ChemComm



COMMUNICATION

View Article Online



Cite this: Chem. Commun., 2025, **61**, 4042

Received 14th November 2024 Accepted 28th January 2025

DOI: 10.1039/d4cc06061j

rsc.li/chemcomm

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

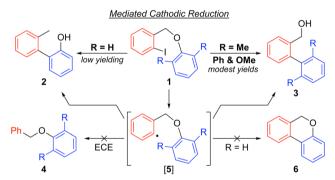
James E. Pearce, Da Jack Hodgson, Da Ana A. Folgueiras-Amador, Da Johanna A. Fish, 📭 Robert C. Carroll, 📭 Simon J. Coles, 📭 Philip J. Parsons, 📭 Richard C. D. Brown ** and David C. Harrowven ** **

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.

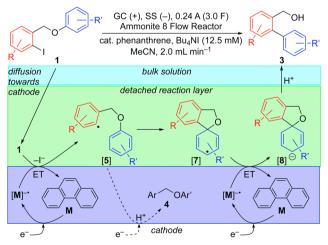
Benzyl ortho-iodoaryl ethers are commonly used as precursors to benzo[c]chromenes, e.g. $1 \rightarrow 6$, through cyclisations induced by palladium catalysis, or radical formation. Of these, the former usually proceed in high yield through ortho-cyclisation. In contrast, reactions via radical intermediates 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] \rightarrow [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

^a Chemistry, University of Southampton, Highfield, Southampton, SO17 1BI, UK. E-mail: R.C.Brown@soton.ac.uk, dch2@soton.ac.uk

^b 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

Communication ChemComm

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) $7a + [M]^{\bullet -} \rightarrow 8a + [M]$ 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-h9

Table 2 Yield of biaryl 3i given when varying the stated parameter⁹

Phenanthrene ^a mol% (yield)	Bu ₄ NI ^a equiv. (yield)	charge ^a F (yield)	Flow rate ^a mL min ⁻¹ (yield)
0 (22%) 5 (51%) 20 (58%) 100 (57%)	0.25 (54%) 1.0 (55%) 1.5 (56%) 2.0 (58%)	2.0 (55%) 2.5 (56%) 4.0 (50%)	0.5 (45%) 1.0 (60%) 1.5 (61%) 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. $7 \rightarrow 14$, 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. $1p \rightarrow$ **4p**, and reduction of the benzyl alcohol product, e.g. $1x \rightarrow 3x \rightarrow$ 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 2,6difluoro-analogue 1ae was subjected to electrolysis (Scheme 4). In this case the major product, isolated in 33% yield, was ChemComm Communication

Table 3 Isolated yields of biaryls 3j-x from the mediated electrochemical radical-to-polar crossover reactions of 2-iodobenzyl aryl ethers 1j-x9

Table 4 2,2',6,6'-substituted biaryls formed by electrochemical radicalto-polar crossover reactions⁹

^a From the corresponding bromide.

3-fluoro-2-(o-tolyl)-phenol 19, implicating an unprecedented reductive rearrangement of spirocyclic radical intermediate 7ae to 6H-benzo[c]chromene 18. Although biaryl 19 was formed as an oil, its identity was confirmed by X-ray analysis using the

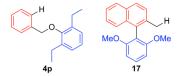
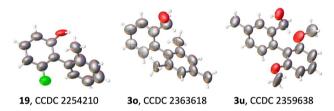


Fig. 1 By-products evidencing ECE reduction, product iodination and product reduction as competing side reactions.

Scheme 4 An unexpected rearrangement leading to 3-fluoro-2-(otolyl)-phenol 19



Representative examples of X-ray analysis undertaken using the crystalline sponge method. 120

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-topolar 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, ¹H NMR, ¹³C 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 ¹H and ¹³C NMR spectra.

Conflicts of interest

Communication

There are no conflicts of interest to declare.

