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Research Article

# Electrochemical Nickel-Catalyzed C(sp$^2$)-H Functionalization of Tropones with Aldehydes

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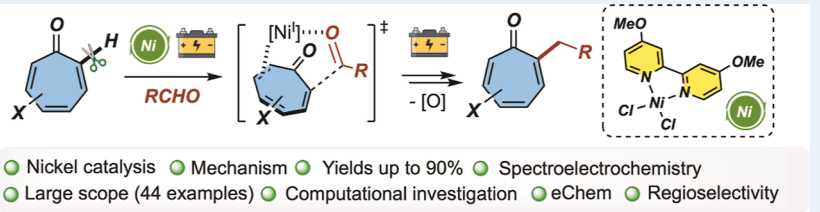


**ABSTRACT:** A direct electroreductive functionalization of tropones employing aldehydes as alkylating agents is reported. This C(sp$^2$)-H functionalization process leverages the mediation of electroactive nickel complexes, enabling a wide range of both native and substituted tropones (44 examples) to be alkylated selectively at the $\alpha$-position in high yields (up to 90%). Combined electrochemical, spectroelectrochemical, and computational analyses disclosed the whole mechanistic pathway and revealed the key role played by reduced Ni complexes in activating the tropone core toward condensation with the aldehydes.

**KEYWORDS:** *electrosynthesis, nickel-catalysis, tropones, aldehydes, DFT calculations, cyclovoltammetry*

## INTRODUCTION

Tropone and tropolone derivatives are widely distributed in naturally occurring compounds and bioactive ingredients.[1] Colchicine, purpurogallin, harringtonolide, and roseobacticide B are representative examples of densely polycyclic scaffolds that include the cycloheptatrienone scaffold (Figure 1a).[2] Not surprisingly, attention to tropone synthetic chemistry grew rapidly leading to the publication of elegant total syntheses of tropone-based bioactive compounds.

However, from a synthetic viewpoint, the peculiar seven-membered structure combined with its nonbenzenoid aromaticity appoints tropo(lo)nes as nontrivial platforms to generate chemical complexity. As such, they call for innovative synthetic organic transformations.

Nowadays, the existing portfolio of tropone chemistry primarily focuses on dearomative cycloaddition reactions[3] or the de novo assembly of the 7-membered ring.[4] Conversely, investigations into chemical tropone decorations, via direct C−H functionalization, still remains largely elusive.[5] Impracticability of Friedel−Crafts-type transformations (tropone features an overall electron-poor aromatic core); atypical reactivity of the formal C═O unit (tropone is better represented as tropylium oxide), and high propensity toward dearomatization processes represent the most stringent traits that still narrow this scenario (Figure 1b).

To overcome these issues, we propose a new functionalization strategy built upon considering a chemical conceptual analogy between $\alpha,\beta$-unsaturated carbonyls (i.e., cyclohexanone or

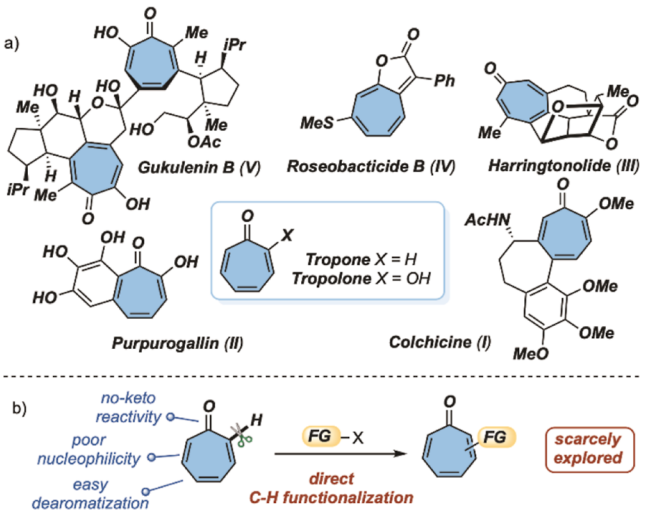


**Figure 1.** (a) Tropo(lo)nes: ubiquitous platforms for bioactive structures. (b) Main shortcomings that still limit the functionalization of tropone via C−H functionalization.

