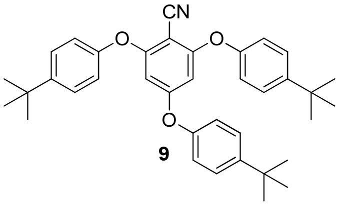
4-(4-*tert*-Butylphenoxy)benzonitrile 7



7

This was prepared according to the ***Representative procedure B*** from Bu_4NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 4-fluorobenzonitrile **6** (0.242 g, 2.00 mmol) and **1** (0.489 g, 2.20 mmol) at 110 °C in $scCO_2$ (23 MPa). Purification by flash column chromatography (1:10 EtOAc-hexane) gave diaryl ether **7** as colorless crystals (0.427 g, 85%); mp 92-94 ºC (from EtOAc-hexane) (lit.[28] 89-91 ºC); R_f 0.48 (1:10 EtOAc-hexane); ν_{max}(solid)/cm^{-1} 2962, 2871, 2221, 1605, 1591, 1493, 1362, 1296, 1247, 1202, 1167, 1108, 1014, 875, 851 and 831; δ_H (400 MHz; DMSO-d_6) 1.29 [9 H, s, C(C*H*$_3$)$_3$], 7.06 (4 H, dd, *J* 1.5 and 8.5, Ar-*H*), 7.47 (2 H, d, *J* 8.5, Ar-*H*) and 7.81 (2 H, d, *J*, 8.5, Ar-*H*). The ν_{max} data is in agreement with literature values.[28]

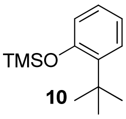
2,4,6-Tris(4-*tert*-butylphenoxy)benzonitrile 9



9

This was prepared according to ***Representative procedure B*** from Bu_4NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 2,4,6-trifluorobenzonitrile **8** (0.126 g, 0.800 mmol) and **1** (0.587 g, 2.64 mmol) at 110 °C in $scCO_2$ (23 MPa). Purification by flash column chromatography (1:10 EtOAc-hexane) gave the diaryl ether **9** as colorless crystals (0.394 g, 90%). A sample was recrystallized from EtOAc-MeOH for chemical analyses; mp 133-135 ºC (from EtOAc-MeOH); R_f 0.34 (1:10 EtOAc-hexane); (Found: C, 81.2; H, 7.5; N, 2.6. $C_{37}H_{41}NO_3$ requires C, 81.1; H, 7.5; N, 2.6%); ν_{max}(Neat)/cm^{-1} 2961, 2906, 2869, 2228, 1578, 1504, 1477, 1433, 1364, 1343, 1214, 1175, 1129, 1108, 1051, 1014, 910, 833 and 732; δ_H (400 MHz; DMSO-d_6) 1.19 [9 H, s, C(C*H*$_3$)$_3$], 1.26 [18 H, s, C(C*H*$_3$)$_3$], 5.88 (2 H, s, Ar-*H*), 6.83 (2 H, d, *J* 8.5, Ar-*H*), 7.03 (4 H, d, *J* 8.5, Ar-*H*), 7.26 (2 H, d, *J* 8.5, Ar-*H*) and 7.39 (4 H, d, *J* 8.5, Ar-*H*); δ_C (101 MHz; $CDCl_3$) 31.3, 31.4, 34.3, 34.5, 88.9, 99.3, 113.4, 119.4, 119.7, 126.7, 126.8, 148.0, 148.2, 151.9, 152.1, 162.7 and 163.2; *m/z* (ES) 565.3425 [$(M+NH_4)^+$. $C_{37}H_{45}N_2O_3$ requires *M*, 565.3425], 547 (EI, M^+, 25%), 532 (53), 476 (37), 460 (11), 259 (25) and 117 (18).

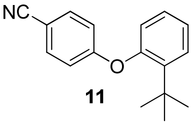
(2-*tert*-Butylphenoxy)trimethylsilane 10



10

This was prepared according to the ***Representative procedure A*** from 2-*tert*-butylphenol (5.00 g, 33.3 mmol), 1,1,1,3,3,3-hexamethyldisilazane (2.69 g, 16.6 mmol) and TMSCl (0.362 g, 3.33 mmol) at 150 °C. Distillation under reduced pressure gave the TMS-protected phenol **10** as a colorless liquid (6.31 g, 85%); bp 53 ºC (0.5 mm Hg) [lit.[26] 85.5 ºC (1 mm Hg)]; ν_{max}(film) cm^{-1} 2958, 2912, 1598, 1575, 1487, 1441, 1249, 1092, 1053, 921, 841 and 751; δ_H (400 MHz; CDCl$_3$) 0.37 [9 H, s, Si(C*H*$_3$)$_3$], 1.39 [9 H, s, C(C*H*$_3$)$_3$], 6.78 (1 H, dd, *J* 1.0 and 8.0, Ar-*H*), 6.90 (1 H, dt, *J* 1.0 and 8.0, Ar-*H*), 7.10 (1 H, dt, *J* 1.5 and 7.5, Ar-*H*) and 7.30 (1 H, dd, *J* 1.5 and 7.5, Ar-*H*); *m/z* (GC-MS, EI) 222.1 (M$^+$. $C_{13}H_{22}OSi$ requires 222.1).

