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Acyl radicals generated from aldehydes with NHPI as electrocatalyst: aldehydes and alcohols as carbon-centered radical precursors†

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In this work, we describe how *N*-hydroxyphthalimide (NHPI) promotes hydrogen atom transfer from aldehydes under electrocatalytic chemical conditions. This involves the generation of phthalimide-*N*-oxyl (PINO), which abstracts an acyl hydrogen to produce acyl radicals from aldehydes. These acyl radicals then react with oximes or another PINO radical to form redox-active esters (RAEs). Additionally, we detail a Giese-type reaction with electron-deficient alkenes via electrochemical reduction of the generated RAE derivatives. This process produces sp³-carbon centered radicals from aldehydes. We also extend this method to aliphatic alcohols, involving a multi-step electrochemical process to form carbon-centered radicals from readily available alcohols.

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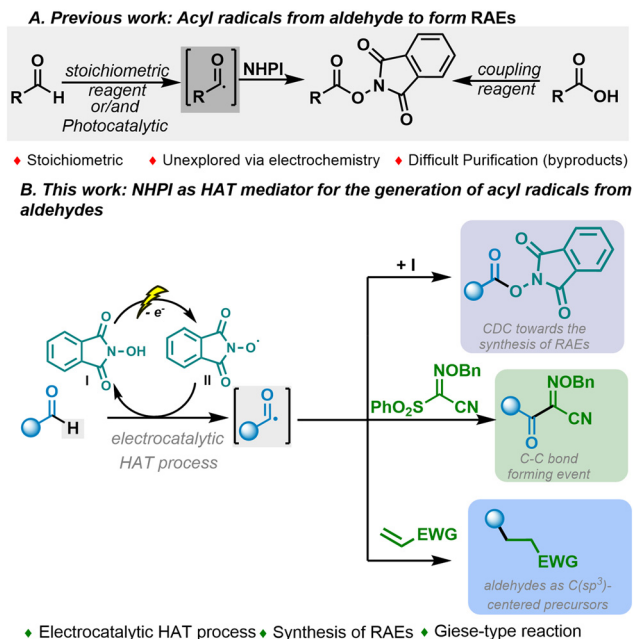
Introduction

Nowadays, there is increasing demand from society for the development of new synthetic strategies that are more sustainable, environmentally friendly and exhibit high atom economy.¹ In this context, the selective functionalization of C–H bonds has attracted enormous attention from both the chemical industry and academia as it has clearly been recognized as one of the prime challenges in modern synthetic chemistry.² Inspired by visible light driven HAT processes,^{2i,3} electrochemistry, which has experienced a renaissance in the past decade,⁴ has also emerged as a new means for the *in situ* generation of HAT abstractors from various redox mediators with the ability to activate C–H bonds.⁵ From this point of view, various systems have been studied in the past few years. However, it should be highlighted that there are only a few methods that describe direct C–H functionalization using a HAT mediator under electrochemical conditions.^{5,6} These methods are even fewer if we consider those that use the generated carbon-centered radical for the formation of new C–C bonds promoted by substoichiometric amounts of the HAT

promoter since the field is dominated by the oxidation of alcohols, and oxygenation, halogenation and azidation reactions.⁷

Acyl radicals are an interesting class of carbon-centered radicals due to their valuable synthetic applications towards the construction of carbonyl compounds.⁸ Although these radicals can be accessed by abstraction of carbonylic hydrogen,⁹ less straightforward approaches have also traditionally been used when the generation of acyl radicals was performed under electrochemical conditions, such as the cleavage of prefunctionalised RCO-X or carbonylation reactions.^{8,10} Despite the great efforts that have been made towards the generation of acyl radicals under electrochemical conditions, the direct electrogeneration of acyl radicals from aldehydes remains challenging and its widespread generation and application are yet to be achieved.¹¹ Therefore, the development of an electrochemically driven process that would directly abstract hydrogen from aldehydes to generate acyl radicals would be highly desirable. In this context, redox-active esters (RAEs) are very useful radical precursors in organic synthesis,¹² and their syntheses are carried out either by esterifying carboxylic acids with *N*-hydroxyphthalimide¹³ or by forming acyl radicals with stoichiometric reagents,¹⁴ with both methods requiring superstoichiometric amounts of reagents (Scheme 1A). Although important advancements have been made towards the synthesis of RAEs from aldehydes through cross dehydrogenative type strategies,¹⁴ the need for the use of harsh reaction conditions (high temperatures),^{14b,e,d} metal promoters^{14c,f} and stoichiometric amounts of oxidants^{14a,c,e,d} may still hamper their broad applicability. Therefore, the synthesis of redox active esters from aldehydes by using a hydrogen atom transfer mediator, with

