Diaryl ether synthesis in supercritical carbon dioxide in batch and continuous flow modes†

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Received (in Cambridge, UK) 19th May 2008, Accepted 27th June 2008
First published as an Advance Article on the web 6th August 2008
DOI: 10.1039/b808374f

A high yielding, batch mode synthesis of diaryl ethers and sulfides by an S_NAr fluoride-mediated process in $scCO_2$ has been developed; the use of a polymer-supported imidazolium fluoride reagent in batch mode led to the development of a fixed-bed continuous flow process, with high conversions.

Diaryl ethers occur widely in biologically active pharmaceuticals and agrochemicals as synthetically challenging natural products, as well as in commercially available engineering plastics.[1–3] Several synthetic methods have been developed to prepare this important class of compounds.[4]

Supercritical carbon dioxide ($scCO_2$) has been promoted as a non-flammable, environmentally benign alternative to the conventional solvents used in organic synthesis.[5–7] In its supercritical state (P_c = 73.8 bar, 7.4 MPa, T_c = 31 °C),[8] CO_2 has a substantial liquid-like dissolving power;[9] its very low viscosity and high gas-like diffusivity enable effective mass and heat transfer.[9,10] Most chemical manufacturing processes rely on batch mode techniques, but there has recently been an upsurge of interest in continuous flow processes, which have the potential to reduce manufacturing costs.[10–12] From an industrial perspective, the highly advantageous properties of $scCO_2$ are its easy separation from the products of a reaction and its purification by controlled decompression. A practical industrial example is the heterogeneous hydrogenation process developed by Poliakoff.[13] We have recently described a continuous flow Suzuki–Miyaura coupling reaction[14] in $scCO_2$, in the presence of an immobilized PdEnCat™ catalyst.[15]

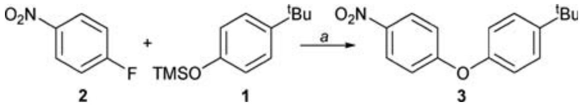
In this Communication, we report a high-yielding, fluoride-mediated diaryl ether synthesis in $scCO_2$. We also describe the translation of a batch to a continuous flow process.

Our starting point was the CsF-mediated S_NAr reaction of aryl silyl ethers with aryl fluorides to give diaryl ethers.[16] To test this concept in batch mode in $scCO_2$, the reaction between TMS-protected phenol **1**[17] and fluoronitrobenzene **2** (Table 1) was investigated. The use of TMS-protected phenol resulted in the formation of gaseous TMS-F, which was miscible with $scCO_2$ under the reaction conditions.

No reaction occurred in $scCO_2$ when a catalytic (5 mol%) amount of CsF was used (entry 1, Table 1); however, the use of Bu_4NF afforded a 20% yield of **3** (entry 2, Table 1).[18] A dramatic enhancement in yield was observed when a combination of Bu_4NBr and CsF (5 mol%) was used (entry 3, Table 1). A larger quantity of Bu_4NBr (20 mol%) proved to be even more effective (entry 4, Table 1). We have previously noted the potential for tetra-alkylammonium salts to promote organometallic cross-coupling reactions in $scCO_2$, and we attributed this to a "catalytic effect" as a result of the ionic liquid nature[19] of the CO_2-expanded Bu_4NBr liquid phase.[20] We observed an expanded liquid phase in the batch mode reactions that was consistent with related similar observations.[21,22]

The scope of the newly developed Bu_4NBr/CsF aryl ether coupling protocol was then explored, as detailed in Table 2. Difluoro-substituted nitrobenzene **4** reacted in high yield with silyl phenol **1** (entry 1, Table 2), which shows that multiple substitution is not slow in $scCO_2$, provided that activation is

Table 1 Synthesis of the diaryl ether **3** in $scCO_2$[a]



Entry	Fluoride salt	Yield (%)[b]
1	CsF (5 mol%)	< 1
2	Bu_4NF (5 mol%)[c]	20
3	Bu_4NBr (5 mol%) + CsF (5 mol%)	91
4	Bu_4NBr (20 mol%) + CsF (5 mol%)	97

[a] Reagents and conditions: 2.00 mmol **2**, 2.20 mmol **1**, fluoride salt (5 mol%), $scCO_2$ (*ca.* 21 MPa), 10 cm^3 reaction vessel, 90 °C, 16 h. [b] Yield (GC) against mesitylene (reference). [c] 1.0 M solution in THF.

