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# Electrochemical Asymmetric Radical Functionalization of Aldehydes Enabled by a Redox Shuttle

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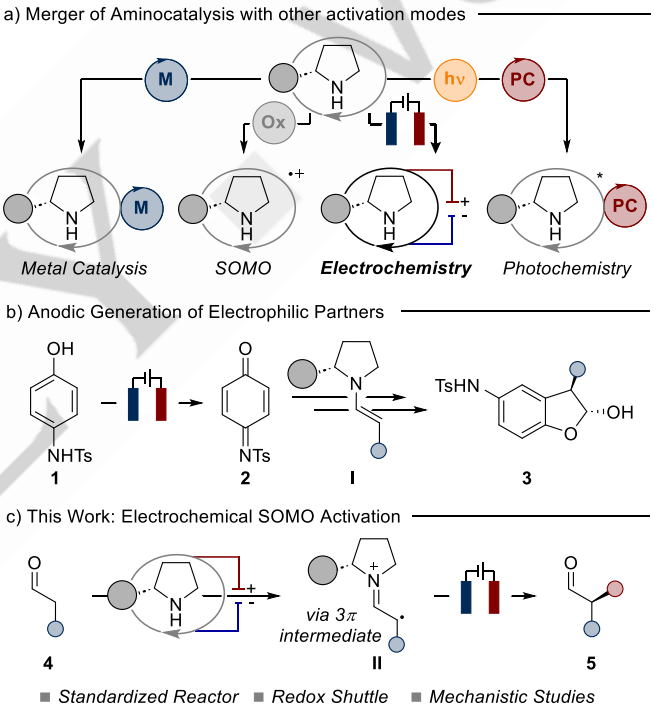
**Abstract:** Aminocatalysis is a well-established tool that enables the production of enantioenriched compounds under mild conditions. Its versatility is underscored by its seamless integration with various synthetic approaches. While the combination of aminocatalysis with metal catalysis, photochemistry, and stoichiometric oxidants has been extensively explored, its synergy with electrochemical activation remains largely unexplored. Herein, we present the successful merger of electrochemistry and aminocatalysis to perform SOMO-type transformations, expanding the toolkit for asymmetric electrochemical synthesis. The methodology harnesses electricity to drive the oxidation of catalytically generated enamines, which ultimately partake in enantioselective radical processes, leading to α-alkylated aldehydes. Crucially, mechanistic studies highlight how this electrochemical strategy is enabled by the use of a redox shuttle, 4,4'-dimethoxybiphenyl, to prevent catalyst degradation and furnishing the coveted compounds in good yield and high enantioselectivity.

In the realm of asymmetric organic synthesis, organocatalysis stands out as a widely acknowledged and established approach. It presents eco-friendly, cost-efficient, and operationally uncomplicated alternatives to the conventional methods involving metal or bio-catalysts.[1] Over the years, aminocatalysis,[2] has garnered significant attention for its application in the construction of complex molecular architectures.[3] Beyond its classic utilization, aminocatalysis serves as an exceedingly versatile tool of molecular activation, extending its application through synergistic coupling with other various activating modes and providing unprecedented synthetic opportunities (Scheme 1a).[4] For instance, aminocatalysis has been coupled with transition metal-catalysis, providing an effective method that takes advantage of the complementary properties of the two distinct catalytic systems.[5] On top of polar transformations, aminocatalysis has been used also to drive radical reactions.[6] Specifically, the coupling with over-stoichiometric quantities of oxidants gives rise to Singly Occupied Molecular Orbital (SOMO) radical cationic species.[7] This pioneering approach opened new synthetic and mechanistic opportunities in both asymmetric organocatalysis and radical processes, albeit using toxic and dangerous oxidizing compounds such as cerium ammonium nitrate. Further, aminocatalysis has been also merged with photochemical tools[8]




**Scheme 1.** a) Merger of aminocatalysis with metal catalysis, SOMO activation, electrochemistry and photochemistry. b) Electrochemistry as a tool to generate electrophilic partners in enamine mediated processes. c) Merger of aminocatalysis with electrochemistry to promote SOMO-type processes.