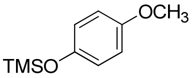
4-(2-*tert*-Butylphenoxy)benzonitrile 11



11

This was prepared according to the ***Representative procedure B*** from Bu$_4$NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 4-fluorobenzonitrile **6** (0.242 g, 2.00 mmol) and **10** (0.489 g, 2.20 mmol) at 110 °C in scCO$_2$ (22 MPa). Purification by flash column chromatography (1:10 EtOAc-hexane) gave the diaryl ether **11** as colorless crystals (0.342 g, 68%). A sample was recrystallized from hexane for chemical analyses; mp 118-120 ºC (from hexane); R_f 0.43 (1:10 EtOAc-hexane); ν_{max}(solid)/cm^{-1} 2996, 2959, 2911, 2871, 2223, 1599, 1501, 1481, 1439, 1241, 1192, 1165, 1086, 877, 839 and 772; δ_H (500 MHz; CDCl$_3$) 1.38 [9 H, s, C(C*H*$_3$)$_3$], 6.88 (1 H, dd, *J* 1.5 and 8.0, Ar-*H*), 7.02 (2 H, d, *J* 9.0, Ar-*H*), 7.18 (1 H, dt, *J* 1.5 and 8.0, Ar-*H*), 7.23 (1 H, dt, *J* 1.5 and 8.0, Ar-*H*), 7.47 (1 H, dd, *J* 1.5 and 8.0, Ar-*H*) and 7.62 (2 H, d, *J*, 9.0, Ar-*H*); δ_C (126 MHz; CDCl$_3$) 30.2, 34.7, 105.5, 118.1, 118.9, 121.5, 125.0, 127.5, 127.8, 134.1, 141.8, 153.6 and 161.8; *m/z* (ES) 251.2 (M$^+$. $C_{17}H_{17}NO$ requires *M*, 251.1).

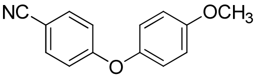
(4-Methoxyphenoxy)trimethylsilane 12



12

This was prepared according to the ***Representative procedure A*** from 4-methoxyphenol (7.00 g, 56.4 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (5.01 g, 31.0 mmol) at 130 °C. Distillation under reduced pressure gave the TMS-protected phenol **12** as a colorless liquid (9.59 g, 87%); bp 56 ºC (0.5 mm Hg) [lit.,[29] 81.5 ºC (3 mm Hg)]; ν_{max}(film) cm^{-1} 2997, 2958, 2906, 2835, 1506, 1252, 1233, 1039, 912, 844 and 752; δ_H (500 MHz; CDCl$_3$) 0.26 [9 H, s, Si(C*H*$_3$)$_3$], 3.78 (3 H, s, C*H*$_3$) and 6.79 (4 H, s, Ar-*H*); *m/z* (GC-MS, EI) 196.1 (M$^+$. $C_{10}H_{16}O_2Si$ requires 196.1). The ν_{max} and δ_H data are in agreement with literature values.[30]

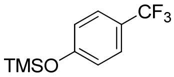
4-(4-Methoxyphenoxy)benzonitrile 13



13

This was prepared according to ***Representative procedure B*** from Bu_4NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 4-fluorobenzonitrile **6** (0.242 g, 2.00 mmol) and **12** (0.432 g, 2.20 mmol) at 110 °C in $scCO_2$ (23 MPa). Purification by flash column chromatography (1:2 EtOAc-hexane) gave the diaryl ether **13** as colorless crystals (0.396 g, 88%). A sample was recrystallized from EtOAc-hexane for chemical analyses; mp 109-110 ºC (from EtOAc-hexane) (lit.[31] 107.5 ºC); R_f 0.63 (1:2 EtOAc-hexane); ν_{max}(solid)/cm^{-1} 2957, 2837, 2226, 1600, 1494, 1231, 1196, 1166, 1102, 1033, 874, 834 and 757; δ_H (500 MHz; $CDCl_3$) 3.85 (3 H, s, C*H*$_3$), 6.96 (4 H, t, *J* 9.0, Ar-*H*), 7.02 (2 H, d, *J* 9.0, Ar-*H*) and 7.59 (2 H, d, *J* 9.0, Ar-*H*); *m/z* (ES) 225.1 (M$^+$. $C_{14}H_{11}NO_2$ requires *M*, 225.1).

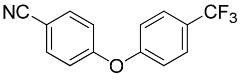
(4-(Trifluoromethyl)phenoxy)trimethylsilane 14



14

This was prepared according to the ***Representative procedure A*** from 4-hydroxybenzotrifluoride (5.00 g, 30.8 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (2.74 g, 17.0 mmol) at 100 °C. Distillation under reduced pressure gave the TMS-protected phenol **14** as a colorless liquid (6.38 g, 88%); bp 34 ºC (0.6 mm Hg) [lit.[25] 59 ºC (3 mm Hg)]; ν_{max}(film) cm^{-1} 2964, 1612, 1518, 1322, 1273, 1256, 1160, 1118, 1102, 1066, 907, 837, 754 and 703; δ_H (400 MHz; $CDCl_3$) 0.31 [9 H, s, Si(C*H*$_3$)$_3$], 6.92 (2 H, d, *J* 8.5, Ar-*H*) and 7.52 (2 H, d, *J* 8.5, Ar-*H*); *m/z* (GC-MS, EI) 234.1 (M$^+$. $C_{10}H_{13}F_3OSi$ requires 234.1).

