RESEARCH ARTICLE doi.org/10.1002/adsc.9592 ADVANCED SYNTHESIS & CATALYSIS

Electrochemical Chemo- and Regioselective Heterofunctionalization of Tropones via C(sp^2)—H Derivatization

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Abstract: A general electrochemical synthetic procedure for the site-selective heterofunctionalization of activated tropones is documented. Detailed voltametric analysis and quantum chemistry calculations enabled the development of a predictive model for the process efficiency, accounting for both reactivity and regioselectivity. Mono- and poly-halogenation, nitration, sulfonation, and thiocyanation protocols are successfully executed starting from inexpensive sodium salts under oxidative electrolytic conditions (35 examples, isolated yields up to 95%, faradaic efficiencies up to 95%). The implementation of an iterative electrochemical/metal-catalyzed cross-coupling synthetic strategy, along with the adaptation of the protocol for the preparation of biologically relevant tropolone derivatives, underscores the generality and robustness of the methodology.

Keywords: electrosynthesis, functionalization, mechanistic interpretation, regioselectivity, tropone

1. Introduction

The introduction of heteroatoms onto aromatic rings, via electrophilic aromatic substitution, has continuously been standing as one of the grounding milestones of synthetic organic chemistry. Besides altering the electronic and steric properties of the core itself, these groups often serve for further functionalization and conjugation.[1] For example, arene decoration with halogens frequently anticipates subsequent metal-catalyzed cross-couplings to install new C—C bonds, while N—, O—, and S—connectivity may serve as a linkage to a diverse range of branches.[2]

Categorizing this ample scenario based on reactivity profiles, two major strategic courses can be identified: the employment of nucleophilic or electrophilic precursors. The first consists of cheap, abundant, and easy-to-handle inorganic salts, such as halogenides, nitrites, sulphinates, sulphides, azides, etc. These, however, often represent a thermodynamic sink, rendering the functionalization of electron-poor arenes a challenging task.[3] On the other hand, electrophilic molecular halogens,

N-halosuccinimides, nitronium ion, sulfuric anhydride, etc., show exquisite reactivity but are frequently toxic or require very harsh conditions for their preparation. These shortcomings limit the broad applicability and often require special handling and dedicated equipment (**Figure 1**a).[4] A valuable alternative to both "polar" approaches is represented by radical species,[5–11] which could be conveniently generated by oxidation of the corresponding anions. Here, electrochemistry has emerged as a powerful tool to realize this oxidative process in a clean and sustainable way.[12] This technique relies solely on electricity for the efficient anodic generation of transient electrophilic radical species, and it offers an unparalleled opportunity to modulate the intrinsic chemical behavior through precise adjustment of applied conditions.

In the realm of "flat-land" (i.e., arenes), tropone and tropolones are gaining growing credit both as platforms to develop new synthetic methodologies[13] and as starting materials for the preparation of naturally occurring and bioactive compounds.[14] Despite the large volume of efforts invested toward the "dearomative" functionalization of the nonbenzenoid aromatic core, the seek for direct functionalization protocols of the seven-membered ring, via direct C(sp^2)—H functionalization, is still in its infancy.

Our scientific interests in electroorganic synthetic chemistry[15] and gold-catalyzed aromatic functionalization[16] enabled the discovery of unique and complementary reaction profiles of tropones/tropolones toward polar as well as radical species (Figure 1A).[17] In particular, we elucidated that by selecting the reaction modality (polar vs radical), it was possible to intrinsically steer the regiochemistry of the functionalization: radical at C(7) and polar at C(5). Despite the undoubted synthetic values, all the reported protocols dealt with a single C—H functionalization, leaving site-selective approaches to multiple decorations undisclosed.

