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.

Graphical Abstract
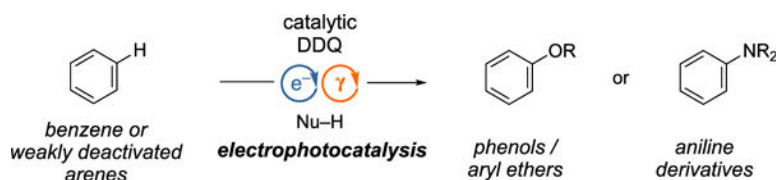
The electrophotocatalytic C-H heterofunctionalization of arenes with high chemoselectivity at both batch and flow conditions is demonstrated.

Keywords

Electrophotocatalysis; electrochemistry; photochemistry; hydroxylation; alkoxylation; amination

Direct C–H functionalization provides a time-, effort-, and resource-economical approach to synthesize substituted arenes from simple precursors (Figure 1A).[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

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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 DDQ (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 1B).[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 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 electrophotocatalyst[9–11] for S_NAr reactions with non-traditional 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 DDQ (**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 $TBABF_4$ and acetic acid. Under these conditions, phenol (**11**) was generated in 43% yield (entry 1). Changing the electrolyte to $LiClO_4$ 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 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 1–2). 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 electron-rich ring (entries 7–10). Although these conditions 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**.

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 (equation 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]
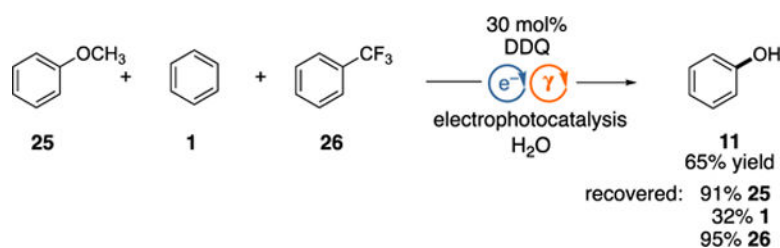
$$\tag{1}$$

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 set-up (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.

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

Supplementary Material

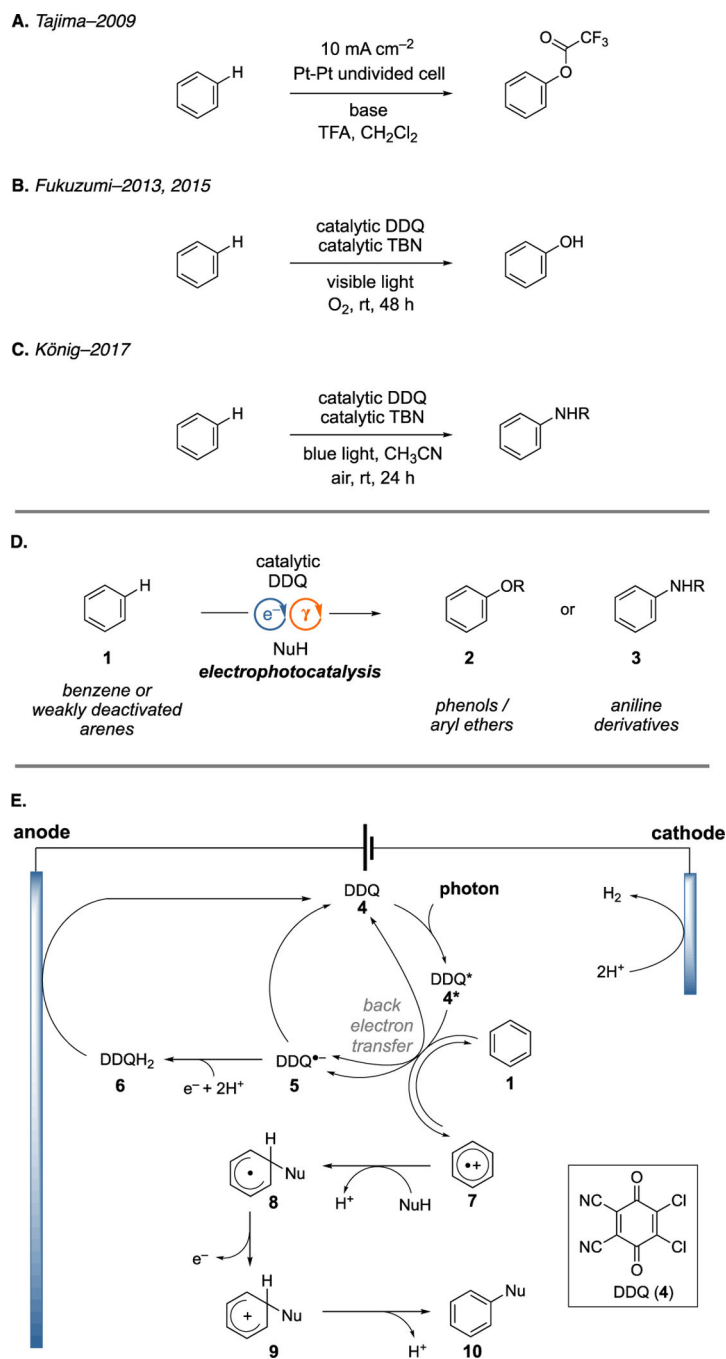Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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A. *Tajima–2009*

