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Enantioselective organocatalytic electrochemical α-chlorination of aldehydes

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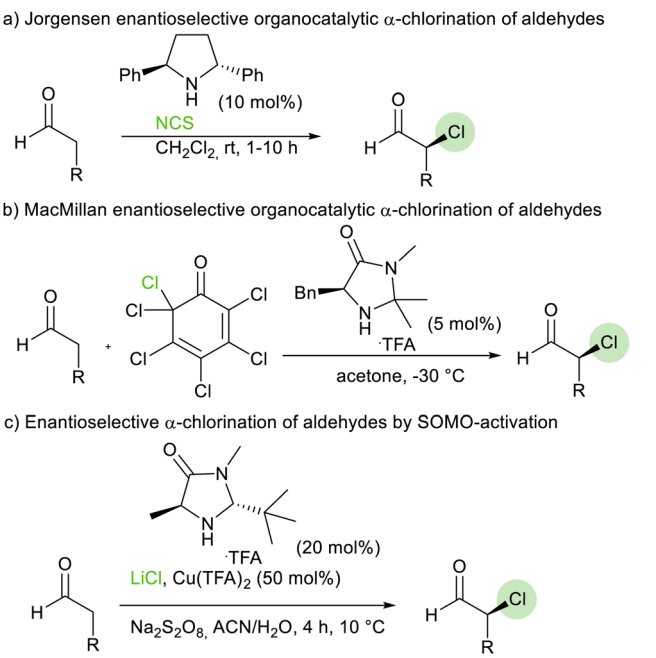
The enantioselective organocatalytic α-chlorination of aldehydes using electrochemistry to activate the enamine intermediate through a SOMO strategy was investigated. Based on mechanistic insights, an improved procedure was developed that directly employs $CuCl_2$ in the electrochemical reaction. Under the optimized setup (potentiostatic conditions of 1 V, glassy-carbon electrodes, and a 0.2 M solution of $LiClO_4$), in the presence of catalytic amounts of a chiral imidazolidinone organocatalyst, the aldehyde reacts with copper chloride(II) and leads to the formation of the corresponding α-chlorinated aldehydes in high yields with high enantioselectivities (up to 97% ee). Thanks to the electrochemical approach, stoichiometric amounts of chemical oxidants were successfully replaced by electrons, enabling a more sustainable and efficient catalytic stereoselective reaction. In addition, the transformation was successfully translated to a continuous flow process, which significantly enhanced productivity and reduced the reaction time to just 1.73 minutes, and the reaction was also performed on a gram scale.

Introduction

Halogenation is a key process for the synthesis of highly functionalized organic compounds, enabling the introduction of halogen atoms into specific positions of molecules to modulate their reactivity and properties. Among the various methodologies for the introduction of a halogen atom into organic compounds, one of the most versatile approaches consists of the introduction of a chlorine atom at the α-position of carbonyl compounds,[1] a strategy that has been effectively applied in many catalytic stereoselective transformations. For instance, simple aldehydes can be easily converted into aziridines, chlorohydrins, epoxides, or α-hydroxy acids through *in situ* derivatization of the corresponding α-chlorinated aldehydes.[2]

In 2004, Jørgensen[3] and MacMillan[4] independently reported the organocatalytic enantioselective direct α-chlorination of unbranched aliphatic aldehydes using *N*-chlorosuccinimide (NCS) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one, respectively, as chlorinating agents (Scheme 1a and b). In the first approach, Jørgensen demonstrated that readily available organocatalysts such as L-proline amide or (2*R*,5*R*)-diphenylpyrrolidine could promote the formation of α-chloroaldehydes with yields up to 99% and an enantiomeric excess (ee) of 95%. On the other hand, following MacMillan's methodology, where a chiral imidazolidinone is used as the organocatalyst, enantioenriched α-chlorinated aldehydes were synthesized in up to 94% yield and 95% ee. In 2009, as a further development, MacMillan and co-workers reported an innovative SOMO-catalyzed methodology for



Scheme 1 Recent examples of enantioselective organocatalytic α-chlorination of aldehydes.

