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Electrochemical C(sp^3)–H functionalization of ethers *via* hydrogen-atom transfer by means of cathodic reduction†

Leonardo Rapisarda,[a] Andrea Fermi, *[ab] Paola Ceroni, [ab] Riccardo Giovanelli,[ab] Giulio Bertuzzi*[ab] and Marco Bandini *[ab]

The chemo- and stereoselective electrochemical allylation/alkylation of ethers is presented *via* a C(sp^3)–H activation event. The electrosynthetic 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(sp^3)–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(sp^3)–H functionalizations.[3]

In very recent times, the organic synthetic community has faced the (re)emerging of organic electrosynthesis (*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(sp^3)–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, electrophilic[7] 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

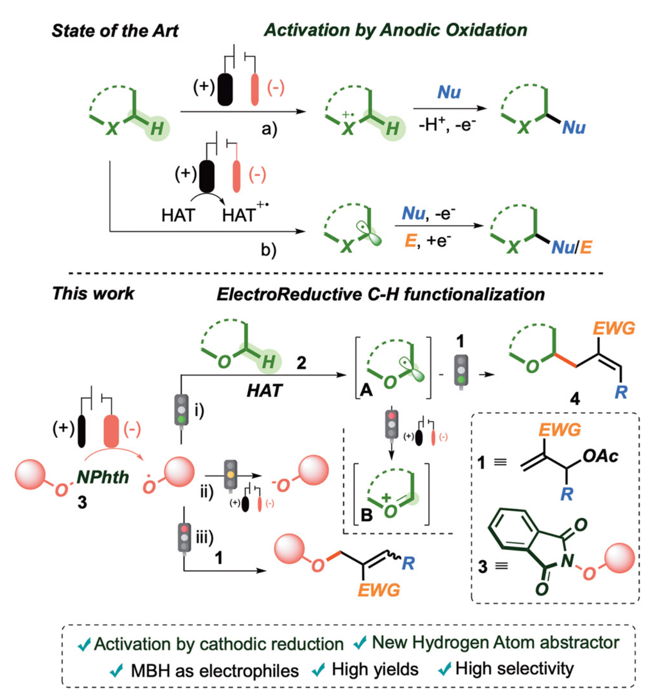

Fig. 1 State of the art in the eChem promoted C–H activation procedures (*i.e.* direct and indirect anodic oxidation (top)). The present electroreductive methodology (bottom).

[a] Dipartimento di Chimica "Giacomo Ciamician", Alma Mater Studiorum – Università di Bologna, via Selmi 2, 40126, Bologna, Italy. E-mail: marco.bandini@unibo.it

[b] Center for Chemical Catalysis – C3, Alma Mater Studiorum – Università di Bologna Via Selmi 2, 40126, Bologna, Italy

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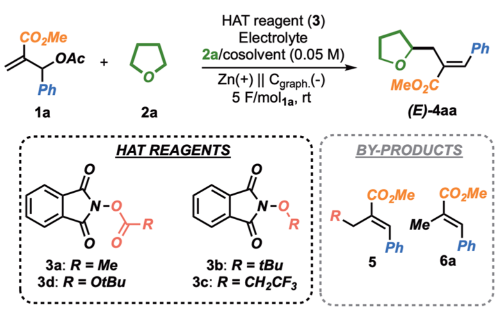
and productive employment of oxidant species as hydrogen atom abstractors in a strongly reductive environment.

Inspired by our recent results on selective radical-based transformations[9] 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, $TEABF_4$ 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]