Notes and references

- 1 (a) M. Kitamura, K. Ohmori, T. Kawase and K. Suzuki, Angew. Chem., Int. Ed., 1999, 38, 1229; (b) R. Grigg, V. Savic and V. Tambyrajah, Tetrahedron Lett., 2000, 41, 3003; (c) T. Harayama, H. Yasuda, T. Akiyama, Y. Takeuchi and H. Abe, Chem. Pharm. Bull., 2000, 48, 861; (d) K. Ohmori, M. Tamiya, M. Kitamura, H. Kato, M. Oorui and K. Suzuki, Angew. Chem., Int. Ed., 2005, 44, 3871; (e) D. C. Harrowven, T. Woodcock and P. D. Howes, Angew. Chem., Int. Ed., 2005, 44, 3967; (f) L.-C. Campeau, M. Parisien, A. Jean and K. Fagnou, J. Am. Chem. Soc., 2006, 128, 581; (g) M. Tamiya, K. Ohmori, M. Kitamura, H. Kato, T. Arai, M. Oorui and K. Suzuki, Chem. - Eur. J., 2007, 13, 9791; (h) H. Kelgtermans, L. Dobrzanska, W. Dehaen and L. Van Meervelt, Org. Lett., 2012, 14, 5200; (i) T. Matsukihira, T. Kida, K. Hidaka, S. Saga, M. Takemura, A. Yonoki, T. Nishimori, Y. Horino, T. Harayama, Y. Takeuchi and H. Abe, Heterocycles, 2013, 87, 2555; (j) G. Bringmann, N. Manchala, T. Büttner, B. Hertlein-Amslinger and R. Seupel, Chem. - Eur. J., 2016, 22, 9792; (k) R. Cano, J. M. Pérez, D. J. Ramón and G. P. McGlacken, Tetrahedron, 2016, 72, 1043; (l) Y. Tanji, N. Mitsutake, T. Fujihara and Y. Tsuji, Angew. Chem., Int. Ed., 2018, 57, 10314; (m) Y. An, B.-S. Zhang, Z. Zhang, C. Liu, X. Y. Gou, Y.-N. Ding and Y.-M. Liang, Chem. Commun., 2020, 56, 5933.
- 2 Radical cyclisations of benzyl 2-iodoaryl ethers have been induced with (i) Bu₃SnH: (a) D. C. Harrowven, M. I. T. Nunn, N. A. Newman and D. R. Fenwick, Tetrahedron Lett., 2001, 42, 961; (ii) KOtBu and a nitrogen heterocycle: (b) D. S. Roman, Y. Takahashi and A. B. Charette, Org. Lett., 2011, 13, 3242; (c) S. Zhou, G. M. Anderson, B. Mondal, E. Doni, V. Ironmonger, M. Kranz, T. Tuttle and J. A. Murphy, Chem. Sci., 2014, 5, 476; (d) S. Chen, W. Chen, Y. Chen, Z. Liu, T. Mu, P. Wang and Z. Yan, RSC Adv., 2020, 10, 14500; (e) C.-L. Sun, Y.-F. Gu, W.-P. Huang and Z.-J. Shi, Chem. Commun., 2011, 47, 9813; (f) H. Yang, L. Zhang and L. Jiao, Chem. - Eur. J., 2017, 23, 65; (iii) KOtBu, DMSO and blue light: (g) M. E. Budén, M. D. Heredia, M. Puiatti and R. A. Rossi, Org. Biomol. Chem., 2022, 20, 228; (iv) with boron reagents: (h) S. Pinet, V. Liautard, M. Debiais and M. Pucheault, Synthesis, 2017, 4759; (i) A. B. Waghamare, R. K. Raut, N. Patel and M. Majumdar, Eur. J. Inorg. Chem., 2022, E202200089; (v) by photocatalysis: (j) P. Herr, F. Glaser, L. A. Büldt, C. B. Larsen and O. S. Wenger, J. Am. Chem. Soc., 2019, 141, 14394; (vi) with Me₄NI: (k) K. Nozawa-Kumada, K. Nakamura, S. Kurosu, Y. Iwakawa, C. Denneval, M. Shigeno and Y. Kondo, Chem. Pharm. Bull., 2019, 67, 1042.
- 3 The cyclisation has also been conducted photochemically via triplet aryl cation intermediates, see: W. Sun, L. Wilding-Steele, R. C. D. Brown and D. C. Harrowven, Chem. Commun., 2023, 59, 10797.
- 4 For excellent reviews covering the mechanisms of cathodic reduction of aryl halides see: (a) J.-M. Savéant, Adv. Phys. Org. Chem.,

