Electro-Oxidative Platform for Nucleophilic α-Functionalization of Ketones

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Abstract:

The significance of α-functionalization of carbonyl compounds arises from its frequent use in synthetic organic chemistry. Consequently, there is a substantial and constant demand for the creation of strategies that facilitate the efficient execution of such valuable transformation. In this context, herein is presented a universal electrochemical oxidative platform for the α-derivatization of ketones with nucleophiles, employing an umpolung reactivity. This approach has been successfully employed in five distinct transformations involving C-C and C-X bond formation via straightforward nucleophilic substitution or cycloaddition reaction pathways. Furthermore, the implementation of this methodology in flow using a commercially available reactor demonstrated its inherent scalability.

Main text:

α-functionalization of carbonyl compounds stands as a pivotal retrosynthetic strategy, playing an important role in the construction of complex molecular structures within the realm of natural product synthesis and the broader landscape of synthetic organic chemistry.[1,2] The traditional protocols depicted for the α-functionalization of ketones have been classically dominated by enolate chemistry. Indeed, the recognition of the synthetic value of nucleophilic enolates has rendered them as reactants of choice for the versatile construction of C−C and C−X (with X = heteroatom) bonds at the α-position of a ketonic moiety, often using electrophilic reagents. In this regard, over-reaction is a longstanding obstacle in these protocols; in addition, prior synthesis of electrophilic reagents is required to enable such processes.

Alternatively, umpolung type reactivity for α-functionalization of carbonyl compounds can be seen as a more efficient and practical strategy due to the direct use of nucleophiles with no need for prior activation, therefore expanding the scope of functionalities that can be tolerated. In this context, oxidative umpolung of enolates has emerged as an interesting platform. In such umpolung strategies, enolates are transformed into electrophiles, typically using hypervalent iodine reagent or *in-situ* triflation, thus promoting their coupling with nucleophiles.[3-9]

Complementary, electrochemistry offers a selective platform to achieve functionalization of ketones using oxidative umpolung processes. Such processes were described several times in the electrosynthesis literature. An initial report by Shono and co-workers described the electro-oxidative desaturation of ketones for the synthesis of α,β-desaturated carbonyls.[10-12]

Mechanistically, direct anodic oxidation of enol ether starting materials led to a polarity switch by generating an electrophilic radical-cation intermediate, followed by deprotonation at the β-position to obtain the desaturated product. In the past decades, Moeller has acquired a rich record of electrochemical studies focusing on the *intramolecular* oxidative umpolung of enol ethers with electron-rich alkenes, alcohols and amines.[13-16] These methodologies were utilized for the synthesis of several natural products and unique skeletons, demonstrating their effectiveness.[17,18] However, moving to the intermolecular spaces, such reactivity is still underdeveloped and limited. Cantillo and co-workers have recently reported the α-arylation of non-substituted acetophenone derivatives with electron-rich arenes through direct anodic oxidation.[19] In this work, the authors developed a two-step protocol for the *in-situ* formation of a terminal silyl-enol ether, followed by its oxidation, to generate a postulated radical-cation intermediate. Such intermediate then reacts with electron-rich arene to forge the desired C-C bond. Although the described methodology is a milestone in this area, it is limited to terminal aryl-conjugated enol ethers and reported only with electron-rich arenes as nucleophiles. During the preparation of this manuscript, a similar method was reported, this time describing the α-fucntionalization of aryl-ketones with 1,3-diketones.[20]

Herein, we describe a general electro-oxidative umpolung platform towards the formal nucleophilic α-functionalization and α-cycloaddition of alkyl ketones. Under these conditions, efficient intermolecular couplings have been achieved in the presence of 1,3-dicarbonyls, alkenes, and chloride as nucleophiles. A single-pass flow protocol was also developed on a gram-scale using a commercially available reactor. Overall, the flow reaction conditions offered better reactivity and shorter reaction time with no supporting electrolyte needed.