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Scheme 1 Previous work (A) and this work (B).

the potential to synergistically act as a reagent under electrochemical conditions, would be an ideal process that leads to the formation of H_2 as the sole byproduct.^{15,16}

Herein, we describe the use of *N*-hydroxyphthalimide (NHPI) as a hydrogen atom transfer mediator to generate acyl radicals (Scheme 1B). These versatile carbon-centered radicals have been exploited for the formation of C–C bonds and the synthesis of RAEs when the electrochemically generated *N*-oxy radical is additionally used to trap the acyl radical. Moreover, when performed in the presence of a deactivated alkene, the *in situ* generated RAE can be electrochemically reduced to generate a sp^3 -carbon-centered radical with the ability to perform a Giese-type reaction. This one-pot transformation opens the opportunity for considering aldehydes as alkyl radical precursors.

Results and discussion

Optimization of the model reaction

We began the study by choosing octanal (**1a**) as the model precursor and oxime ether **2a** as the ideal substrate for trapping the acyl radical due to its known versatility¹⁷ (Table 1, entry 1). By using an electrochemical system with graphite as the working electrode and nickel foam as the counter electrode under 1 mA constant current for 12 h in an undivided cell with KCl as the electrolyte in a 3 : 1 mixture of MeCN and H_2O , compound **3a** was isolated in good yield (61%, entry 1). With the aim of developing a synthetically useful electrochemical system for generating acyl radicals, various parameters such as solvents, electrolytes, electrode materials and electrochemical parameters have been studied and summarized, as shown in Table 1. Firstly, the addition of an alternative electrolyte was

Table 1 Optimization of the electrocatalytically generated acyl radical^a

	Deviation from optimized conditions	Yield ^b (%)
1	No deviation	72 (61)
2	TBAPF ₄	69
3	LiClO ₄	43
4	2.5 mA 3 h vs. 1 mA 12 h	28
5	H_2O vs. MeCN/ H_2O 3 : 1	6
6	MeCN vs. MeCN/ H_2O 3 : 1	34
7	MeCN/ H_2O 1 : 1 vs. MeCN/ H_2O 3 : 1	10
8	GRC (–) vs. Ni _{foam} (–)	7
9	Zn (–) vs. Ni _{foam} (–)	3
10	Pt (–) vs. Ni _{foam} (–)	8
11	NHPI 0.2 equiv. vs. 0.5 equiv.	53
12	No NHPI	0
13	No current	0

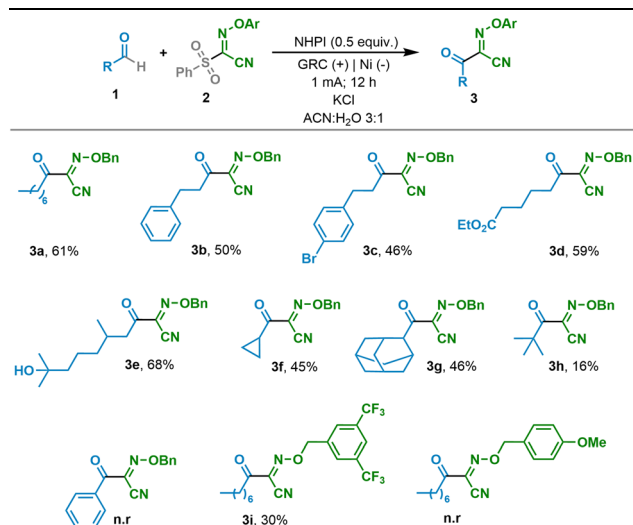
^a Standard reaction conditions: 0.1 mmol of **2a** and 0.4 mmol of octanal in 3 mL MeCN : H_2O 3 : 1 with KCl (0.1 mmol), under an air atmosphere, were set at constant current of 1 mA for 12 h at room temperature. ^b Yields determined by ¹H-NMR using 1,3,5-trimethoxybenzene as the internal standard. Isolated yields in brackets.