such as direct photoexcitation of catalytically generated intermediates,[9] or with the aid of a photocatalyst,[10] to enable redox neutral radical transformations under very mild conditions. However, despite the demonstrated versatility of aminocatalysis within the radical domain, its integration with electrochemistry has been notably underexplored.[11] In contrast, electrochemistry has found successful synergy with asymmetric metal catalysis[12] and biocatalysis.[13] This divergence is particularly striking when compared to the recognized potential of merging organocatalysis with electrochemistry, a highlighted research area in the current decade.[14] In the context of aminocatalysis, particularly in enamine-mediated transformations, a breakthrough has been made by the group of Jørgensen (Scheme 1b).[11c] Their work



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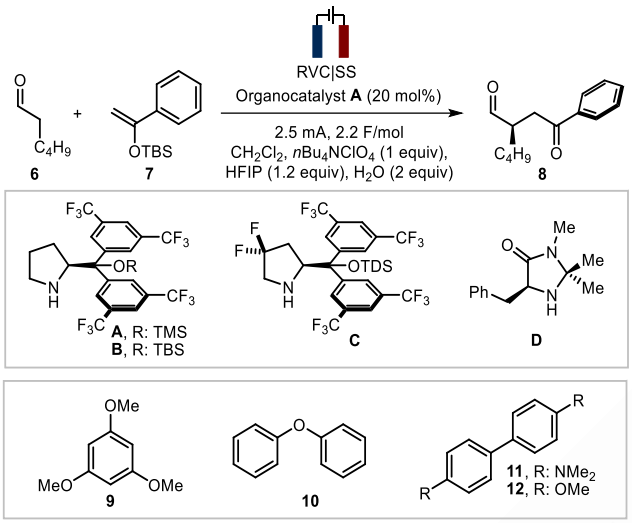
demonstrated the exploitation of anodic oxidation to convert *para*-hydroxy-*N*-tosyl aniline **1** into electrophile **2**, which could be later trapped by enamine **I** to ultimately yield compound **3**. This seminal example underscores the potential for leveraging electrochemistry to diversify the array of transiently generated electrophiles in enamine-promoted transformations. Following this contribution, several research groups have used electricity to broaden the spectrum of transiently generated electrophiles in enamine-promoted transformations.[11e-h]

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




| Entry | Deviation From Reaction Conditions | Yield (%) | e.r. |
|---|---|---|---|
| 1 | None | 34 | 90:10 |
| 2 | **9**-**11** as redox shuttles (50 mol%) | 15-63 | 90:10 |
| **3** | **12 as redox shuttle (50 mol%)** | **70 (67)** | **90:10** |
| 4[b] | **12** as redox shuttle, **B** as organocatalyst | 45 | 77:23 |
| 5[b] | **12** as redox shuttle, **C**-**D** as organocatalysts | 5< | - |
| 6[b] | **12** as redox shuttle, *n*Bu$_4$NBF$_4$ or *n*Bu$_4$NPF$_6$ as electrolytes | 34-61 | 90:10 |
| 7[b] | **12** as redox shuttle, no water | 18 | 90:10 |
| 8[b] | **12** as redox shuttle, graphite instead of RVC | 22 | 90:10 |
| 9[b] | No Organocatalyst **A** | - | - |
| 10[b] | No Electricity | - | - |

[a] Reactions performed on a 0.4 mmol scale of compound **7**, using 3 equivalents of hexanal **6**. Yields were determined by $^1$H NMR analysis, using trichloroethylene as internal standard. Yield after isolation is reported in parenthesis. Enantiomeric ratio of **8** was determined by UPC$^2$ analysis. [b] 50 mol% of **12**. TBS: *tert*-butyldimethylsilyl. RVC: reticulated vitreous carbon. SS: stainless steel. HFIP: hexafluoroisopropanol. TMS: trimethylsilyl. TDS: Thexyl-dimethylsilyl

Nevertheless, the application of electrochemistry appears predominantly confined to the generation of in situ electrophilic species, limiting its capacity to enable radical reactions analogous to those achievable through classical SOMO activation. Herein, we report the successful use of electrochemistry to produce 3π intermediate **II** (Scheme 1c) upon anodic single electron transfer (SET) from in-situ generated enamine **I**, and its use in the asymmetric α-alkylation of aldehydes. The effective realization of this process relies on the use of a key biphenyl derivative that, acting as a redox shuttle,[15] prevents parasitic pathways such as catalyst degradation.

