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Asymmetric cyclopropanation *via* an electro-organocatalytic cascade†

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We report an iminium ion-promoted, asymmetric synthesis of cyclopropanes *via* an electrocatalytic, iodine-mediated ring closure. The mild, controlled electrochemical generation of electrophilic iodine species in catalytic quantities prevents organocatalyst deactivation, while also eliminating the need for halogenating reagents, thus simplifying traditional synthetic approaches.

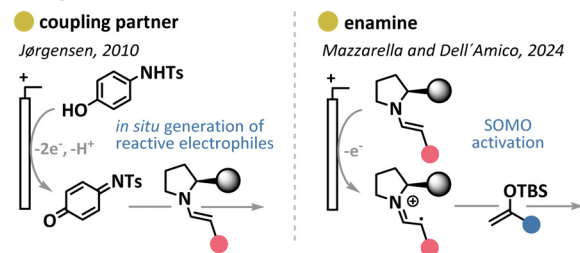
Over the past two decades, amino-organocatalysis has been extensively employed in the development of asymmetric reactions, exploiting both polar and radical pathways, while combining organocatalysis with metal- and photocatalysis has enabled unconventional transformations.¹ Electrochemistry, in turn, offers a greener approach to synthesizing simple molecules and performing late-stage functionalization of complex targets.² Thus, merging aminocatalysis with electrochemistry presents a highly attractive strategy that could unlock novel enantioselective reactivities in a more sustainable manner.³ However, electrochemical aminocatalysis has been demonstrated feasible only *via* asymmetric enamine-mediated pathways, which can be categorized into two main strategies (Scheme 1a). The first involves the *in situ* electrochemical generation of electrophilic partners, which subsequently react with enamines,⁴ while the second is based on the single-electron oxidation of the enamine intermediate, leading to the formation of a radical cation.⁵ A major limitation of such transformations stems from the oxidative degradation of chiral organocatalysts or their intermediates under electrochemical conditions. To address this, Mazzarella and Dell'Amico recently employed redox shuttles for a milder, indirect single-electron transfer (SET) oxidation of the enamine intermediate, thereby protecting the catalyst from oxidative damage.^{5c} In another approach, the Hao Xu group designed a bifunctional, diarylprolinol-based chiral electrocatalyst, which acts both as a

redox mediator for substrate electrooxidation and a promoter for asymmetric induction through the enamine formation.^{4f}

Despite these advances, electrochemical aminocatalysis involving the formation of an iminium ion remains underexplored to the best of our knowledge. Inspired by the concept of constructing cyclopropane rings electrochemically,⁶ particularly *via* halogen-mediated reactions,^{6c-i} we sought to develop an asymmetric cyclopropanation under electrochemical conditions to demonstrate the proof-of-principle that electrochemistry is compatible with iminium ion organocatalysis. Considering our group's expertise in Michael-initiated ring closure (MIRC) reactions⁷ and electrochemical transformations,⁸ we selected an established protocol for asymmetric cyclopropanation *via* iminium ion catalysis that previously utilized a cascade process

a) Enamine-promoted electrochemical transformations

through direct or indirect anodic oxidation of:



b) Asymmetric organocatalyzed cyclopropanation



Scheme 1 (a) Asymmetric organocatalytic electrochemical strategies. (b) Asymmetric cyclopropanation *via* MIRC.

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involving α,β -unsaturated aldehydes and halogenated Michael donors as a benchmark reaction (Scheme 1b).⁹ Importantly, streamlining this protocol to employ simple malonates, while performing the ring-closure cascade using electrocatalytically generated electrophilic halogen species, would improve atom economy for the overall process by eliminating the additional step for the synthesis of halogenated Michael donors that involves stoichiometric amounts of electrophilic halogen sources.

