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Electrochemical C(sp³)-H functionalization of ethers *via* hydrogen-atom transfer by means of cathodic reduction†

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The chemo- and stereoselective electrochemical allylation/alkylation of ethers is presented *via* a C(sp³)-H activation event. The electrochemical protocol enables the realization of a large library of functionalized ethers (35 examples) in high yields (up to 84%) *via* cathodic activation of a new type of redox-active carbonate (RAC), capable of triggering HAT (Hydrogen-Atom-Transfer) events through the generation of electrophilic oxy radicals. The process displayed high functional group tolerance and mild reaction conditions. A mechanistic elucidation *via* voltammetric analysis completes the study.

The chemical manipulation of unreactive C(sp³)-H bonds is among the most rapid synthetic tools to achieve key building blocks from the chemical feedstock. It also represents an extraordinary synthetic challenge, given the inertness of the C-H bonds towards selective functionalizations.¹ In this landscape, the “radical approach”, based on Hydrogen-Atom-Transfer (HAT) methodologies, is currently paralleling the well consolidated transition metal catalyzed “two-electron manifold” strategies.² As a matter of fact, HAT can effectively combine pivotal aspects such as selectivity, simplicity, and sustainability in site-selective C(sp³)-H functionalizations.³

In very recent times, the organic synthetic community has faced the (re)emerging of organic electrochemistry (*i.e.* eChem) for the generation and functionalization of radical species.⁴ However, despite its undoubted advantages in terms of rapid and productive chemical diversification, eChem has been rarely adopted in HAT-based C(sp³)-H functionalizations. As a matter of fact, the field is dominated by halogenation, oxygenation and azidation reactions *via* anodic Shono oxidation of (mostly)

amines (Fig. 1, top a).⁵ On the contrary, direct intermolecular HAT processes, for the production of key reactive intermediates and subsequent nucleophilic,⁶ or, more rarely, electrophilic⁷ trapping have been scarcely documented (Fig. 1, top b). In addition, the few reported strategies proceed through anodic oxidation for the formation of the hydrogen-atom abstractor.

The development of complementary electrochemical functionalization of unactivated C-H bonds, triggered by cathodic reduction, would expand significantly the portfolio of chemical diversity accessible through eChem.⁸ The challenge in this strategy lies in the intrinsic difficulty towards the generation

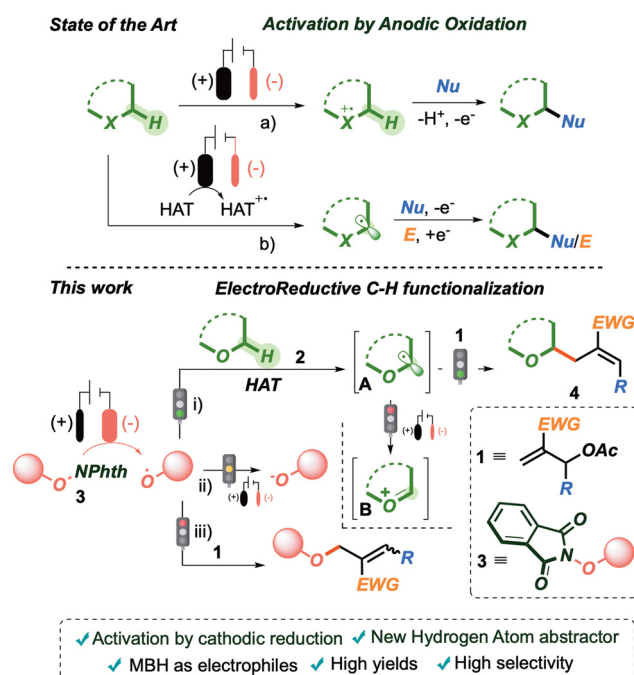


Fig. 1 State of the art in the eChem promoted C-H activation procedures (*i.e.* direct and indirect anodic oxidation (top)). The present electroreductive methodology (bottom).

