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# The electrosynthesis of highly encumbered biaryls from aryl *o*-iodobenzyl ethers by a radical to polar crossover sequence†‡

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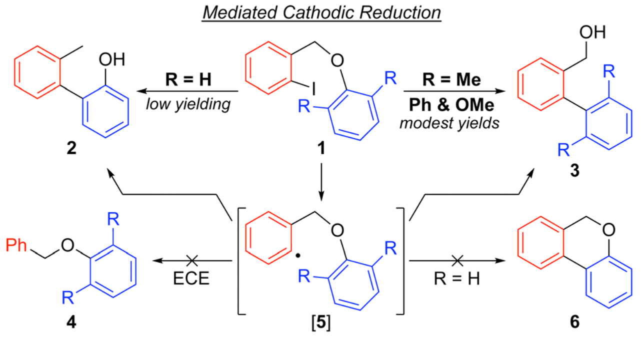
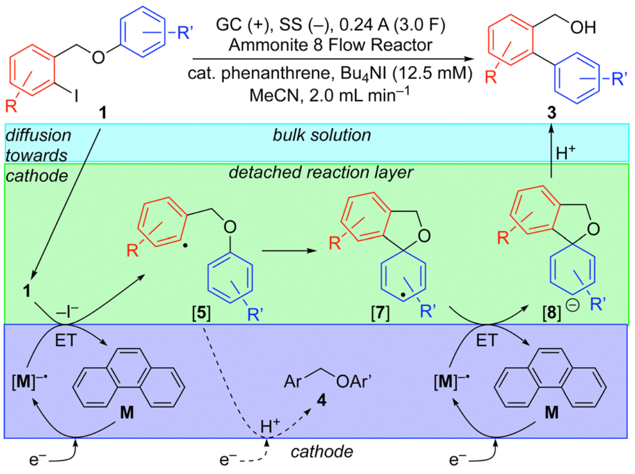
**Highly encumbered 2,2′,6-tri- and 2,2′,6,6′-tetra-substituted biaryls are readily prepared from aryl *ortho*-iodobenzyl ethers through mediated cathodic reduction under flow. The reaction proceeds *via* the stepwise transfer of two electrons: the first to induce loss of iodide and a radical cyclisation, and the second to induce a polar fragmentation.**

Benzyl *ortho*-iodoaryl ethers are commonly used as precursors to benzo[*c*]chromenes, *e.g.* **1** → **6**, through cyclisations induced by palladium catalysis,[1] or radical formation.[2,3] Of these, the former usually proceed in high yield through *ortho*-cyclisation. In contrast, reactions *via* radical intermediates usually give cyclisation to **6** in low to modest yield due to competing processes such as iodide reduction to **4** or *ipso*-cyclisation and fragmentation (Scheme 1).[2] Cathodic reductions of aryl iodides also proceed *via* the corresponding radical intermediate.[4] However, at the highly negative cathode potentials required, reduction of aryl radicals is extremely facile such that direct cathodic ECE reduction to the aryl anion is usually observed.[5–7]

We recently showed how reductive radical cyclisation reactions of aryl halides could be effected electrochemically in flow using a strongly reducing catalytic mediator.[5,6] The role of the mediator was shown to be key in ensuring that the generated aryl radical intermediate was formed away from the cathode, in a region where the flux of mediator radical anion $[\mathbf{M}]^{\bullet-}$ leaving the cathode intercepts the flux of substrate coming toward it.[5,6] By analogy, we envisioned an extension of the method to cathodic reductions of benzyl *ortho*-iodoaryl ethers **1** where a radical cyclisation [**5**] → [**7**] might be followed by reduction to [**8**] and a polar fragmentation to biaryl **3** (Scheme 2).[8] Herein, we describe our realisation of that sequence, its scope and limitations (Scheme 1).



Scheme 1 Summary of mediated cathodic reductions of benzyl *o*-iodoaryl ethers.



Scheme 2 Use of phenanthrene as a mediator to control the sequenced addition of two electrons from the cathode to the substrate.[9]

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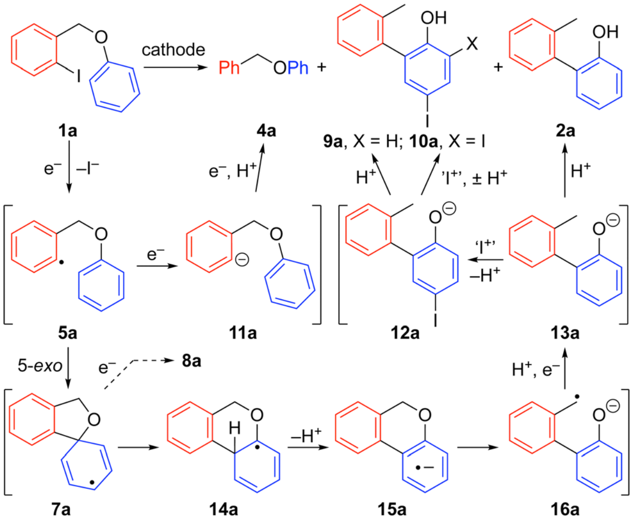
† In memory of Prof. Pierre Duhamel.