In this direction, our attention was caught by a recently disclosed class of nucleophilic tropones, featuring amino groups as traceless umpolung activating "tags" at C(2)-position.[18] In particular, by postulating a competence of 2-aminotropones **1** toward the trapping of electrophilic radicals, we planned to realize a direct electrochemical heterofunctionalization protocol that would be of utmost importance to further expand the attractiveness of the titled seven-membered scaffold in synthetic organic chemistry.[19] In this context, our working plan relied on the generation of electrophilic radicals via anodic oxidation of cheap and readily available inorganic salts that could lead to a productive

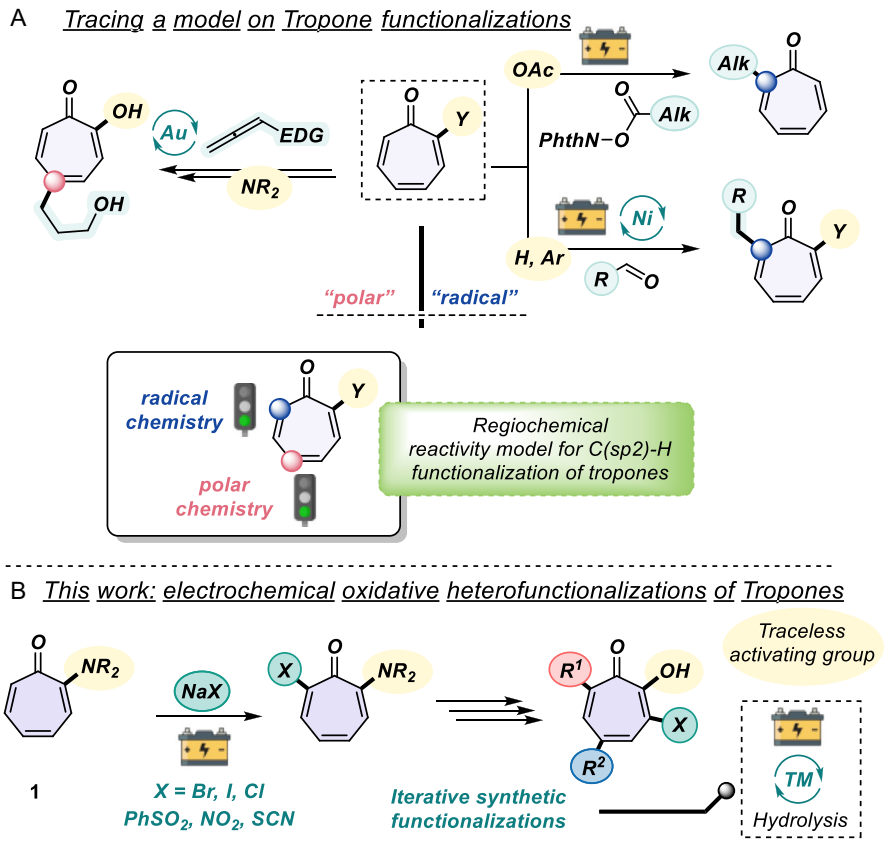


Figure 1. A) Building a regiochemical model for the direct C—H functionalization of tropone/tropolones. B) The present strategy: highly efficient, chemo- and regioselective mono- and polyfunctionalization of (tracelessly) activated tropones by means of an oxidative electrochemical approach.

functionalization when the oxidation of the anions takes place at lower voltages compared to the tropone derivative (Figure 1B). As a matter of fact, dealing with single-electron-transfer oxidation of the arene as the first electrochemical event could trigger uncontrolled dimerization/polymerization of the starting material. If successful, the way toward a single and unified strategy to the direct electrochemical mono- and poly-heterofunctionalization of tropones would be traced.

2. Results and Discussion

We therefore considered several anions as precursors of fundamental functional groups, namely: halides (i.e., bromide, iodide, and chloride),[5] benzenesulphinate,[6] nitrite,[7] thiocyanate,[8] trifluoromethanesulphinate,[9] azide,[10] and 2-naphthalenethiolate.[11] These, taken as the most convenient form in terms of availability and solubility (organic or alkaline metal salts, or respective acid), were subjected to a comparative cyclovoltammetry analysis together with **1a**.