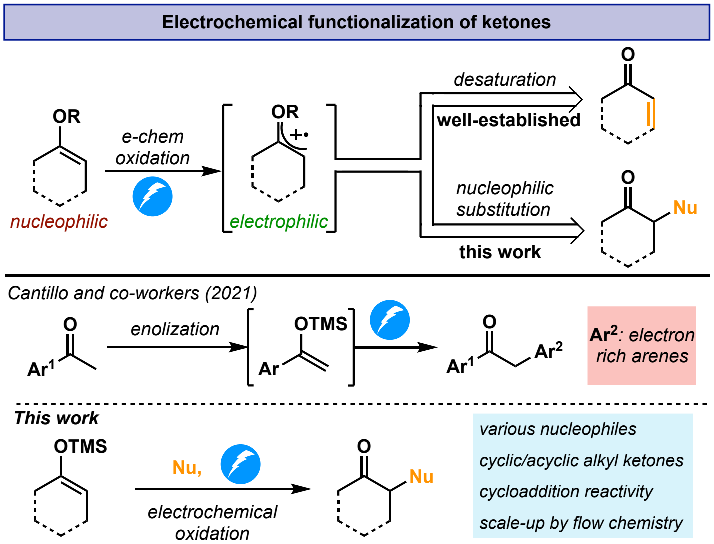
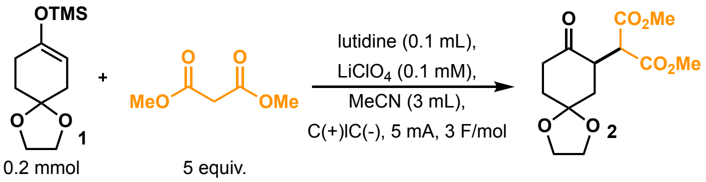


Figure 1: Previous examples of electro-oxidative umpolung processes for the functionalization of ketones and "This work" for a general electro-oxidative platform for alkyl ketones nucleophilic functionalization.

TMS-enol ether **1** and dimethylmalonate were selected for the optimization of the electro-oxidative nucleophilic α-functionalization of ketones. A summarized overview is provided in Table 1. Our prior experience in the context of electrochemically driven desaturation reaction development served as a template for this study.[12,21] Rigorous assessments were conducted on electrolytes, electrodes, solvents, and nucleophile amount. Exploration of various electrolytes showcased that those lacking redox activity and nucleophilic characteristics were most advantageous (Table 1, entries 1-4). Particularly, $LiClO_4$ exhibited the highest yield. Subsequently, a foray into multiple anodic materials determined that a graphite anode delivered optimal reactivity (Table 1, entries 5-7). The cost-effectiveness and efficiency of graphite ultimately prompted its selection as electrode material. Among the assortment of screened solvents, DMA and DMF were potential candidates; however, MeCN demonstrated superior performance across a broad range of substrates (Table 1, entries 9-10). Other solvents such as acetone, resulted in no conversion towards the desired product due to limited electrolyte solubility (Table 1, entry 8). The evaluation of different bases revealed that heteroaromatic amines were the most promising to afford the desired reactivity (Table 1, entries 11-13). Notably, among all the bases tested, 2,6-lutidine at a concentration of 3.5% (v/v) emerged as the most favorable option. Various equivalents of the nucleophile were explored to refine the reaction conditions (Table 1, entries 14-16). Employing 1 or 2.5 equivalents of malonate resulted in 25% and 63% yields, respectively. It is worth mentioning that dimerization of the ketone was observed as a side product in those cases. Consequently, the optimal outcome was achieved when employing 5 equivalents of methyl-malonate. Control experiments showed that the final set of conditions tolerates exogenous air and moisture, leads to completion after 3-4 F/mol, and can be set up in minutes using a simple undivided cell and a commercial potentiostat (Table 1, entry 17).

Optimization of the electrochemical α-functionalization of ketones



entry	deviation from above	yield (%)
1	none	86
2	$TBABF_4$ instead of $LiClO_4$	ND
3	$NaSbF_6$ instead of $LiClO_4$	35
4	$TBAPF_6$ instead of $LiClO_4$	6
5	RVC instead of graphite anode	67
6	platinium anode instead of graphite anode	71
7	nickel foam anode instead of graphite anode	ND
8	acetone instead of MeCN	ND
9	DMF instead of MeCN	6
10	DMA instead of MeCN	9
11	Et_3N instead of lutidine	ND
12	collidine instead of lutidine	79
13	pyridine instead of lutidine	35
14	1 equiv. of dimethyl-malonate	25
15	2.5 equiv. of dimethyl-malonate	63
16	6 equiv. of dimethyl-malonate	86
17	non-anhydrous MeCN	85
18	no lutidine	ND
19	no $LiClO_4$	ND
20	no electrolysis	ND

Table 1: Optimization of the electro-oxidative nucleophilic functionalization of enol-ether **1** and dimethylmalonate. n.d.: not detected.

