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Electrophotocatalytic C–H Heterofunctionalization of Arenes

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Abstract: The electrophotocatalytic heterofunctionalization of arenes is described. Using 2,3-dichloro-5,6-dicyanoquinone (DDQ) under a mild electrochemical potential with visible-light irradiation, arenes undergo oxidant-free hydroxylation, alkoxylation, and amination with high chemoselectivity. In addition to batch reactions, an electrophotocatalytic recirculating flow process is demonstrated, enabling the conversion of benzene to phenol on a gram scale.

Direct C-H functionalization provides a time-, effort-, and resource-economical approach to synthesize substituted arenes from simple precursors.^[1] While transition metal catalyzed strategies have arguably been the most well-studied approach to accomplish such transformations,^[2,3] reactions initiated by single-electron oxidation of the arene have also been explored. The oxygenation of arenes by direct electrolysis has long been known (e.g. Figure 1A), although these approaches tend to suffer from low yield, selectivity, and scope.^[4] More recently, visible-light photocatalysis has enabled a number of powerful methods for arene functionalization that do not require the use of metals or metal-directing groups.^[5] Because these photoredox reactions are typically initiated by single-electron oxidation of the arene ring, they tend to be performed with relatively electron-rich substrates due to their lower oxidation potentials. In contrast, it has proven more challenging to achieve such reactions with weakly electron-deficient or electron-neutral arenes, for example those bearing halogen atoms or benzene (1) itself, because of their relatively high oxidation potentials. A notable exception was reported by Fukuzumi, who described the visible-light-induced hydroxylation of benzene (1) using DDO (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (4), which has a sufficiently high excited state redox potential to achieve the single-electron oxidation of benzene (Figure 1 B).^[6,7] Despite the groundbreaking nature of this discovery, this process was limited to the small-scale hydroxylation of benzene with a relatively high catalyst loading (30-100 mol%). Subsequently, König showed that DDQ photocatalysis could achieve the direct amination of arenes using nucleophiles such as carbamates and ureas, greatly expanding the utility of this chemistry (Figure 1C).^[8] However, the relatively high catalyst loading and the use of tert-butyl nitrite and air, which forms a potentially explosive mixture, were not

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ideal. We hypothesized that adaptation to an electrophotocatalytic strategy might address some of the issues noted above and thus enable a range of useful arene C-H functionalizations.

We recently demonstrated the use of DDQ as an electro-photocatalyst $^{\left[9-11\right]}$ for $S_{N}Ar$ reactions with non-traditional

10 mA cm⁻² Pt-Pt undivided cell

A. Tajima–2009





Figure 1. A) Example of oxygenation of benzene by direct electrolysis. B) DDQ photocatalyzed hydroxylation of benzene. C) DDQ photocatalyzed amination of benzene. D) Electrophotocatalytic arene heterofunctionalization. E) Mechanistic rationale.

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substrates under mild conditions.^[10b] Given that success, and the Fukuzumi and König precedents, we speculated that this electrophotocatalytic approach might be adapted to realize an efficient arene heterofunctionalization strategy (Figure 1D). We anticipated that the process would operate by a mechanism akin to the previous reports, wherein photoexcited DDQ effects single electron transfer (SET) oxidization of an arene 1 to furnish a radical cation 7 that can undergo nucleophilic capture. The key difference is that DDO (4) would be regenerated by anodic oxidation of the reduced $DDQH_2$ (6), with concomitant cathodic reduction of protons to form hydrogen gas completing the electrochemical reaction. Thus, this electrophotocatalytic setup obviates the need for a traditional oxidant like TBN. In this Communication, we demonstrate the electrophotocatalytic heterofunctionalization of arenes, including hydroxylation, alkoxylation, and amination reactions, both in batch and in a recirculating flow process.

We first examined the electrophotocatalytic coupling of benzene (1) and water to form phenol (11) (Table 1). Our initial condition choice was based on our previous study^[10b] and entailed subjecting benzene, 20 equivalents of water, and 10 mol% DDQ (4) to a 1.5 V controlled potential in an undivided cell (carbon cathode, Pt anode) under visible light irradiation (blue LED strip) in the presence of TBABF₄ and acetic acid. Under these conditions, phenol (11) was generated in 43% yield (entry 1). Changing the electrolyte to LiClO₄ resulted in an appreciably higher yield (55%, entry 2), while lower catalyst loading resulted in diminished yield (36% yield, entry 3). The catalyst, potential, and light were necessary for this reaction (entries 4-6) which confirmed the process was actually electrophotocatalytic. The product yield was significantly diminished without the addition of acetic acid (entry 7). With further screening, we found that a higher yield (80%) could be realized by using more equivalents of water (50 equiv) and a longer reaction time of 48 h (entry 8). Importantly, when we attempted the same reaction by direct electrolysis without catalyst and light using up to 3.0 V