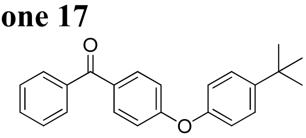
4-(4-(Trifluoromethyl)phenoxy)benzonitrile 15



15

This was prepared according to the ***Representative procedure B*** from Bu_4NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 4-fluorobenzonitrile **6** (0.242 g, 2.00 mmol) and **14** (0.515 g, 2.20 mmol) at 110 °C in $scCO_2$ (3200 psi). Purification by flash column chromatography (1:5 EtOAc-hexane) gave starting material 4-fluorobenzonitrile **6** and the diaryl ether **15** (0.128 g, 28%); R_f 0.44 (1:5 EtOAc-hexane); δ_H (400 MHz; DMSO-*d*$_6$) 7.24 (2 H, d, *J* 9.0, Ar-*H*), 7.30 (2 H, d, *J* 8.5, Ar-*H*), 7.81 (2 H, d, *J* 8.5, Ar-*H*) and 7.89 (2 H, d, *J* 9.0, Ar-*H*); *m/z* (GC-MS, EI) 263.1 (M$^+$. $C_{14}H_8F_3NO$ requires *M*, 263.1).

(4-*tert*-Butylphenoxy)benzophenone 17

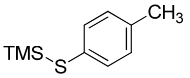


17

This was prepared according to the ***Representative procedure B*** from Bu_4NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 4-fluorobenzophenone **16** (0.400 g, 2.00 mmol) and **1** (0.489 g, 2.20 mmol) at 110 °C in $scCO_2$ (22 MPa). Purification by flash column chromatography (1:5 EtOAc-hexane) gave the diaryl ether **17** as colorless crystals (0.496 g, 75%). A sample was recrystallized from MeOH for chemical analyses; mp 78-79 ºC (from

MeOH); *R*f 0.51 (1:5 EtOAc-hexane); (Found: C, 83.7; H, 6.7. $C_{23}H_{22}O_2$ requires C, 83.6; H, 6.7%); *ν*max(solid)/cm^{-1} 3046, 2954, 1646, 1594, 1497, 1307, 1282, 1253, 1149, 1109, 937, 922, 849, 830, 794, 739, 731, 697 and 666; δ_H (500 MHz; $CDCl_3$) 1.37 [9 H, s, C(C*H*$_3$)$_3$], 7.05 (4 H, d, *J* 8.5, Ar-*H*), 7.43 (2 H, d, *J* 8.5, Ar-*H*), 7.50 (2 H, t, *J* 7.5, Ar-*H*), 7.59 (1 H, t, *J* 7.5, Ar-*H*), 7.80 (2 H, d, *J* 8.5, Ar-*H*) and 7.84 (2 H, d, *J*, 8.5, Ar-*H*); δ_C (126 MHz; $CDCl_3$) 31.4, 34.4, 116.9, 119.7, 126.8, 128.2, 130.3, 131.6, 132.1, 132.4, 138.0, 147.6, 152.9, 162.0 and 195.5; *m/z* (ES) 331.1693 [(M+H)$^+$. $C_{23}H_{23}O_2$ requires *M*, 331.1693], 330 (EI, M$^+$, 31%), 315 (82), 236 (5), 210 (11), 200 (12), 135 (37), 123 (31) 105 (100), and 95 (23).

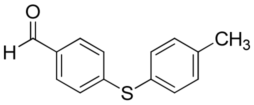
(*p*-Tolylthio)trimethylsilane 19



19

This was prepared according to ***Representative procedure A*** from *p*-thiocresol (6.87 g, 55.3 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (5.36 g, 33.2 mmol) at 120 °C. Distillation under reduced pressure gave the TMS-protected thiophenol **19** as a colorless liquid (7.51 g, 69%); bp 51 ºC (1 mm Hg) [lit.[32] 59-60 ºC (1 mm Hg)]; δ_H (500 MHz; $CDCl_3$) 0.28 [9 H, s, Si(C*H*$_3$)$_3$], 2.34 (3 H, s, C*H*$_3$), 7.08 (2 H, d, *J* 8.0, Ar-*H*) and 7.31 (2 H, d, *J* 8.0, Ar-*H*); *m/z* (GC-MS, EI) 196.1 (M$^+$. $C_{10}H_{16}SSi$ requires *M*, 196.1). The δ_H data is in agreement with literature values.[33]

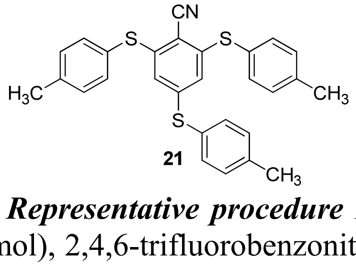
4-(*p*-Tolylthio)benzaldehyde 20



20

This was prepared according to the ***Representative procedure B*** from Bu_4NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 4-fluorobenzaldehyde **18** (0.248 g, 2.00 mmol) and **19** (0.432 g, 2.20 mmol) at 110 °C in $scCO_2$ (22 MPa). Purification by flash column chromatography (1:10 EtOAc-hexane) gave the diaryl ether **20** as colorless crystals (0.393 g, 86%); mp 69-70 ºC (from EtOAc-hexane) (lit.[34] 69-71 ºC); *R*f 0.27 (1:10 EtOAc-hexane); *ν*max(solid) cm^{-1} 2850, 1693, 1584, 1557, 1488, 1409, 1381, 1301, 1206, 1165, 1077, 1011, 806 and 691; δ_H (400 MHz; DMSO-*d*$_6$) 2.36 (3 H, s, C*H*$_3$), 7.18 (2 H, d, *J* 8.0, Ar-*H*), 7.27 (2 H, d, *J* 8.0, Ar-*H*), 7.40 (2 H, d, *J* 8.0, Ar-*H*), 7.73 (2 H, d, *J* 8.0, Ar-*H*) and 9.87 [1 H, s, *H*(C=O)].

