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

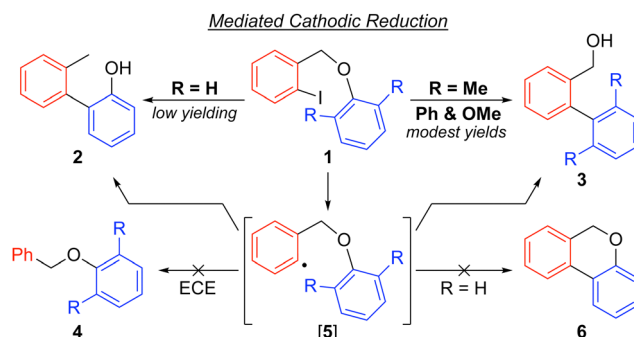
James E. Pearce,<sup>a</sup> Jack Hodgson,<sup>a</sup> Ana A. Folguez-Amador,<sup>a</sup> Johanna A. Fish,<sup>a</sup> Robert C. Carroll,<sup>a</sup> Simon J. Coles,<sup>a</sup> Philip J. Parsons,<sup>b</sup> Richard C. D. Brown<sup>a\*</sup> and David C. Harrowven<sup>a\*</sup>

**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.**

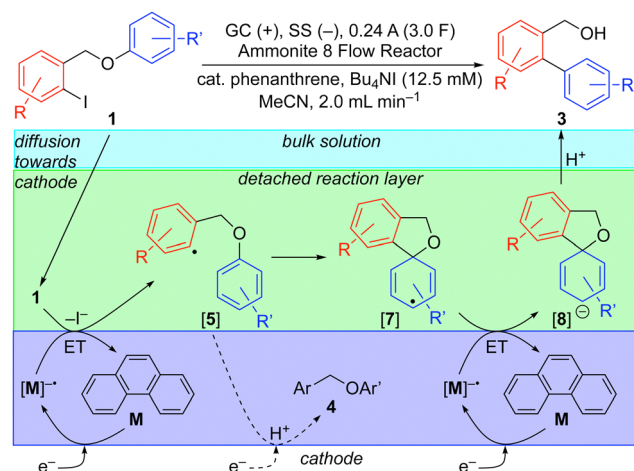
Benzyl *ortho*-iodoaryl ethers are commonly used as precursors to benzo[*c*]chromenes, *e.g.* **1** → **6**, through cyclisations induced by palladium catalysis,<sup>1</sup> or radical formation.<sup>2,3</sup> Of these, the former usually proceed in high yield through *ortho*-cyclisation. In contrast, 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).<sup>2</sup> Cathodic reductions of aryl iodides also proceed *via* the corresponding radical intermediate.<sup>4</sup> 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.<sup>5–7</sup>

We recently showed how reductive radical cyclisation reactions of aryl halides could be effected electrochemically in flow using a strongly reducing catalytic mediator.<sup>5,6</sup> 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 [M]<sup>•–</sup> leaving the cathode intercepts the flux of substrate coming toward it.<sup>5,6</sup> 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).<sup>8</sup> 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.<sup>9</sup>

<sup>a</sup> Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK.  
E-mail: R.C.Brown@soton.ac.uk, dch2@soton.ac.uk

<sup>b</sup> Department of Chemistry, Imperial College London, White City Campus, W12 0BZ, UK

† 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>





**Table 3** Isolated yields of biaryls **3j–x** from the mediated electrochemical radical-to-polar crossover reactions of 2-iodobenzyl aryl ethers **1j–x**<sup>9</sup>

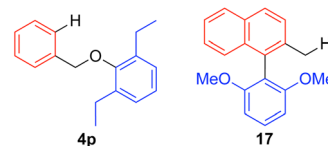
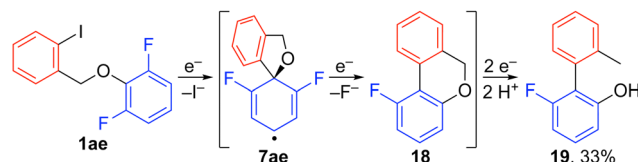
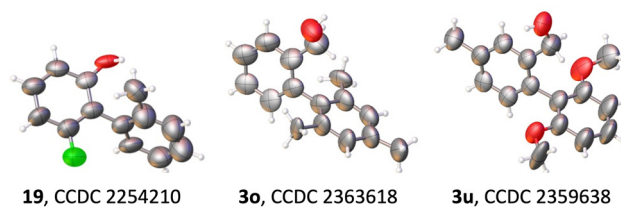


**Table 4** 2,2',6,6'-substituted biaryls formed by electrochemical radical-to-polar crossover reactions<sup>9</sup>



<sup>a</sup> From the corresponding bromide.

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

**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.<sup>12c</sup>

recently introduced crystalline sponge technique,<sup>12</sup> which proved applicable to all of the biaryls surveyed (Fig. 2 and ESI†).<sup>12c</sup>

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 Folguez-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, <sup>1</sup>H NMR, <sup>13</sup>C NMR, LRMS, HRMS and X-ray data have been included, where applicable, in



the ESI<sup>†</sup> for both the products and starting materials detailed herein. These data include copies of the recorded <sup>1</sup>H and <sup>13</sup>C NMR spectra.

## Conflicts of interest

There are no conflicts of interest to declare.

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