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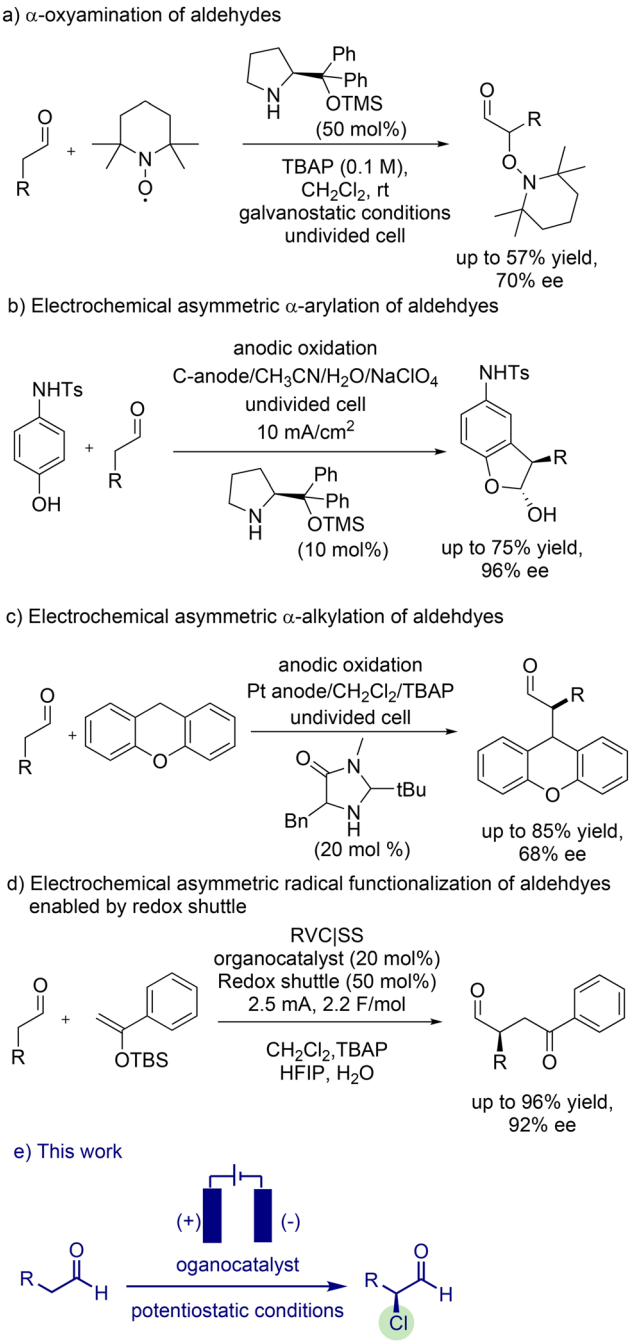
achieving the same transformation, employing a cheap nucleophilic chlorine source such as NaCl or LiCl in the presence of $Cu(TFA)_2$.[5] In this case, the chiral enamine formed by the interaction of the chiral organocatalyst with the unbranched aliphatic aldehyde undergoes direct oxidation to its radical cation form through a single electron transfer (SET) process.

This oxidation is promoted by the presence of copper trifluoroacetate and an excess of the chemical oxidizer $Na_2S_2O_8$, resulting in the formation of α-chlorinated aldehydes with yields and stereochemical efficiency comparable to those previously reported (Scheme 1c).

Given the recent emergence of electrochemistry as an innovative tool in organic chemistry for promoting redox transformations[6] and providing an alternative to conventional chemical oxidants,[7] we envisioned the possibility of adopting this approach to replace the chemical oxidants typically used in α-chlorination of aldehydes. However, while the application of electrochemistry in the asymmetric metal catalysis[8] and biocatalysis fields[9] is well established, the exploration of asymmetric organocatalysis combined with electrochemistry remains confined to a few examples with only a limited number of enantioselective electrochemical transformations reported so far.[10]

In 2009, Jang and co-workers reported a pioneering protocol combining organocatalysis with electrochemistry for the α-oxyamination of aldehydes using a substoichiometric amount of pyrrolidine for the racemic transformation and the Hayashi–Jørgensen catalyst to induce enantioselectivity, albeit with modest results (Scheme 2a).[11] One year later, Jørgensen employed the same chiral organocatalyst to develop a direct regio- and stereoselective protocol for the synthesis of *meta*-substituted anilines through the α-functionalization of aldehydes with anilines, achieving good yields and excellent enantioselectivities.[12] The process consists of the formation of a quinone by anodic oxidation of the aniline, which subsequently reacts with a nucleophilic enamine generated by the interaction of an aliphatic unbranched aldehyde with the Hayashi–Jørgensen organocatalyst. While this transformation yields excellent results, the electrochemical focus was oriented towards the generation of the electrophilic species rather than SOMO activation of the enamine (Scheme 2b). Through a different approach, in the same year, Jang and co-workers reported the first example of an electrochemical SOMO-activated reaction using the anodically generated radical cation of an enamine compound to promote an asymmetric electrochemical α-alkylation of aldehydes in the presence of xanthene (Scheme 2c).[13] Recently, Dell'Amico and co-workers developed an electrochemical stereoselective organocatalytic α-functionalization of aldehydes *via* SOMO activation of the enamine, employing 4,4-dimethoxybiphenyl as a redox shuttle. In this approach, galvanostatic conditions and the redox shuttle are crucial to prevent catalyst degradation and ensure excellent yields and enantiomeric ratios (Scheme 2d).[14]

Inspired by these works, we wish to report here our studies on the stereoselective catalytic α-chlorination of aldehydes under electrochemical conditions, by electrochemical SOMO activation of enamines generated in the presence of catalytic amounts of a chiral imidazolidinone (Scheme 2e).