We initiated our investigation using cinnamic aldehyde **1a** and dimethyl malonate **2a** as model substrates, with organocatalyst **I** (20 mol%) in a simple undivided cell setup, featuring a graphite (G) anode and a stainless-steel (SS) cathode, under galvanostatic conditions (Table 1). Following the work of the Nikishin group,¹⁰ preliminary experiments were conducted in ethanol with catalytic amounts of tetraethylammonium iodide as a halogen source and acid additives (see Table S1 in ESI†). The reproducibility of the reaction improved significantly when ethanol was replaced by dichloromethane as the solvent, with hexafluoroisopropanol (HFIP) and water as additives, and tetrabutylammonium perchlorate as the electrolyte. HFIP serves as a protons source for the cathodic reaction and was found to stabilize iminium ions,¹¹ while water most likely plays a role in the formation and hydrolysis of the iminium ion. The optimal reaction time for our transformation was determined to be 5 hours (Table 1, entry 1). Upon completion of the reaction, we observed the intermediate **4a** (up to 32%) in some instances, which results from the nucleophilic addition of malonate **2a** to the iminium

ion, along with the byproduct **5a** (7–24% yield). The formation of **5a** has previously been reported in the aminocatalyzed synthesis of **3a**, arising from a base-induced retro-Michael reaction of the cyclopropane adduct.^{9b} Prolonging the reaction time to 16 hours led to further conversion of the product **3a** into **5a** (Table 1, entry 2). Lowering the amount of tetraethylammonium iodide or substituting it with other halogen sources reduced the yield (entries 3–6). To address the partial catalyst decomposition caused by oxidation,^{5c,12} we explored the use of presumably more stable aminocatalysts **II–VI**.¹³ Unfortunately, none of these catalysts improved the yield of the desired product and all showed some degree of decomposition, as confirmed by GC-MS and NMR analyses of the crude reaction mixtures (Table 1, entry 7). Substituting the cathode material with graphite or platinum significantly suppressed cyclopropane **3a** formation (Table 1, entry 8), and using acetonitrile as the solvent also lowered the yield (entry 9). Without a halogen source, the reaction yielded only the Michael adduct **4a** with excellent enantioselectivity (96% ee, Table 1, entry 10), while no reaction occurred in the absence of the organocatalyst (entry 11). Lastly, a control experiment confirmed that electricity is essential for cyclopropane ring formation (entry 12).

With the optimal conditions established, we investigated the substrate scope for the cascade electro-organocatalytic cyclopropanation (Scheme 2). Aromatic α,β -unsaturated aldehydes (**1**) reacted efficiently with malonate (**2a**) under the optimized conditions, yielding the corresponding cyclopropanes (**3a–j**) with excellent stereoselectivity (94–98% ee and >20:1 d.r. in all cases). Notably, cyclopropanes **3b–3g**, containing electron-deficient substituents in the aromatic ring, were isolated in moderate to good yields. Potentially sensitive to electrochemical conditions nitro- or methoxy- groups were tolerated in the reaction (**3f**, **3g**, **3i**). However, in the case of 4-methoxycinnamaldehyde, rapid formation of the byproduct **5i** was observed at room temperature (Scheme 4a). To suppress the side product formation, the reaction was performed at 0 °C, which improved the yield of cyclopropane **3i**, with 24 hours identified as the optimal reaction time. Similarly, cyclopropane **3j**, bearing an electron-donating alkyl group, was obtained at a lower temperature. We then explored different nucleophilic reaction partners. Dibenzyl malonate reacted smoothly, yielding product **3k** with results comparable to those obtained with dimethyl malonate. When 1,3-ketoester was used as the nucleophile, cyclopropane **3l** was obtained in only 1.5 hours, though with moderate yield and diastereoselectivity. Furthermore, we were pleased to obtain biologically relevant spirooxindoles **3m** and **3n** with good diastereoselectivity.¹⁴

Based on our observations and previous studies, we propose a plausible mechanism, as depicted in Scheme 3. First, in the organocatalytic cycle, condensation of the chiral aminocatalyst **I** with cinnamic aldehyde **1a** occurs forming an iminium ion (**i**). Upon Michael addition of malonate **2a** to the iminium ion (**i**), an enamine (**ii**) is generated, which may hydrolyze to intermediate **4a**. Electrooxidation of iodide occurs at the anode, forming electrophilic iodine species, which are captured by the enamine (**ii**).¹⁵ The iodinated iminium ion (**iii**) then undergoes intramolecular alkylation, releasing iodide anion back into the electrocatalytic cycle and forming an iminium ion (**iv**).