We started our investigation (Table 1) by exploring the asymmetric electrochemical coupling of aldehyde **6** with silyl enol ether **7** in the presence of organocatalyst **A** in an undivided electrochemical cell (IKA Electrasyn 2.0). After evaluating potential reaction conditions (see Supporting Information) and based on previous works in the field of SOMO-aminocatalysis,[7] we found that the desired compound was obtained in 34% yield and 90:10 enantiomeric ratio (e.r., entry 1) when employing reticulated vitreous carbon as anode, stainless steel as cathode, $CH_2Cl_2$ as solvent, $H_2O$ and HFIP as additives,[16] and *n*Bu$_4$NClO$_4$ as electrolyte under galvanostatic conditions (2.5 mA and 2.2 F/mol). Notably, at the end of the reaction, we observed complete degradation of organocatalyst **A**, likely through an oxidative anodic pathway.[17] To solve this issue, and inspired by Sevov's work on mitigating overreduction in electrochemical reductive cross couplings,[18] we sought to protect organocatalyst **A** from overoxidation by integrating a redox shuttle. Ideally, this species would possess a redox potential between the enamine and the aminocatalyst, thus preventing the undesired oxidation of the aminocatalyst while not interfering with the productive electron transfer from **I** (*vide infra*). We identified electron-rich aromatic cores as promising candidates.[9e,19] While the use of 50 mol% of compounds **9**-**11** (entry 2) afforded the desired compound with low to good yields, the use of compound **12** (entry 3) proved to be optimal, delivering **8** in 67% yield and an identical enantiomeric ratio. Aminocatalyst **A** proved to be the optimal catalyst for this electrochemical protocol, as the use of a catalyst adorned with a more encumbering silyl protecting group (**B**, entry 4) promoted the reaction with a lower chemical efficiency and enantioselectivity, while the use of less nucleophilic catalysts (**C** and **D**, entry 5) completely suppressed the reactivity. The use of different electrolytes such as *n*Bu$_4$NBF$_4$ or *n*Bu$_4$NPF$_6$ (entry 6) also proved detrimental in terms of chemical efficiency, as well as when not employing water as additive (entry 7) or the use of a different carbon material for the anode such as graphite (entry 8). Finally, we confirmed that the reaction necessitates both aminocatalyst **A** (entry 9) and electricity (entry 10) to proceed.

With the optimal reaction conditions in hand, we set on investigating the generality of this process (Scheme 2). First, we combined enol ether **7** with an array of different aldehydes (**14**-**19**). Both heptanal, isovaleraldehyde, and 2-cyclohexylacetaldehyde successfully reacted, affording the target products (**14**-**16**) in moderate to good yields and enantioselectivities, proving the amenability of this method also to branched and cyclic aldehydes. Furthermore, aldehydes bearing