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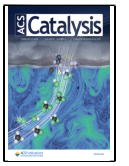
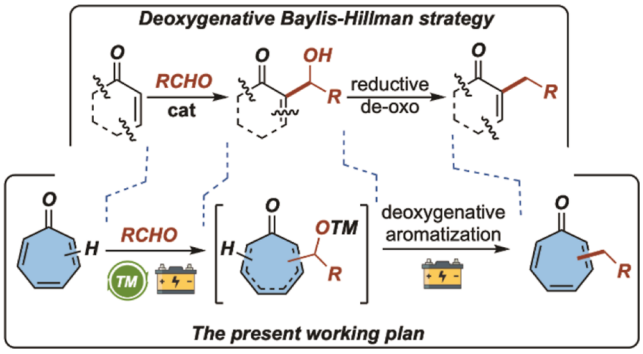


methyl acrylate) and tropones, with a focus on the well-established deoxygenative Baylis–Hillman strategy (Scheme 1-up), where after the (redox-neutral) Baylis–Hillman reaction has taken place, a following distinct reductive deoxygenation step is carried out.[6]

**Scheme 1. Present Electrochemical Strategy for the Direct Access of C–H Functionalization of Tropones Gets Inspired by the Deoxygenative BH Reaction**




In particular, we hypothesized that direct C–C bond formation on the seven-membered ring could be achieved under reductive electrochemical conditions using aldehydes as convenient alkylating agents[7] and low-oxidation state transition metals (TMs) to trigger a cross-electrophile-coupling-like strategy.[8] In addition, the formation of metal-alkoxide intermediates could facilitate the situ final deoxygenation stage without the need for exogenous stoichiometric reducing agents (Scheme 1-bottom).

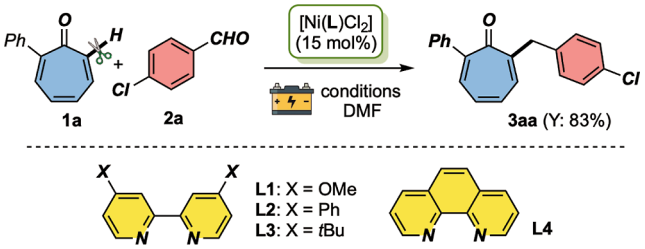
The feasibility of this working plan is strongly substantiated by our recent experience in proving electroreductive cross-electrophile couplings as an excellent enabling technology for the efficient functionalization of both Morita-Baylis–Hillman[9] and tropone derivatives.[10]

## METHODS

In particular, due to the well-established efficiency of nickel complexes in mediating electrocatalytic organic transformations,[11] we preliminarily targeted readily available and air-stable bispyridil-Ni(II) complexes [Ni(**L**)$Cl_2$] in the presence of 2-phenyl-tropone **1a** and *p*-Cl-benzaldehyde **2a** as model substrates. Remarkably, the presence of a catalytic amount of a nickel complex (15 mol %) proved essential to guarantee synthetically useful conversions (entry 1 vs entries 2–5). In detail, by means of the sacrificial anode strategy (Zn), isolated yields up to 83% on the site-selective $\alpha$-alkylation of **1a** were recorded (entry 2, Table 1). Here, 4,4′$(OMe)_2$-bpy (**L1**) appeared as the ligand of selection among those tested (**L1–4**). Moreover, from the electrode-couple screening, it is worth mentioning that a metal cathode and a Zn anode are essential to get a productive outcome, with the Ni(−)/Zn(+) couple proving superior with respect to all other combinations tested (i.e., W/Zn, C/Zn, SS/Zn, and Ni/Mg, entry 2 vs entries 6–9).

Additionally, optimal reaction conditions involved constant current electrolysis (CCE, $I$ = 2 mA) providing 4 F/mol with reference to the limiting reagent **2a**, stoichiometrically necessary to react all reagent **1a** (entries 2 vs entries 10 and 11), and using tetraethylammonium tetrafluoroborate ($TEABF_4$) as the electrolyte (entries 2 vs entries 12 and 13).