Table 1: Optimization studies

1	+	$H_2O \qquad \frac{10 \text{ mol% E}}{\text{Blue L}} \\ \text{E}_{cell} = 1 \\ C (+) P \\ \text{AcOH, elec} \\ \text{CH}_3O \\ \text{CH}$	DDQ (4) ED .5 V et (-) etrolyte	ОН 11	+	H ₂
Entry	Time [h]	Electrolyte (equiv)	Other		Yield [%	6] ^[a,b]

		•• • • •	•	
1	28	$TBABF_4$ (1)	_	43
2	28	LiClO₄ (6)	-	55
3	28	LiClO₄ (6)	5% DDQ	36
4	28	LiClO ₄ (6)	no catalyst	0
5	28	LiClO₄ (6)	no light	0
6	28	LiClO₄ (6)	no electrolysis	< 5
7	28	LiClO ₄ (6)	no acid	8
8	48	LiClO ₄ (6)	50 equiv H ₂ O	80
9	48	LiClO₄ (6)	direct electrolysis ^[a]	0
10	96	LiClO ₄ (6)	4 mmol scale	66 (52) ^[c]

[a] See Supporting Information for detailed procedures. [b] Yields were determined by UPLC. [c] Isolated yields.

constant voltage, no phenol was observed (entry 9). Using the optimized conditions but longer reaction time (96 h), the reaction could be scaled up (entry 10).

Using the optimized conditions, the generality of the hydroxylation reaction was explored (Table 2). Bromoarene products 12 and 13 were obtained in 55% and 50% yields with 10:1 to 4:1 regioselectivity, respectively (entries 1 and 2). Meanwhile, both 1,3- and 1,2-dichlorobenzene underwent hydroxylation with complete regioselectivity (entries 3 and 4). Benzophenone and 3-methylacetophenone also reacted, furnishing phenol 16 in 46% yield and 17 in 52% yield, respectively (entries 5 and 6). Despite the fact that these electron-deficient arenes were reactive to the hydroxylation procedure, substrates with two electronically differentiated arenes were exclusively functionalized on the more electronrich ring (entries 7-10). Although these are obviously strongly oxidizing conditions, potentially sensitive functionality in the form of Boc-protected peptides (entries 11 and 12) or free hydroxyl groups (entry 13) were tolerated, allowing for the production of phenols 22-24.

Table 2: Electrophotocatalytic hydroxylation of arenes with water.



[a] See Supporting Information for detailed procedures. [b] Isolated vields.

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To further demonstrate the selectivity of this protocol, we subjected a mixture of anisole (25), benzene (1), and trifluorotoluene (26) to the electrophotocatalytic hydroxylation procedure [Eq. (1)]. In this case, phenol (11) was generated exclusively while the other two arenes were left untouched by these conditions. Intermediate 4^* is insufficiently oxidizing to remove an electron from arenes with very high oxidation potentials, while alkoxybenzenes or phenols also do not undergo reaction, likely due to a rapid back-electron transfer process that outcompetes nucleophilic attack to the transient radical cation intermediate.^[6]



In addition to the use of water to generate phenols, we found that other nucleophiles could also be utilized (Table 3). For example, the reaction of benzene with various alcohols led to the formation of aryl ether products 25, 27-30 (entries 1-5). Methoxylation to generate 31 was readily achieved (entry 6), and the deuterated analogue 32 could also be accessed (entry 7). Alternatively, benzoic acid (entry 8) or N-Boc alanine (entry 9) furnished aryl esters 33 and 34. In terms of nitrogen nucleophiles, benzamide (entry 10), ethyl carbamate (entry 11), urea (entry 12), and acetamide (entry 13) reacted with benzene in varying yields. Amines were not productive (e.g. entry 14), likely due to the acidic conditions. On the other hand, diphenylsulfonimide readily participated (entry 15). Using ethylcarbamate, a variety of halogenated arenes could be derivatized (entries 16-19). Meanwhile, tert-butylcarbamate was also productive to furnish adduct 46 in 62% yield (entry 20).

To enable further scale up of this process, we adapted this method to a continuous flow system.^[12] Although continuous flow has proven to be highly advantageous for photoredox catalysis, it has only just recently been adapted for electrophotocatalysis.^[9j,k,m] Because in the current reactions the photochemical portion of the process is much slower than the electrochemical one, we were able to couple a small electrochemical cell with one or more photochemical chambers using an inexpensive peristaltic pump. Using the hydroxylation of benzene as a representative reaction, we employed a flow setup (Figure 2) with a residence time of 3 min and a 1.5 V controlled potential undivided cell, with which phenol (11) was formed in 65% yield on a 0.4 mmol scale in 18 h (Figure 2B). For a larger scale (4 mmol), a longer reaction time was needed; however, by equipping two photoreactor channels the reaction time could be reduced with minimal impact on yield (Figure 2C). Equipping three flow channels further decreased the reaction time to 22 h and improved the yield (Figure 2D). Notably, using the three channel set-up, a 15 mmol scale reaction delivered a 56% yield of phenol (11) in 60 h.