Scheme 2 Electrochemical stereoselective organocatalytic α-functionalization of aldehydes.

Results and discussion

We started our preliminary investigation by examining the reactivity of dihydrocinnamic aldehyde **1** as a model substrate in the presence of LiCl as the chlorine source. At first, cyclic

voltammetry was performed on a 1 : 1 mixture of LiCl and aldehyde **1**. By recording voltammograms using a Rodeostat apparatus in a 0.2 M $LiClO_4$ acetonitrile solution, it was found that both compounds show irreversible oxidation peaks at 1.16 V *vs.* Ag/Ag^+ and 2.18 V *vs.* Ag/Ag^+, respectively (for details, see the SI).

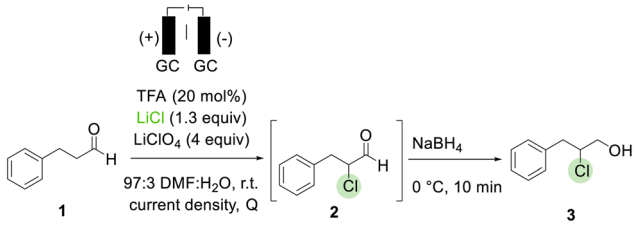
Since LiCl has a lower oxidation potential, we hypothesized that α-chlorination of aldehyde **1** could be achieved through the *in situ* generation of $Cl^•$ under galvanostatic conditions. This approach is in agreement with the well-known electrophilic nature of the chlorine radical, which readily reacts with electron-rich aromatic compounds.[15]

Therefore, we initially performed a screening of the current density and the total charge from 2 to 5 F mol^{-1} to find out the best galvanostatic reaction conditions for this transformation. This investigation was performed under ambient atmosphere using 1 mmol of compound **1** in the presence of a catalytic amount of trifluoroacetic acid, in an undivided cell, using glassy-carbon electrodes, as both anode and cathode, and with 1.3 equivalents of LiCl in a 0.4 M solution of $LiClO_4$. The reaction medium was switched from acetonitrile to a 97 : 3 DMF : H_2O solution to improve the chemical efficiency of the process (see the SI). After 16 hours of reaction, the resulting α-chlorinated aldehyde **2** was directly reduced to alcohol with 6 equivalents of $NaBH_4$, and the product was isolated by chromatographic purification. The data are presented in Table 1. Increasing the current density from 1.5 mA cm^{-2} to 6 mA cm^{-2} while applying a total charge of 2 F mol^{-1} resulted in a decrease in product yield (entries 1–4). Reducing the current density to 1.5 mA cm^{-2} and increasing the total charge to 3 F mol^{-1} afforded product **3** with a 56% yield (entry 5). A higher total charge (4 F mol^{-1}, entry 6) proved to be advantageous for the reaction, affording **3** in 68% yield. However, a further increase in the total charge resulted in a lower yield (entry 7). The reaction conditions of entry 6 were selected for further studies; in particular, in order to investigate the stereochemical outcome of the α-chlorination of hydrocinnamaldehyde **1**, enantiopure imidazolidinone-based organocatalysts **A** and **B** were evaluated (Table 2).[5]

Both organocatalysts were tested at room temperature and at 0 °C; however, no significant enantiomeric excess was observed under these conditions. The best results were obtained using catalyst **A**, where compound **3** was isolated in 65% yield with moderate enantioselectivity after 16 h of reaction time (30% ee, entry 1). However, performing the reaction at 0 °C resulted in lower yields and no significant change in the stereochemical efficiency, while no enantioselectivity was observed at all when catalyst **B** was employed (Table 2). According to these findings, the reaction protocol was slightly modified. Cyclic voltammetry measurements indicated that the co-presence of copper(II) bis(trifluoroacetate) and LiCl in the reaction medium could facilitate the *in situ* formation of $CuCl_2$, which is likely to act as the primary chlorine source (see below for further comments); therefore, we decided to investigate the direct use of $CuCl_2{\cdot}2H_2O$ as an alternative chlorine donor. The electrochemical behaviour of the resulting mixture was then investigated by cyclic voltammetry analysis (Fig. 1).