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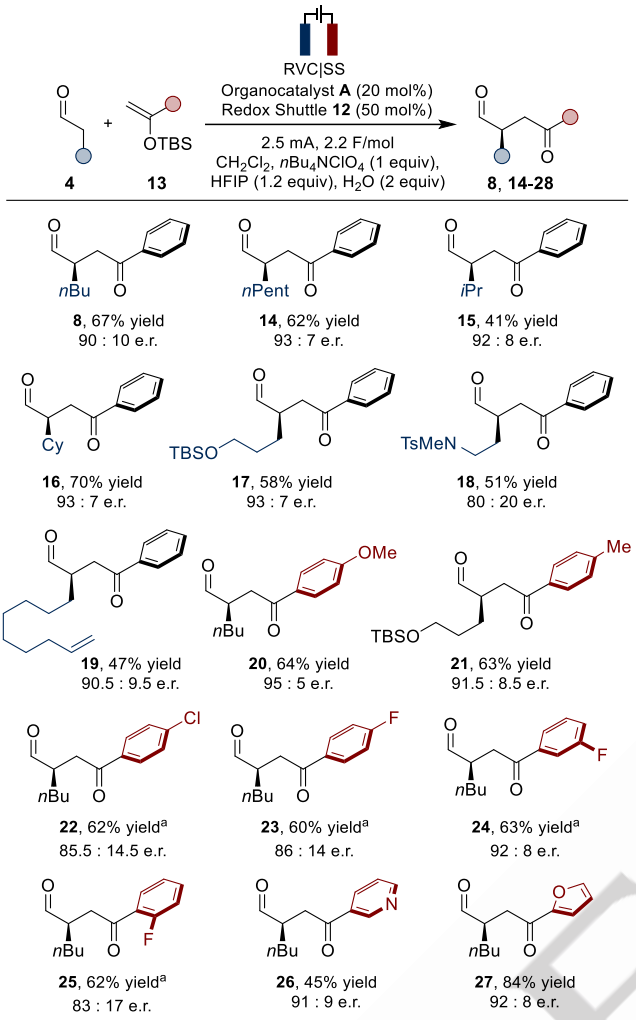
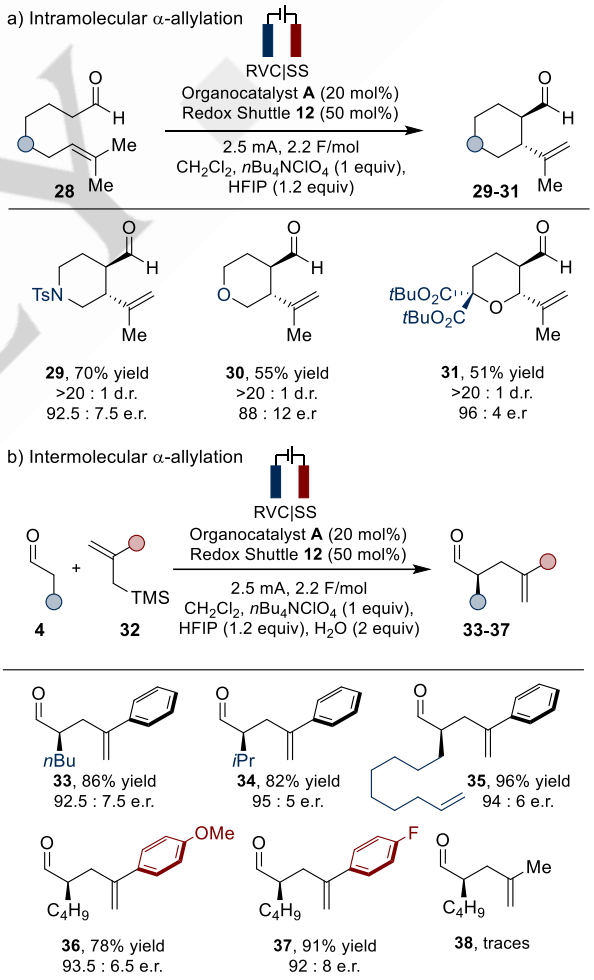



**Scheme 2.** Survey of aldehydes **4** and silyl enol ethers **13** that can participate to the electrochemical protocol. Reactions performed on a 0.4 mmol scale (0.1 M) of compound **13**, using 3 equiv. of aldehydes **4**. Yields and enantiomeric ratios refer to isolated products. [a] 1 equiv. of **12** was used. Ts: tosyl.

possibly sensitive moieties such as oxygen, nitrogen and olefin functionalities, were swiftly converted into the corresponding products (**17**-**19**) without any undesired over-functionalization. As a limitation to the method, the use of α-branched aldehydes did not afford the coveted products. Subsequently, we evaluated the scope of the silyl enol ethers amenable to this electrochemical protocol. In general, the reaction seems to be very general and not sensitive of the electronic nature of the substituent on the aromatic ring as both electron-donating (**20** and **21**) and electron-withdrawing groups (**22** and **23**) were well tolerated. Furthermore, both *meta*- and *ortho*-substituted derivatives (**24** and **25**) afforded the desired compound with similar chemical efficiency. Finally, the method is also amenable to the use of silyl enol ethers bearing either an electron-poor or an electron-rich heteroaromatic group (**26** and **27**).