Table 1 Reaction condition optimization

#	Deviation from reaction conditions	Yield, %			ee 3a , ^b %
		3a ^c	4a	5a	
1	None	59	—	12	96
2	1.0 mA, 16 h	48	—	24	96
3	<i>n</i> Bu ₄ NI instead of Et ₄ NI	47	4	7	97
4	I ₂ instead of Et ₄ NI	29	—	—	94
5	<i>n</i> Bu ₄ NBr instead of Et ₄ NI	6	21	—	nd
6	0.1 equiv. of Et ₄ NI	39	14	7	98
7	II–VI as organocatalyst	38–46	—	Traces	70–92
8	Pt or G as cathode	9	29–32	—	nd
9	CH ₃ CN instead of CH ₂ Cl ₂	30	9	—	94
10	No halogen source	—	33	—	—
11	No organocatalyst	—	—	—	—
12	No electricity	—	49	—	—

^a Yields were determined by ¹H NMR analysis of the crude reaction mixture using trimethoxybenzene as an internal standard. ^b Enantiomeric excess of **3a** was determined by chiral HPLC analysis. ^c Diastereomeric ratio of **3a** was determined by ¹H NMR analysis of the crude reaction mixture and was for all entries >20:1. n.d.: not determined.

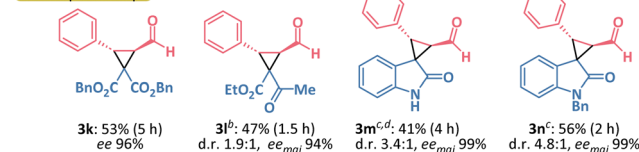




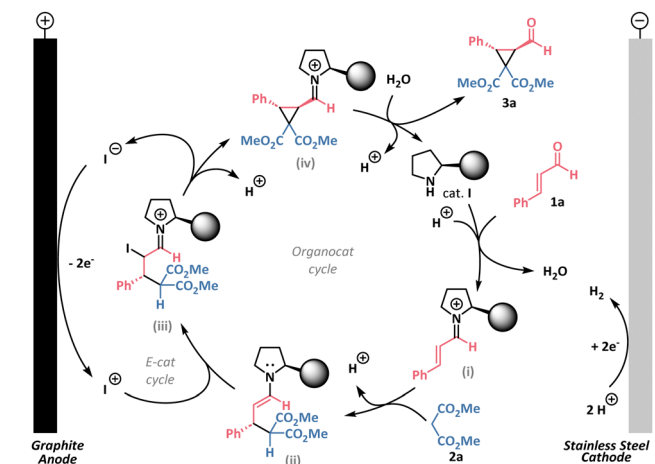
Electrophiles scope



Nucleophiles scope



Scheme 2 Substrate scope of the electro-organocatalytic cyclopropanation. Yields and enantiomeric excess refer to isolated products. ^aThe reaction was performed at 0 °C. ^bYield and d.r. were determined by ¹H NMR analysis of the crude reaction mixture using trimethoxybenzene as an internal standard. The yield of the isolated major diastereomer is 30%. ^cYields, d.r. and ee of products **3m** and **3n** correspond to the isolated products after *in situ* reduction to the corresponding alcohols with sodium borohydride. ^dThe reaction was performed at -10 °C.



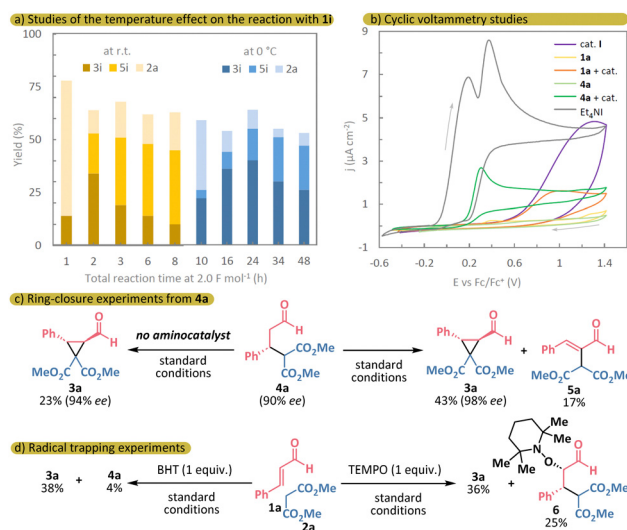
Scheme 3 Proposed mechanism.

Subsequent hydrolysis of the iminium ion (**iv**) yields the desired product **3a** and regenerates the organocatalyst **I**. Under certain conditions, the intermediate (**iv**) can undergo a retro-Michael reaction, leading to the formation of the byproduct **5a**.