The recorded oxidation potentials (three-electrode cell, $LiClO_4$ electrolyte, data reported vs the Fc/Fc^+ couple, **Figure 2**A) originate from two families of electroactive compounds, giving rise to a thumb rule for the selection of which ions could be potentially suitable for the present protocols. Indeed, the ones showing a E_p lower or in close proximity to the oxidation of **1a** (0.46 V), namely bromide (0.43 V), iodide (0.02 V), benzenesulphinate (0.19 V), nitrite (0.32 V), and thiocyanate (0.44 V)

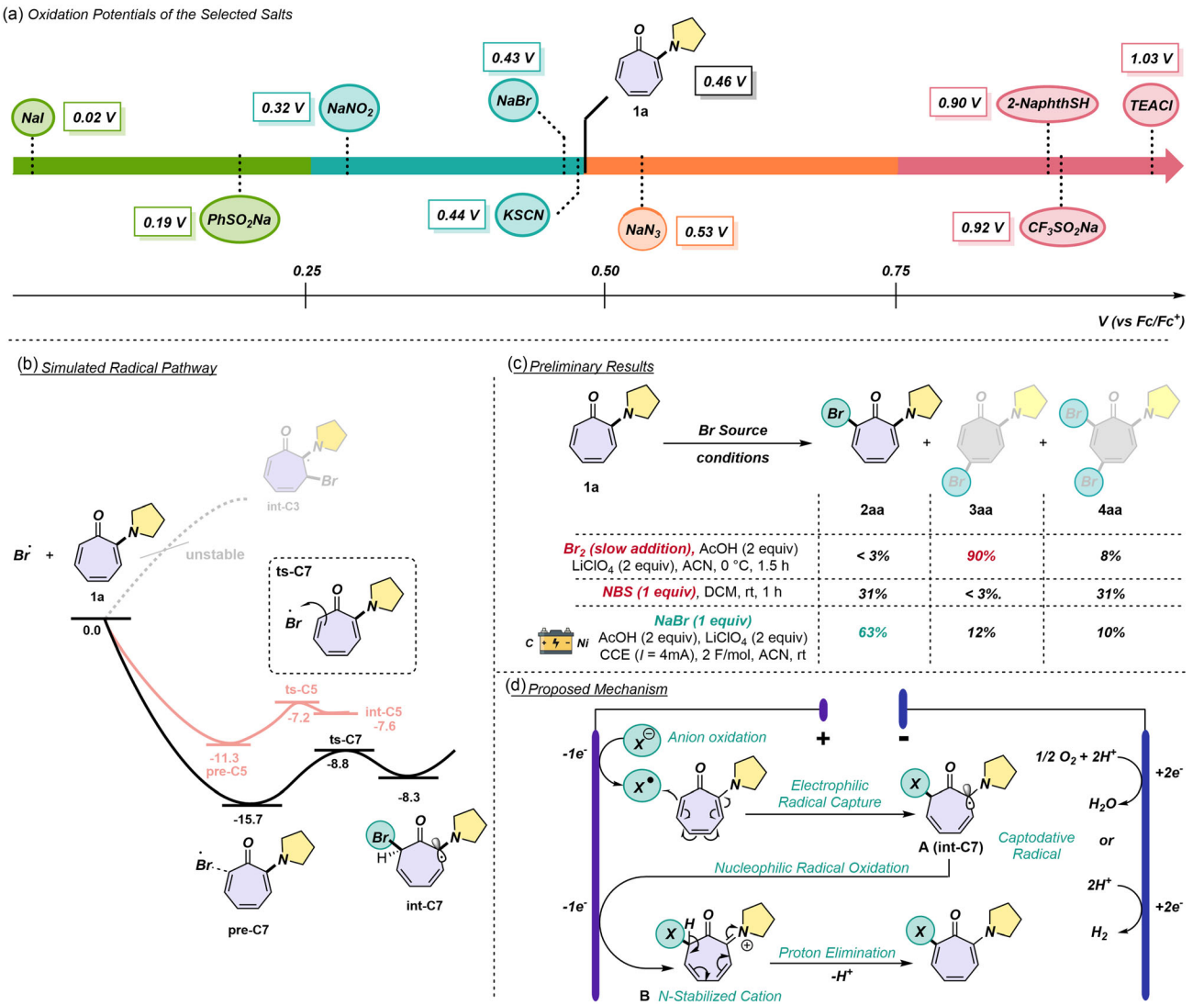


Figure 2. A) Oxidation potentials (vs Fc/Fc^+) of the selected salts. For the experimental conditions and CV curves, see the Supporting Information. B) Suggested reaction mechanism computed at the DLPNO-CCSD(T)/Def2TZVP/PCM(ACN)//M06/Def2svp/PCM(ACN) level of theory. The energies are reported in kcal/mol and correspond to relative ΔG with respect to the starting materials. C) Preliminary results on the bromination of **1a** (for specific reaction conditions see the Supporting Information). D) Proposed reaction mechanism (TEAI = tetraethylammonium iodide, TEACl = tetraethylammonium chloride).

could be predicted as competent, while chloride (1.03 V), trifluoromethanesulphinate (0.92 V), azide (0.53 V), and naphthalenethiolate (0.90 V) could be suggested as unproductive.

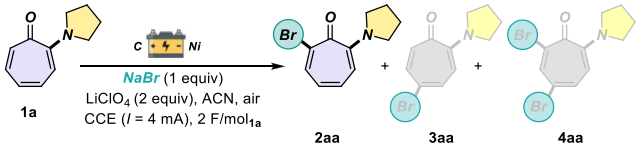
To test the feasibility of our working hypothesis, we selected the bromination with NaBr as a general model reaction. Based on Figure 2A, bromination should be a challenging functionalization, yet most productive, as its oxidation potential (NaBr, 0.43 V) resulted quite close to that of **1a**. Additionally, our choice to employ 2-aminotropone **1a** was dictated by the presence of three different nucleophilic positions (i.e., C(3), C(5), and C(7)) that pose severe regioselective interrogatives which needed careful considerations. In this direction, we have already demonstrated that **1a** can selectively capture cationic species at the C(5)-position,[17c] so we moved to predict, by means of combined density functional theory (DFT)/DLPNO-CCSD(T) calculations (see SI for details, DFT), whether this is also the case with electrophilic radicals.