‡ Electronic supplementary information (ESI) available: Experimental accounts with spectral details and copies of NMR spectra. CCDC 2359638 and 2363618. See DOI: https://doi.org/10.1039/d4cc06061j

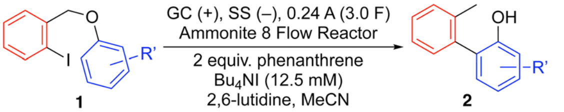


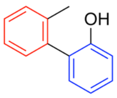
Scheme 3 A mechanistic rational for the formation of the products isolated from the mediated electrochemical reaction of 2-iodobenzyl phenyl ether **1a**.

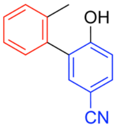
Early studies of the reaction using 2-iodobenzyl phenyl ether **1a** (R = R′ = H) had proved disappointing with a myriad of conditions giving rise to complex product mixtures from which we were unable to isolate the anticipated biaryl **3a** (R = R′ = H). Rather, the products identified were benzyl phenyl ether **4a** and phenols **2a**, **9a** and **10a** (Scheme 3), suggesting that the envisioned electron transfer (ET) **7a** + $[\mathbf{M}]^{\bullet-}$ → **8a** + **[M]** was outpaced by its neophyl rearrangement to the fused ring system **14a.**[10] Subsequent deprotonation to **15a**, fragmentation to **16a** and reduction to **13a** then provides access to phenol **2a** and the iodinated phenols **9a** and **10a.**

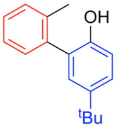
Attempts to improve the yield of phenol **2a** by addition of 2,6-lutidine met with partial success but its chromatographic separation from other by-products proved intractable leading to low isolated yields.[11] Indeed, this problem was encountered in a myriad of analogous reactions of 2-iodobenzyl aryl ethers (*e.g.* **1a-h**), with some allowing isolation of the corresponding phenol (**2a-h**) in low yield (Table 1).

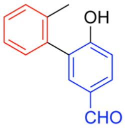
Table 1 Isolated yields of phenols **2a–h** from the phenanthrene mediated electrochemical reactions of 2-iodobenzyl aryl ethers **1a-h**[9]

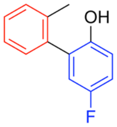


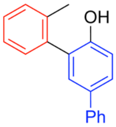

**2a**, 27%

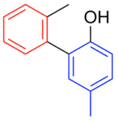

**2b**, 20%


**2c**, 25%


**2d**, 9%


**2e**, 37%


**2f**, 5%


**2g**, 15%

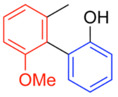
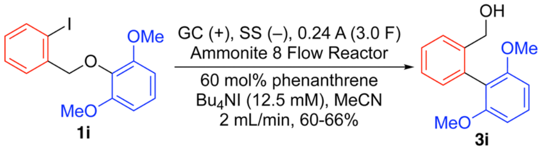
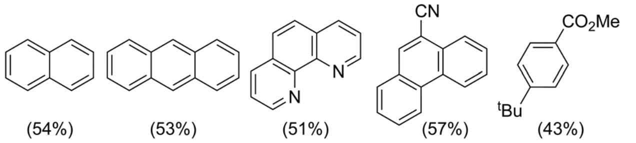

**2h**, 21%

Table 2 Yield of biaryl **3i** given when varying the stated parameter[9]



| Phenanthrene[a] mol% (yield) | $Bu_4NI$[a] equiv. (yield) | charge[a] F (yield) | Flow rate[a] mL $min^{-1}$ (yield) |
|---|---|---|---|
| 0 (22%) | 0.25 (54%) | 2.0 (55%) | 0.5 (45%) |
| 5 (51%) | 1.0 (55%) | 2.5 (56%) | 1.0 (60%) |
| 20 (58%) | 1.5 (56%) | 4.0 (50%) | 1.5 (61%) |
| 100 (57%) | 2.0 (58%) | | 3.0 (63%) |

Alternative mediators @ 60 mol% (yield)[a]



[a] Yields estimated by analysis of $^1H$ NMR spectra of crude reaction mixtures with DMT as an internal standard. Other conditions were as stated in Scheme 1.

