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Electrochemical Site-Selective Alkylation of Tropones via Formal C(sp^3)–C(sp^2) Coupling Reaction

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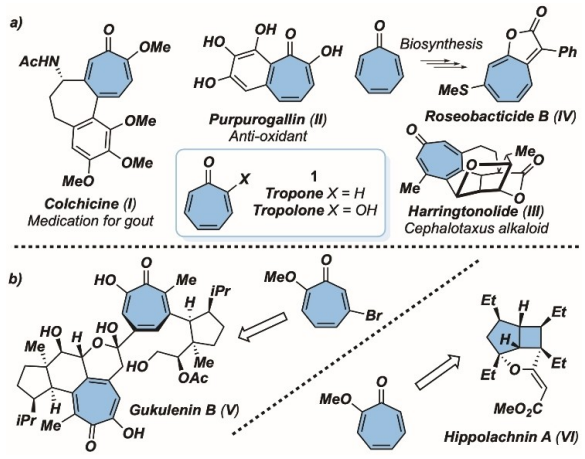
Abstract: The first site-selective electrochemical alkylation of tropones is realized by reacting 2-acetoxytropones and redox-active-esters (RAEs). The electroreductive protocol enables the preparation of mono- and disubstituted tropones in high yields (up to 71%) under very mild conditions. Dedicated voltammetric measurements served for the identification of 2-acetoxytropones as a class of valuable trapping agents of nucleophilic radical species and shed light on the whole mechanistic profile. Wide tolerance towards functional groups (27 examples) and application to late-stage functionalization of a bioactive compound (*i.e.* Colchicine analogue), emphasize the synthetic impact of the present methodology.

Keywords: Electrosynthesis; Alkylation; Tropone; Redox active esters; Mechanistic investigation

Tropones (**1**) are seven-membered-ring ketones belonging to the class of non-benzenoid aromatic molecules, historically contributing to the recognition and generalization of the concept of aromaticity.[1] Far from being a mere structural fascination, the tropone scaffold can be encountered in a variety of naturally occurring and biologically active molecules.[2] Among them, Colchicine (**I**) is an effective medication for the treatment of gout,[3] Purpurogallin (**II**) is commonly utilized as an anti-oxidant in non-edible oils[4] and Harringtonolide (**III**), displays anti-viral, anti-fungal, and anti-cancer activities.[5] Additionally, tropone itself serves as a building block in various bio-syntheses (*i.e.* Roseobacticide B **IV**, Scheme 1a)[6] and it constitutes a unique platform in the total synthesis of complex molecular scaffolds.[7] Herein, the cycloheptatrienone motif can be retained in the target compound as recently demonstrated by the group of Nicolau in the synthesis of Gukulenin B (**V**),[7d] or employed in successive structural modifications, as exemplified by Trauner and Winter in the preparation of Hippolachnin A (**VI**).[7c]

Despite this undoubted wide interest, the available chemical portfolio for the manipulation of tropones still remains quite narrow and mainly confined to cycloaddition reactions.[8] Contrarily, direct and site-selective protocols (*i.e.* alkylations) for the tropone skeleton decoration are still rare and scattered in scope.[9] As a matter of fact, three methodologies directed to the obtainment of 2-alkyltropones have been documented so far: i) the reaction of 2-benzyloxytropone with mixed alkyl-zinc reagents, as reported by Knochel (limited to secondary alkyl groups);[10] ii)



Scheme 1. a) Examples of naturally occurring and bioactive compounds based on tropone (**I**–**IV**); b) Tropone derivatives as a key platform in total synthesis.