[20] The results, shown in Figure 2B, suggest that, on the contrary, the capture of a bromine radical should occur selectively at the C(7)-position due to the increased stability of the resulting allylic radical intermediate (black path). In particular, the bromine radical approaches **1a** and forms the dipole radical precomplex **pre-C7**, which is stabilized by 15.7 kcal mol^{-1}. Subsequently, a C─Br covalent bond is formed, which requires an activation energy of only 6.9 kcal mol^{-1}. **Int-C7** is, thus, formed, which is stabilized by 10.6 kcal mol^{-1} with respect to the starting reagents. The path for substitution at **C5** is similar, but the involved intermediates and transition states are systematically less stable (red path). Finally, the C(3)-bromination proved energetically unfeasible due to the high instability of the α-amino radical intermediate **int-C3**.

Taken together, these data suggest that the target electrochemical bromination reaction is feasible and potentially very selective. We, thus, moved to verify these hypotheses by running three bromination reactions under different conditions: i) Br_2; ii) *N*-bromosuccinimide (NBS); and iii) electrochemical oxidation of NaBr (Figure 2C). Interestingly, while electrophilic bromination with Br_2 gave selectively product **3aa** (90% yield), along with di-halogenated **4aa** (8% yield), the use of NBS showed major regioselectivity toward the C(7)-position (**2aa**, 31% yield) but poor yield and chemoselectivity (equimolar amount of **4aa** being formed). Gratifyingly, the electrochemical protocol[21] resulted in good accordance with the predictions, giving 63% yield of C(7)-adduct **2aa** predominantly (5.3:1 ratio with **3aa** and 10% yield of **4aa**). These findings confirmed a complementary regioselectivity between the electrochemical (radical) protocol and the polar (Br_2) one. Furthermore, a superior chemoselectivity was observed in comparison to NBS, as the slow and controlled generation of the reactive species, intrinsic to the electrochemical setup, allows to easily discriminate between **1a** and **3aa** for the radical capture.