10 mA cm^{-2}
Pt-Pt undivided cell

base
TFA, CH$_2$Cl$_2$

B. *Fukuzumi–2013, 2015*

catalytic DDQ
catalytic TBN

visible light
O$_2$, rt, 48 h

C. *König–2017*

catalytic DDQ
catalytic TBN

blue light, CH$_3$CN
air, rt, 24 h

D.

catalytic
DDQ

NuH
electrophotocatalysis

1
*benzene or
weakly deactivated
arenes*

or

2
*phenols /
aryl ethers*

3
*aniline
derivatives*

E.

anode   cathode

DDQ **4**   **photon**   H$_2$

DDQ* **4***

*back
electron
transfer*

DDQH$_2$ **6**   e$^-$ + 2H$^+$ DDQ$^{\bullet-}$ **5**   **1**

2H$^+$

H
| Nu
8   H$^+$ NuH   **7**

e$^-$

H
| Nu
9   H$^+$ **10**

DDQ (**4**)

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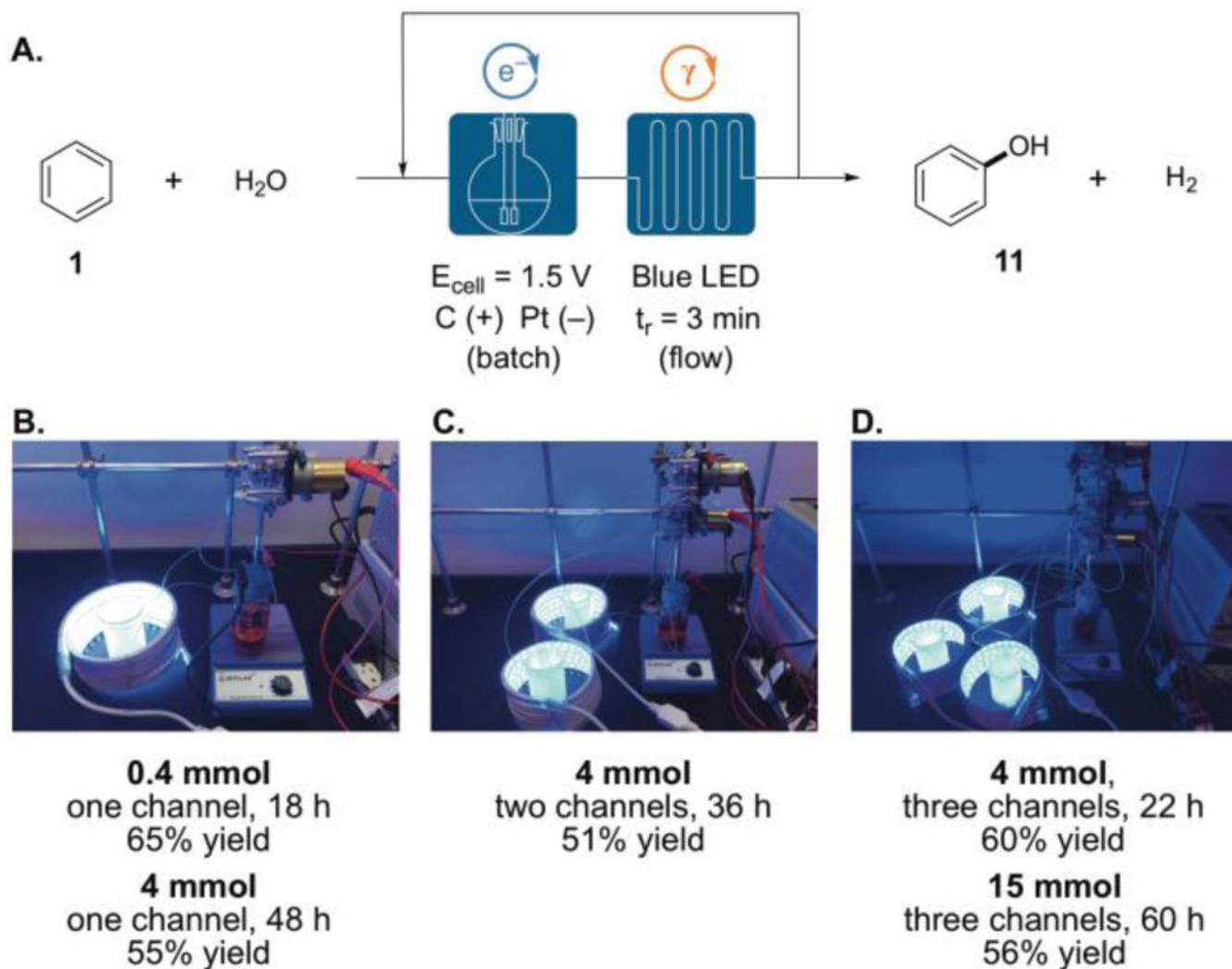
Figure 2.
(A) Electrophotocatalytic hydroxylation of benzene in flow using (B) one, (C) two, or (D)
three photo reactor channels.