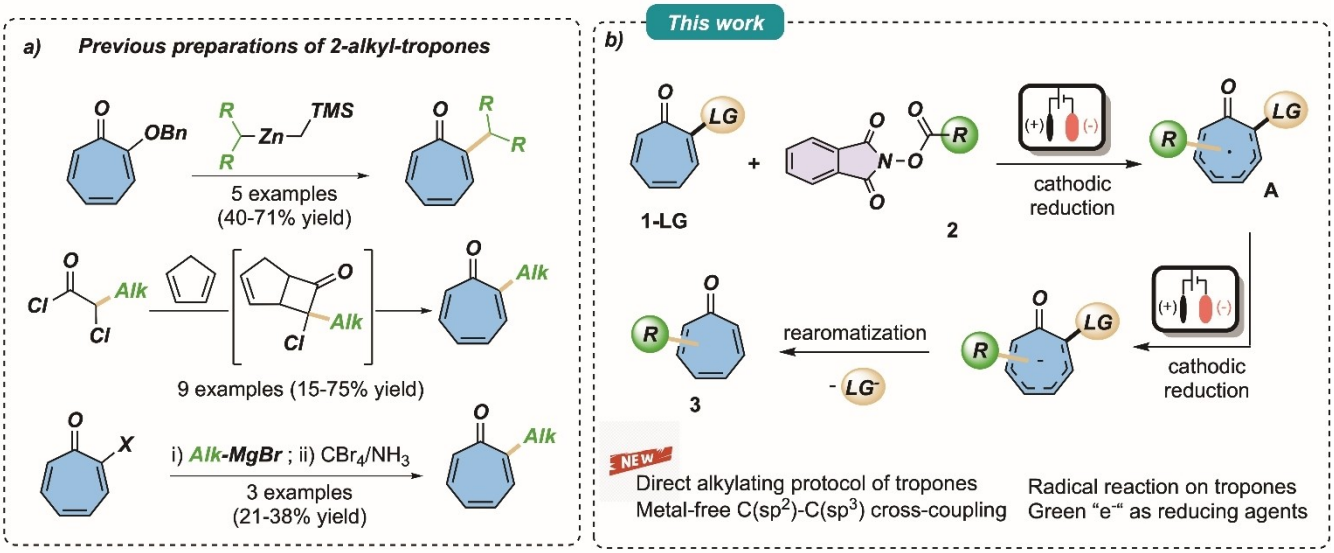
the chloroketene-cyclopentadiene cycloaddition followed by hydrolysis (multi-step approach)[11] and iii) the addition of Grignard reagents to tropone (followed by oxidation) or to 2-fluorotropone, resulting in low yield and poor selectivity (Scheme 2a).[12]

Therefore, the request for robust, direct and selective C-alkylations of the non-benzenoid aromatic scaffold is still urgent. Here, nucleophilic C-alkylation reactions are largely dominated by a "polar scenario" based on harsh organo-lithium, organo-zinc and Grignard reagents, featuring lack in functional group tolerance, easy preparation and usability under mild conditions. On the other hand, the use of radical chemistry for the realization of complex organic transformations is currently emerging as a very convenient, or, in some cases, even the sole synthetic choice, to a given preparative task.[13]

In this scenario, decarboxylative processes for the formation of nucleophilic alkyl radicals from carboxylic acids/derivatives offer the possibility to draw from a boundless pool of native or synthetic starting materials,[14] and relies on innovative enabling techniques for their implementation under very convenient and widely tolerant conditions.[15] Here, also based on our recent interests on the generation and selective use of radical species in organic synthesis (either under catalytic or electroChem conditions),[16,17] we speculated on the realization of a **general α-alkylation of tropones** via a still unknown electrochemical "radical approach".[18]

Our working hypothesis relies on the utilization of an activated form of tropone (**1**) being able to undergo the addition of nucleophilic radicals, generated by the electrochemical reduction of *N*-hydroxyphthalimide esters (Redox-Active Esters, RAEs, **2**)[19] and, consequently, restore the aromaticity by eliminating a pre-installed leaving group (LG) at the α-position (Scheme 2b). Overall, the realization of a metal-free C-(sp^2)–C(sp^3) cross coupling methodology on tropone derivatives would be conveniently obtained by exploiting "green" electrons as traceless reducing agents.

The main challenge in designing the titled electrochemical cross-electrophile coupling relies on the accomplishment of chemoselective cathodic events. Here, it turned out as pivotal the identification of an activated tropone **1-LG** featuring an adequate electrophilic profile to undergo radical trapping but, at the same time, less prone to reduction with respect to



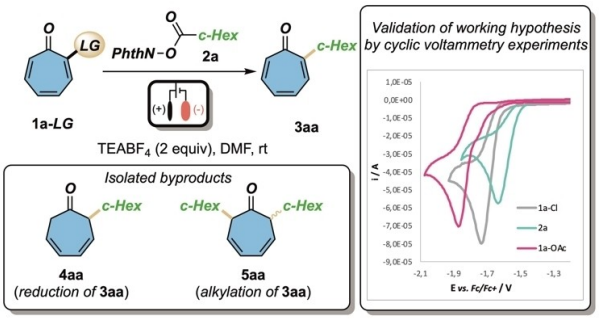
Scheme 2. a) Known methodologies for the preparation of 2-alkyl-tropones; b) Present working hypothesis for the direct alkylation of tropones with electrochemically generated nucleophilic radicals (LG: leaving group, TMS: trimethylsilyl, Alk: alkyl).