With the optimized conditions in hand, we first assessed the ketone scope (Figure 2). Regarding ketone substrates, cyclic (from 5-12 membered rings), acyclic, and aryl conjugated derivatives were tolerated. Substituents at the β- and γ-positions are all compatible (**2**, **5** and **9**), as well as Lewis-basic heteroatoms (**4** and **10**), acid-labile ketals (**2**), electron-rich arenes, TBS protected alcohols (**5**), and Boc-protected amines (**4**). Next, we examined several 1,3 dicarbonyl compounds and discovered that diones nucleophiles work under the reaction conditions to obtain tri-ketone compounds. Similar to malonates, diones were also efficiently coupled with both cyclic and acyclic ketones (**10** and **11**). Unfortunately, due to subsequent intramolecular reactions, malononitrile and Meldrum's acid did not furnish the desired product under the reaction conditions (intramolecular cyclization was detected).

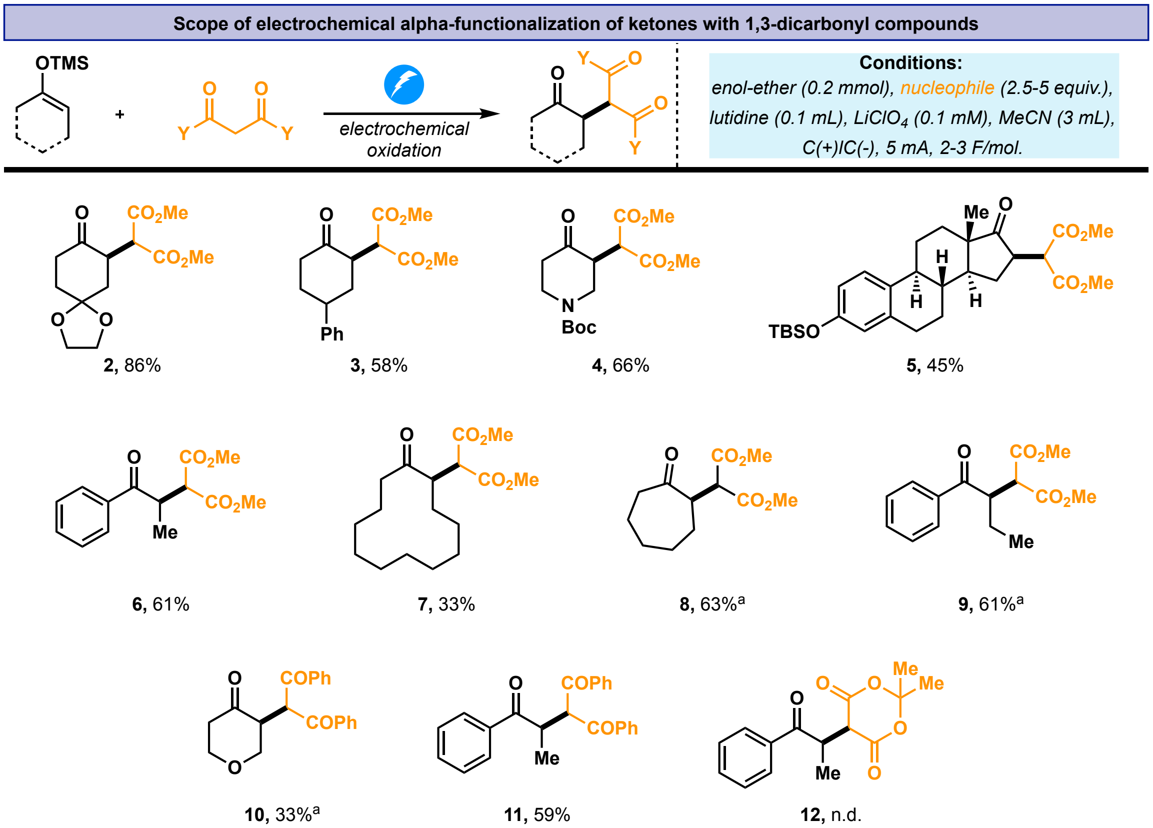
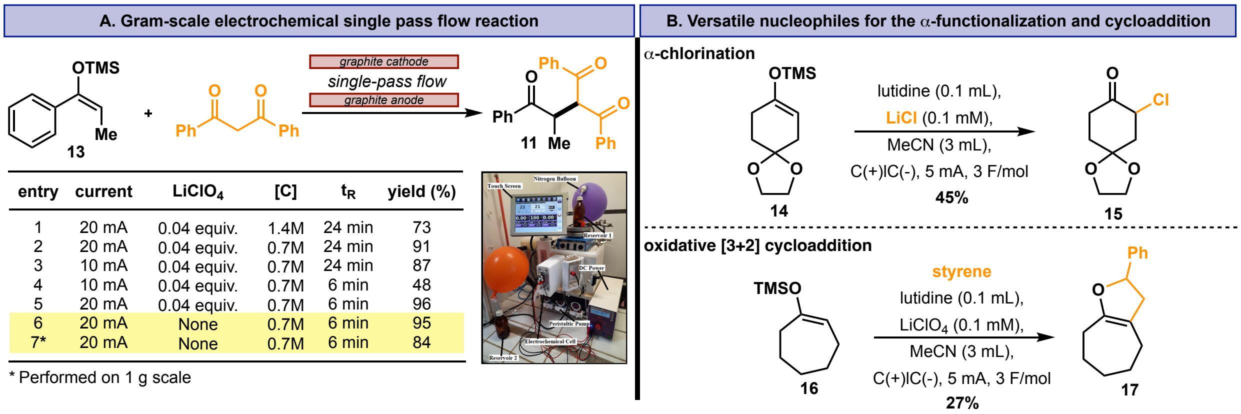