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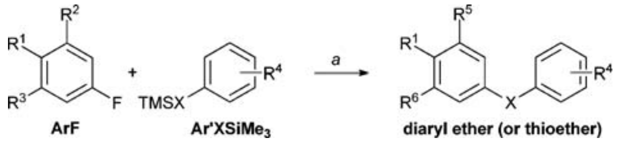
† Electronic supplementary information (ESI) available: Representative experimental procedures for batch and continuous flow mode processes in $scCO_2$, and characterisation data for new compounds. See DOI: 10.1039/b808374f

Table 2 Coupling of ArF with Ar′XSiMe$_3$ in the presence of Bu$_4$NBr/CsF in scCO$_2$



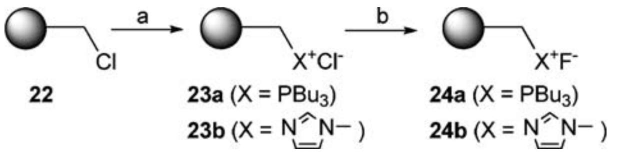
Entry[a]	ArF	Ar′XSiMe$_3$	Diaryl ether product	T/°C	Yield (%)[b]
1[c]	**4** (R^1 = NO$_2$, R^2 = F, R^3 = H)	**1** (X = O, R^4 = 4-^{t}Bu)	**5** (R^5 = O-(4-C$_6$H$_4$^{t}Bu), R^6 = H)	90	96
2	**6** (R^1 = CN, R^2 = R^3 = H)	**1** (X = O, R^4 = 4-^{t}Bu)	**7** (R^5 = R^6 = H)	110	85
3[d]	**8** (R^1 = CN, R^2 = R^3 = F)	**1** (X = O, R^4 = 4-^{t}Bu)	**9** (R^5 = R^6 = O-(4-C$_6$H$_4$^{t}Bu))	110	90
4	**6** (R^1 = CN, R^2 = R^3 = H)	**10** (X = O, R^4 = 2-^{t}Bu)	**11** (R^5 = R^6 = H)	110	68
5	**6** (R^1 = CN, R^2 = R^3 = H)	**12** (X = O, R^4 = 4-OCH$_3$)	**13** (R^5 = R^6 = H)	110	88
6	**6** (R^1 = CN, R^2 = R^3 = H)	**14** (X = O, R^4 = 4-CF$_3$)	**15** (R^5 = R^6 = H)	110	28
7	**16** (R^1 = COPh, R^2 = R^3 = H)	**1** (X = O, R^4 = 4-^{t}Bu)	**17** (R^5 = R^6 = H)	110	75
8	**18** (R^1 = CHO, R^2 = R^3 = H)	**19** (X = S, R^4 = 4-CH$_3$)	**20** (R^5 = R^6 = H)	110	86
9[e]	**8** (R^1 = CN, R^2 = R^3 = F)	**19** (X = S, R^4 = 4-CH$_3$)	**21** (R^5 = R^6 = S-(4-C$_6$H$_4$CH$_3$))	110	95

[a] Reagents and conditions: 2.00 mmol ArF, 2.20 mmol Ar′XSiMe$_3$, 0.10 mmol CsF, 0.40 mmol Bu$_4$NBr, scCO$_2$ (*ca.* 22 MPa), 10 cm^3 reaction vessel, 16 h. [b] Isolated yield. [c] 1.00 mmol **4**, 2.20 mmol **1**, 0.10 mmol CsF, 0.40 mmol Bu$_4$NBr. [d] 0.80 mmol **8**, 2.64 mmol **1**, 0.10 mmol CsF, 0.40 mmol Bu$_4$NBr. [e] 0.80 mmol **8**, 2.64 mmol **19**, 0.10 mmol CsF, 0.40 mmol Bu$_4$NBr.