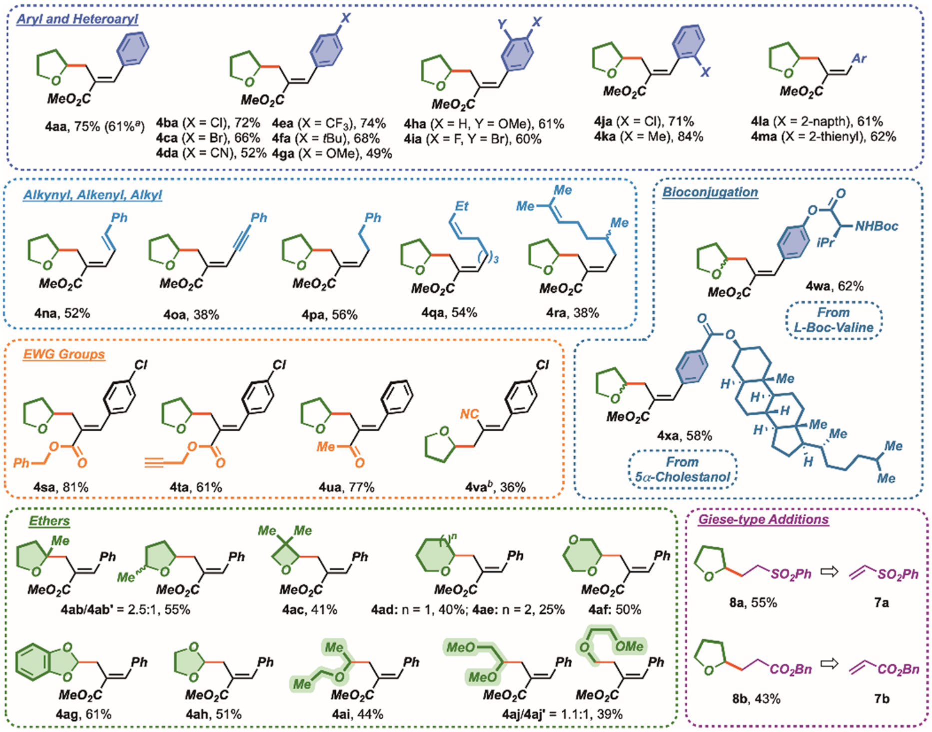
Entry	2a : cosolvent	3 : electrolyte	Electrolysis	Yield[b] [%]
1	1 : 2 (DMF)	**3a** : $TEABF_4$	CCE (I = 4 mA)	18 (35/21)
2	1 : 2 (DMF)	**3b** : $TEABF_4$	CCE (I = 4 mA)	— (—/17)
3	1 : 2 (DMF)	**3c** : $TEABF_4$	CCE (I = 4 mA)	— (—/13)
4	1 : 2 (DMF)	**3d** : $TEABF_4$	CCE (I = 4 mA)	34 (—/12)
5	1 : 2 (DMF)	— : $TEABF_4$	CCE (I = 4 mA)	— (—/13)
6	5 : 1 (DMF)	**3d** : $TBAPF_6$	CCE (I = 4 mA)	46 (—/11)
7	5 : 1 (DMF)	**3d** : $LiBF_4$	CCE (I = 4 mA)	50 (—/8)
8	5 : 1 (ACN)	**3d** : $LiBF_4$	CCE (I = 4 mA)	53 (—/—)
9	5 : 1 (ACN)	**3d** : $LiBF_4$	CCE (I = 2 mA)	63 (—/—)
10	**5 : 1 (ACN)**	**3d : $LiBF_4$**	**CVE (V = 5 V)**	**75 (—/—)**
11	5 : 1 (ACN)	**3d** : $LiBF_4$	CVE (V = 3 V)	30 (—/—)
12	5 : 1 (ACN)	**3d** : $LiBF_4$	CVE (V = 7 V)	63 (—/—)

[a] All reactions were carried in the Electrasyn 2.0 apparatus (undivided cell, see ESI for details). [b] Isolated yields after flash chromatography. In brackets yields of **5** and **6a**, respectively (^{1}H NMR by internal standard). *E*/*Z* ratios were determined *via* ^{1}H-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 $TBAPF_6$ (entry 6) or $LiBF_4$ (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 5α-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



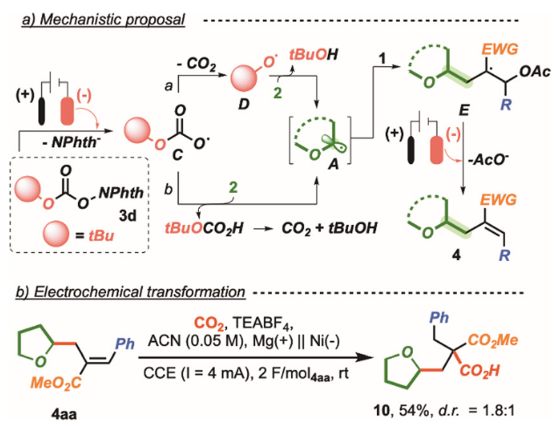
Scheme 1 Scope of the protocol for MBH acetates (**1**, Conditions **A**: Table 1, entry 10) and ethers (**2**, Conditions **B**, Table 1, entry 6). *E*/*Z* ratios were determined *via* ^{1}H-NMR spectroscopy on the reaction crude mixtures and were found to be ≥13 : 1 (see ESI† for details). [a] Reaction 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 Et_2O (**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 Boc_2O/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*BuOCO$_2^\bullet$ **C**[16] 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 monoelectronic 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•) 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*BuOCO$_2^{\bullet}$ (**3d**) and Me• (**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(sp^3)–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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