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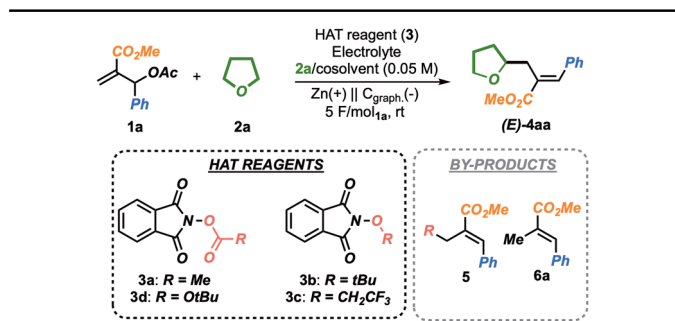


and productive employment of oxidant species as hydrogen atom abstractors in a strongly reductive environment.

Inspired by our recent results on selective radical-based transformations⁹ and discoveries on the suitability of Morita-Baylis-Hillman (MBH) acetates **1** as electrophilic radical acceptors in eChem allylation strategies,¹⁰ we introduce an unprecedented electrochemical allylation/alkylation of simple and abundant ether feedstocks **2**, proceeding under cathodic reduction. The strategy relies on a HAT manifold and leads to the discovery of a novel precursor of hydridic hydrogen atom abstractors, prone to HAT events on simple ethers (α -oxy radical **A**) and capable of overriding further reduction and direct addition to electrophilic MBH **1** (Fig. 1 bottom i vs. ii and iii).¹¹ Importantly, the application of a sacrificial anode strategy would effectively suppress the oxidation of **A** to the corresponding oxonium cations **B**.

To primarily test the feasibility of our hypothesis, we selected *N*-acetoxy-phthalimide **3a** as the model HAT reagent.¹² Encouragingly, when **3a** was subjected to a constant current electrolysis (4 mA, TEABF₄ as electrolyte, *C*_{graph.} cathode and Zn anode, 2.5 F mol_{3a}⁻¹), in the presence of **1a** and a 2a/DMF (1:2) solvent mixture, the desired product **4aa** was isolated in 18% yield as a single *E* isomer (Table 1, entry 1). However, **4aa** was obtained in combination with **5aa**, arising from the direct addition of the methyl radical (from **3a**) onto **1a** (35% yield), along with **6a** (21% yield), as the result of an undesired reduction of **1a**.

Table 1 Optimization of the reaction conditions^a



Entry	2a:cosolvent	3: electrolyte	Electrolysis	Yield ^b [%]
1	1:2 (DMF)	3a: TEABF ₄	CCE (<i>I</i> = 4 mA)	18 (35/21)
2	1:2 (DMF)	3b: TEABF ₄	CCE (<i>I</i> = 4 mA)	— (—/17)
3	1:2 (DMF)	3c: TEABF ₄	CCE (<i>I</i> = 4 mA)	— (—/13)
4	1:2 (DMF)	3d: TEABF ₄	CCE (<i>I</i> = 4 mA)	34 (—/12)
5	1:2 (DMF)	—: TEABF ₄	CCE (<i>I</i> = 4 mA)	— (—/13)
6	5:1 (DMF)	3d: TBAPF ₆	CCE (<i>I</i> = 4 mA)	46 (—/11)
7	5:1 (DMF)	3d: LiBF ₄	CCE (<i>I</i> = 4 mA)	50 (—/8)
8	5:1 (ACN)	3d: LiBF ₄	CCE (<i>I</i> = 4 mA)	53 (—/—)
9	5:1 (ACN)	3d: LiBF ₄	CCE (<i>I</i> = 2 mA)	63 (—/—)
10	5:1 (ACN)	3d: LiBF ₄	CVE (<i>V</i> = 5 V)	75 (—/—)
11	5:1 (ACN)	3d: LiBF ₄	CVE (<i>V</i> = 3 V)	30 (—/—)
12	5:1 (ACN)	3d: LiBF ₄	CVE (<i>V</i> = 7 V)	63 (—/—)

