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Electrochemical 1,2-hydrogen atom transfer functionalizations of *N*-(benzyloxy)phthalimides†

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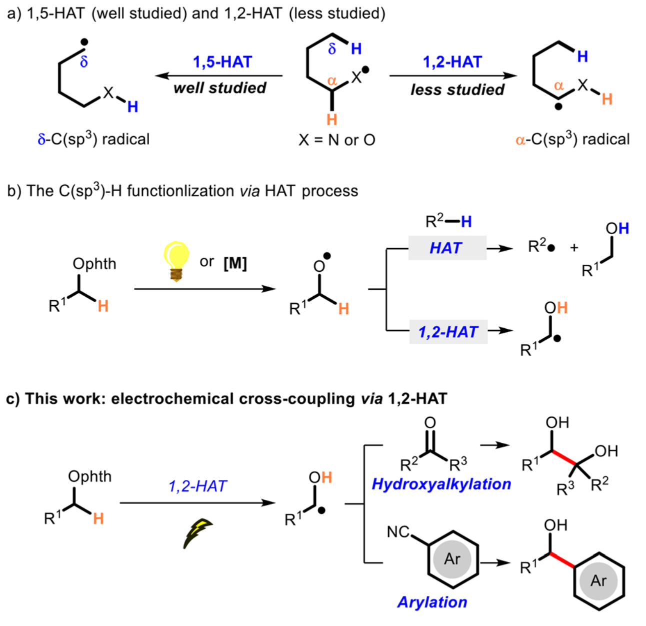
We report a straightforward, catalyst-free method for the cathodic benzylic C–H hydroxyalkylation/arylation of *N*-(alkyloxy)phthalimides with ketones or cyanopyridines. The reaction is driven by an electrochemically induced 1,2-hydrogen atom transfer involving alkoxy radicals generated by O–N bond cleavage. This protocol provides an efficient approach for the synthesis of a wide range of valuable unsymmetrical 1,2-diols and diarylmethanols.

Hydrogen atom transfer (HAT) has emerged as a practical and powerful strategy for the C(sp^3)–H radical functionalization, which has been widely applied in synthetic organic chemistry.[1] Among the various HAT reactions, heteroatom-centered radicals, such as $O^•$, $N^•$, are recognized for their versatility as intermediates in HAT, facilitating the generation of C(sp^3) radicals through intermolecular or intramolecular 1,2- or 1,5-HAT reactions (Scheme 1a).[2,3] For instance, intramolecular 1,5-HAT can effectively produce δ-C(sp^3) radicals through the preferred six-membered ring transition-state,[4] which has been employed in a variety of functionalizations, including heteroarylation,[5] alkylation,[6] and allylation.[7] In contrast, the intramolecular 1,2-HAT reaction is less reported, with only a few examples observed to form C(sp^3)–C bonds. This is partly due to the higher activation energy required for the 1,2-HAT processes.[8] To the best of our knowledge, the initiation of 1,2-HAT processes has been achieved using transition-metal catalysts, including Ir, Ag, Cu, and Ni catalysts,[9] or through photocatalytic reactions (Scheme 1b).[10] Despite these advances, the development of a mild and sustainable approach to initiate 1,2-HAT processes, especially for the formation of α-C(sp^3)–C bonds adjacent to heteroatoms in organic chemistry, is still a worthwhile avenue for investigation.

Organic electrochemistry has been regarded as a sustainable and safe redox reagent that can generate radical species, thereby obviating the need for stoichiometric amounts of oxidants and reductants.[11] Recently, a number of chemists have employed an electrochemically driven HAT strategy to achieve the functionalization of C(sp^3)–H bonds.[12] For example, several kinds of different HAT reagents, such as *N*-hydroxyphthalimide (NHPI) derivatives,[13] quinuclidine,[14] sulfonamide,[15] benzimidazole,[16] and azide,[17] have been reported to promote the intermolecular HAT reactions through anodic oxidation. In addition, several studies have revealed the 1,5-HAT reaction of heteroatom-centered radicals under anodic oxidation.[18] A notable recent example is the electrochemical allylation/alkylation of ethers *via* intermolecular HAT of alkoxy radicals under cathodic reduction, as described by the Bertuzzi and Bandini group.[19] However, the 1,2-HAT reaction of oxygen-centered radicals remains less investigated.[20] Therefore, the exploration of electrochemical functionalization of oxygen-



Scheme 1 The functionalization of C(sp^3)–H *via* HAT process.