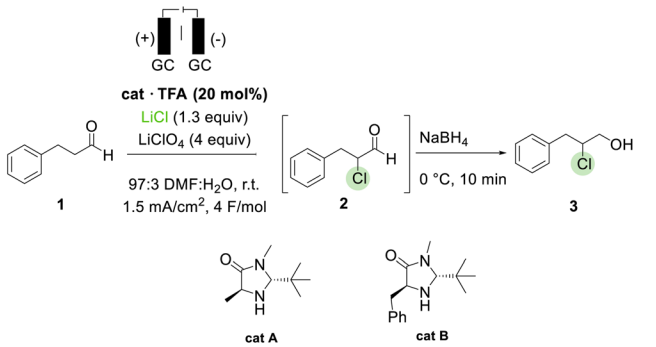
When a stoichiometric amount of catalyst **A** is added to a 5 mM solution of aldehyde **1** in 0.2 M solution of $LiClO_4$ in CH_3CN (red line, Fig. 1), a new irreversible oxidation peak appears at 0.7 V *vs.* Ag/Ag^+, which is assigned to the *in situ* generation of the enamine. Additionally, the cyclic voltammetry study, performed after the addition of a stoichiometric amount of $CuCl_2{\cdot}2H_2O$ to the mixture (blue line, Fig. 1), revealed the presence of two oxidation peaks and two reduction peaks, corresponding to the Cu^0/Cu^I and Cu^I/Cu^{II} oxidation/reduction transitions. Noteworthily, an increase in the anodic current of the enamine species was observed, con-

Table 1 Preliminary investigation of electrochemical α-chlorination of dihydrocinnamic aldehyde **1**



Entry	Current density (mA cm^{-2})	Q (F mol^{-1})	**3** yield (%)
1	1.5	2	45
2	3	2	37
3	4.5	2	32
4	6	2	27
5	1.5	3	56
6	1.5	4	68
7	1.5	5	45

Table 2 Preliminary investigation of stereoselective electrochemical α-chlorination of dihydrocinnamic aldehyde **1**



Entry	Catalyst	Temp. (°C)	**3** yield (%)	**3** ee[a] (%)
1	**A**	25	65	30
2	**A**	0	23	33
3	**B**	25	62	<5
4	**B**	0	17	<5

[a] Enantiomeric excesses were determined with HPLC using a chiral stationary phase.

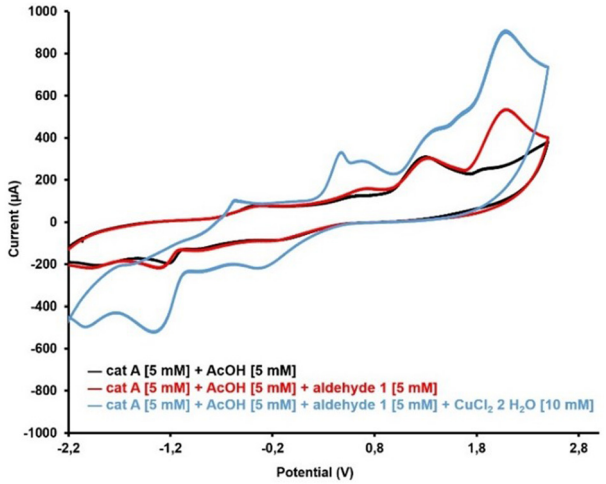


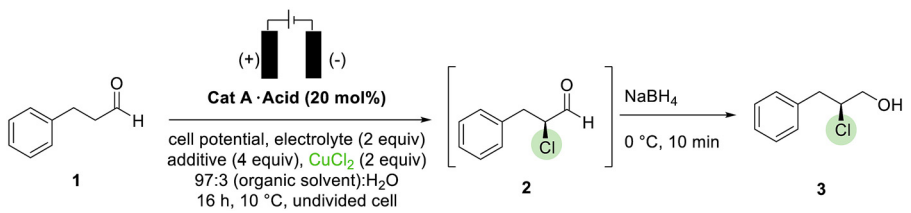
Fig. 1 Cyclic voltammetry of organocatalyst **A** (5 mM) recorded in a 0.2 M solution of $LiClO_4$ (black line). Cyclic voltammetry of a stochiometric amount of organocatalyst **A** (5 mM) and aldehyde **1** (5 mM) in the presence of a catalytic amount of acetic acid (0.5 mM) recorded in a 0.2 M solution of $LiClO_4$ (red line). Cyclic voltammetry of a stochiometric amount of organocatalyst **A** (5 mM) and aldehyde **1** (5 mM) in the presence of a catalytic amount of acetic acid (0.5 mM) and $CuCl_2$ (5 mM) recorded in a 0.2 M solution of $LiClO_4$ (blue line). GC rod as the working electrode, Pt foil as the counter electrode and Ag/Ag^+ as the reference electrode with a scan rate of 0.1 V s^{-1}.

sistent with the role of the Lewis acid in promoting enamine formation.