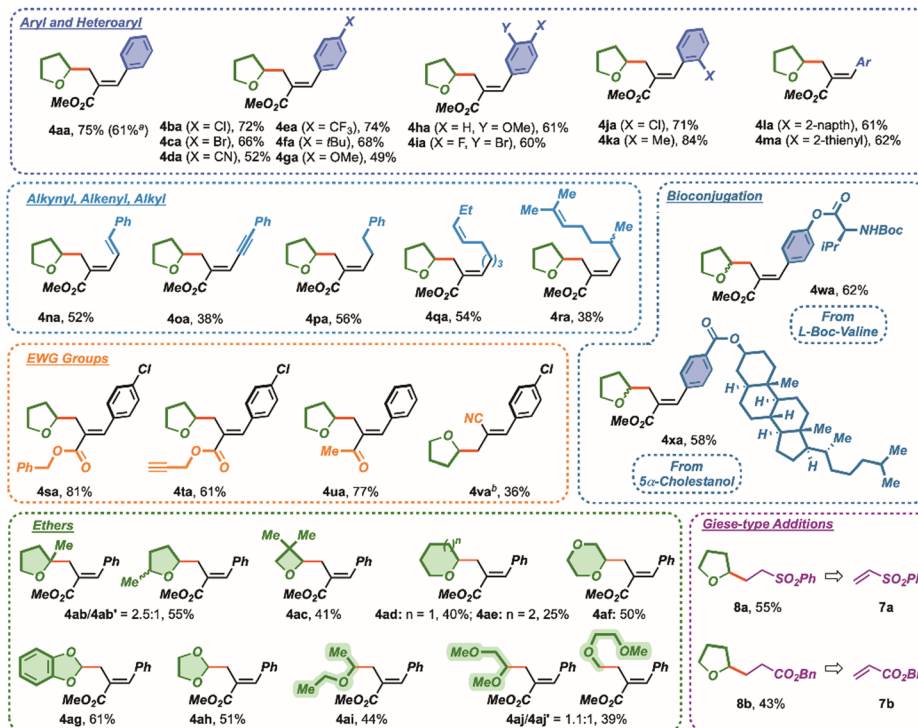
^a All reactions were carried in the ElectroSyn 2.0 apparatus (undivided cell, see ESI for details). ^b Isolated yields after flash chromatography. In brackets yields of **5** and **6a**, respectively (¹H NMR by internal standard). *E/Z* ratios were determined via ¹H-NMR spectroscopy on the reaction crude mixtures (>25:1). CCE: constant current electrolysis; CVE: constant voltage electrolysis.

To validate the hypothesis that an electrophilic radical precursor could improve the reaction outcomes, *N*-*tert*-butoxyphthalimide **3b** (entry 2) and *N*-trifluoroethoxyphthalimide **3c** (entry 3) were tested under the conditions described in entry 1. Disappointingly, no product was formed in both cases. We thus speculated that, moving from ether- to more reactive carbonate-derivatives could facilitate the reduction- β -scission of the phthalimide adduct. Accordingly, we synthesized carbonate **3d**, for which we propose the acronym RAC, standing for Redox-Active-Carbonate.¹³ Delightfully, the employment of this RAC in the eChem protocol led to the isolation of **4aa** in 34% yield (entry 4) along with minor quantities of **6a** (12%), as an indication that the cathodic events involved mainly **3d**. As expected, the use of electrophilic alkoxy radicals completely suppressed the formation of **5ad**. Interestingly, RAC **3d** represents a valuable complement to peroxide-based reagents, intrinsically more difficult to reduce (see Fig. S2, ESI[†]), providing new opportunities within the electrochemical HAT scenario.

Importantly, a blank experiment in the absence of **3d** was shown not to produce **4aa**, even in trace amounts (entry 5). Then, higher amounts of THF in the solvent mixture (entry 6) increased the yield (46% yield), by likely facilitating the capture of the electrophilic radical generated by **3d**. For solubility reasons, electrolytes such as TBAPF₆ (entry 6) or LiBF₄ (entry 7) were preferred, with the latter being optimal. Interestingly, a co-solvent switch from DMF to ACN was found to suppress the formation of **6a** (entry 8). Finally, if lowering the operating current from 4 mA to 2 mA was already found beneficial (63% yield, entry 9),¹⁴ a switch to constant voltage electrolysis (CVE, 5 V) allowed us to reach the optimal 75% yield in **4aa** (entry 10, Conditions A). Further tuning of the reaction voltage was found to be detrimental (entries 11 and 12).