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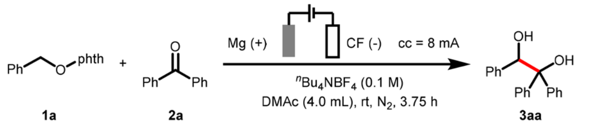
centered α-C(sp^3)–H bonds through the 1,2-HAT would significantly broaden the synthetic applications of alkoxy radicals in organic electrochemistry. Herein, we present a simple and metal-free cathodic benzylic C–H hydroxyalkylation/arylation of *N*-(alkyloxy)-phthalimides through 1,2-HAT of alkoxy radicals (Scheme 1c). This electrochemically driven HAT strategy offers mild reaction conditions and a wide substrate scope, resulting in the synthesis of diverse 1,2-diols and diarylmethanols.

We initially explored the reaction parameters using benzylic alcohol-derived *N*-alkoxyphthalimide **1a** and benzophenone **2a** as the model substrates (Table 1). Gratifyingly, the reaction yielded the desired 1,2-diol product **3aa** in 78% when conducted in DMAc at a constant current of 8 mA, employing TBAB as the electrolyte in an undivided cell with a magnesium anode and a carbon felt cathode (entry 1). Increasing or decreasing the constant current was found to be less effective and gave slightly lower yields of desired product **3aa** (entry 2). Reducing the reaction time to 3 hours did not improve the yield of product **3aa**, whereas extending it to 5 hours led to a 57% yield (entry 3). Other sacrificial anodes, including Zn, Al and stainless steel, proved less effective than the Mg anode (entry 4). When $^n\mathrm{Bu_4NI}$, $^n\mathrm{Bu_4NBr}$ or $^n\mathrm{Bu_4NCl}$ were used as electrolytes, significant decreased yields of the desired product **3aa** were obtained (entry 5). Increasing the amount of **1a** to 3.0 equivalents did not improve the yield (entry 6). Notably, no product **3aa** was observed under air conditions, indicating the reaction was air-sensitive (entry 7). Finally, a control experiment confirmed that electricity was essential for the synthesis of 1,2-diols (entry 8).

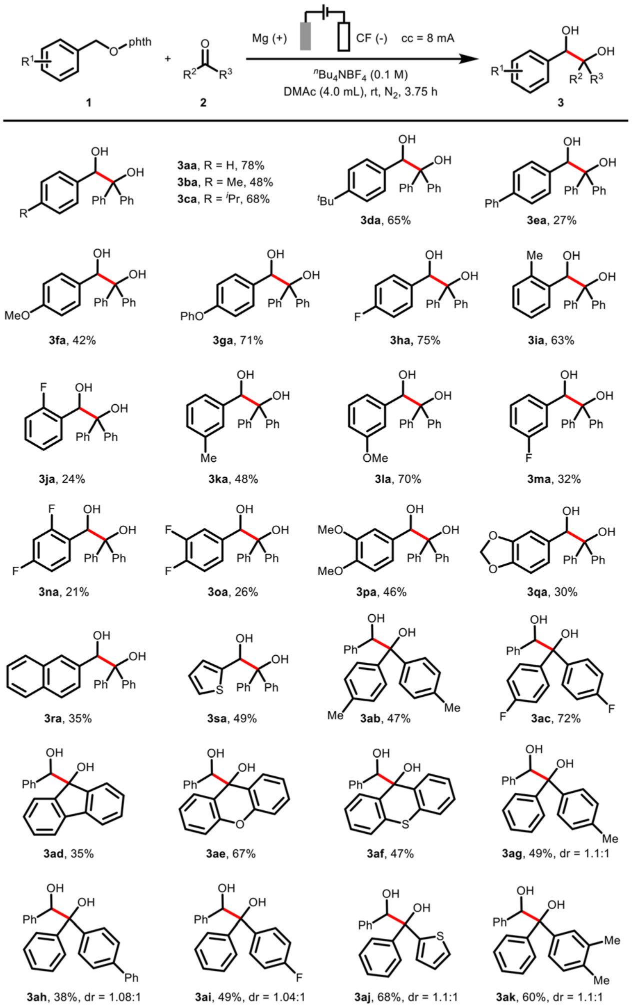
With the optimal reaction conditions in hand, we probed the substrate scope of *N*-(benzyloxy)phthalimides **1** and ketones **2** (Scheme 2). Using benzophenone **2a** as a coupling partner, a series of *para*-substituted *N*-(benzyloxy)phthalimides (such as methyl, i-propyl, *t*-butyl, phenyl, methoxy, phenoxy, and fluoro substitutions) underwent the electrochemical cross-coupling reaction smoothly, and the desired products **3ba–3ha** were isolated in 27–75% yields. The *ortho*-substituted methyl and fluoro *N*-(benzyloxy)phthalimides were also compatible and gave the desired products **3ia** and **3ja** in 63% and 24% yields, respectively. Moreover, *meta*-substituted *N*-(benzyloxy) phthalimides were efficiently converted to the corresponding 1,2-diols **3ka–3ma**, with yields ranging from 32–70% for substrates containing methyl, methoxy, and fluorine groups. Additionally, *N*-(benzyloxy)phthalimides bearing multiple substituents could also give the desired products **3na–3pa** in 21–46% yields. Notably, the substrate derived from pepper alcohol smoothly participated in the reaction, affording the corresponding product **3qa** in 30% yield. 2-Naphthalene- and thiophen-substituted substrates were also tested and gave the