The combined cyclic voltammetry (CV) analysis, quantum chemistry calculations, and preliminary experimental data suggest the operating mechanism, depicted in Figure 2D. Oxidation of the target anion gives rise to an electrophilic radical that is intercepted by **1a** to form a highly stabilized radical intermediate **A.** This benefits from multiple resonance forms (diene) and a captodative effect from the synergistic interaction with the pyrrolidine and the keto-group. **A** can be further oxidized to iminium ion **B** that, upon proton elimination, gives rise to final product **2**.[22] Reduction of oxygen or protons (produced by the electrochemical reaction) can occur as cathodic events to counterbalance the overall anodic process.[23] Importantly, the formation of electrophilic dimers (radical–radical coupling), or cationic species (radical oxidation), although frequently reported in similar electrochemical processes,[24] can be ruled out in all present cases where a high C(7) regioselectivity (products **2**) is observed, as the latter species (i.e., molecular bromine) would render C(5)-functionalized adducts **3**.

In order to maximize both yield and the regi-o/chemoselectivity, we then moved to the optimization of the electrochemical protocol (**Table 1**). A survey of reaction parameters revealed that the best chemical

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

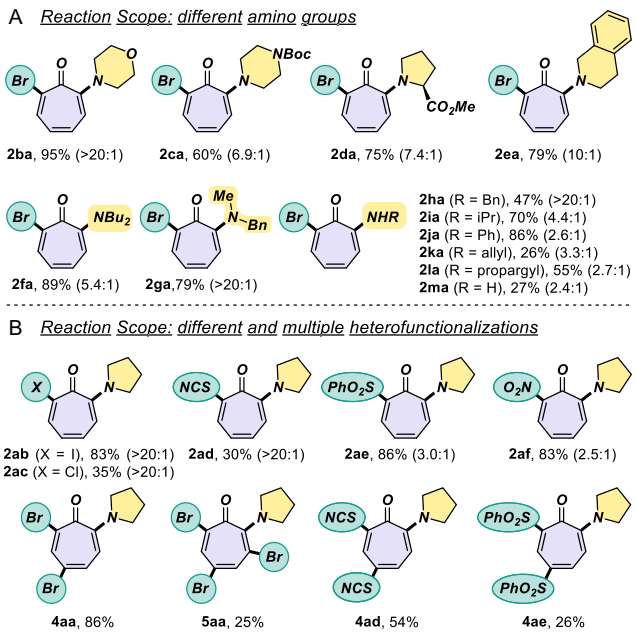


Entry	Deviation from optimal conditions	Y **2aa** [%][b)]	Y **3aa**/**4aa** [%][b)]
1	None	93[c)]	3/–
2	Reaction run under Ar	67	13/11
3	Reaction run under Ar, AcOH (2 equiv)	63	12/10
4	Pt(+) instead of $C_{graph.}$(+)	60	10/6
5	GC(+) instead of $C_{graph.}$(+)	68	8/17
6	$C_{graph.}$(−) instead of Ni(−)	63	10/13
7	Ag(−) instead of Ni(−)	86	–/10
8	DMF instead of ACN	75	10/6
9	DMSO instead of ACN	60	4/6
10	$TEABF_4$ instead of $LiClO_4$	54	4/8
11	LiBr (2 equiv) instead of NaBr, no $LiClO_4$	73	10/14

[a)] All reactions were carried out in the ElectraSyn 2.0 apparatus by means of an undivided cell at room temperature. **1a**:NaBr:electrolyte = 1:1:2, [**1a**] = 0.05 M;
[b)] Yield calculated by ^{1}H NMR analysis on the crude mixture, with CH_2Br_2 as the internal standard;
[c)] Isolated yield after flash chromatography. (DMF: dimethylformamide; DMSO: dimethyl sulfoxide; ACN: acetonitrile).

outcome was achieved with stoichiometric amounts of NaBr as brominating agent, by running the reaction under air in CH_3CN as the solvent (entries 8, 9) and using $LiClO_4$ as supporting electrolyte. Optimal electrochemical parameters also involved: galvanostatic electrolysis ($I = 4$ mA), with a Ni (cathode) and $C_{graphite}$ (anode) electrode couple (entries 4–7), and a stoichiometric amount of electrons (2 F mol^{-1}). In this case, a faradaic efficiency close to 100% was observed. Interestingly, atmospheric oxygen was proven to promote reduction of H^+ as the main cathodic event (entries 2 and 3, see Figure S2, Supporting Information for details) and the presence of Li salts as supporting electrolytes showed improved yields and selectivity (entry 1 vs 10),[25] while the usage of sole LiBr as both electrolyte and brominating agent worsened the results, considerably (entry 11).