Since the Cu^{II}/Cu^{I} reduction occurs at −0.3 V *vs.* Ag/Ag^+ and the oxidation potential of the enamine is 0.7 V *vs.* Ag/Ag^+, we investigated the α-chlorination of aldehyde **1** in the presence of $CuCl_2{\cdot}2H_2O$ with a cell potential of 1 V.

The results are summarized in Table 3. Typical reaction conditions are as follows: 1 mmol of aldehyde, 20 mol% of organocatalyst as the acetate or trifluoroacetate salt, and 2 equivalents of $CuCl_2{\cdot}2H_2O$. The reaction was performed over 16 hours at 10 °C in an undivided cell with glassy-carbon electrodes as both anode and cathode, using different electrolytes and additives. To identify the optimal solvent, $LiClO_4$ was used as the electrolyte and LiTFA as the additive. When 97 : 3 DMF : H_2O was employed, compound **3** was obtained in 54% yield with 91% ee (entry 1). Replacing DMF with CH_3CN improved the chemical outcome of the transformation, affording the product in 89% yield and 92% ee (entry 2). The roles of the acid, the additive, and the electrolyte were then evaluated. Replacing TFA with acetic acid led to comparable results (entry 2 *vs.* entry 3). When the reaction was performed without $LiClO_4$, alcohol **3** was isolated in 64% yield and 89% ee (entry 4), whereas only trace amounts were observed in the absence of LiTFA (entry 5). Furthermore, replacing $LiClO_4$ with *t*-Bu_4NPF_6 led to a slight decrease in the yield (entry 6). Increasing the cell potential to 2 V resulted in the deposition of metallic copper on the cathode surface, with a consequent decrement of the yield (entry 7). Additionally, replacing glassy-carbon electrodes with Pt-foil as both anode and cathode improved the chemical outcome of the reaction, providing **3** in 74% yield and 90% ee (entry 8). Reducing the reaction time from 16 h to 8 h proved to be detrimental, since the desired product was isolated in 57% yield and 92% ee (entry 9, Table 3). Upon using only one equivalent of $CuCl_2$ (instead of 2 equivalents), the formation of Cu(0) and passivation of the electrode were observed, due to the reduction of Cu(II) to Cu(I) and from Cu(I) to Cu(0), thus resulting in only 50% yield (entry 10). Even lower yields were observed with catalytic amounts of

Table 3 Optimization studies of the electrochemical α-chlorination of aldehyde **1** in the presence of chiral organocatalyst **A**



Entry	Electrolyte	Additive	Acid	Cell potential (V)	Electrodes	Organic solvent	Time (h)	**3** yield[a] (%)	**3** ee[b] (%)
1	$LiClO_4$	LiTFA	AcOH	1	GC(−)||GC(+)	DMF	16	54	91
2	$LiClO_4$	LiTFA	AcOH	1	GC(−)||GC(+)	ACN	16	89	92
3	$LiClO_4$	LiTFA	TFA	1	GC(−)||GC(+)	ACN	16	84	91
4	None	LiTFA	AcOH	1	GC(−)||GC(+)	ACN	16	64	89
5	$LiClO_4$	—	AcOH	1	GC(−)||GC(+)	ACN	16	<5	n.d.
6	*t*-Bu_4NPF_6	LiTFA	AcOH	1	GC(−)||GC(+)	ACN	16	67	88
7	$LiClO_4$	LiTFA	AcOH	2	GC(−)||GC(+)	ACN	16	45	91
8	$LiClO_4$	LiTFA	AcOH	1	Pt(−)||Pt(+)	ACN	16	74	90
9	$LiClO_4$	LiTFA	AcOH	1	GC(−)||GC(+)	ACN	8	57	92
10[c]	$LiClO_4$	LiTFA	AcOH	1	GC(−)||GC(+)	ACN	16	50	90
11[d]	$LiClO_4$	LiTFA	AcOH	1	GC(−)||GC(+)	ACN	16	30	89

[a] Isolated yields obtained by flash chromatography after *in situ* reduction of aldehyde **2** with $NaBH_4$. [b] Enantiomeric excesses were determined with HPLC using a chiral stationary phase. [c] Reaction performed with 1 equiv. of $CuCl_2$. [d] Reaction performed with 0.5 equiv. of $CuCl_2$.

copper(II) chloride. For the sake of comparison, it is worth mentioning that the reaction performed in the presence of a nickel catalyst afforded the product in good yields but with no enantioselectivity, thus highlighting the importance of the copper salt in the stereochemical outcome of the reaction. With the nickel catalyst, the reaction did not proceed without electricity.