Table 1 Optimization of reaction conditions[a]



Entry	Variation from standard conditions	Yield of **3aa** (%)
1	None	78[b]
2	6 mA or 10 mA instead of 8 mA	66/62
3	3 h or 5 h instead of 3.75 h	52/57
4[c]	Zn, Al or SS instead of Mg anode	29/0/0
5	$^n\mathrm{Bu_4NI}$, $^n\mathrm{Bu_4NBr}$, $^n\mathrm{Bu_4NCl}$ instead of $^n\mathrm{Bu_4NBF_4}$	47/30/37
6	3.0 equivalents of **1a**	68
7	Air instead of N_2	Trace
8	No electricity	0

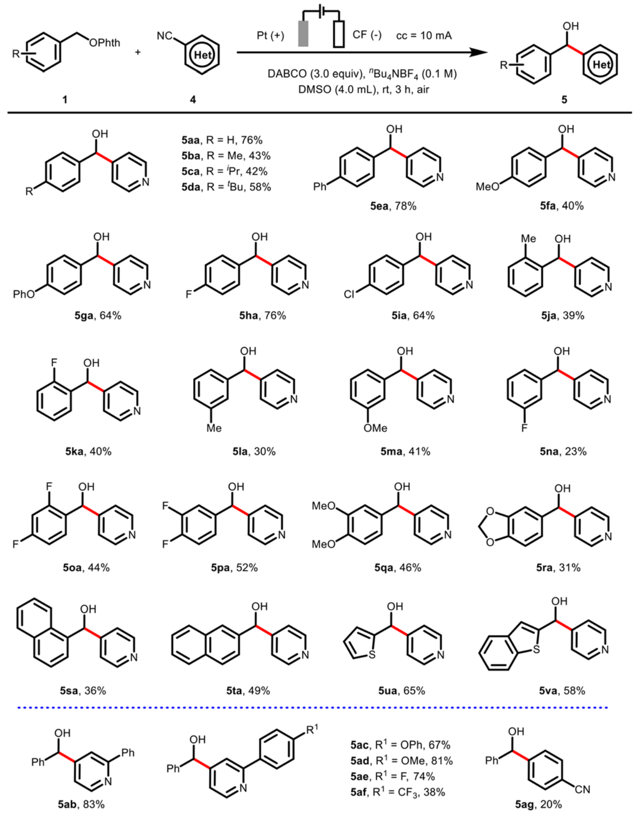
[a] Standard conditions: undivided cell, magnesium (Mg) anode, carbon felt (CF) cathode, constant current = 8 mA, **1a** (2 equiv.), **2a** (0.2 mmol), $^n\mathrm{Bu_4NBF_4}$ (2 equiv.), DMAc (4 mL), N_2, r.t., 3.75 h. Yield was determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [b] Isolated yield. [c] Reactions were performed at 10 mA.



Scheme 2 Scope of the electrochemical 1,2-HAT of *N*-(benzyloxy) phthalimides with ketones. Reaction conditions: undivided cell, magnesium (Mg) anode, carbon felt (CF) cathode, constant current = 8 mA, **1** (2 equiv.), **2** (0.2 mmol), $^n\mathrm{Bu_4NBF_4}$ (2 equiv.), DMAc (4 mL), N_2, r.t., 3.75 h.

corresponding coupling products **3ra** (35%) and **3sa** (49%). Subsequently, we turned our attention to the scope of diarylketone derivatives. Symmetrical diarylketone derivatives, including 4,4′-dimethylbenzophenone, 4,4′-difluorobenzophenone, 9-fluorenone, xanthone, and thioxanthen-9-one, successfully coupled with *N*-(benzyloxy)phthalimide to result the corresponding 1,2-diols **3ab–3af** in 35–72% yields. Furthermore, unsymmetrical diarylketones were employed to form 1,2-diols **3ag–3ak** in 38–68% yields and nearly 1 : 1 diastereoselectivity.