The scope of the bromination reaction was then assessed by applying the optimal conditions to a range of tropones featuring different amino activating groups (**1b**–**m**, **Scheme 1**A). Tertiary (both symmetrical, unsymmetrical, cyclic, and noncyclic, **1b**–**g**) as well as secondary (both aliphatic **1h**, **1i**, **1k**, **1l,** and aromatic **1j**) amines showed excellent competence in undergoing the target electrochemical heterofunctionalization (yield up to 95% and C(7):C(5) selectivity up to 20:1). Interestingly, the unsubstituted primary amine **1m** was also capable to furnish the corresponding C(7)-bromo derivative in moderate efficiency.



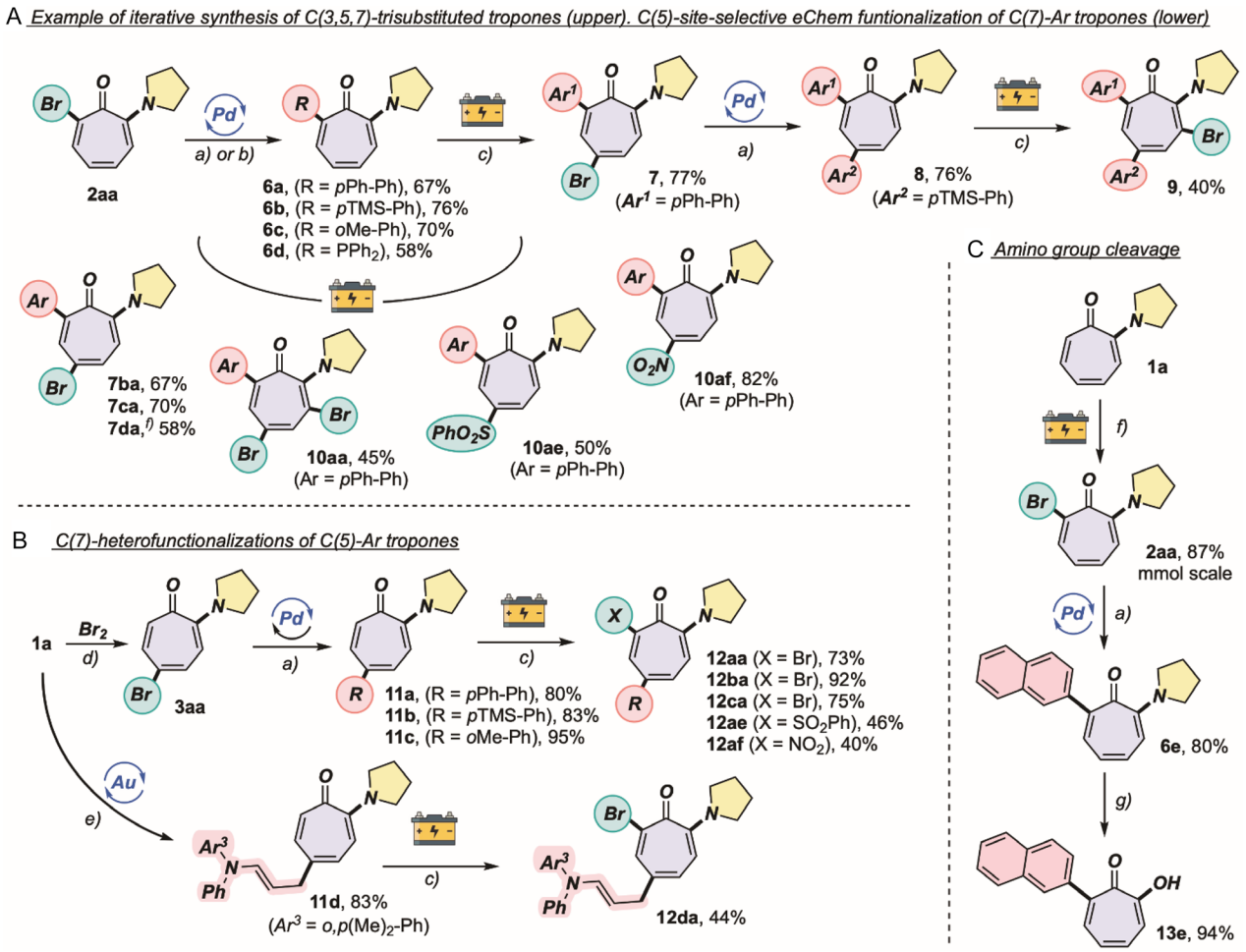
Scheme 1. A) Scope of different α-aminotropones **1** in the electrochemical bromination protocol. In brackets the **2**:**3** ratio is reported. All reactions were carried out under optimal conditions (Table 1, entry 1), see General Procedure **A** in the Supporting Information for details. B) Other heterofunctionalization products. For specific reaction conditions, see General Procedure **B** in the Supporting Information.