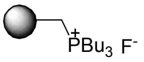
2,4,6-Tris-*p*-tolylsufanylbenzonitrile 21



21

This was prepared according to ***Representative procedure B*** from Bu_4NBr (0.129 g, 0.400 mmol), CsF (0.0152 g, 0.100 mmol), 2,4,6-trifluorobenzonitrile **8** (0.126 g, 0.800 mmol) and **19** (0.518 g, 2.64 mmol) at 110 °C in $scCO_2$ (23 MPa). Purification by flash column chromatography (1:5 EtOAc-hexane) gave the trithioether **21** as colorless crystals (0.357 g, 95%). A sample was recrystallized from EtOAc-MeOH for chemical analyses; mp 146-147 ºC (from EtOAc-MeOH); R_f 0.37 (1:5 EtOAc-hexane); (Found: C, 71.7; H, 4.9; N, 2.8. $C_{28}H_{23}NS_3$ requires C, 71.6; H, 4.9; N, 3.0%); ν_{max}(Neat)/cm^{-1} 2922, 2211, 1594, 1544, 1512, 1488, 1400, 1376, 1202, 1177, 1104, 1051, 1016, 834, 806 and 706; δ_H (400 MHz; DMSO-*d*$_6$) 2.33 [3 H, s, C*H*$_3$], 2.35 [6 H, s, C*H*$_3$], 6.14 (2 H, s, Ar-*H*), 7.01 (2 H, d, *J* 8.0, Ar-*H*), 7.05 (2 H, d, *J* 8.0, Ar-*H*), 7.14 (4 H, d, *J* 8.0, Ar-*H*) and 7.24 (4 H, d, *J* 8.0, Ar-*H*); δ_C (126 MHz; $CDCl_3$) 21.3, 21.4, 105.0, 115.1, 121.2, 125.8, 126.5, 130.3, 130.5, 134.8, 135.0, 139.6, 139.7, 145.8 and 146.8; *m/z* (ES) 470.1063 [(M+H)$^+$. $C_{28}H_{23}NS_3$ requires *M*, 470.1065], 471 (EI, (M+H)$^+$, 100%), 458 (18), 443 (13), 347 (13), 255 (37), 149 (22), 135 (21) and 123 (48).

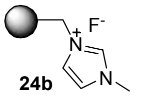
Merrifield resin-supported phosphonium fluoride 24a



24a

To a Schlenk tube were added the Merrifield resin **22** (8.00 g, 1.24 mmol Cl/g, 200-400 mesh) and chlorobenzene (N_2-bubbled, 70 cm^3) at room temperature. After the suspension was left overnight, excess chlorobenzene was decanted and Bu_3P (20.1 g, 99.2 mmol) was added under a N_2 atmosphere. The suspension was left at 100 °C with occasional stirring for 48 h. After the suspension was cooled to room temperature, it was diluted with CH_2Cl_2 and the liquid phase was decanted. Another portion of CH_2Cl_2 was added and the suspension was filtered. The resin beads were washed with CH_2Cl_2 overnight using a soxhlet extraction apparatus. Drying under reduced pressure at 60 °C gave the Merrifield resin-supported phosphonium chloride **23a** (9.63 g) which was used immediately. Elemental analysis showed that the P content of **23a** was 3.2%, which corresponds to 1.0 mmol P/g; δ_C (polymer gel; 101 MHz; $CDCl_3$) 13.5, 18.5 (d, J_{CP} 38), 23.7 (d, J_{CP} 30), 40.5, 44.5 (br s) and 127.8 (br s); δ_P (polymer gel; 162 MHz; $CDCl_3$) 32.4. To a Schlenk tube were added the resin **23a** (1.50 g) and MeOH (10 cm^3) at room temperature. After the suspension was left overnight at 60 °C, CsF (0.565 g, 3.72 mmol) was added. The suspension was stirred at 60 °C for 24 h and then cooled to room temperature. The resin beads were filtered and washed with MeOH (100 cm^3). Drying under reduced pressure at 60 °C gave the Merrifield resin-supported phosphonium fluoride **24a** (1.38 g). Elemental analysis showed that the total Cl content of **24a** was 0.5%, which corresponds to 0.1 mmol Cl/g.

Merrifield resin-supported imidazolium fluoride 24b



24b

Macroporous Merrifield resin **22** (7.00 g, 1.20 mmol Cl/g, 100-200 mesh) and 1-methylimidazole (6.90 g, 84.0 mmol) were suspended in chlorobenzene (42 cm^3) and heated at 120 °C for 60 h. After allowing to cool to ambient temperature, the suspension was diluted with CH_2Cl_2 and the liquid phase decanted with a syringe. Another portion of CH_2Cl_2 was added and the suspension was filtered. The resulting resin beads were washed with CH_2Cl_2 overnight using a soxhlet apparatus. Drying under reduced pressure at 60 °C gave the Merrifield-resin supported imidazolium chloride **23b** (7.78 g) which was used immediately. The imidazolium chloride resin **23b** (5.50 g) and CsF (2.01 g, 13.2 mmol) were suspended in MeOH (36 cm^3) and heated at 60 °C for 72 °C. The suspension was allowed to cool to ambient temperature, and the resin beads were filtered and washed with MeOH (100 cm^3). Drying under reduced pressure at 60 °C gave the Merrifield resin-supported imidazolium fluoride **24b** (5.10 g). Elemental analysis showed a 4-methylimidazole loading of 1.2 mmol/g and a Cl^- content of 0.65 mmol/g (implying an F^- content of 0.55 mmol/g).