Meanwhile, the evolution of hydrogen occurs at the cathode as the counter half-reaction. Thus, the reaction mechanism involves two catalytic cycles, and balancing their rates is crucial for efficient product formation. The electrochemical cycle is controlled by current density, while the organocatalytic cycle can be influenced by temperature (see kinetic studies in Fig. S4 in ESI†).

To better understand the reaction mechanism, we first measured the oxidation potentials of the main reaction components using cyclic voltammetry (Scheme 4b). Iodide exhibits two distinct oxidation peaks at potentials of +0.19 V and +0.38 V, with the first oxidation occurring at the lowest potential in the system. However, the enamine (**II**), formed from the intermediate **4a** and organocatalyst **I**, shows an oxidation peak at +0.27 V, which is lower than iodine's second oxidation peak, suggesting that it may undergo SET oxidation under the reaction conditions. The other reaction components have higher oxidation potentials than iodide and are unlikely to undergo anodic oxidation. Nevertheless, decomposition of the free catalyst through reaction with electrophilic iodine species *via* Grob-type fragmentation is also possible.^{6d,11a}

We then conducted several control experiments. In the reaction with stoichiometric amounts of molecular iodine or *N*-iodosuccinimide under the standard conditions, but without applying electricity, no conversion of the starting materials was detected, and organocatalyst **I** began to decompose. This suggests that controlled electrocatalytic generation of electrophilic iodine likely protects the catalyst from Grob-type fragmentation. Next, we attempted to form the cyclopropane ring under our electrochemical conditions using the pre-synthesized intermediate **4a**.¹⁶ After the addition of 2.0 F mol⁻¹ over 5 hours,



Scheme 4 (a) Temperature effect studies. Separate reactions with 2.0 F mol⁻¹. (b) Cyclic voltammetry measurements. Voltammograms recorded in 0.1 M *n*Bu₄NPF₆ CH₃CN solution with Ag/Ag⁺ reference electrode and realigned with respect to Fc/Fc⁺ couple. Arrows indicate the direction of the potential scan. (c) Electrochemical ring closure of pre-synthesized intermediate **4a**. (d) Experiments with TEMPO and BHT as presumed radical scavengers.



43% of the desired product **3a** was formed, along with 17% of the byproduct **5a** (Scheme 4c). Interestingly, after 1 hour of reaction, the intermediate **4a** partially fragmented back to cinnamic aldehyde **1a** and dimethyl malonate **2a** (40% NMR yield). This demonstrates the reversibility of the Michael addition step and highlights the complex kinetics of the overall process (see Fig. S5 in ESI†). In the absence of the organocatalyst, the product **3a** was formed less efficiently, with a yield of 23%, and no formation of **1a** or **2a** was observed.

To determine whether the reaction mechanism has a polar or radical nature, we conducted control experiments with radical scavengers (Scheme 4d). The reaction with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) under our electrochemical conditions resulted in only minor suppression of the product **3a** formation (36% NMR yield), and a TEMPO-adduct **6** was observed (25% NMR yield) (see Scheme S2 in ESI† for the alternative radical pathway).^{6f} However, electrochemical experiments using TEMPO as a radical trap can produce ambiguous results, as TEMPO can be oxidized to its *N*-oxoammonium salt under electrochemical conditions and react with the enamine (**ii**) in a polar manner.¹⁷ We then switched to dibutylhydroxytoluene (BHT) as a more reliable radical scavenger in electrochemistry and still observed the formation of cyclopropane **3a** (38% NMR yield), with only 4% of **4a** detected in the crude NMR, indicating that no quenching of the potential enamine radical cation occurred. These results, combined with the earlier experiment demonstrating ring closure in the absence of the aminocatalyst directly from the intermediate **4a**, suggest a predominantly polar mechanistic pathway in the electrochemical catalytic cycle.

In conclusion, we demonstrated the successful integration of electrochemistry with iminium ion organocatalysis to achieve highly enantioselective cyclopropanation. This streamlined process enhances atom economy by eliminating the need for pre-synthesized halogenated Michael donors. Mechanistic studies, supported by cyclic voltammetry and control experiments, suggest a predominantly polar pathway in the electrochemical catalytic cycle, driven by anodic iodide oxidation.

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Data availability

The data supporting this article are included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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