We then moved to validate the thumb rule proposed in Figure 2A in order to expand the portfolio of functional groups to accommodate the tropone scaffold (Scheme 1B). Not surprisingly, on the basis of the electrochemical responses, iodination toward **2ab** was achieved in high yield (83%) and selectivity (C(7):C(5) > 20:1) using tetraethylammonium iodide (TEAI) as the iodide source. The introduction of an –SCN group (**2ad**) proved to be more challenging, as the formation of doubly substituted compound **4ad** was very difficult to avoid, probably due to the slightly activating nature of this group on the arene core. Indeed, direct double functionalization toward **4ad** proceeded in higher yield (vide infra). Sulfonation (**2ae**) and nitration (**2af**) proceeded smoothly in high yields in the presence of $PhSO_2Na$ (86%) and $NaNO_2$ (83%), respectively. Importantly, the introduction of electron-withdrawing groups at the tropone core has no precedents in literature, due to the electrophilic nature of native tropone and the instability of the nucleophilic variants (2-alkoxy or 2-aminotropones) toward the strongly acidic conditions (i.e., sulfonitric mixture, fuming oleum, etc.).

These results show that all the anions tested, displaying a lower oxidation potential with respect to **1a**, proved competent in the present protocol, validating our model. Contrarily, azidation with NaN_3, trifluoromethylation with Langlois' reagent and thiolation with 2-thionaphthol failed to render the respective products, as predicted by the oxidation potential higher than that of 0.46 V (vs Fc/Fc^+). However, when a chlorination with tetraethylammonium chloride (TEACl) was attempted, the desired product **2ac** was obtained, albeit in low yield (35%). In this case, the significant increase in the cell voltage recorded could result in partial oxidation of the chloride ion, along with a massive decomposition of **1a**.

To further demonstrate the effectiveness of the present electrochemical method, we aimed at direct access to multiple functionalizations, also inspired by the formation of **4aa** as a byproduct in the bromination reactions. Indeed, by simply doubling the equivalents of NaBr and electrons (4 F mol^{-1}), product **4aa** was achieved in high yield (86%), with exquisite faradaic efficiency. On the contrary, the one-pot C(3,5,7)-tri-bromination reaction resulted more challenging to be realized starting from **1a**, as the requested prolonged reaction time led to an inevitable voltage increase and lost in chemoselectivity. Nonetheless, the desired tribrominated **5aa** was isolated in 25% yield. Double thiocyanation (**4ad**, 54% yield) and double sulfonation (**4ae**, 26% yield) were also possible. Interestingly, in all cases, the second functionalization proceeded selectively at the C(5)-position, suggesting this as the second most reactive one in the present protocol.