After having established this phenacylation protocol, we wondered whether we could expand this electrochemical SOMO approach also to the α-allylation of aldehydes (Scheme 3). First, we assessed the feasibility of this approach to an intramolecular level (Scheme 3a), using aldehydes adorned with a pendant olefin (**28**). These compounds, during the SOMO activation, would be involved in cyclization and deprotonation steps, yielding the corresponding cyclic derivatives.[7l] Indeed, when reacted under similar reaction conditions with respect to the α-phenacylation (see Supporting Information for further details), derivatives bearing a sulfonamide, ether and ester functionalities afforded the desired products with good chemical efficiency, perfect control over the diastereoselectivity and in satisfactory enantioselectivities (**29**-**31**). These encouraging results led us exploring the feasibility of an intermolecular α-allylation strategy (Scheme 3b), employing allyl silane **32** as the substrate. To our delight, 2-phenylallyltrimethylsilane could be coupled with different aldehydes such as hexanal, isovaleraldehyde and 10-undecenal (**33**-**35**), further proving that branched aldehydes and potentially sensitive functionalities are well-tolerated under this electrochemical protocol. Moreover, both electron-rich and electron-poor allyl silanes could be converted into the corresponding products (**36** and **37**) in satisfactory yields and enantioselectivities. As a limitation, the use of methallyltrimethylsilane did not provide product **38**.




**Scheme 3.** a) Survey of aldehydes **28** that can participate to the intramolecular α-allylation. b) Survey of aldehydes **4** and allyl silanes **32** that can participate to the intermolecular α-allylation. Reactions performed on a 0.4 mmol scale (0.1 M) of compound **13**, using 3 equivalents of aldehydes **4**. Yields and enantiomeric ratios refer to isolated products.



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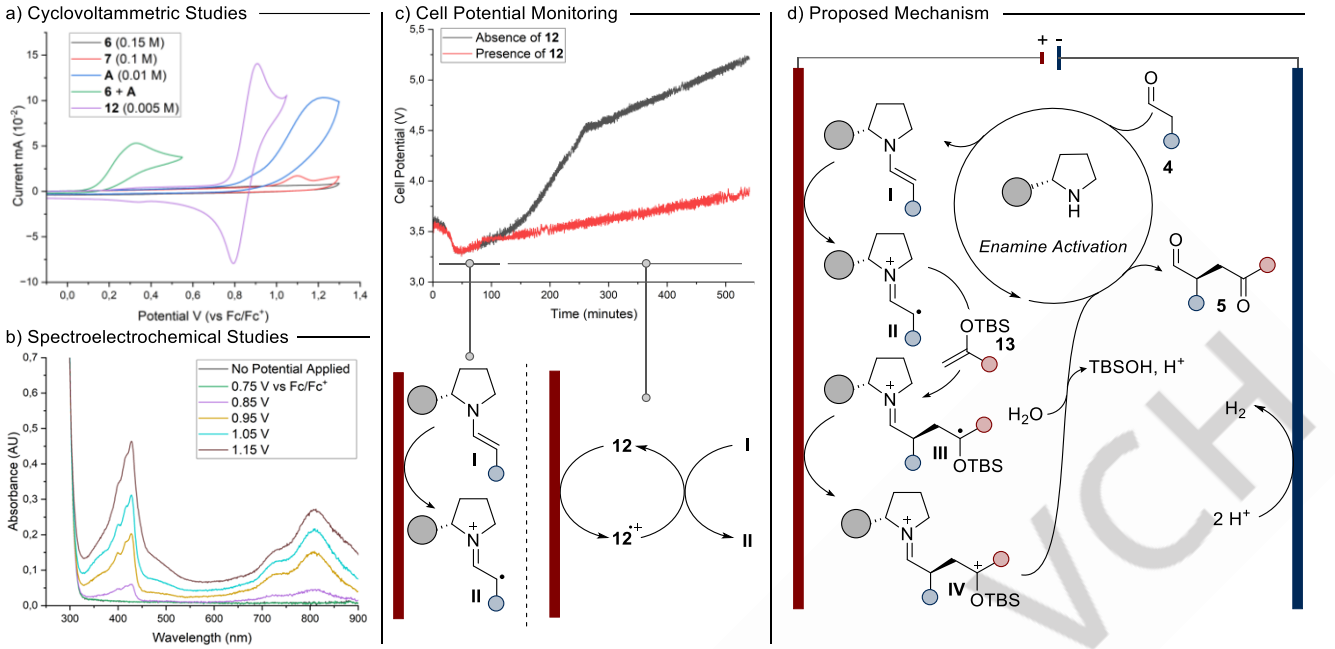


**Scheme 4.** Mechanistic studies and suggested mechanism for the aminocatalytic electrochemical enantioselective α-enolation of aldehydes. a) Cyclovoltammetric studies. b) Spectroelectrochemical characterization of the radical cation of the redox shuttle. c) Cell potential monitoring in the presence and absence of redox shuttle. d) Proposed mechanism.