**Table 1. Optimization of the Reaction Conditions**[a]




| run | L | electrolysis conditions | yield **3aa** (%)[b] |
|---|---|---|---|
| 1 | [c] | Ni/Zn, 2 mA, 4 F/mol, $TEABF_4$ | 15 |
| 2 | **L1** | Ni/Zn, 2 mA, 4 F/mol, $TEABF_4$ | 83 |
| 3 | **L2** | Ni/Zn, 2 mA, 4 F/mol, $TEABF_4$ | 39 |
| 4 | **L3** | Ni/Zn, 2 mA, 4 F/mol, $TEABF_4$ | 65 |
| 5 | **L4** | Ni/Zn, 2 mA, 4 F/mol, $TEABF_4$ | 60 |
| 6 | **L1** | W/Zn, 2 mA, 4 F/mol, $TEABF_4$ | 75 |
| 7 | **L1** | SS/Zn, 2 mA, 4 F/mol, $TEABF_4$ | 54 |
| 8 | **L1** | C/Zn, 2 mA, 4 F/mol, $TEABF_4$ | NR |
| 9 | **L1** | Ni/Mg, 2 mA, 4 F/mol, $TEABF_4$ | traces[d] |
| 10 | **L1** | Ni/Zn, 3 mA, 4 F/mol, $TEABF_4$ | 26 |
| 11 | **L1** | Ni/Zn, 1.5 mA, 4 F/mol, $TEABF_4$ | 41 |
| 12 | **L1** | Ni/Zn, 2 mA, 4 F/mol, $LiBF_4$ | 24 |
| 13 | **L1** | Ni/Zn, 2 mA, 4 F/mol, TEACl | <10 |

[a]All reactions were carried out in an ElectraSyn 2.0 apparatus by means of undivided cell strategy at room temperature. Anhydrous conditions and inert atmosphere (i.e. $N_2$) were applied. **1a**/**2a**/electrolyte = 2:1:1.5, [**2a**]: 0.05 M. [b]Isolated yield after flash chromatography. [c]In absence of Ni-catalyst. [d]Extensive decomposition of **1a** was observed in the reaction crude. NR: no reaction.

The generality of the present electrochemical procedure was then assessed by subjecting a range of $\alpha$-substituted tropones (**1b–s**) as well as native tropone **1t** to reductive alkylating conditions with a family of aldehydes **2b–s** (aromatic as well as aliphatic). The obtained results are summarized in Scheme 2.

Aromatic aldehydes (**2b-n**) proved competent as benzylating agents regardless of the nature of the substituents and their positions (Scheme 2 upper). In particular, strong as well as mild electron-withdrawing groups (EWGs: F, $CF_3$, and Cl) could be accommodated at ortho-, meta-, and para-positions, ensuring satisfying levels of chemical outcomes (yield up to 77%). Analogously, aldehydes carrying electron-donating units (EDGs: alkyl, phenyl, and OMe) on the aromatic ring and benzofused carbonyls (**2c,d**) underwent the $\alpha$-benzylation of 2-phenyltropone **1a** in synthetically useful yields (44–81%). Interestingly, the alkylation methodology could also be extended to aliphatic aldehydes (**2o,s**). In this regard, linear and branched alkyl chains could be conveniently introduced in the seven-membered ring unit via direct activation of the C($sp^2$)-H bond (yield up to 52%). A range of $\alpha$-aryltropones was also compatible with this protocol (**1b–r**, Scheme 2 center), allowing combinations of substituted $\alpha$-aryl and $\alpha$-benzyl units without affecting the corresponding C–H functionalization/alkylation process. Notably, a wide range of functional groups (e.g., TMS, Ac, and CN) and heteroaromatic arenes were tolerated under these conditions, yielding the desired compounds **3** in moderate to very high yields (up to 83%). An excursion away from the starting aromatics also showed that $\alpha$-acetamide groups are compatible with this approach (**3sb**).