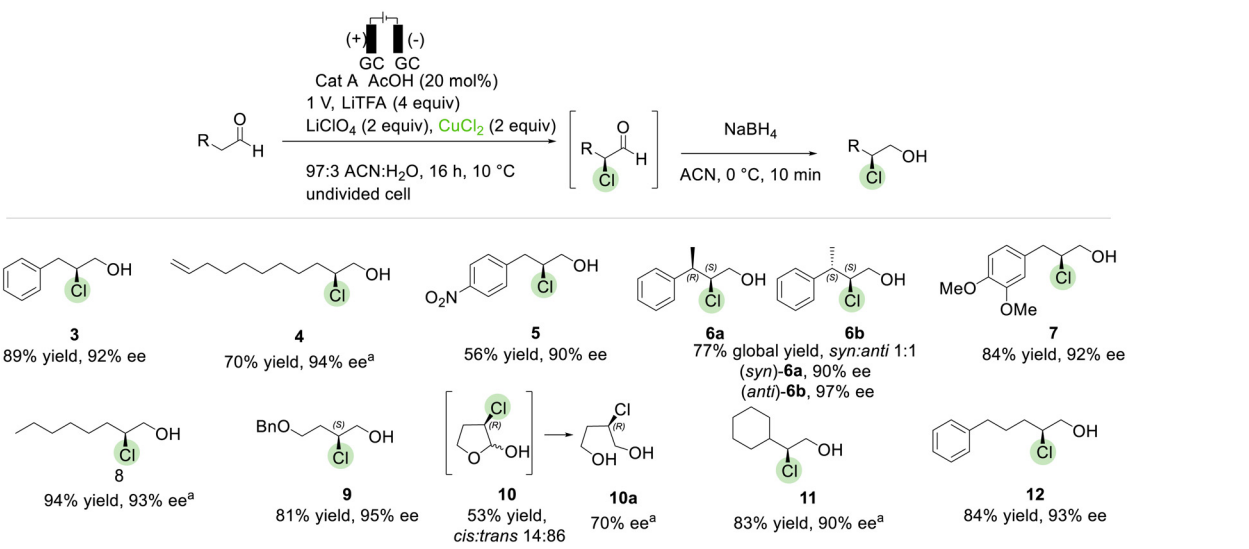
Under the optimized electrochemical reaction conditions (Table 3, entry 2), the scope of the reaction was then investigated. As shown in Scheme 3, linear, cyclic and arenyl aldehydes proved to be suitable substrates for this transformation. Products **4**, **8**, **9**, **11** and **12**, derived from linear and cyclic aliphatic aldehydes, were obtained with excellent enantioselectivities (90–95% ee) and higher yields compared to chloroalcohols **3**, **5**, **6**, and **7**, which originate from dihydrocinnamic aldehyde derivatives. Among the aromatic substrates, those bearing an electron-withdrawing group on the aromatic ring exhibited higher yields than those with electron-donating groups (*e.g.*, compound **5** *vs.* compound **7**).

Product **6**, derived from the reaction of a β-substituted aldehyde, was obtained as a 1 : 1 *syn* : *anti* diastereoisomeric mixture, with 90% ee for the *syn*-**6** isomer and 97% ee for the *anti*-**6** isomer. The reaction of 4-benzyloxybutanal afforded compound **9** in 81% yield with 95% ee, while the α-chlorination of 2-hydroxytetrahydrofuran led to the formation of the corresponding chlorinated aldehyde **10** in 53% yield, isolated as a cyclic acetal in a 14 : 86 *cis* : *trans* ratio.

Reduction with $NaBH_4$ and derivatization with naphthoyl chloride enabled the determination of the enantiomeric excess of the corresponding alcohol **10a**, which was found to be 70%. The result, along with the observation that compound **10** exhibits the (*R*)-configuration at the stereocenter bearing the chlorine atom, suggests that the free hydroxyl group plays a crucial role in influencing the stereochemical outcome of the transformation.

To gain a mechanistic understanding of the enantioselective electrochemical α-chlorination of aldehydes, a series of control experiments, cyclic voltammetry studies and radical trapping experiments were conducted. The results of the studies are reported in Table 4. In the absence of the organocatalyst, the α-chlorination of aldehyde **1** fails to proceed (entry 1); however, without electricity, the transformation still occurs, affording compound **3**, although with a lower yield and enantioselectivity (58% yield, 85% ee, entry 2). This suggests that while the organocatalyst is essential for the reaction to proceed under electrochemical conditions, the process can still occur without the electrical input, albeit with a lower efficiency.