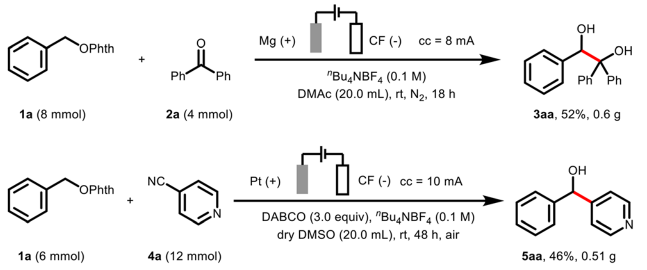
To further demonstrate the diversity of this electrochemical method, we evaluated the feasibility of cyanopyridines as coupling partners in the electrochemical 1,2-HAT coupling, aiming to synthesize heteroaryl-containing diarylmethanols. We were pleased to find that this method could effectively yield a range of heteroaryl-containing diarylmethanols (Scheme 3). For example, the reaction of *N*-(benzyloxy)phthalimide (**1a**) and 4-cyanopyridine (**4a**) with DABCO as the sacrificial reagent led to the desired diarylmethanol product **5aa** in 76% yield. In addition to the simple *N*-(benzyloxy)phthalimide, this process was applicable to a variety of *N*-(benzyloxy)phthalimides bearing electron-rich and electron-poor substituents, affording the desired products **5ba–5ia** in 40–78% yields. Both *meta*- and *ortho*-substituted *N*-(benzyloxy)phthalimides were well-tolerated, and gave products **5ja–5na** in 23–41% yields. The application of multi-substituted substrates resulted in the corresponding alcohol products **5oa–5ra** in 44–52% yields. Furthermore, the use of naphthalene- or heterocyclic-substituted *N*-(benzyloxy)phthalimides as coupling partners delivered products **5sa–5va** in 36–65% yields. On the other hand, a series of cyanopyridines smoothly underwent the electroreductive arylation, providing the desired products **5ab–5af** in 38–83% yields. Additionally, 1,4-dicyanobenzene could also take part in this reaction to form the product **5ag**, albeit in a lower yield of 20%.



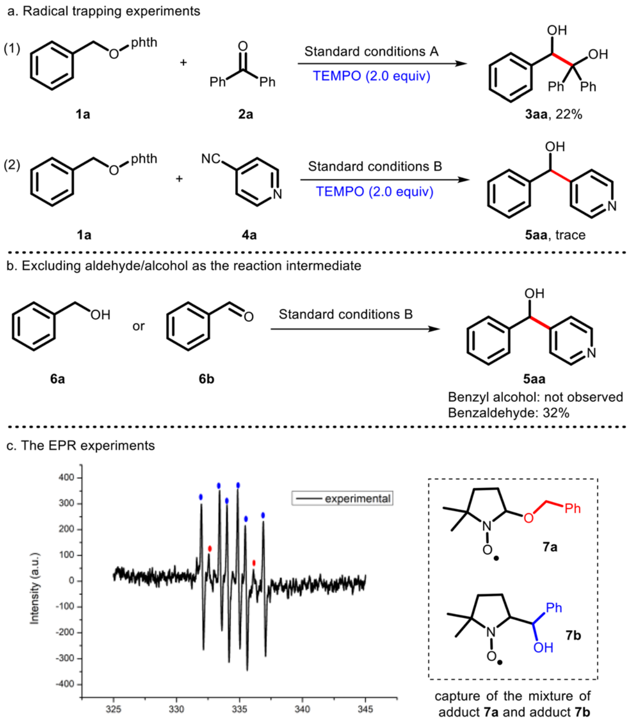
Scheme 3 Scope of the electrochemical 1,2-HAT of *N*-(benzyloxy) phthalimides with cyanopyridines. Reaction conditions: undivided cell, platinum plate (Pt) anode, carbon felt (CF) cathode, constant current = 10 mA, **1** (0.2 mmol), **4** (2 equiv.), DABCO (3 equiv.), ^{n}Bu$_4$NBF$_4$ (2 equiv.), DMSO (4 mL), air, r.t., 3 h.

Next, we evaluated the scalability of the electroreductive cross-coupling strategy by conducting the reaction on a 5 mmol scale, employing **1a** and **2a**, or **4a** as substrates. The corresponding products **3a** and **5a**, were successfully obtained with yields of 52% and 46%, respectively (Scheme 4). These results highlight the practicality and efficacy of this method for the synthesis of 1,2-diols and diarylmethanols under electrochemical conditions.