studied. KCl showed the best results (entries 2 and 3 and the ESI[†]). We then tested the reaction at a higher intensity and a shorter reaction time, and the desired product was obtained with a significantly lower efficiency (entry 4). Different solvent systems (entries 5–7) were then evaluated. Thus, when MeCN or H_2O was used as the sole solvent, the performance of the electrochemical system was substantially worsened (entries 5 and 6). A mixture of MeCN : H_2O in 3 : 1 proportion was then identified as optimal, as a different ratio of the solvent system was shown to lead to worse results (entry 7). Electrode material selection had a significant impact on the reaction. Counter electrodes other than nickel foam, such as those based on graphite, platinum or zinc, did not satisfactorily lead to the desired α -dicarbonylic product, with all affording the desired product in less than 10% yield (entries 9 and 10). We then tried to reduce the loading of NHPI (entry 11). Although the reaction proceeded remarkably well with only 20 mol% of the electrocatalyst (53%), 50 mol% of it was established as optimal in order to allow and facilitate the general progress of the studied reaction. Finally, the reaction did not take place in the absence of the electrochemical mediator or electrical current (entries 12 and 13).

Substrate scope

Once the reaction conditions had been optimized, a variety of aldehydes were tested under the electrochemical reaction conditions in an undivided cell with the aim of studying the influence of the nature of the aldehyde on its electrochemical behaviour (Table 2). At first, various linear aldehydes were

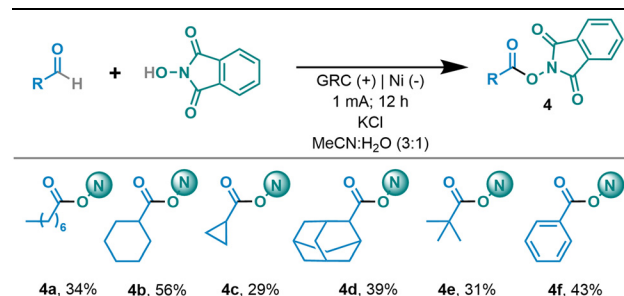


Table 2 Substrate scope of the electrochemical HAT promoted carbon–carbon bond forming reaction^a

^a Reaction conditions: **1** (0.4 mmol) and **2** (0.1 mmol), NHPI (0.05 mmol) and KCl (0.1 mmol) in MeCN:H₂O (3 : 1, 3 mL), r.t., under air, undivided cell (GRC (+), Ni_{foam} (-)) at constant current (1.0 mA) for 12 h. Isolated yields.

studied under the optimized reaction conditions. Thus, the carbon–carbon bond forming event through a HAT process took place efficiently and the desired products were obtained in good yields (**3a–e**). It should be highlighted that aromatic bromides (**3c**), which could get access to more versatile products upon further derivatizations, esters (**3d**) and free alcohols (**3e**) were found to be compatible with the electrochemical reaction conditions. More sterically hindered aldehydes decorated with an α -disubstituted carbon chain were also subjected to the electrochemical reaction. Thus, cyclopropyl and adamantyl decorated aldehydes led to the final product in synthetically useful yields (**3f** and **3g**, respectively). A more sterically congested *tert*-butyl derivative was observed to react less efficiently and afforded the desired product in a low yield (**3h**). Aromatic aldehydes although consumed during the reaction did not lead to the desired product under the optimized reaction conditions. Benzylic or secondary and primary decorated amine aliphatic aldehydes were also incompatible with the present optimized reaction conditions. The electronics of the aromatic ring of the oxime partner were also considered. While an electron-poor phenyl ring led to a significantly lower yield (**3i**), its electron-rich analogue did not afford the desired product.

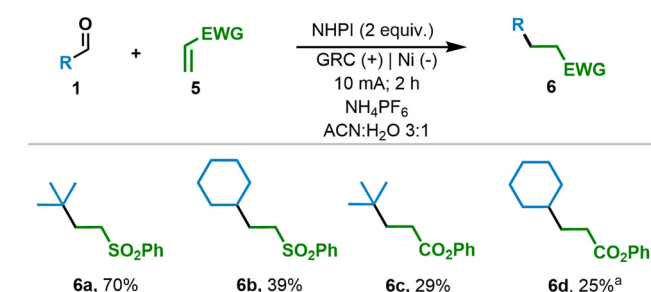
As mentioned above, with the aim of further exploiting the electrocatalytically generated acyl radicals, we envisioned the possibility of generating a redox active ester by exploiting the *N*-oxyl radical generated from NHPI not only to catalytically generate the acyl radical but also to quench it to form the carbon heteroatom bond, giving rise to the redox active ester. Therefore, after optimizing the reaction conditions (see the ESI†), we were able to obtain the desired RAE by simply coupling the aldehydes and NHPI (Table 3). It should be high-

Table 3 Substrate scope of the electrochemical HAT promoted synthesis of redox active esters^a

^a Reaction conditions: **1** (0.4 mmol), NHPI (0.05 mmol) and KCl (0.1 mmol) in MeCN:H₂O (3 : 1, 3 mL), r.t., under air, undivided cell (GRC (+), Ni_{foam} (-)) at constant current (1.0 mA) for 12 h. Isolated yields.

lighted that primary, secondary and tertiary decorated aliphatic aldehydes were compatible and led to the desired RAEs in synthetically useful yields (**4a–4e**). In addition, benzaldehyde was efficiently coupled with the electrochemically generated PINO to yield the corresponding ester (**4f**).