As a follow-up experiment, the reaction was performed using the Autolab system, where the oxidation potential was precisely set to the enamine value of 0.7 V by means of a reference electrode (Ag/AgCl). This controlled setup led to a slight improvement in the reaction outcome, delivering compound **3** in 78% yield and 91% ee after 8 hours of electrolysis (Table 4, entry 3 *vs.* Table 3, entry 1). Additionally, it was found that LiTFA can be replaced by a combination of LiCl and TFA, as demonstrated in entry 4. The ability of compound **1** to undergo α-chlorination, albeit with low efficiency, in the absence of electricity suggests the involvement of a chemical oxidizing agent in the reaction mixture. This led us to investigate the role of $CuCl_2$ in the reaction mechanism. Since the oxidation potential of $CuCl_2$ is 0.5 V *vs.* Ag/Ag^+ (Cu^I/Cu^{II}), and



Scheme 3 Scope of the enantioselective electrochemical chlorination of aldehydes. Electrochemical reaction conditions: 1 mmol scale of aldehyde, 20 mol% of organocatalyst **A**, 20 mol% of AcOH and 300 μL of distilled water in 10 mL of ACN, undivided cell. Isolated yields were obtained by flash chromatography after *in situ* reduction with $NaBH_4$. Enantiomeric excess was determined with HPLC using a chiral stationary phase. [a] ee was evaluated on the naphthoyl derivative.

Table 4 Control experiments designed to elucidate the reaction mechanism

Entry	Electrolyte (equiv.)	Additive (equiv.)	Cell potential (V)	Catalyst	Electrodes	**3** yield[a] (%)	**3** ee[b] (%)
1	$LiClO_4$ (2)	LiTFA (3)	1	—	GC(−)|GC(+)	—	—
2	$LiClO_4$ (2)	LiTFA (4)	—	**A**	—	58	85
3	$LiClO_4$ (2)	LiTFA (4)	0.7	**A**	GC(−)|GC(+) *vs.* Ag/AgCl	78	91
4	$LiClO_4$ (2)	LiCl (1.5) + TFA (1.5)	1	**A**	GC(−)|GC(+)	85	90

[a] Reaction performed for 16 hours, on a 1 mmol scale of aldehyde **1**, 20 mol% of organocatalyst **A**, 20 mol% of AcOH and 300 μL of distilled water in 10 mL of ACN, undivided cell. Isolated yields obtained by flash chromatography after *in situ* reduction of aldehyde **2** with $NaBH_4$. [b] Enantiomeric excess was determined with HPLC using a chiral stationary phase.

the enamine of **1** has an oxidation potential of 0.7 V *vs.* Ag/Ag^+, copper chloride(II) cannot act as a direct oxidizing agent.

However, it was observed that in the presence of LiTFA salt, $CuCl_2$ undergoes an anion exchange process, generating $Cu(TFA)_2$, as illustrated in the equilibrium shown in eqn (1):

$$CuCl_2 + 2LiTFA \rightleftarrows Cu(TFA)_2 + 2LiCl \quad (1)$$

The *in situ* generated $Cu(TFA)_2$ acts as a single-electron transfer (SET) chemical oxidizing agent, enabling the α-chlorination of aldehydes even in the absence of an external electrical input.

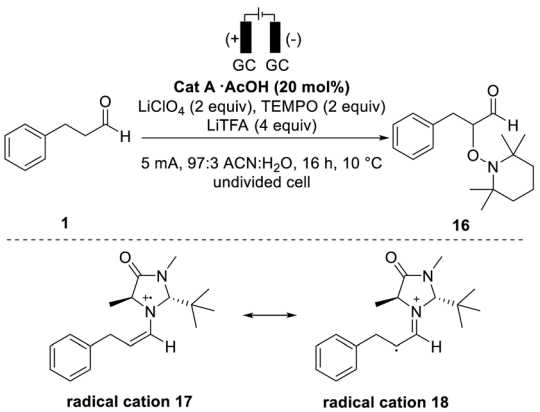
However, since this process generates only a small amount of $Cu(TFA)_2$, product **3** is obtained in lower yields compared to the electrochemical process (for further details and CV studies, see the SI).

To further confirm the generation of enamine-radical intermediates in the proposed SOMO catalysis mechanism, the α-chlorination of aldehyde **1** was performed under galvanostatic conditions in the presence of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) as a radical scavenger. A constant current of 5 mA was applied to the system. Under these conditions, compound **16** was detected *via* APCI-MS, which is consistent with the interception of a radical species, presumably the enamine-derived radical cation **17** (Scheme 4).