At this juncture we decided to apply the reaction to 2-iodobenzyl 2,6-dimethoxyphenyl ether **1i** in the hope that the *ortho*-substituents on the aryl ether would supress neophyl rearrangement (*e.g.* **7** → **14**, Scheme 3) and allow the reaction set out in Scheme 2 to take place. Pleasingly, electrolysis of **1i** under an array of conditions led to the anticipated biaryl **3i** in moderate to good yield and showed that the reaction was resilient to change with respect to various parameters (the mediator, its concentration, charge and flow rate, Table 2). The scope of the reaction for the synthesis of 2,2′,6-trisubstituted biaryls was next demonstrated with successful preparations of 2,6-dialkylbiaryls bearing inductive and mesomeric donor and withdrawing substituents at various centres, **3j-q** (Table 3). Similarly, 2,6-dialkoxybiaryls **3r-u**, terphenyl **3v**, and the related condensed aromatics **3w** and **3x** could be accessed in modest yield using the procedure.

The formation of the highly encumbered biaryl **3x** prompted us to extend the reaction to other 2,2′,6,6′-tetrasubstituted biaryls. Pleasingly, each of the reactions studied performed well, giving the anticipated products **3y-ad** in appreciable yield (Table 4).

Notably, purification of the biaryl products **3** from impurities was seldom problematic as much of the remaining mass balance was comprised of compounds that were readily removed by column chromatography. For the most part, the byproducts given co-eluted with phenanthrene and/or recovered starting material so their purification and isolation was not pursued. $^1H$ NMR analysis of non-polar fractions, in some cases, provided evidence for competing ECE reduction of the starting material, *e.g.* **1p** → **4p**, and reduction of the benzyl alcohol product, *e.g.* **1x** → **3x** → **17** (Fig. 1 and ESI‡). The latter suggests that ethereal bonds in the starting materials **1**, and any ECE products **4**, may also be reduced leading to non-polar and volatile byproducts.

Finally, a surprising observation was made when the 2,6-difluoro-analogue **1ae** was subjected to electrolysis (Scheme 4). In this case the major product, isolated in 33% yield, was

Table 3 Isolated yields of biaryls **3j-x** from the mediated electrochemical radical-to-polar crossover reactions of 2-iodobenzyl aryl ethers **1j-x**[9]

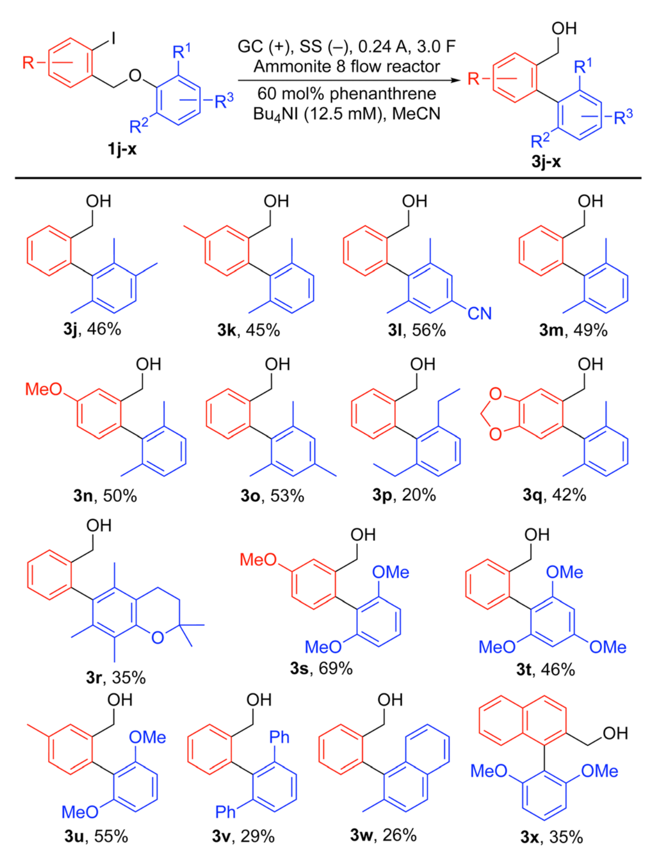
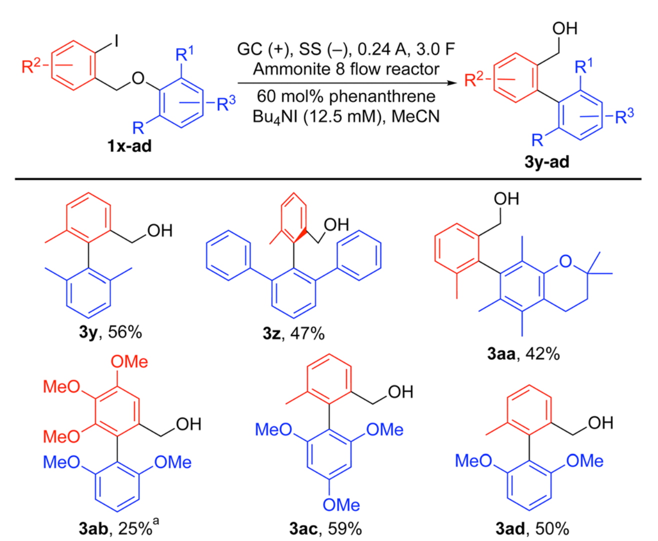