Although $\alpha$-substituted tropones were initially targeted aiming to exploit the higher stability of the corresponding alkylated compounds, we then turned our attention toward the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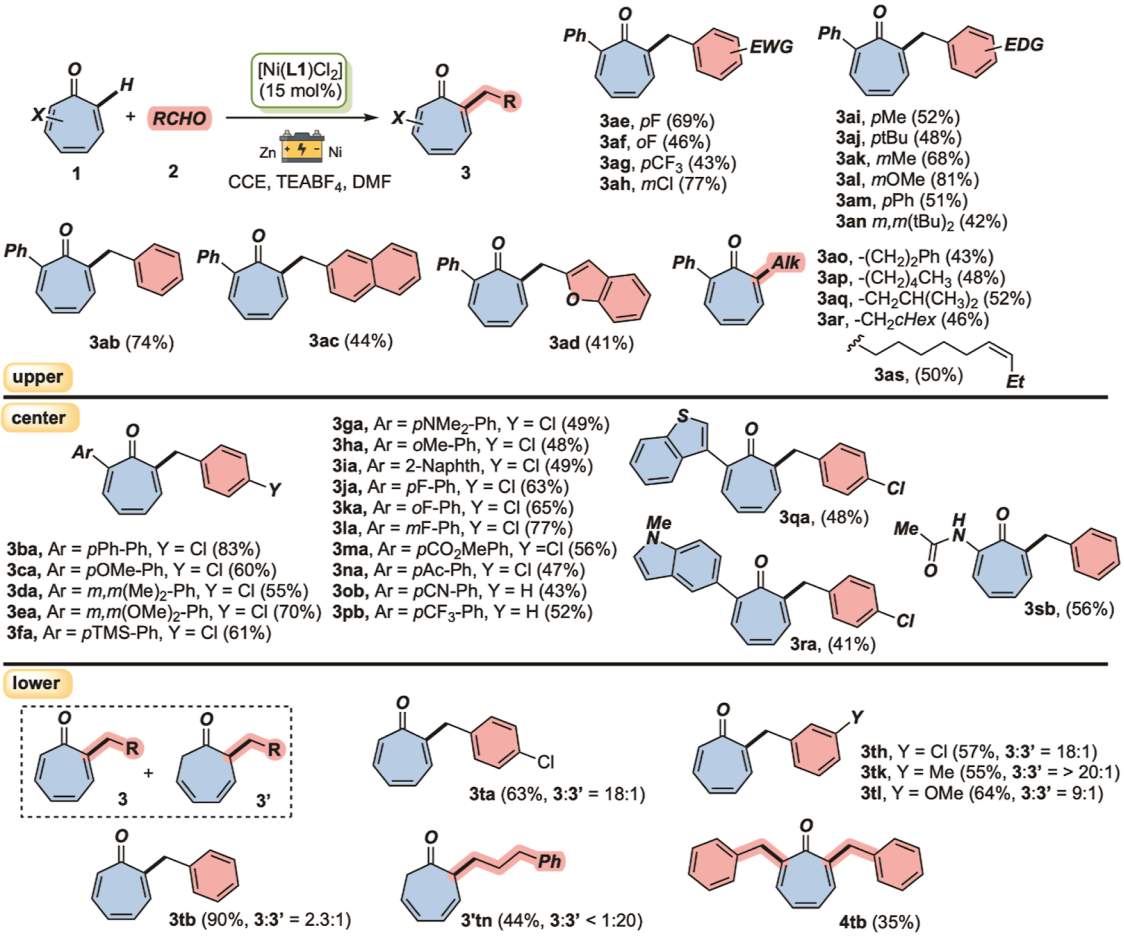
**Scheme 2. Scope of the Reaction. Upper: Screening of Different Aldehydes (1b-s) as Alkylating Agents. Center: Screening of Diversely $\alpha$-substituted Tropones. Lower: Testing the Unsubstituted Tropone 1t under Optimal Mono- and di-alkylating Electrochemical Conditions. All Reactions Were Carried out under Optimal Conditions Described in Table 1, Entry 2**