[a] See Supporting Information for detailed procedures. [b] Isolated yields. [c] Yields were determined by UPLC. [d] Without AcOH.

In conclusion, we have developed an electrophotocatalytic procedure for the C-H hydroxylation, alkoxylation, and amination of arenes with high chemoselectivity.^[13] Using DDQ as an electrophotocatalyst, water, alcohols, acids, amides or carbamates can be appended to arenes

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Figure 2. A) Electrophotocatalytic hydroxylation of benzene in flow using B) one, C) two, or D) three photoreactor channels.

without the use of external oxidants. This work thus adds a new set of tools to the arsenal of direct C-H functionalization protocols.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkoxylation · amination · electrophotocatalysis · hydroxylation · photochemistry

- a) J.-Q. Yu, Z. Shi, *C-H Activation*, Springer, Berlin, Heidelberg, 2010; b) H. M. L. Davies, D. Morton, *J. Org. Chem.* 2016, *81*, 343–350.
- [2] a) J. Hartwig, Organotransition Metal Chemistry: From Bonding to Catalysis, University Science Books, Sausalito, CA, 2010; For selected recent reviews: b) P. Gandeepan, L. Ackermann, Chem 2018, 4, 199–222; c) S. Rej, Y. Ano, N. Chatani, Chem. Rev. 2020, 120, 1788–1887.
- [3] Examples of direct arene heterofunctionalization: a) S.-i. Niwa, M. Eswaramoorthy, J. Nair, A. Raj, N. Itoh, H. Shoji, T. Namba, F. Mizukami, *Science* 2002, 295, 105–107; b) Y. Morimoto, S. Bunno, N. Fujieda, H. Sugimoto, S. Itoh, *J. Am. Chem. Soc.* 2015, 137, 5867–5870; c) J. W. Han, J. Jung, Y.-M. Lee, W. Nam, S. Fukuzumi, *Chem. Sci.* 2017, 8, 7119–7125; d) For a review on catalytic phenol production: R. J. Schmidt, *Appl. Catal. A* 2005, 280, 89–103.
- [4] For selected examples of electrochemical arene heterofunctionalization: a) T. Tajima, Y. Kishi, A. Nakajima, *Electrochim. Acta* 2009, 54, 5959-5963; b) L. Eberson, E. Oberrauch, *Acta Chem. Scand. B* 1981, 35, 193-196; c) Y.-H. So, J. Y. Becker, L. L. Miller, J. Chem. Soc. Chem. Commun. 1975, 262-263; d) L. Eberson, K. Nyberg, J. Am. Chem. Soc. 1966, 88, 1686-1691.

[5] For selected reviews: a) S. Fukuzumi, K. Ohkubo, Org. Biomol. Chem. 2014, 12, 6059-6071; b) N. A. Romero, D. A. Nicewicz, Chem. Rev. 2016, 116, 10075-10166; c) S. Crespi, M. Fagnoni, Chem. Rev. 2020, 120, 9790-9833; For selected examples: d) D. P. Hari, P. Schroll, B. König, J. Am. Chem. Soc. 2012, 134, 2958-2961; e) J. W. Beatty, J. J. Douglas, K. P. Cole, C. R. J. Stephenson, Nat. Commun. 2015, 6, 7919-7925; f) N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, Science 2015, 349, 1326-1330; g) K. A. Margrey, J. B. McManus, S. Bonazzi, F. Zecri, D. A. Nicewicz, J. Am. Chem. Soc. 2017, 139, 11288-11299.