Table 4 2,2′,6,6′-substituted biaryls formed by electrochemical radical-to-polar crossover reactions[9]



[a] From the corresponding bromide.

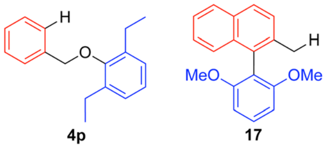
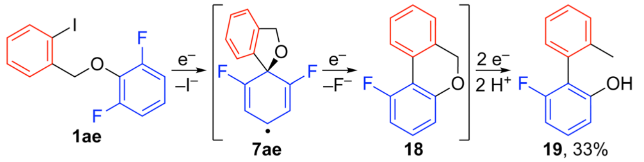


Fig. 1 By-products evidencing ECE reduction, product iodination and product reduction as competing side reactions.



Scheme 4 An unexpected rearrangement leading to 3-fluoro-2-(*o*-tolyl)-phenol **19**.

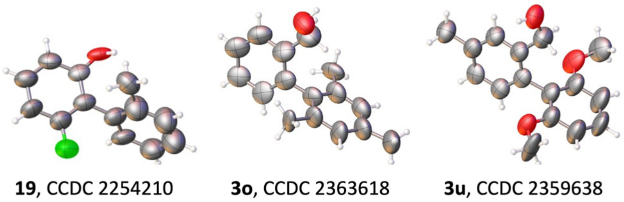


Fig. 2 Representative examples of X-ray analysis undertaken using the crystalline sponge method.[12c]

3-fluoro-2-(*o*-tolyl)-phenol **19**, implicating an unprecedented reductive rearrangement of spirocyclic radical intermediate **7ae** to 6*H*-benzo[*c*]chromene **18**. Although biaryl **19** was formed as an oil, its identity was confirmed by X-ray analysis using the recently introduced crystalline sponge technique,[12] which proved applicable to all of the biaryls surveyed (Fig. 2 and ESI‡).[12c]

In conclusion, mediated electrosynthesis provides a means to control the rate at which sequential electron additions to a substrate occur. By slowing the transfer of a second electron to the substrate, the transient aryl radical has time to react with the proximal arene. From a synthetic perspective, the method provides rapid access to highly substituted biaryls, including 2,2′,6,6′-tetrasubstituted biaryls, in modest yield. Notably, flow electrochemistry is widely seen as an emerging sustainable method and the required aryl *o*-iodobenzyl ethers are easy to prepare at low cost (as detailed in the ESI‡). We are currently looking to develop further reductive electrochemical radical-to-polar crossover, and higher, cascade reaction sequences.

James E. Pearce conducted the bulk of the experimental work with support from Jack Hodgson, Ana Folgueiras-Amador, Johanna Fish and Philip Parsons. Crystalline Sponge X-ray analyses were conducted by Robert Carroll under the supervision of Simon Coles. The corresponding authors conceived of, and supervised, the project as a whole. We gratefully acknowledge financial support from EPSRC [EP/P013341/1, EP/W02098X/1 and EP/K039466/1], Pareon Chemicals Ltd and the European Regional Development Fund [ERDF Interreg Va programme (Project 121)].

## Data availability

Experimental accounts and MP, IR, $^1$H NMR, $^{13}$C NMR, LRMS, HRMS and X-ray data have been included, where applicable, in the ESI‡ for both the products and starting materials detailed herein. These data include copies of the recorded $^1$H and $^{13}$C NMR spectra.

## Conflicts of interest

There are no conflicts of interest to declare.

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