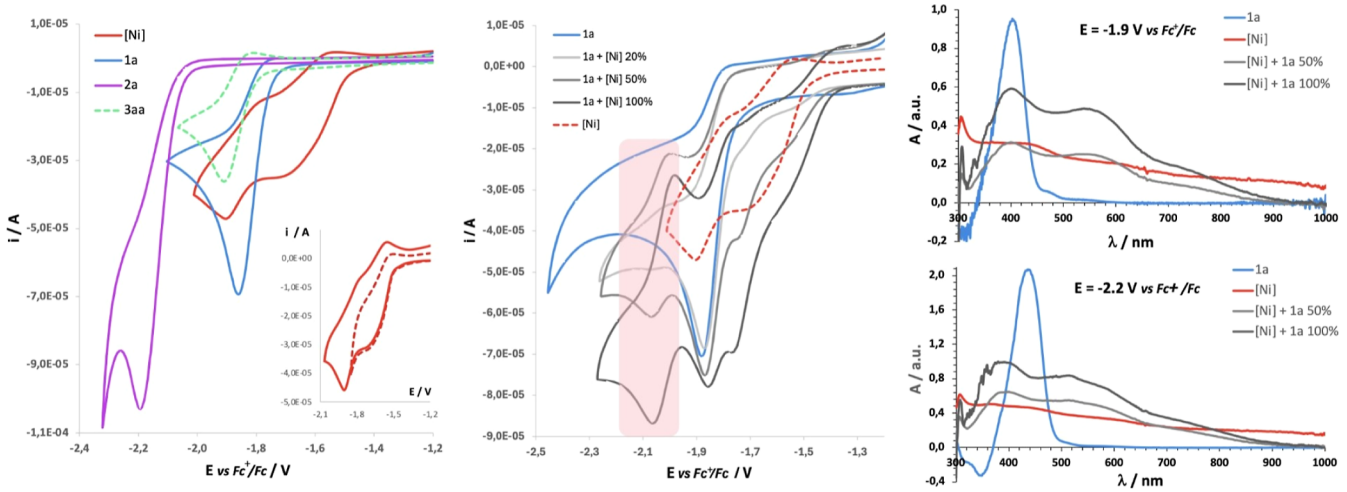




**Figure 2.** CV responses of (a) various species participating in the electrochemical reaction (inset highlights the two reduction processes of [Ni]) and (b) for subsequent addition of [Ni] in a solution containing a fixed amount of **1a** (pink bar highlights the new reversible reduction process ascribable to the intermediate of the reaction). Figure also reports UV−vis spectra recorded in the various solutions during the polarization of the electrode at (c) −1.9 V and (d) − 2.2 V vs $Fc^+/Fc$.

more challenging native tropone **1t** as a platform for the benzylation protocol (Scheme 2 lower).

Satisfyingly, the electrochemical $\alpha$-alkylation of the unsubstituted tropone was found to be highly efficient with a range of both aromatic and aliphatic aldehydes. In particular, combined chemical yields up to 90% (including partially reduced cycloheptadienones **3'**) were recorded. The use of tropone **1t** also inspired us to challenge our protocol with a one-pot double



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alkylation strategy. Interestingly, by using an excess of benzaldehyde (**2b**), the 2,7-dibenzylated tropone **4tb** was isolated in an unoptimized yield (35%).

In order to initiate the investigation of the reaction mechanism, cyclovoltammetric analyses were first conducted on the various reaction components. As observed from the voltammetric responses collected (3-electrode cell, Figure 2a), the [Ni(**L1**)$Cl_2$] complex ([**Ni**]) shows two reduction processes, the first occurring at −1.75 V vs the $Fc^+$/Fc redox couple, and the second one at −1.90 V. Therefore, the first reduction of this complex occurs at lower potentials with respect to the process involving both **1a** (−1.87 V) and **2a** (−2.18 V), suggesting that the catalytic cycle is initiated by a monoelectronic reduction of the starting Ni(II) complex to furnish a Ni(I) intermediate.

Then, to get further details about the initial stages of the reaction machinery, we conducted additional voltammetric experiments of the [**Ni**]-**1a** mixture, by systematically increasing the concentration of [**Ni**] in a solution at a fixed concentration of **1a** (Figure 2b).[12] A new peak appearing in the voltammograms of these mixtures suggests the formation of a new species showing a reversible reduction with $E_{1/2}$ = −1.98 V vs $Fc^+$/Fc (see the pink area in Figure 2b).