RAEs **2**.[20] To this aim, a dedicated voltammetric analysis led us to select readily available 2-chlorotropone **1 a-Cl** and 2-acetoxytropone **1 a-OAc** as potential radical acceptors, in combination with RAE **2 a** as radical generator. In particular, **2 a** showed a cathodic reduction at less negative potential (−1.63 V *vs* Fc/Fc^+) with respect to **1 a-Cl** (−1.73 V vs. Fc/Fc^+) and **1 a-OAc** (−1.87 V vs. Fc/Fc^+), foreseeing the desired selectivity (Figure of Table 1). In addition, measurements performed at different scan rates (up to 3 Vs^{-1}) evidences the very high reactivity of the radical species generated via electrochemical reduction of **2 a** (see supporting information).

Based on these promising findings, **1 a-Cl** and **2 a** (1.5 equiv.) were subjected to a constant current electrolysis (2 mA, 3 F/$mol_{1a\text{-}Cl}$) using a graphite (C) cathode and a Zn sacrificial anode and 0.1 M $TEABF_4$ as the supporting electrolyte in DMF (Table 1, entry 1).

Interestingly, the desired product **3 aa** was isolated in 15% yield. Here, the identification of side-products **4 aa** and **5 aa**, revealed the tendency of **3 aa** to undergo a cathodic over-reduction/alkylation sequence under these conditions (see Figure S3 for voltammetric analysis of **3 aa**).

Table 1. Optimization of the reaction conditions.[a]



Entry	**1 a**:**2 a** (F/mol_{1a})	*LG*	*A*(+)||*C*(−)	*I* [mA]	Yield [%] of **3 aa** (**4 aa**/**5 aa**)[b]
1	1:1.5 (3)	Cl	Zn||$C_{(g)}$	2	15 (10/7)
2	1:1.5 (2)	Cl	Zn||$C_{(g)}$	2	30 (–/–)
3	1:1.5 (2)	Cl	Zn||SS	2	17 (8/5)
4	1:1.5 (2)	Cl	Zn||Ag	2	38 (–/–)
5	1:1.5 (2)	Cl	Mg||Ag	2	–
6	1:1.5 (2)	OAc	Zn||Ag	2	53 (7/4)
7	1.5:1 (1.5)	OAc	Zn||Ag	2	59 (–/–)
8	2:1 (1)	OAc	Zn||Ag	2	64 (–/–)
9	2:1 (1)	OAc	Zn||Ag	3	71 (–/–)
10	2:1 (0.75)	OAc	Zn||Ag	3	48 (–/–)

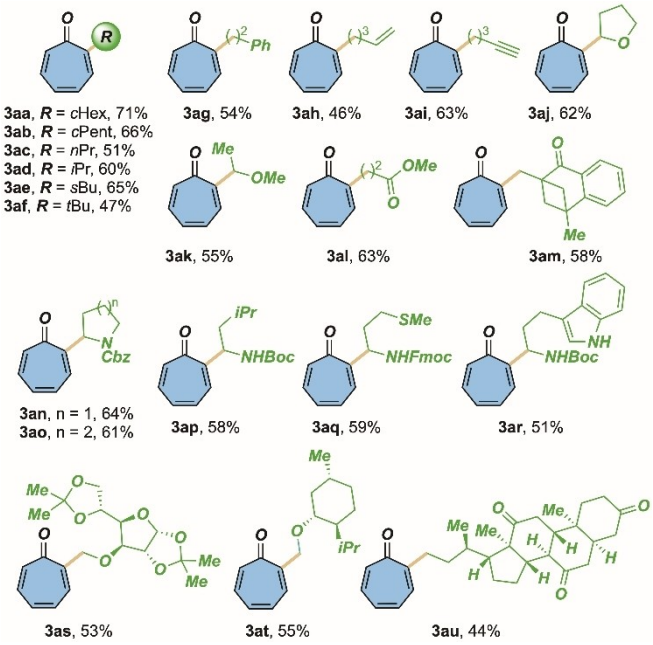
[a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis (CCE, A: anode, C: cathode).

[b] Isolated yields after flash chromatography. (PhthN: phthalimide).