Given the encouraging results achieved and the synthetic potential of the developed method and considering the well-known ability of redox active esters to be electrochemically reduced,¹³ we speculated that under our optimized reaction conditions, the generated RAE might be *in situ* reduced, generating the corresponding alkyl radical upon decarboxylation. Therefore, considering that currently the primary application of redox active esters is to serve as precursors to generate sp^3 -carbon-centered radicals, we envisioned the possibility of extending the applicability of the method for generating the above-mentioned radical species directly from aldehydes. Thus, we studied the reaction of aldehydes in the presence of NHPI, which served as the catalyst and reagent, and vinyl sulfone, which served as the Giese acceptor (Scheme 2). To our delight, aldehydes as precursors of secondary and tertiary alkyl radicals performed efficiently, leading to the Giese adduct in moderate to good yields in the presence of vinyl sulfone and the phenyl ester (**6a–6d**).

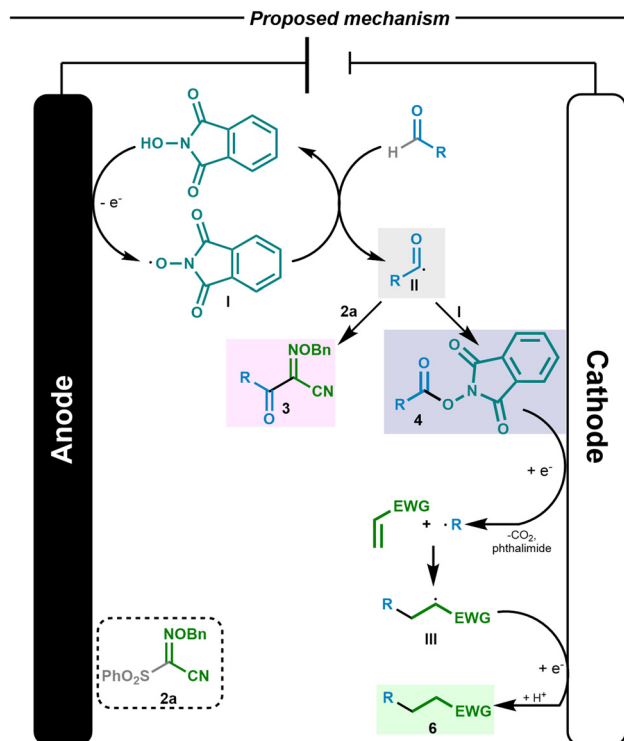


Scheme 2 Giese reaction using aldehydes as radical precursors. Reaction conditions: **1** (0.3 mmol) and **5** (0.1 mmol), NHPI (0.2 mmol) and NH_4PF_6 (0.1 mmol) in MeCN:H₂O (3 : 1, 3 mL), r.t., under air, undivided cell (GRC (+), Ni_{foam} (-)) at constant current (10 mA) for 2 h. Isolated yields. ^b 4 h.



In addition, to expand this method, we envisioned the possibility of taking it one step further. Our approach would again take advantage of the versatility of the *N*-hydroxy radical derivatives generated electrochemically.^{5a,16a} We propose a double oxidation process to generate the oxoammonium intermediate (shown to be feasible for similar substrates, $E_{ox} < 1.0$ V vs. NHE).^{5a} Once the active species is generated, an aliphatic alcohol derivative will form an adduct at the nitrogen atom of the oxoammonium species, followed by intramolecular hydride transfer to regenerate NHPI and the organic aldehyde. The aldehyde *in situ* generated would then trigger the acyl radical process, leading to the formation of the RAE and its subsequent reduction/decarboxylation to give rise to the sp^3 carbon-centered radical. This overall process enables alcohols to serve as precursors of aliphatic carbon-centered radical species (Scheme 3). Therefore, after optimizing the reaction conditions (see the ESI†), we were able to obtain the desired RAE from a primary alcohol and NHPI (Scheme 3A). We then investigated alcohols as radical precursors in Giese-type reactions. Alcohols proved to be efficient precursors for tertiary, secondary and primary alkyl radicals, leading to the Giese adduct in synthetically useful yields (**6b** and **6e–g**). It should be highlighted that primary alkyl radicals can be generated and they performed efficiently, in contrast to known alternatives.