sufficient. Electron deficient 4-fluorobenzonitrile (**6**) afforded only a 25% yield of ether **7** at 90 °C, but gave an 85% yield at 110 °C. By comparison, the corresponding reaction using 4-*tert*-butyl phenol in the presence of excess Cs$_2$CO$_3$ in scCO$_2$ (110 °C) gave **7** in 6% yield. This procedure demonstrates the power of the new process, using scCO$_2$ as a solvent. Trifluoro-substituted benzonitrile **8** reacted with silyl phenol **1** (entry 3, Table 2) to give **9** in high yield. Along with various fluorobenzenes, sterically and electronically diverse TMS-ethers were also examined (entries 4–6, Table 2).

However, the TMS-ether of 4-hydroxybenzotrifluoride (**14**) afforded diaryl ether **15** in only 28% yield, owing to the poor nucleophilicity of the corresponding phenoxide anion. Fluorobenzophenone **16** was converted to diaryl ether **17** in 75% yield, indicating that an aryl ketone is also sufficiently activating for the reaction to occur at 110 °C. The reaction is not limited to diaryl ethers, but is more widely applicable; for example, TMS-protected thiophenol **19** gave diaryl thioether **20** in high yield (86%). The reaction between trifluoro-substituted benzonitrile **8** and TMS-protected thiophenol **19** also proceeded in excellent yield to give trithioether **21**.

The reaction conditions described in Table 2 lend themselves to the use of a polymer-supported fluoride reagent, which is an essential prerequisite for the translation to a continuous flow process. The polymer-supported phosphonium fluoride, **24a**, which is known to be more stable than the corresponding ammonium salt,[23] was prepared from the commercially available, gel-type Merrifield resin **22**. Simple nucleophilic substitution of the benzylic chloro-substituent with PBu$_3$ in polymer **22** gave phosphonium chloride salt **23a**, and subsequent ion exchange with CsF afforded polymer-supported phosphonium fluoride **24a** (Scheme 1).



Scheme 1 Preparation of Merrifield resin-supported reagents **24**. Reagents and conditions (a) (**23a**) PBu$_3$, chlorobenzene, 100 °C, 48 h; (**23b**) 1-methylimidazole, chlorobenzene, 120 °C, 48 h; (b) CsF, MeOH, 60 °C, 24 h.

The performance of polymer-supported fluoride **24a** was first evaluated in the diaryl ether coupling reaction (Table 1) in batch mode, before being applied to a continuous flow process. **24a** retained good activity, with yields of over 70% being obtained after five cycles (Table 3). The moderate decrease of yields, compared with those obtained with the Bu$_4$NBr and CsF mixture, could be attributed to mass-transfer limitations caused by the confinement of the reagent. These results were promising for application to a continuous flow process.

Experiments for a 'proof of concept' fixed-bed reactor continuous flow process for the diaryl ether coupling reaction of fluoronitrobenzene **2** and TMS-protected phenol derivative **1** were first performed in a heptane solvent using polymer-supported phosphonium fluoride **24a** (see ESI,† Table 1). In scCO$_2$, initial experiments were performed using the apparatus illustrated in Fig. 1. It is pertinent to mention that the use of a resin derived from the macroporous Merrifield resin was necessary to prevent polymer swelling and column blockage under continuous flow conditions.[24] The pre-mixed liquid reactants were dosed onto a high pressure column, containing the polymer-supported reagent, by means of an HPLC pump

Table 3 Batch reaction of fluoride **2** and ether **1**, using polymer-supported phosphonium fluoride **24a** in scCO$_2$ to give diaryl ether **3**[a]

Entry	Recycle of polymer-supported reagent **24a**	Yield (%)
1	Virgin	56
2	1st	84
3	2nd	77
4	3rd	81
5	4th	72
6	5th	72

[a] Reagents and conditions: 2.00 mmol **2**, 2.20 mmol **1**, **24a** (0.500 g), scCO$_2$ (*ca.* 21 MPa), 10 cm^3 reaction vessel, 90 °C, 16 h.