These issues were initially tackled by lowering the total charge furnished to the reaction (2 mA, 2 F/$mol_{1a\text{-}Cl}$) and holding the same reaction stoichiometry (30% yield, entry 2). Under these conditions, further attempts to improve the reaction efficiency elected Zn(+)\|\|Ag(−) as the best performing couple of electrodes (entries 3–5), enabling the isolation of **3 aa** in yield up to 38%. Although these conditions precluded the formation of over-reduction products **4 aa** and **5 aa**, a major degradation of **1 a-Cl** was detected in the reaction crude. This evidence suggested that along with the reaction course (decrease in **2 a** concentration), the electroreductive process could gradually lose in chemoselectivity, by triggering uncontrolled reactions of **1 a-Cl** via single-electron-transfer processes.

The proximity of the reduction peaks observed in the voltammetric responses of **2 a** and **1 a-Cl** supports this statement. Therefore, we hypothesized that the employment of the more electron-rich **1 a-OAc** could face this shortcoming. Remarkably, when 2-acetoxytropone was employed, a net increase in chemical yield was recorded (entry 6, 53% yield). Further advances in the reaction conditions regarded the stoichiometry of the process and the electrolytic conditions that led to the optimal 71% yield with a current value of 3 mA and **1 a-OAc**:**2 a** 2:1 ratio (entry 9, see SI for a full screening of current values). Importantly, by furnishing a sub-stoichiometric number of electrons (entry 10) a considerable drop in isolated yield was observed (48%) showing a charge-dependent behavior of the process and thus suggesting radical chains as unlikely for the present machinery.

The generality of the present electrochemical alkylation was then tested by engaging several different radical precursors **2** to optimal conditions (Scheme 3). Primary (**2 c**), secondary (**2 a**, **2 b**, **2 d**, **2 e**) and tertiary (**2 f**) radicals reacted promptly and regioselectively (exclusive α-alkylation was recorded) with **1 a-OAc** to render products **3 aa**–**3 af** in up to 71% yield. Additionally, a range of functional groups such as arenes (**3 ag**), alkenes (**3 ah**), alkynes (**3 ai**), esters (**3 al**) and ketones (**3 am**)[21] was efficiently accommodated on the radical framework, unraveling a highly tolerant protocol. Subsequently, the compatibility of the protocol towards α-oxy radicals, as well as α-amino radicals was ascertained. As a matter of fact, cyclic (**2 j**) and acyclic (**2 k**, from lactic acid) nucleophilic α-oxy radicals were found to be competent nucleophilic alkylating agents (55–62% yield). Analogously, proteogenic amino-acid-derived RAEs **2 n**–**2 r** were productively engaged under optimal conditions, providing a simultaneous validation towards amino protecting groups tolerance (*i.e.* Boc, Fmoc and Cbz) and functional groups (*i.e.* sulfides and unprotected indole) compatibility (51–64% yield). Finally, RAEs **2 s**–**2 u**, containing a protected form of *D*-glucofuranose, dehydrocholic acid and (−)-menthol, respec-

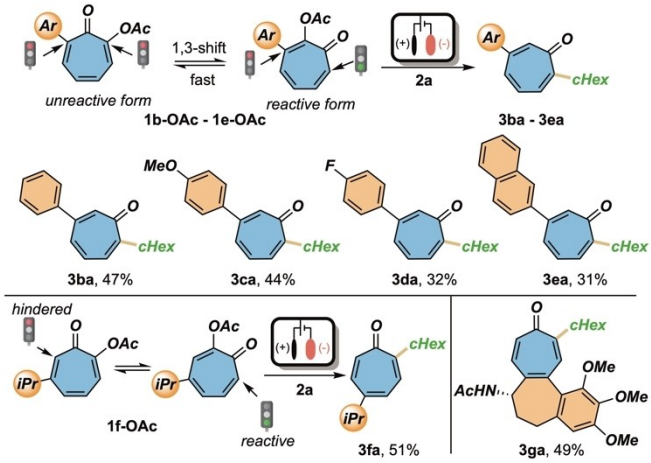


Scheme 3. Scope of the reaction: screening of radical alkylating agents **2**.

tively, were subjected to optimal conditions as representative late-stage electrochemical bioconjugation examples. Remarkably, the corresponding products **3as**–**3au** were isolated in 44–55% yield.

Interestingly, the utilization of 2-acetoxytropones **1-OAc** as starting materials offers the unique opportunity to exploit the fluxionality of the acetyl group in testing the reactivity of substituted tropones.[22] For example, it can be effectively employed for opening new perspectives in the utilization of 2,7-disubstituted tropones by generating *in situ* a reactive form (Scheme 4). To prove this hypothesis, a range of 7-aryl-2-acetoxytropones **1b-OAc**–**1e-OAc**[23] were readily accessed (see SI for synthetic details and single crystal X-ray characterization of **1b-OAc**) and subjected to optimal alkylating conditions with **2a**. Satisfyingly, four different 6-aryl-2-alkyl-tropones **3ba**–**3ea** were obtained in moderate yields (up to 47%).