Diaryl ether synthesis with the polymer-supported phosphonium fluoride 24a in batch reaction mode

To a 10 cm^3 Hastelloy reactor (for $scCO_2$ reaction) were added **2** (0.282 g, 2.00 mmol), **1** (0.489 g, 2.20 mmol) and a pouch (made of 500 mesh stainless steel screen) which contained the resin **24a** (0.500 g) at room temperature. After purging with N_2 the reactor was sealed, charged to approximately 2/3 full with liquid CO_2 and heated to 90 °C. At this temperature the pressure was 21 MPa. After 16 h the reactor was allowed to cool to room temperature and the CO_2 vapour was released by bubbling it into cyclohexane (40 cm^3). The vessel was then rinsed with another portion of cyclohexane (20 cm^3) and the rinse solution was combined with the bubbled solution. The pouch was put into a vial and rinsed further with cyclohexane (10 cm^3). The cyclohexane solution was then decanted by pipette. This sequence was repeated three more times. The decanted cyclohexane solutions were combined with the bubbled solution. After mixing with a known amount of mesitylene (*ca.* 0.0580 g), an aliquot (0.2 μL) of the solution was injected into the GC. The yield was calculated based on the pre-acquired calibration curve. The chemical identity of the product **3**, which was separated by preparative TLC technique, was confirmed by IR spectroscopy through comparison with the authentic material. After analysis, the wet pouch was used in subsequent recycling tests.

Diaryl ether synthesis in continuous-flow reaction mode

A mixture of **2** (5.7 mmol) and **1** (6.2 mmol) was delivered at a dose rate of 0.01 cm^3 min^{-1} to a high-pressure column [15 cm (L) x 0.62 cm (id)], containing dry imidazolium resin **24b** (0.74 g), using a Thermo Separation Products ConstaMetric® 3200 HPLC pump (matched to the pressure of the continuous flow apparatus). The temperature of the column was maintained at 110 °C using thermocouple-controlled heating tape. A Jasco™ PU-1580-CO_2 CO_2 delivery pump, operating in continuous pressure mode at a pressure of 26 MPa, was used to pass $scCO_2$ through the reactor column at a flow rate of 0.32 cm^3 min^{-1}. The eluate was vented into a collection vessel containing ethyl acetate. Regular aliquots were collected and analyzed by GC to provide a conversion yield of diaryl ether product **3**.

Upon periodic dosing of small quantities of the reagents onto the column, virtually no material was observed in the eluent. This suggests that in order for the observed conversions to have been attained column saturation had been realized. The disappointing mass balance still observed after saturation could potentially be due to product and reagent precipitation in the column, although further study is needed.

GC monitoring experiments

Conversion yields were determined by gas chromatography. From the peak areas of diaryl ether **3** and aryl fluoride **2** in the chromatogram, the conversion was calculated using a pre-acquired calibration curve (see Fig. 1). The table below gives details of the method used for sample analysis. Absolute yields were acquired by co-injection of a known amount of mesitylene and the resultant peak areas compared to a pre-acquired calibration curve (not shown).

Temp (°C)	Rate (°C)	Hold (min)	Time (min)
100	-	5	5
200	10	10	25
250	50	5	31

Figure 1. Calibration curve for diaryl ether 3 versus aryl fluoride 2

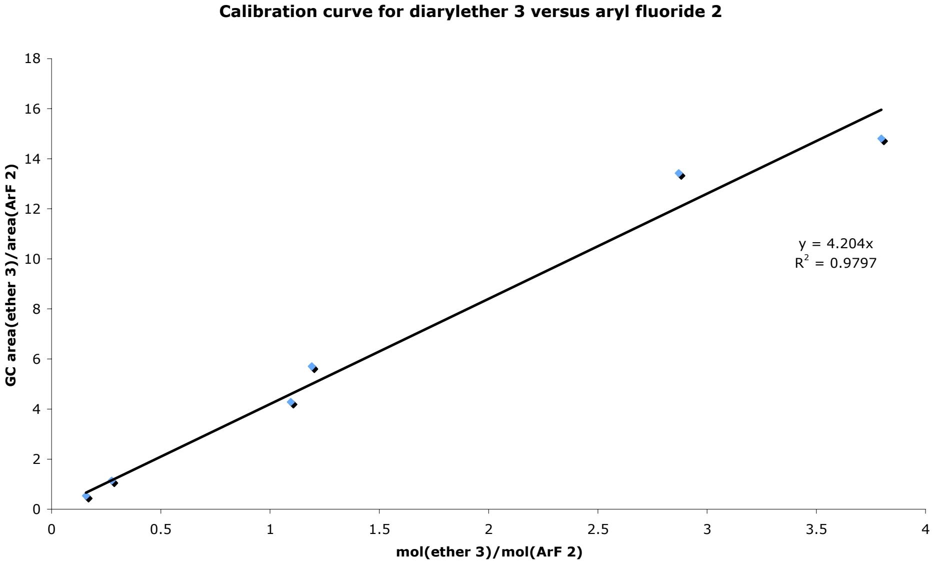


Figure 2. GC Chromatogram for Table 4, entry 1 (elapsed time of 1 h, conversion 69%)