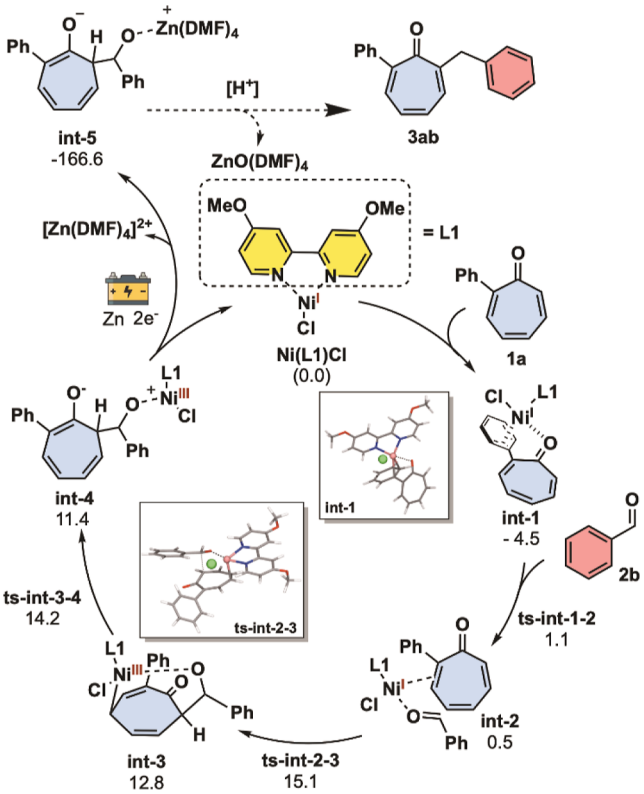
This could be ascribed to a [**Ni**]-**1a** intermediate being formed during the electrochemical reaction, increasing in intensity along with an increasing concentration of [**Ni**]. This new species is reduced at a more negative potential than the starting complex [**Ni**] and also at a different potential than that expected for the free **L1** (−2.72 V), allowing for its observation by CV analyses. A similar electrochemical process was also observed by adding **1a** to a solution containing a fixed concentration of [**Ni**] (see Figure S1). This new electroactive organo-nickel intermediate was therefore postulated as a key for the formation of **3aa** upon reaction with **2a** (vide infra on mechanistic investigation). To corroborate this hypothesis, we recorded UV−vis spectra of solutions containing either **1a**, [**Ni**] or mixtures of the two species while polarizing a Pt grid working electrode (spectra recorded at the various potentials are reported in Figure S2). Interestingly, spectra recorded right before (-1.90 V, Figure 2c) and after (−2.20 V, Figure 2d) the reversible reduction peak associated with the [**Ni**]-**1a** intermediate,[13] evidenced that this new species exhibits a main absorption at 560 nm in the neutral form (−1.90 V), or one at 520 nm after being reduced (−2.20 V). Furthermore, the lower intensity of the adsorption recorded at 400 nm (i.e., reduction of **1a**) when analyzing the mixture suggests that the starting tropone is involved in the reaction with [**Ni**]. Through computational exploration (vide infra), we have found a [**Ni**] complex whose simulated UV−vis absorption bands in the oxidation state Ni(I) correlate well with those found in these experiments (Figure S3−top). As a result, we have collected experimental and computational indications that in the initial stages of the reaction, Ni(II) is reduced to Ni(I), which subsequently reacts to form a complex with **1a,** resulting in an organo-nickel intermediate.

These intriguing results prompted us to perform a computational investigation to gain further insights into the underlying mechanism and the nature of the organo-nickel species involved. We employed density functional theory (DFT) calculations conducted at the SMD[14] (DMF) M06[15] /def2svp(p)[16] level of theory, using the Gaussian 09 software[17] (see the Supporting Information for the full computational protocol). The results of the electrochemical tests suggested a reaction initiated by the Ni(I) species.