Figure 2: Scope of the electro-oxidative nucleophilic functionalization reaction with 1,3-dicarbonyls. [a] NMR yield. n.d.: not detected.

One of the main advantages of electrosynthesis relies on its facile and sustainable scalability. In this context, the scalability of the reported method was evaluated using propiophenone-derived silyl enol ether **13** on a 1-gram scale reaction (Figure 3A) with diphenylpropanedione to afford triketone **11**. For this purpose, we used a commercially available single-pass flow system (Vapourtec reactor). We first optimized the reaction on a small scale (0.2 mmol) to facilitate the transfer to the flow reactor. Accordingly, a lower amount of electrolyte was used to avoid any risk of clogging, the electrolysis was also set to 10 mA to get a higher reaction rate in single-pass mode, and a flow rate of 0.1 mL/min was used to have a sufficient residence time. Then, we evaluated the impact of concentration, reaction time, current, and electrolyte concentration. First, a substrate concentration screen was found to be optimal with 0.7 M to give 73% product (Figure 3A, entries 1-2). Next, the use of a 20 mA current proved to be ideal. A reaction time of 6 min instead of 24 min afforded the best result with 96% isolated product **11**. Notably, this reaction can be carried out without supporting electrolyte to exhibit a similar yield (95%) keeping the other reaction parameters unchanged (Figure 3A, entry 6). Finally, scale-up to 1 gram using the same reaction conditions afforded the desired product in 84% isolated yield. Such a result highlights the efficiency of the reported method for large-scale experiments.

In a broader context, the modification of ketones has demonstrated extensive applications within the realm of organic synthesis.[22-25] Thus, we wondered if our electro-oxidative platform would enable the versatile diversification of ketones (Figure 3B). Pleasingly, *α*-chlorination of ketones was successfully achieved using lithium chloride instead of $LiClO_4$ as an electrolyte, resulting in a 45% yield of chlorinated product **15**. Beyond the *α*-functionalization reactivity, we recognized the applicability of this methodology in oxidative cycloaddition reactions. Through this approach, we uncovered a formal [3+2] cycloaddition reaction employing styrene as a coupling partner and leading to the formation of phenyl dihydrofurane **17** in 27% yield.



entry	current	$LiClO_4$	[C]	t_R	yield (%)
1	20 mA	0.04 equiv.	1.4M	24 min	73
2	20 mA	0.04 equiv.	0.7M	24 min	91
3	10 mA	0.04 equiv.	0.7M	24 min	87
4	10 mA	0.04 equiv.	0.7M	6 min	48
5	20 mA	0.04 equiv.	0.7M	6 min	96
6	20 mA	None	0.7M	6 min	95
7*	20 mA	None	0.7M	6 min	84

* Performed on 1 g scale

Figure 3: a) Gram-scale single-pass flow scale-up using a Vapourtec flow reactor b) Versatile functionalization of ketones with other coupling partners.

This work provides a new perspective on how an electrochemical approach, inspired by decades of intramolecular electro-oxidative umpolung reactivities, can be used in the context of efficient α-functionalization of ketones with a variety of applications in modern organic synthesis. This electro-oxidative protocol can be performed in an undivided cell, on multiple scales, without strict removal of air or water, and in the absence of expensive reagents and stoichiometric oxidants. Overall, this strategy led to the development of three different reactions for the functionalization of alkyl ketones, including C-C and C-Cl bond formations as well as a [3+2] cycloaddition. These reactions were applied across dozens of substrates, demonstrating the high functional group tolerance and efficiency of this electrochemical methodology.

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