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- [6] a) K. Ohkubo, A. Fujimoto, S. Fukuzumi, J. Am. Chem. Soc.
 2013, 135, 5368-5371; b) K. Ohkubo, K. Hirose, S. Fukuzumi, Chem. Eur. J. 2015, 21, 2855-2861.
- [7] A related photocatalytic arene hydroxylation/ amination reaction that requires UV light has also been reported. Y.-W. Zheng, B. Chen, P. Ye, K. Feng, W. Wang, Q.-Y. Meng, L.-Z. Wu, C.-H. Tung, J. Am. Chem. Soc. 2016, 138, 10080-10083.
- [8] a) S. Das, P. Natarajan, B. König, *Chem. Eur. J.* 2017, 23, 18161–18165; For a recent review, see: b) P. Natarajan, B. König, *Eur. J. Org. Chem.* 2021, https://doi.org/10.1002/ejoc.202100011.
- [9] For examples of electrophotocatalysis or photoelectrocatalysis, see: a) J.-C. Moutet, G. Reverdy, J. Chem. Soc. Chem. Commun. 1982, 654-655; b) R. Scheffold, R. Orlinski, J. Am. Chem. Soc. 1983, 105, 7200-7202; c) H. Tateno, S. Iguchi, Y. Miseki, K. Sayama, Angew. Chem. Int. Ed. 2018, 57, 11238-11241; Angew. Chem. 2018, 130, 11408-11411; d) H. Yan, Z.-W. Hou, H.-C. Xu, Angew. Chem. Int. Ed. 2019, 58, 4592-4595; Angew. Chem. 2019, 131, 4640-4643; e) F. Wang, S. S. Stahl, Angew. Chem. Int. Ed. 2019, 58, 6385-6390; Angew. Chem. 2019, 131, 6451-6456; f) L. Zhang, L. Liardet, J. Luo, D. Ren, M. Grätzel, X. Hu, Nat. Catal. 2019, 2, 366-373; g) W. Zhang, K. Carpenter, S. Lin, Angew. Chem. Int. Ed. 2020, 59, 409-417; Angew. Chem. 2020, 132, 417-425; h) N. G. W. Cowper, C. P. Chernowsky, O. P. Williams, Z. K. Wickens, J. Am. Chem. Soc. 2020, 142, 2093-2099; i) X. Lai, X. Shu, J. Song, H.-C. Xu, Angew. Chem. Int. Ed. 2020, 59, 10626-10632; Angew. Chem. 2020, 132, 10713-10719; j) Y. Qiu, A. Scheremetjew, L. H. Finger, L. Ackermann, Chem. Eur. J. 2020, 26, 3241-3246; k) P. Xu, P. Chen, H.-C. Xu, Angew. Chem. Int. Ed. 2020, 59, 14275-14280; Angew. Chem. 2020, 132, 14381-14386; l) L. Niu, C. Jiang, Y. Liang, D. Liu, F. Bu, R. Shi, H. Chen, A. D. Chowdhury, A. Lei, J. Am. Chem. Soc. 2020, 142, 17693-17702; m) H. Yan, J. Song, S. Zhu, H.-C. Xu, CCS Chem. 2021, 3, 317–325; n) S. Wu, J. Žurauskas, M. Domanski, P. S. Hitzfield, V. Butera, D.J. Scott, J. Rehbein, A. Kumar, E. Thyrhaug, J. Hauer, J. P. Barham, Org. Chem. Front. 2021, 8, 1132 - 1142.
- [10] For examples of electrophotocatalysis from our group, see: a) H. Huang, Z. M. Strater, M. Rauch, J. Shee, T. J. Sisto, C. Nuckolls, T. H. Lambert, Angew. Chem. Int. Ed. 2019, 58, 13318–13322; Angew. Chem. 2019, 131, 13452–13456; b) H. Huang, T. H. Lambert, Angew. Chem. Int. Ed. 2020, 59, 658–662; Angew. Chem. 2020, 132, 668–672; c) H. Huang, Z. M. Strater, T. H. Lambert, J. Am. Chem. Soc. 2020, 142, 1698–1703; d) H. Kim, H. Kim, T. H. Lambert, S. Lin, J. Am. Chem. Soc. 2020, 142, 2087–2092; e) T. Shen, T. H. Lambert, Science 2021, 371, 620–626.
- [11] For selected reviews and highlights, see: a) L. Capaldo, L. L. Quadri, D. Ravelli, Angew. Chem. Int. Ed. 2019, 58, 17508–17510; Angew. Chem. 2019, 131, 17670–17672; b) J. P. Barham, B. König, Angew. Chem. Int. Ed. 2020, 59, 11732–11747; Angew. Chem. 2020, 132, 11828–11844; c) J. Liu, L. Lu, D. Wood, S. Lin, ACS Cent. Sci. 2020, 6, 1317–1340; d) Y. Yu, P. Guo, J.-S. Zhong, Y. Yuan, K.-Y. Ye, Org. Chem. Front. 2020, 7, 131–135; e) T. H. Meyer, I. Choi, C. Tian, L. Ackermann, Chem 2020, 6, 2484–2496.

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- [12] a) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* 2016, *116*, 10276–10341; b) M. Elsherbini, T. Wirth, *Acc. Chem. Res.* 2019, *52*, 3287–3296.
- [13] During the review of this manuscript, a preprint describing a closely related method appeared: Z.-W. Hou, H. Yan, J. Song, H.-C. Xu, 2021, DOI 10.26434/chemrxiv.13718392.v1.

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