To elucidate the identity of the Ni species, we calculated UV−vis spectra for the [Ni(I)(**L1**)Cl] catalyst and compared them with the experimental spectra shown in Figure 2. The calculated absorption peaks for [Ni(I)] at 376 and 442 nm (Figure S3, top) closely align with the experimental values of 365 and 440 nm. Then, we next investigated the formation of a [**Ni**]-**1a** species, as suggested by the spectro-electrochemical investigation. Here, our calculations showed that a $\pi$-O-chelated organonickel complex **int-1** is formed in a barrierless exothermic process, stabilized by 4.5 kcal/mol. **Int-1** has a chelating-like coordination mode of the Ni(I) metal center with **1a** through contacts involving the $\pi$-electron cloud of the phenyl ring ($\eta^2$-like hapticity) and the lone pair of the oxygen atom of the tropone core. The computational spectra showed a good agreement with the experimental ones (Figure S3, bottom) with absorption peaks at 430, 572, 604, and 607 nm.

In the next step, the Ni-center (**int-2**, Scheme 3) is proposed to act as a tethering unit to bring in proximity benzaldehyde **2b**

**Scheme 3. Suggested Reaction Mechanism Computed at the DFT (M06/def2svp(p)) Level of Theory. The Energies Are Reported in Kcal/mol and Correspond to Relative $\Delta G$ (Reported Below Minima Structures) and $\Delta G^{+2}$ (Reported Next/below Arrows)**




(weak Ni−O coordination) and tropone **1a** (interacting with the $\varepsilon$−$\zeta$ double bond). This coordination results in a net transfer of electron-density from the metal center to the tropone as supported by the electrostatic potential and the NBO charges computed on **int-2** and **int-3** (Figure S5). In particular, upon nickel coordination (**int-2**), the tropone unit carries a negative charge of −0.43 au, while the aldehyde is unperturbed (+0.06 a.u). This interaction leads to an overall umpolung of reactivity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of the tropone and triggers the consequent nucleophilic condensation to the aldehyde (**ts-int-2−3**: 15.1 kcal/mol).[18,19] The consequent C−C bond formation event occurs exclusively at the $\alpha$-carbon of tropone, leading to the organo-Ni(III) **int-3** eventually featuring a C($\delta$)-Ni bond. Next, the weak Ni−C bond is broken with an activation energy of only 1.4 kcal/mol and a new Ni(III)−O alkoxide **int-4** is obtained.

At this point, the final electrochemical reduction of Ni(III) to Ni(I) restores the catalytically active species and a Zn−Ni ion-exchange, between **int-3** and the Zn(II) ions liberated from the sacrificial anode,[22] affords the zinc-alkoxide **int-5** through a strongly exothermic step. This last intermediate is ready to furnish the final product either directly or assisted by the mild acidic media used during the work-up process.

Finally, due to the well-known propensity of organonickel species to react via single-electron-transfer (SET) processes,[20,21] we investigated the possibility of a SET event occurring in our case, by using Marcus Theory[23] and the methodology described in the reference (Figure S4).[24] Interestingly, the single-electron-transfer alternative that would turn **1a** into a nucleophilic species, able to trap the electrophilic aldehyde, proved unlikely as it requires an activation energy of 30.9 kcal/mol for the initial step: **1a** + [**Ni(I)**] → [**1a**]$^{-\bullet}$ + [**Ni(II)**]$^{+}$.

## CONCLUSIONS

In conclusion, the combined use of nickel catalysis and electrosynthesis has been documented as an efficient strategy to accomplish a general $\alpha$-alkylation of tropones via C−H functionalization. The present cross-electrophile coupling involves common aldehydes as alkylating agents. A dedicated spectro-electrochemical study sheds light on the active role of the nickel complex in the redox process. Here, the tropone core proved to be an effective $\pi$-ligand (acceptor) for the Ni-center, prompting an umpolung of reactivity of the seven-member ring. Finally, all of the catalytic mechanism was computed at the DFT level of theory, relying on close agreements with both experimental and spectroscopic analyses. In particular, the respective behavior of the two electrophiles (tropone and aldehyde) in the present cross-coupling as well as the nature of the catalytically active Ni-species have been elucidated.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c07120.

Experimental procedures, characterization data, and additional optimization data (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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## ABBREVIATIONS

BH, Baylis−Hillman; CCE, constant current electrolysis; DFT, density functional theory; EDG, electron-donating; EWG, electron-withdrawing; NBO, natural bond orbital; SET, single-electron transfer; SS, stainless steel; $TEABF_4$, tetraethylammonium tetrafluoroborate; TM, transition metal.

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