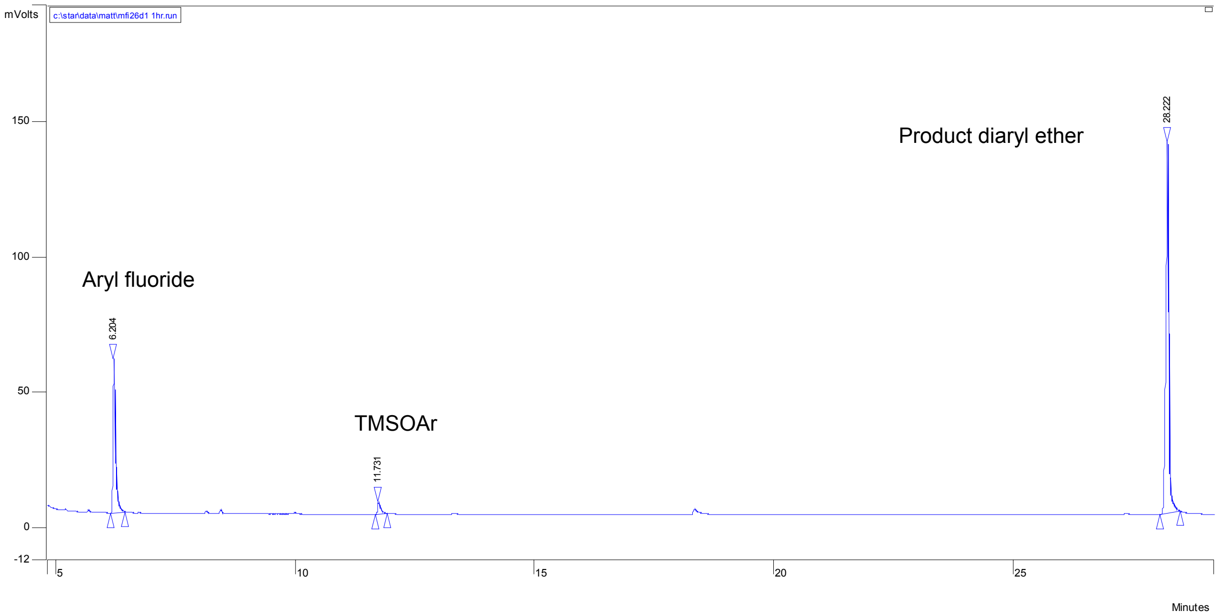


Figure 3. GC Chromatogram for Table 4, entry 2 (elapsed time of 2 h, conversion 61%)

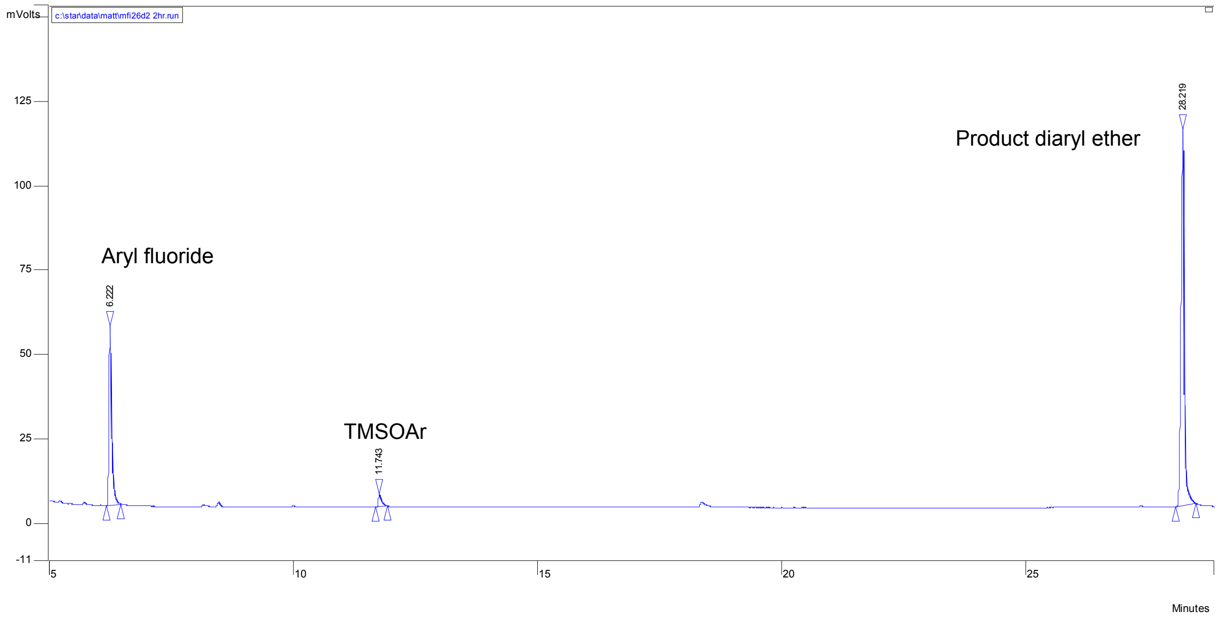


Figure 4. GC Chromatogram for Table 4, entry 3 (elapsed time of 3 h, conversion 61%)