Table 1.

Optimization studies.

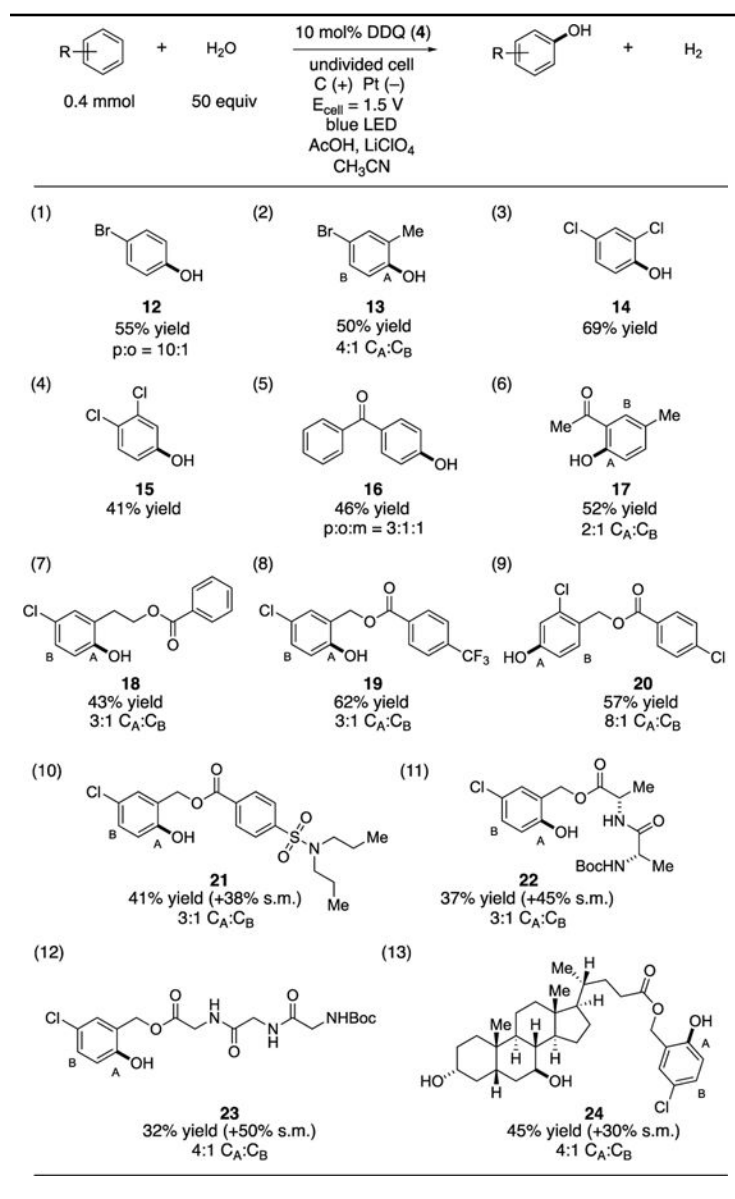| Entry	Time (h)	Electrolyte (equiv)	Other	Yield (%)[a,b]
1	28	TBABF$_4$ (1)	–	43
2	28	LiClO$_4$ (6)	–	55
3	28	LiClO$_4$ (6)	5% DDQ	36
4	28	LiClO$_4$ (6)	no catalyst	0
5	28	LiClO$_4$ (6)	no light	0
6	28	LiClO$_4$ (6)	no electrolysis	<5
7	28	LiClO$_4$ (6)	no acid	8
8	48	LiClO$_4$ (6)	50 equiv. H$_2$O	80
9	48	LiClO$_4$ (6)	direct electrolysis[a]	0
10	96	LiClO$_4$ (6)	4 mmol scale	66 (52)[c]