To understand this reaction, a series of mechanistic experiments were investigated (Scheme 5). The addition of a free radical inhibitor (TEMPO) to the standard reaction led to significant decreased or no yields of the desired product (Scheme 5a). These results indicated that the electrochemical hydroxyalkylation and arylation processes proceed *via* a radical pathway. In addition, the application of benzyl alcohol **6a** instead of *N*-alkoxyphthalimide **1a** led to no arylation product **5aa**, suggesting the alcohol is not related in this transformation. Meanwhile, the reaction of benzaldehyde **6b** and cyanopyridine **4a** resulted in a 32% yield of dialymathanol **5aa**, suggesting a similar reaction pathway through a ketyl radical intermediate (Scheme 5b).[21] Moreover, the EPR analysis of **1a** with DMPO under electroreduction conditions indicated the production of a DMPO-captured alkoxy radical **7a** and ketyl radical **7b** (Scheme 5c).[10d] The use of the *N*-alkoxylpyridinium salt derivative also afforded the α-C–H arylation adductin 38% yield (see ESI, Scheme S1†).[5c,d,22] Furthermore, the kinetic isotope effect (KIE) experiments of hydroxyalkylation and arylation were observed with **1a** and **D-1a**, in which the k_H/k_D ratios were 0.76 and 1.14, respectively (see ESI, Fig. S7 and S8†). These results confirm the intermidiacy of radicals species and intramolecular 1,2-HAT process in this transformation.

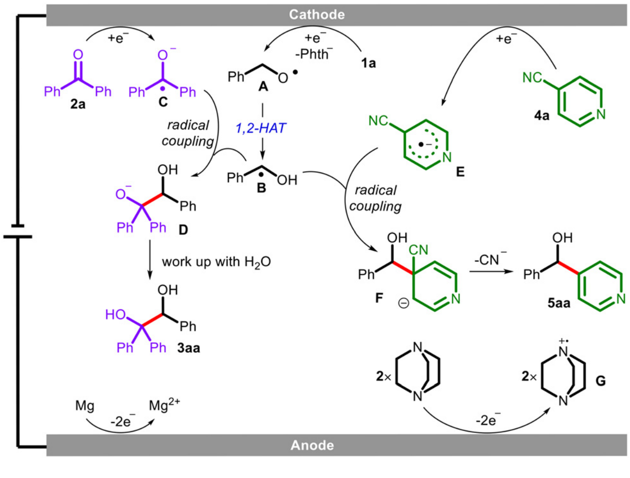


Scheme 4 Scale-up experiments.



Scheme 5 Mechanistic experiments.

Based on these mechanistic studies and previous reports,[10b–e,23] we propose a possible mechanism for this electrochemcial α-C(sp^3)–H hydroxyalkylation/arylation of *N*-(alkyloxy)phthalimides (Scheme 6). The cathodic reduction of *N*-(benzyloxy)phthalimide **1a** results in the formation of the phthalimide anion and a key benzyloxy radical **A.** This radical subsequently undergoes 1,2-HAT to generate the ketyl radical **B.** In the hydroxyalkylation process, the benzophenone **2a** gains a single electron to form radical anion **C** at the cathode. Subsequently, intermediate **B** and **C** undergo radical–radical cross-coupling to produce anion intermediate **D**, followed by protonation to form the final product 1,2-diol **3aa.** Meanwhile, Mg is oxidized to Mg^{2+} at the anode. In the arylation process, the 4-cyanopyridine **4a** is reduced *via* a single-electron transfer (SET) process to generate a radical anion **E** on the cathode. This intermediate **E** couples with the above intermediate **B** to produce anion intermediate **F** and then loss of CN^- to obtain the desired diarylmethanol **5aa.** In this transformation, DABCO works as a sacrificing agent at the anode.



Scheme 6 Proposed mechanism.

Conclusions

In conclusion, we have described a straightforward and efficient electrochemical approach for the cathodic benzylic C–H hydroxyalkylation and arylation of *N*-(alkyloxy)phthalimides, mediated by the 1,2-HAT of alkoxy radicals. This method provides access to a range of valuable 1,2-diols and diarylmethanols in moderate to good yields under mild and straightforward electrolysis conditions. We anticipate that this versatile and efficient electrochemical strategy will broaden the synthetic applications of alkoxy radicals in organic chemistry.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare no competing financial interest.

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