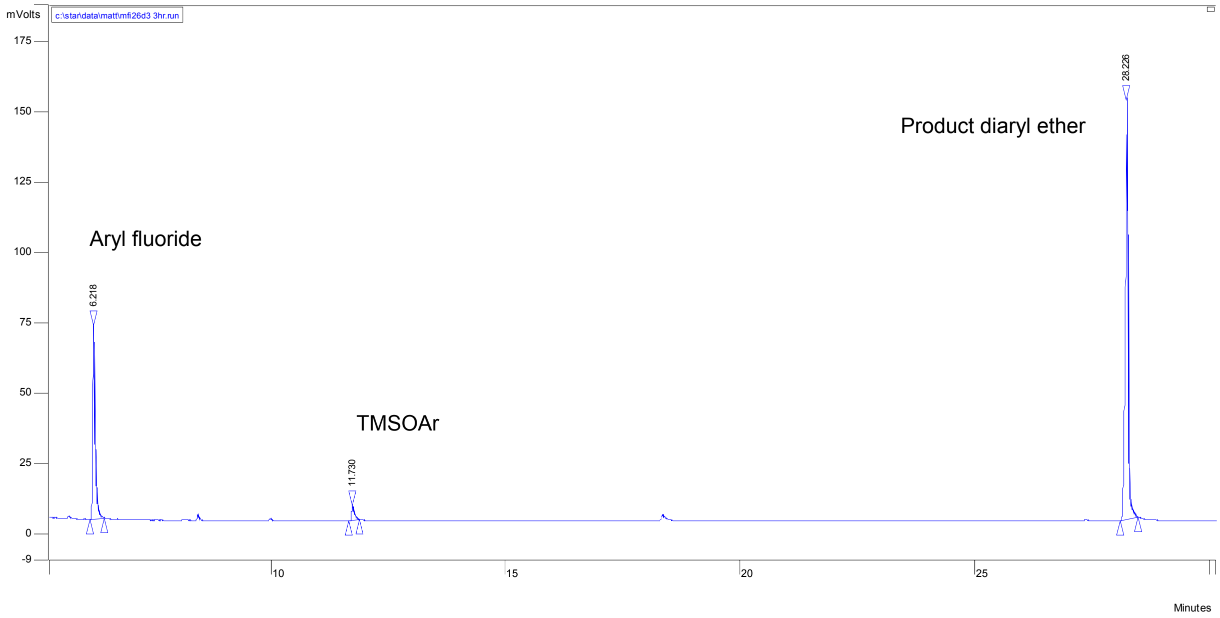


Figure 5. GC Chromatogram for Table 4, entry 4 (elapsed time of 4 h, conversion 96%)

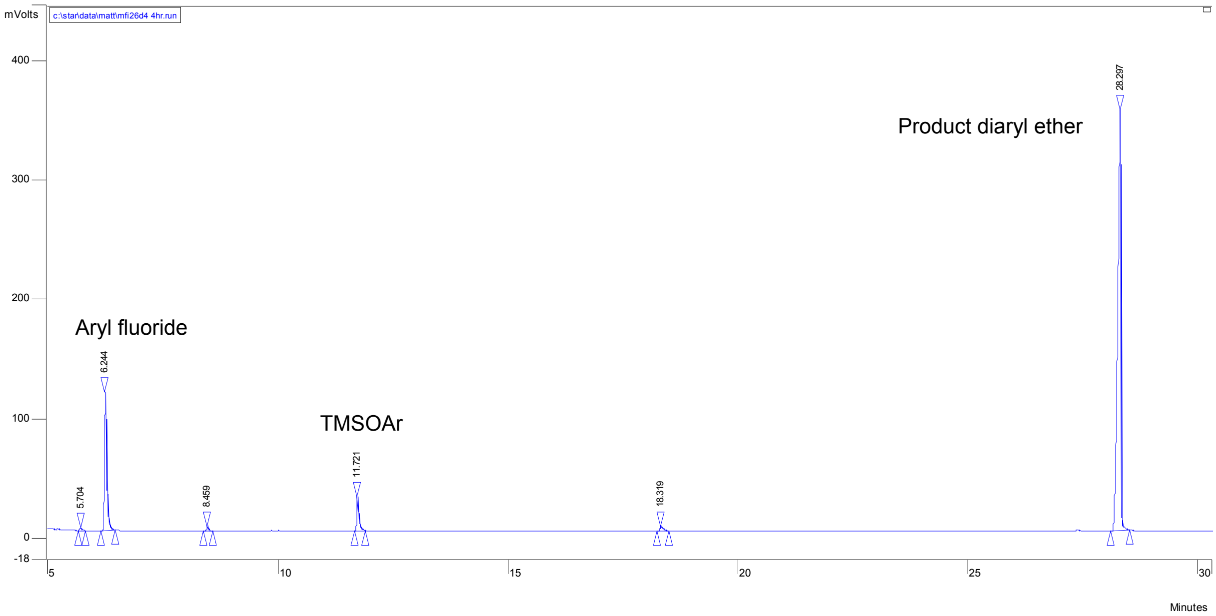


Figure 6. GC Chromatogram for Table 4, entry 5 (elapsed time of 5 h, conversion 96%)