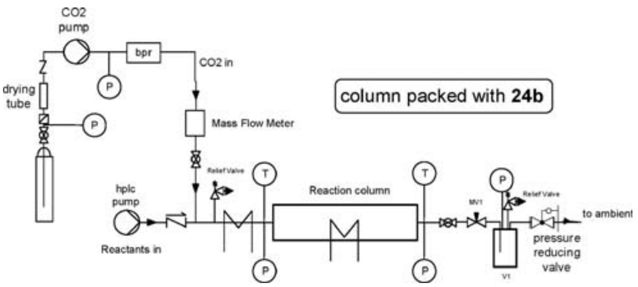


Fig. 1 Schematic of the continuous flow apparatus.

Table 4 Conversion of *para*-nitro fluorobenzene (**2**) into diaryl ether **3** under continuous flow conditions as a function of elapsed time[a]

Entry	Elapsed time/h	Conversion (GC, %)[b]
1	1	69
2	2	61
3	3	61
4	4	96
5	5	96

[a] Reagents and conditions: **2** (1 equiv.), **1** (1.1 equiv.), dose rate 0.01 $cm^3 min^{-1}$, $scCO_2$ flow rate 0.32 $cm^3 min^{-1}$, 110 °C, 26 MPa, 15 cm (L) × 0.62 cm (id) column containing **24b**. [b] Conversion based on a standardized GC comparison of **2** and **3**.

(matched to the pressure of the continuous flow apparatus). A JASCO™ CO_2 delivery pump was used to pass $scCO_2$ at a constant pressure of 26 MPa through the column. The eluate was vented into a collection vessel containing ethyl acetate. Aliquots were collected and analyzed by GC to provide a conversion yield of the diaryl ether product, **3**. The temperature of the column was maintained at 110 °C to accomplish a high conversion to the product. However, under this higher temperature, phosphonium fluoride **24a** appeared to decompose slowly, causing a decreasing conversion, and therefore we adopted a potentially more thermally stable imidazolium fluoride, **24b** (Scheme 1).[25] Pleasingly, high conversions were realized under continuous flow conditions using imidazolium fluoride resin **24b** (Table 4). Optimization revealed the need to maintain the system pressure above 20 MPa, with a minimum $scCO_2$ flow rate of 0.32 $cm^3 min^{-1}$. Further optimization of the flow system is under way to improve upon these promising results. When a material balance was carried out under small-scale continuous flow laboratory conditions, absolute yields of **3** were 2–10%. It is thought that the low isolated yields of product **3** were the result of adsorption of the product and reactants onto the resin, owing to the lower solubilizing power of $scCO_2$ under these conditions. When the column was flushed with toluene for several hours (flow rate 2 $cm^3 min^{-1}$) after the reaction had been running for 5 h, the ratio of product to reactant was identical to that observed in entry 5, Table 4 after 5 h (see ESI†). The qualitative solubilities of aryl fluoride **2** and product **3** were very similar. We have excluded the possibility that the column had not been fully saturated with reactants and product (see ESI†), but this is clearly open to further investigation. Whilst high conversions have been achieved under continuous flow conditions, there is considerable scope for further exploitation of this process technology.

In conclusion, we have demonstrated the high yielding, batch mode synthesis of diaryl ethers by an S_NAr fluoride-mediated process in $scCO_2$. The process is driven by the strength of the Si–F bond, which emerges as a CO_2-miscible side-product. The use of a polymer-supported fluoride reagent in batch mode led to the development of a fixed-bed continuous flow process with high conversions.

We thank AstraZeneca (UK), the Overseas Research Students Awards Scheme (Universities UK), the Cambridge Overseas Trust, the Engineering and Physical Sciences Research Council (UK), the Australian Research Council, VESKI and CSIRO (Australia) for financial support. This project was carried out with partial support from the Materials World Network (NSF/ARC).

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