[a]See SI for detailed procedures.

[b]Yields were determined by UPLC.
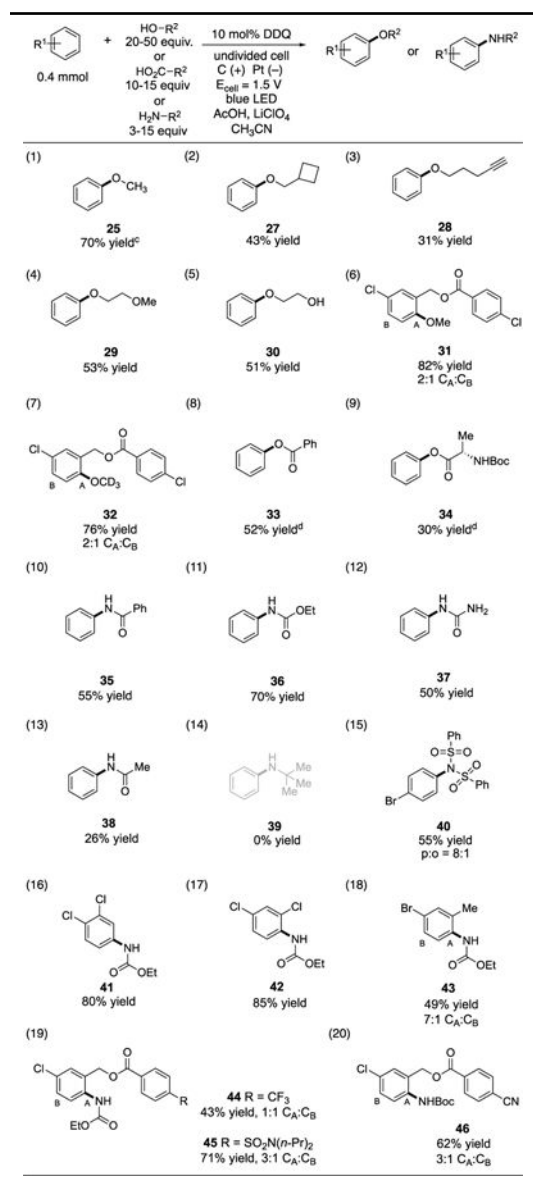
[c]Isolated yields.

Table 2.

Electrophotocatalytic hydroxylation of arenes with water.

(1)

12
55% yield
p:o = 10:1

(2)

13
50% yield
4:1 C_A:C_B

(3)

14
69% yield

(4)

15
41% yield

(5)

16
46% yield
p:o:m = 3:1:1

(6)

17
52% yield
2:1 C_A:C_B

(7)

18
43% yield
3:1 C_A:C_B

(8)

19
62% yield
3:1 C_A:C_B

(9)

20
57% yield
8:1 C_A:C_B

(10)

21
41% yield (+38% s.m.)
3:1 C_A:C_B

(11)

22
37% yield (+45% s.m.)
3:1 C_A:C_B

(12)

23
32% yield (+50% s.m.)
4:1 C_A:C_B

(13)

24
45% yield (+30% s.m.)
4:1 C_A:C_B

[a]See SI for detailed procedures.

[b]Isolated yields.

Table 3.

Electrophotocatalytic heterofunctionalization of arenes.[a,b]