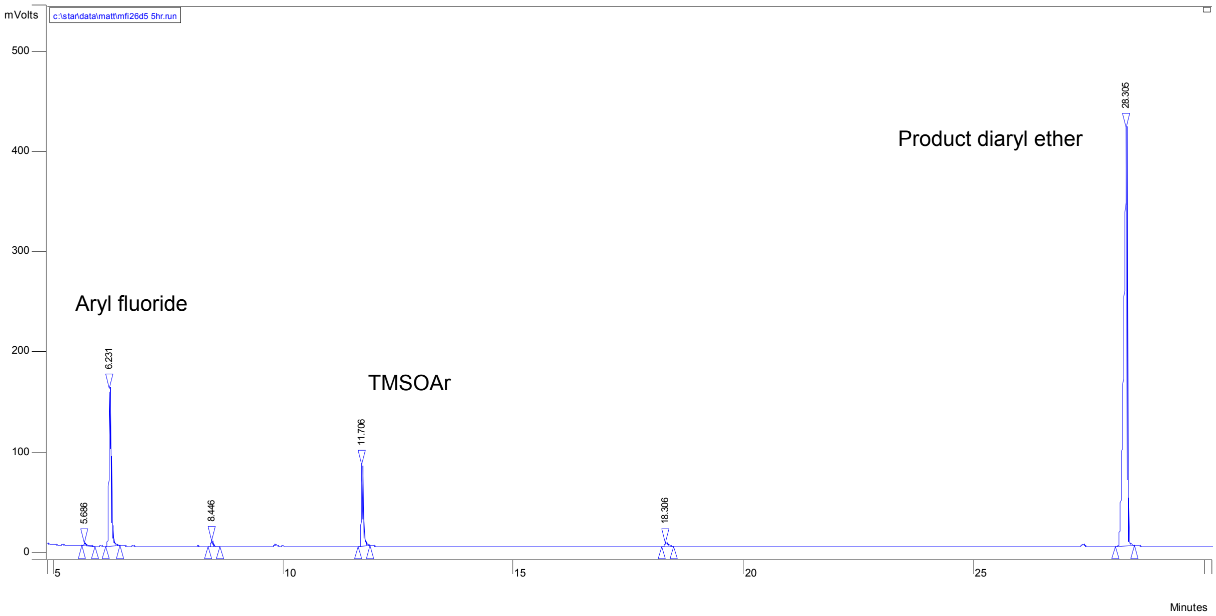


Figure 7. GC chromatogram for eluant after flushing the column with toluene for 2 h (conversion 96%)

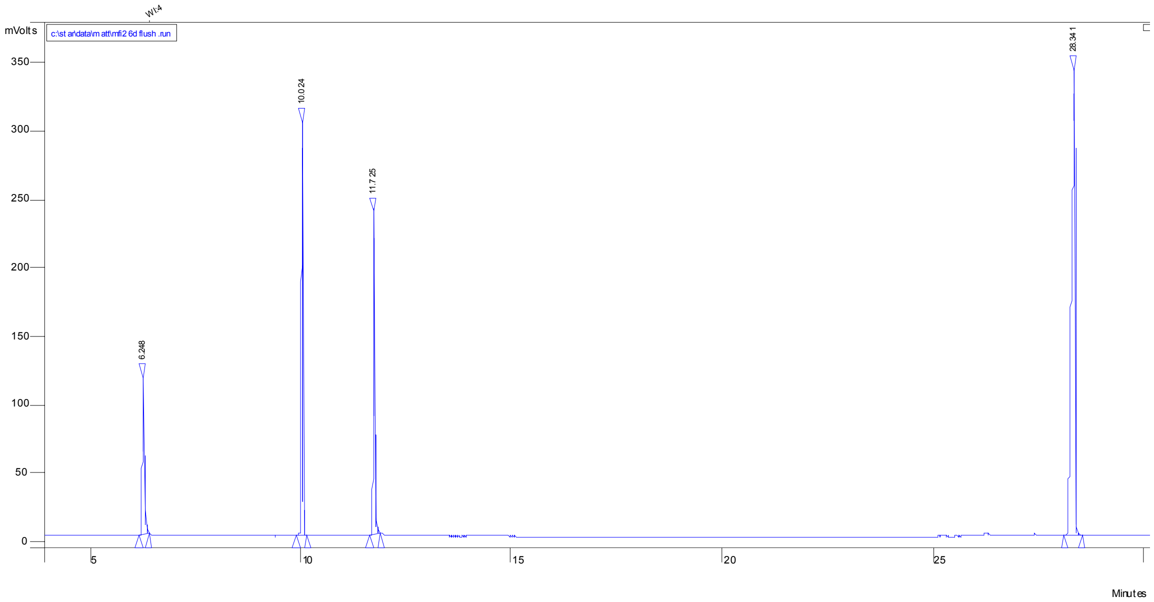


Table 1. Conversion of *p*-nitrofluorobenzene 2 into diaryl ether 3 under continuous flow conditions in heptane.[a]

Entry	Elapsed time, t (h)	T (°C)	Conversion (GC, %)[b]
1	1	90	33
2	2	90	34
3	3	90[c]	31
4	5	110	90
5	9	110	77
6	11	110	83
7	Recycle[d]	110	85[e](69[f])

[a] Reagents and conditions: 50.0 mmol **2**, 55.0 mmol **1**, 0.74 g **24a**, 44.4 mmol octane, 120 cm^3 heptane, flow rate (0.2 cm^3/min), 15 cm (L) x 0.46 cm (id) column. [b] Conversion was calculated from the peak areas of **3** and octane on GC chromatogram. [c] As soon as a sample was collected, reaction temperature was raised to 110 ºC. [d] After the completion of the reaction, the collected product solution was recycled into the column at a flow rate of 0.2 cm^3/min. [e] The overall conversion after the recycle of the product solution. [f] Isolated yield of the diaryl ether **3** after recrystallisation from MeOH.

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