- ed. D. Bethel, Academic Press, New York, 1990, 26, pp. 1-130; (b) J. Grimshaw, Electrochemical Reactions and Mechanisms in Organic Chemistry, Elsevier Science, 2000, pp. 89-157; (c) X. Zeng, Chem. -Eur. J., 2024, 30, e202402220; (d) K. Grudzień, A. Zlobin, J. Zadworny, K. Rybicka-Jasińska and B. Sadowski, Org. Chem. Front., 2024, 11, 5232. For selected examples of cathodic reductive dehalogenation of arvl halides see: (e) J. R. Cockrell and R. W. Murray, J. Electrochem. Soc., 1972, 119, 849; (f) R. N. Renaud, Can. J. Chem., 1974, 52, 376; (g) J. Grimshaw and J. Trocha-Grimshaw, J. Chem. Soc., Perkin Trans. 2, 1975, 215; (h) C. P. Andrieux, J. Badoz-Lambling, C. Combellas, D. Lacombe, J. M. Savéant, A. Thiebault and D. Zann, J. Am. Chem. Soc., 1987, 109, 1518; (i) K. Mitsudo, T. Okada, S. Shimohara, H. Mandai and S. Suga, *Electrochem.*, 2013, **81**, 362; (*j*) J. Ke, H. Wang, L. Zhou, C. Mou, J. Zhang, L. Pan and Y. R. Chi, *Chem. – Eur. J.*, 2019, 25, 6911; (k) C. B. Liu, S. Y. Han, M. Y. Li, X. D. Chong and B. Zhang, *Angew.* Chem., Int. Ed., 2020, 59, 18527; (l) L. Lu, H. Li, Y. Zheng, F. Bu and A. Lei, CCS Chem., 2021, 3, 2669; (m) A. A. Folgueiras-Amador, A. E. Teuten, D. Pletcher and R. C. D. Brown, React. Chem. Eng., 2020, 5, 712.
- 5 J. W. Hodgson, A. A. Folgueiras-Amador, D. Pletcher, D. C. Harrowven, G. Denuault and R. C. D. Brown, Faraday Discuss., 2023, 247, 302.
- 6 A. A. Folgueiras-Amador, A. E. Teuten, M. Salam-Perez, J. E. Pearce, G. Denuault, D. Pletcher, P. J. Parsons, D. C. Harrowven and R. C. D. Brown, Angew. Chem., Int. Ed., 2022, 61, e202203694.
- 7 (a) G. Sun, S. Ren, X. Zhu, M. Huang and Y. Wan, Org. Lett., 2016, 18, 544; (b) Y. Qu, H. Tateno, Y. Matsumura, T. Kashiwagi and M. Atobe, Molecules, 2017, 22, 413; (c) H. Kim, H. Kim, T. H. Lambert and S. Lin, J. Am. Chem. Soc., 2020, 142, 2087; (d) N. G. W. Cowper, C. P. Chernowsky, O. P. Williams and Z. K. Wickens, J. Am. Chem. Soc., 2020, 142, 2093; (e) S. Caby, L. M. Bouchet, J. E. Argüello, R. A. Rossi and J. I. Bardagi, ChemCatChem, 2021, 13, 3001; (f) Y.-J. Chen, T. Lei, H.-L. Hu, H.-L. Wu, S. Zhou, X.-B. Li, B. Chen, C.-H. Tung and L.-Z. Wu, Matter, 2021, 4, 2354; (g) R. Gottlieb and J. L. Neumeyer, J. Am. Chem. Soc., 1976, 98, 7108; (h) J. Grimshaw, R. J. Haslett and J. Trocha-Grimshaw, J. Chem. Soc. Perkin Trans. 1, 1977, 2448; (i) S. Donnelly, J. Grimshaw and J. Trocha-Grimshaw, J. Chem. Soc., Chem. Commun., 1994, 2171; (j) S. Donnelly, J. Grimshaw and J. Trocha-Grimshaw, Electrochim. Acta, 1996, 41, 489.
- 8 (a) F. Xie, F. Han, Q. Su, Y. Peng, L. Jing and P. Han, Org. Lett., 2024, 26, 4427; (b) Y. Wang, Q. Wang, Z. Zhu, W. Qi and Y. Qiu, Sci. Chin. Chem., 2024, 67, 3825.
- 9 Charge density in a single pass flow cell varies along the channel, with a higher value at the start of the channel to a lower value at the end. The working electrode area of the Ammonite 8 flow cell is 20 cm².
- 10 (a) W. H. Urry and M. S. Kharasch, J. Am. Chem. Soc., 1944, 66, 1438. For a review of neophyl and related radical induced aryl migrations see: (b) A. Studer and M. Bossart, Tetrahedron, 2001, 57, 9649.
- 11 (a) K. Midorikawa, S. Suga and J.-I. Yoshida, Chem. Commun., 2006, 3794; (b) K. Kataoka, Y. Hagiwara, K. Midorikawa, S. Suga and J.-I. Yoshida, Org. Process Res. Dev., 2008, 12, 1130.
- 12 The crystal sponge method was first described by (a) Y. Inokuma, S. Yoshioka, J. Ariyoshi, T. Arai, Y. Hitora, K. Takada, S. Matsunaga, K. Rissanen and M. Fujita, Nature, 2013, 495, 461. For a recent review see: (b) N. Zigon, V. Duplan, N. Wada and M. Fujita, Angew. Chem., Int. Ed., 2021, 60, 25204. For details pertaining to examples given in the ESI‡ see: (c) R. C. Carroll, D. C. Harrowven, J. E. Pearce and S. J. Coles, IUCrJ, 2023, 10, 497.