The generality of the methodology was first evaluated by subjecting a series of MBH derivatives (**1b–v**) to the optimal allylation of THF by means of the eChem HAT protocol (Scheme 1). Within the series of aromatic/heteroaromatic acetates (**1a–m**), we were pleased to record good to excellent yields (up to 84%) obtained on the corresponding cinnamates **4** regardless of both electronic properties and position of substituents such as halogens, trifluoromethyl-, cyano-, alkyl- and methoxy-groups. Subjection of **1n** and **1o** to the same protocol resulted in products **4na** (52% yield) and **4oa** (38% yield), featuring a conjugated diene or ene-yne moiety, respectively. In addition, aliphatic MBH acetates **1p**, **1q** and citronellal-derived **1r** were also productively engaged in the disclosed process (38–56% yield). Variation of the electron-withdrawing group to introduce radical-sensitive moieties such as benzylic (**1s**) and propargylic esters (**1t**) or to produce α,β -unsaturated ketones (**4ua**) and nitriles (**4va**) were adequately tolerated (36–81% yield). Importantly, the synthetic relevance of the methodology was verified on late-stage functionalization of derivatized naturally occurring scaffolds, such as *L*-valine derivative **1w** and 5 α -cholestanol derivative **1x**. A survey of ethers **2** in the allylation reaction was then undertaken. This stage posed a significant challenge, since, for each entry, the polarity and the conductivity of the reaction mixture changed markedly. Unfortunately, Conditions A proved too sensitive to the reaction





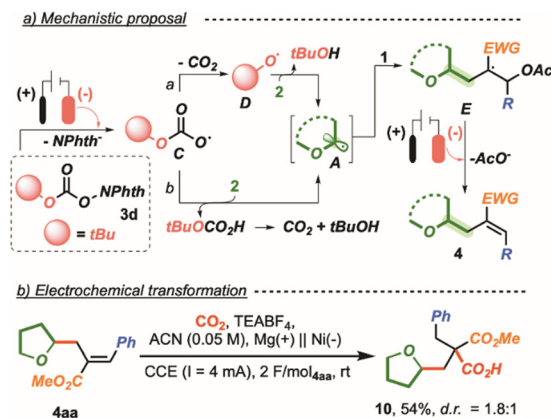
Scheme 1 Scope of the protocol for MBH acetates (**1**, Conditions **A**; Table 1, entry 10) and ethers (**2**, Conditions **B**; Table 1, entry 6). *E/Z* ratios were determined via ¹H-NMR spectroscopy on the reaction crude mixtures and were found to be $\geq 13:1$ (see ESI† for details). ^a Reaction performed on 1.0 mmol scale of **1a** (see ESI† for details). ^b The Z isomer was isolated as the major product (*E/Z* = 1:5). In some cases, variable amounts of starting MBH adducts were recovered untouched.

medium to be employed. A small re-optimization led us to identify another set of parameters (*i.e.* CCE electrolysis, Table 1, entry 6, Conditions **B**).

Therefore, a series of **9** different ethers (**2b–j**) was productively functionalized with acetate **1a** (Conditions **B**). When 2-MeTHF **2b** was engaged in the process, isomers **4ab** and **4ab'** were isolated (55% combined yield, 2.5:1 ratio). Dioxane **2f**, 1,3-benzodioxole **2g** and 1,3-dioxolane **2h** underwent the desired transformation smoothly (50–61% yield). Importantly, in the case of the more reactive **2g** and **2h**, the amount of ether could be decreased to as low as 20 equiv. Finally, acyclic ethers such as Et₂O (**2i**) and 1,2-dimethoxyethane (**2j**) could also be engaged in the present process, although with moderate yields (44% and 39%, respectively).