The availability of C(7)-brominated tropone **5aa** inspired us to investigate the convenient access to C(3,5,7)-trifunctionalized tropones (**10**) via a convenient iterative approach, alternating metal-catalyzed cross-



Scheme 2. A) Functionalization of **2aa** and sequential electrochemical manipulations. B) Preparation and functionalization of **3aa** and sequential electrochemical functionalizations. C) 1-mmol scale process and removal of the activating amino-group. Reaction conditions: a) For the preparation of **6a**–**c**, **11a**–**c,** and **8**: $ArB(OH)_2$ (2 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), Cs_2CO_3 (2 equiv), THF/H_2O (10:1), 70 °C, 3 h (see General Procedure **C** in the Supporting Information for details). b) For the preparation of **6d**, $PHPh_2$ (1.2 equiv), $Pd(OAc)_2$ (5 mol%), dppf (6 mol%) NaOtBu (1.2 equiv), PhMe, 120 °C, 18 h. c) See General Procedure **A** and General Procedure **B** in the Supporting Information for details. d) Br_2 (1 equiv), $LiClO_4$ (2 equiv), AcOH (1 equiv), ACN, 0 °C, 1.5 h. e) See ref. [17c]. f) Isolated as the corresponding phosphine oxide. g) NaOH (6 M), $EtOH/H_2O$, 100 °C, 6 h. THF: tetrahydrofuran.

coupling reactions and electrochemical brominations (**Scheme 2**A). In this way, chemical diversity can be achieved by exploiting the decreasing reactivity order on electrochemical bromination of the tropone core **1a** as follows C(7) > C(5) >> C(3).

At first, by subjecting **2aa** to Pd-catalyzed cross-coupling reactions, a range of C(7)-aryl/phosphino tropones (**6a**–**d**) was isolated in high yields (up to 76%). Then, these species were adopted as starting materials to extend the range of applicability of our functionalization protocol, now targeting position C(5). Mono- (**7aa**–**7da**, up to 70% yield) and dibromination (**8aa**, 45% yield), as well as sulfonation (**7ae**, 50% yield) and nitration (**7af**, 82% yield) reactions could be carried out efficiently. Then we carried out the proposed iterative triple functionalization on compound **7aa**, from which 2-amino-5,7-diaryl tropone **9** and the corresponding C(3)─Br analog **10** could be obtained in synthetically useful yields by means of only two chemical setups.

Thereafter, we took advantage of the regiochemical complementarity of our protocol with Br_2 bromination, preparing **3aa** in 90% yield. This allowed a family of 2-amino-5-aryl tropones **11a–c** to be formed via Suzuki coupling (80%–95%, Scheme 2B). Further chemical complexity was finally accessed directly by adopting our electrochemical oxidative procedure, leading to a selective bromination (**12aa**–**12ca**, up to 92%), sulfonation (**12ae**, 46%), and nitration (**12af**, 40%) with complete C(7)-selectivity. Finally, tropone **11d**,[17c] was also engaged in the electrochemical bromination protocol, obtaining product **12da** in moderate yield.

The robustness of the procedure was then assessed with a 1 mmol-scale reaction on compound **1a**; gratifyingly, no trace of performance loss was observed (87%, Scheme 2C).

Finally, the traceless profile of the activating pyrrolidine unit at the C(2)-position was exploited for the synthesis of biologically relevant naphthyl-tropolone **13e**[26] that was isolated in 65% overall yield (three steps from **1a**) after basic hydrolysis of the pyrrolidine unit.

3. Conclusion

In conclusion, we demonstrated the possibility to realize a general site-selective mono- and poly-heterofunctionalization of activated tropones following an electrochemical oxidative protocol, employing cheap and easy-to-handle sodium salts as precursors of diverse functional groups. A predictive model for the process efficiency and selectivity, based on CV and quantum chemistry calculation studies, was then validated by the tested anions. Finally, we demonstrated how the combination of this electrochemical heterofunctionalization with common complementary halogenation procedures and metal-catalyzed cross-couplings can open a plethora of diversified decorations of the tropone scaffold.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

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