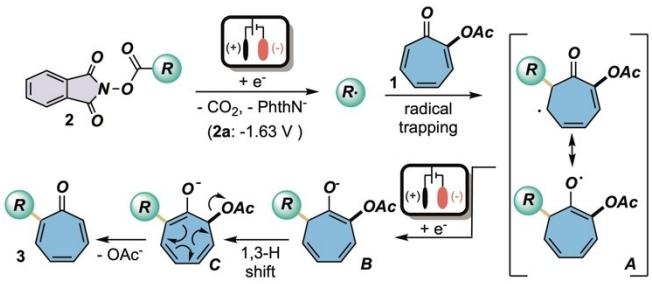
Analogously, acetylated β-thujalpicin **1f-OAc** underwent an electrochemical alkylation process with **2a**, delivering the 2,5-disubstiuted tropone **3af** in 51% yield via site-selective C(sp^2)–C(sp^3) bond forming reaction at the less hindered position. Importantly, the present procedure was also applicable to Colchiceine acetate **1g**,[24] prepared from naturally occurring Colchicine **I** in two steps. A site selective alkylation with **2a** occurred at the less hindered position, resulting in alkylated Colchicine analogue **3ga** as a single isomer in 49% yield. The latter applications underlined the suitability of the present electrochemical methodology for late-stage functionalizations of tropone-based bioactive scaffolds.



Scheme 4. Scope of the reaction: screening of substituted tropones.

The documented electrochemical analyses and the site-specificity recorded on the alkylation of substituted tropones, prompted us to propose the reaction machinery for the present electrochemical functionalization of tropones as depicted in Scheme 5. The experimental evidence led us to conclude that the electroreductive process begins with a monoelectronic cathodic reduction of RAE **2** with consequent fragmentation of the molecule, to deliver a nucleophilic radical species (R•). Therefore, R• is trapped chemoselectively at the most electrophilic α-position of tropone, resulting in the open-shell intermediate **A** stabilized by an extensive delocalized π-system,.[20a] A second cathodic reduction forms the enolic form **B** that can undergo 1,3-hydrogen shift towards isomer **C**, capable of finalizing the re-aromatization step via elimination of the acetoxy unit.

Overall, a formal nucleophilic aromatic substitution (NAS) occurred and the postulated NAS' *vs* NAS regiochemistry is supported by the selectivity recorded starting from functionalized tropones (*i.e.* **1b**–**g**).



Scheme 5. Mechanistic sketch. The electrochemical is finalized by the sacrificial anode oxidation (Zn).

In conclusion, we have documented the first general entry to α-alkyl tropones via a direct and site-selective electrochemical C(sp^3)–C(sp^2) coupling concept. Paving the ways of new tropone chemistry, this protocol shed the first light into radical synthetic transformations of this class of compounds. A wide range of simple (primary, secondary, tertiary) as well as highly decorated alkyl radicals served for the preparation of the target compounds and the use of readily available 2-acetoxytropones enabled the realization of a highly regioselective protocol. Mechanistic elucidation via voltammetric analysis and efficient late-stage functionalization of bioactive scaffolds completed the present investigation.

Experimental section

General Procedure for the electrochemical alkylation of tropone ***1a*** *(*Scheme 3*).* The ElectraSyn vial (5 mL), equipped with a stir bar, was charged with 2-acetoxytropone **1a** (0.30 mmol, 2.0 equiv., 49.2 mg), the desired RAE **2** (0.15 mmol, 1 equiv.) and $TEABF_4$ (0.30 mmol, 65.0 mg). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ag), was inserted into the mixture and closed with a rubber septum. The vessel was evacuated and backfilled with Ar three times, then dry DMF (3.0 mL) was added, and the mixture stirred until complete dissolution of the solids occurred while the mixture was bubbled with Ar (balloon). The reaction mixture was electrolyzed (under Ar, balloon) at a constant current of 3.0 mA, until a total charge of 0.30 mF (2.0 F/mol^2) was reached. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (10 mL) and NH_4Cl(aq) (1 M, 10 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with NH_4Cl(aq) (0.1 M, 3×20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was finally purified by FC to afford pure products **3**.

Acknowledgements

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