Interestingly, the protocol was effectively extended also to electron-poor olefins **7a** and **7b** (Giese-type addition, Conditions **B**) that provided the desired products **8a** and **8b** in up to 55% yield.¹⁵ Furthermore, since the preparation of both starting materials **1** and RAC **3d** relies on the activation of hydroxy moieties, we also demonstrated that compound **4aa** can be isolated in 41% yield (Conditions **B**), *via in situ* activation of both MBH alcohols and *N*-hydroxyphthalimide under Boc₂O/DMAP/THF conditions (see ESI† for details).

Mechanistically, the machinery depicted in Scheme 2a is postulated. In particular, cathodic reduction of **3d** would lead to the *t*BuOCO₂[•] C¹⁶ and phthalimide anion. The alternative fragmentation of **3d** to give a phthalimido radical and



Scheme 2 (a) Tentative reaction mechanism. (b) Electrochemical carboxylation of **4aa**.

*tert*butylcarbonate anion is unlikely, due to the non-productivity of *N*-trifluoroacetoxyphthalimide in the present protocol (see Table S1, ESI†).¹⁷ Subsequently, the radical **C** could undergo direct HAT with ether **2** resulting in the α -oxy radical **A** (path b) or first decompose to the strong electrophilic *tert*butoxyl radical **D** that would then be responsible for the HAT step (path a).¹⁸ Subsequently, the α -oxy radical **A** is postulated to be intercepted, regioselectively, by the electrophilic β -carbon position of **1**, followed by a second mono-electronic cathodic reduction of the so-formed radical intermediate



E^{10} leading to the final α,β -unsaturated ester **4** via elimination of the acetate anion. Here, (i) the absence of compound **5** that would result from the methyl radical trapping of **1** (β -fragmentation of **D** to acetone and Me^\bullet) and (ii) the higher stability of (alkoxycarbonyl)oxyl radicals with respect to alkoxy ones would suggest path b as the most likely one,¹⁹ although the concomitant formation of **D** from the partial decomposition of **3d** cannot be completely excluded.²⁰ Additionally, dedicated labelling studies (THF and THF- d_8) and ON-OFF experiments emphasized the role of the HAT process in the rate-determining-step and underlined the non-prevalence of active background radical chains (see ESI†).

Cyclic voltammetry experiments were then carried out (Fig. S2, ESI†). Both RAC **3d** and RAE **3a** showed very similar redox behaviour, with a first chemically irreversible reduction process with cathodic peaks (E_{pc}) at -1.26 and -1.24 V vs. SCE, respectively. In agreement with literature reports,²¹ this is likely localized on the phthalimide fragment, and it is followed by the N-O bond cleavage with the formation of a phthalimide anion and neutral radicals $t\text{BuOCO}_2^\bullet$ (**3d**) and Me^\bullet (**3a**). On the other hand, ether **3b** is characterized by a first reduction process at $E_{1/2} = -1.43$ V vs. SCE that is not followed by a chemical reaction. Therefore, **3b** is not suitable for its application in the described reaction protocol, not delivering the desired alkoxy radical, useful for the HAT process. Furthermore, MBH acetate **1a** shows a more negative and chemically irreversible reduction process ($E_{pc} = -2.08$ V vs. SCE) and it is therefore out of the available range of applied potentials to perform a redox-driven chemical initiation, in competition with **3**.

Finally, the synthetic versatility of compound **4** was demonstrated by subjecting **4aa** to electrolytic conditions in the presence of 1 atm CO_2 .²² Monomethyl malonate **10** was isolated as the only regioisomer (1.8 : 1 dr) in 54% yield (Scheme 2b).

In conclusion, in the present investigation we have documented eChem C(sp³)-H activation of ethers under cathodic reduction by means of a new redox-active-carbonate (RAC) as an efficient HAT promoter. The use of MBH acetates as electrophilic partners resulted in a regio- and stereoselective protocol for the allylation/alkylation of ethers (35 examples).

Conflicts of interest

There are no conflicts to declare.

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