Following the demonstration of the synthetic utility of this asymmetric electrochemical organocatalytic strategy, we embarked on investigating its mechanism.

Our exploration began with a cyclovoltammetric analysis of the different reaction components (Scheme 4a). While hexanal **6** did not show any oxidation peak within the electrochemical scan range, compounds **7** and **A** showed irreversible oxidation peaks ($E_{pa}$= 1.10 and 1.21 V vs Fc/Fc$^+$, respectively). Notably, upon mixing catalyst **A** and aldehyde **7**, a new oxidation peak at 0.33 V vs Fc/Fc$^+$ appeared, indicative of electron transfer from transiently generated enamine intermediate **I**.[20] Crucially, a cyclovoltammetric analysis of redox shuttle **12** revealed a reversible oxidation peak at 0.84 V vs Fc/Fc$^+$, strategically positioned between the ones of enamine **I** and aminocatalyst **A**. Furthermore, this redox shuttle exhibited remarkable stability under electrochemical conditions, confirmed by its quantitative recovery during the purification step after the electrochemical reactions. Spectroelectrochemical analysis, involving potential-induced changes in the absorption profile of a mixture containing **12** (Scheme 4b), revealed a distinct absorption profile when using 850-1150 mV (vs Fc/Fc$^+$), ascribable to the radical cation of **12**, as supported by TD-DFT calculations (see SI for further details). Notably, upon adding a solution containing aminocatalyst **A** and an excess of hexanal **6**, it was observed that the typical features of the radical cation of **12** disappeared (see SI for further details). This finding suggests that **12**$^{\cdot+}$ could interact with enamine **I** in a SET step, promoting the overall electrochemical functionalization of aldehydes. The use of **12** has a deep influence on the overall cell potential (Scheme 4c). Monitoring the model reaction in the presence of the redox shuttle (conditions as in entry 3, Table 1), revealed a moderate increase in the cell potential during the reaction time, not exceeding 4 V. Conversely, in the absence of **12** (conditions as in entry 1, Table 1), a significantly higher increase in cell potential, up to ~5.5 V, was observed. These results are in agreement with a scenario (*vide infra*) where redox shuttle **12**, at the beginning of the electrochemical process, does not interfere with the anodic electron transfer involving intermediate **I**, while after initial consumption of the enamine could serve to enhance the generation of 3π intermediate **II**. Finally, analysis of the headspace of the reaction mixture (see SI for further details), indicated the formation of molecular hydrogen, hinting at proton reduction happening on the cathode. Collectively, these findings, coupled with precedents in the literature,[7] support our proposed catalytic cycle (Scheme 4d). Condensation of aldehyde **4** and aminocatalyst **A** yields enamine **I**, which is anodically converted into 3π intermediate **II**. The latter interacts with silyl enol ether **13**, affording radical cation **III**, subsequently oxidized to **IV**. Hydrolysis of this intermediate affords target compound **5** and restores the aminocatalyst. Finally, hydrogen evolution takes place on the cathode to close the electrochemical circuit.

In summary, we have reported an asymmetric organocatalytic electrochemical strategy leveraging electricity to promote the α-alkylation of aldehydes. Crucially, this electrochemical strategy requires the use of a redox shuttle to prevent catalyst degradation while affording the target compounds in good yield and enantioselectivity (up to 96% yield and 95:5 enantiomeric ratio). Further applications of this strategy in other organocatalytic fields are currently underway in our laboratory.



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## Supporting Information

The authors have cited additional references within the Supporting Information.[21-31]

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## Authors Contribution

D.M. has conceived the idea, performed the experiments, directed the project and written the manuscript with contribution from all the authors. C.Q and M.V. have performed the experiments. A.S. has contributed to the mechanistic studies. G.P. has performed the crystallographic characterization. L.D. has supervised the work and secured the fundings.

**Keywords:** • Electrosynthesis • Aminocatalysis • Organocatalysis • Redox Shuttle • SOMO Activation

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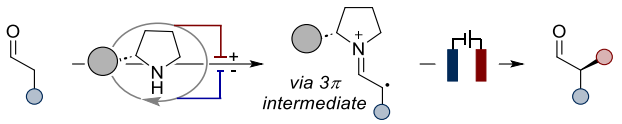


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