A mechanistic proposal of the electrochemical process is depicted in Scheme 4. Based on the literature,^{5a,16a} the alkoxy radical **I** formed through the electrochemical oxidation of NHPI performed the hydrogen atom transfer event from the aldehyde, forming the corresponding acyl radical and regenerating the *N*-oxyl derivative. The radical formed can react either with oxime **2** to form compound **3** or be trapped by another



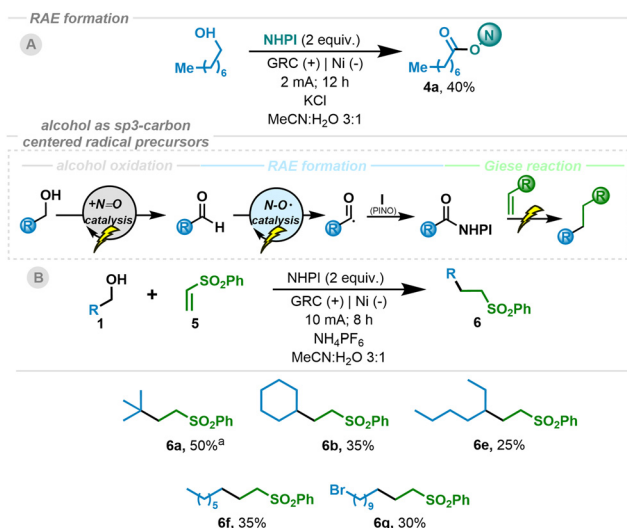
Scheme 4 Proposed reaction mechanism.

alkoxy radical, giving rise to the RAE, as shown in the optimized reaction conditions in Schemes 2 and 3.

The formation of compounds **3** and **4** provide mechanistic evidence for the formation of the acyl radical; trapping the acyl radical using the oxime or a radical scavenger such as PINO (**I**), respectively, would directly lead to these compounds. Once the RAE derivative is formed, it undergoes a well-documented electrochemical reduction, giving rise to the carbon-centered radical upon decarboxylation.¹³ In addition, to further support the source of the sp^3 -carbon-centered radical, we carried out a test reaction (see the ESI†) that showed that under the optimized reaction conditions, RAE **4b** led to the desired Giese-type product **6b** with similar efficiency compared to the reaction involving the aldehyde or the alcohol. Then, a conjugate addition of the radical to the Giese acceptor would take place.¹⁸ The resulting radical species **III** might then be reduced at the cathode and upon protonation, would lead to the Giese type product **6** from the aliphatic aldehyde.

Conclusions

In conclusion, we describe an electrochemical method for generating acyl radicals from aldehydes using NHPI as the promoter. The reaction system has demonstrated its robustness and generality as various aldehydes can be coupled successfully with oximes within this electrochemical system. The *N*-hydroxy radical generated upon anodic oxidation plays a multifunctional role in the present methodology, as it acts as substoi-



Scheme 3 Giese reaction using alcohols as radical precursors. Reaction conditions: **1** (0.4 mmol) and **2** (0.1 mmol), NHPI (0.6 mmol) and NH_4PF_6 (0.1 mmol) in $\text{MeCH}:\text{H}_2\text{O}$ (3:1, 3 mL), r.t., under air, undivided cell (GRC (+), Ni_{foam} (-)) at constant current (10 mA) for 8 h. Isolated yields. ^b Using LiClO_4 as electrolyte.



chiometric promoter of the acyl radical and as a reagent towards the synthesis of redox active esters. Therefore, various RAEs have been prepared by this cross-dehydrogenative type electrochemical methodology using aldehydes as platforms and NHPI as the reagent, avoiding the use of coupling reagents. Moreover, aldehydes and even alcohols have been demonstrated to be valuable sp^3 -carbon-centered radical precursors in Giese type reactions through the electroreduction of RAEs *in situ* generated from them.

Author contributions

R. G. E., J. S. D. S. and R. R. R. carried out the optimization and studied the scope of the reaction. J. A. and J. A. F. S. conceived the project and prepared the manuscript, which was edited by all the other authors.

Data availability

All data supporting the findings of this study, including experimental details and spectroscopic characterization data for all compounds, are available within the article and the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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