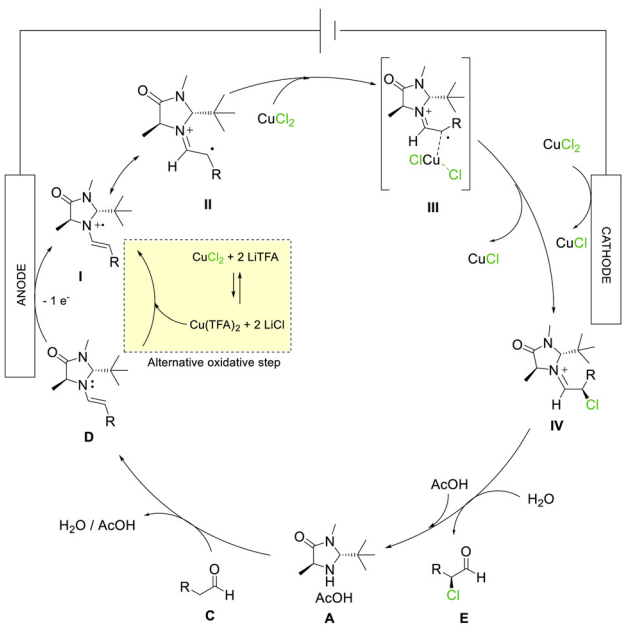
However, it is important to note that TEMPO is known to undergo anodic oxidation to its oxoammonium form under similar electrochemical conditions and may subsequently react with the enamine *via* non-radical pathways. Therefore, although the detection of compound **16** is consistent with the involvement of radical intermediates, it cannot be considered conclusive evidence.

Based on these investigations, a mechanism for the electrochemical enantioselective α-chlorination of aldehydes was proposed and is reported in Scheme 5. The reaction of organocatalyst **A** with aldehyde **C** generates chiral enamine **D**, which can be oxidized through a SET process, leading to the formation of its radical cation form **I** at the anode in the electrochemical pathway. Alternatively, in the non-electrochemical pathway, the same oxidation is facilitated by the *in situ* generated $Cu(TFA)_2$, which acts as the oxidizing agent. Intermediate **I** then interacts with $CuCl_2$ according to the resonance structure **II**, forming species **III**.

According to Kochi's studies,[16] as the radical compound approaches the first coordination sphere of the copper metal, a substitution reaction occurs, where the copper atom is replaced by a chlorine atom. The stereochemical outcome of the process is governed by the chiral organocatalyst, which controls the geometry and the conformational preferences of the enamine and dictates the approach of the reacting species

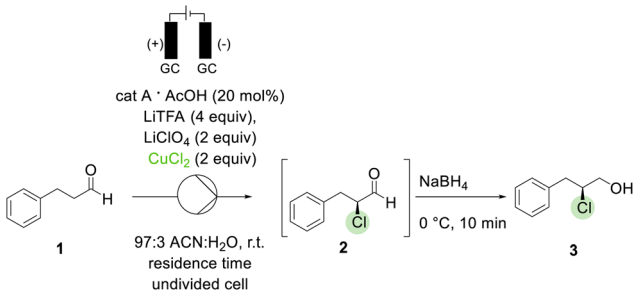


Scheme 4 Radical trap experiment.



Scheme 5 Proposed reaction mechanism.

Table 5 Continuous flow enantioselective catalytic chlorination of aldehyde **1**



Entry	Flow rate (μL min^{-1})	Retention time (min)	**3** yield (%)	**3** ee[a] (%)
1	80	2.81	34	90
2	100	2.25	58	89
3	120	1.87	64	90
4	130	1.73	85	91
5	140	1.61	73	89
6	160	1.40	54	88
7	180	1.25	44	90
8[b]	130	1.73	23	89

[a] Enantiomeric excesses were determined with HPLC using a chiral stationary phase. [b] Reaction performed without electricity.

Table 6 Continuous flow productivities and space time yields

Process	Productivity[a] (mmol h^{-1})	Productivity rel. factor	STY[b] (mmol h^{-1} ml^{-1})	STY rel. factor
Batch[c]	5.56×10^{-2}	1	5.56×10^{-3}	1
Flow[d]	6.64×10^{-1}	11.8	2.95	530

[a] Calculated as moles of product divided by the collection time required to collect the product. [b] Calculated as moles of product in the reactor, divided by residence time and reactor volume. [c] Calculated using data from entry 2 of Table 3. [d] Calculated using data from entry 3 of Table 5.

during the transformation. This results in the release of CuCl and intermediate **IV**, which, upon hydrolysis, releases the final product **E** and regenerates the organocatalyst **A**. To properly balance the electron flow during this process, another equivalent of $CuCl_2$ was used so that the reduction of Cu(II) to Cu(I) occurs at the cathode, in order to avoid the formation of Cu(0) from the CuCl reduction, which would lead to deactivation of the electrode (see Table 3, entry 10). Considering the dual mechanistic pathways, we aimed to assess whether the electrochemical route could offer enhanced efficiency compared to the non-electrochemical pathway.

To this end, the electrochemical α-chlorination of aldehyde **1** was performed under continuous flow conditions,[17] taking advantage of several benefits of flow chemistry, including enhanced reaction control and faster reaction times.[18]

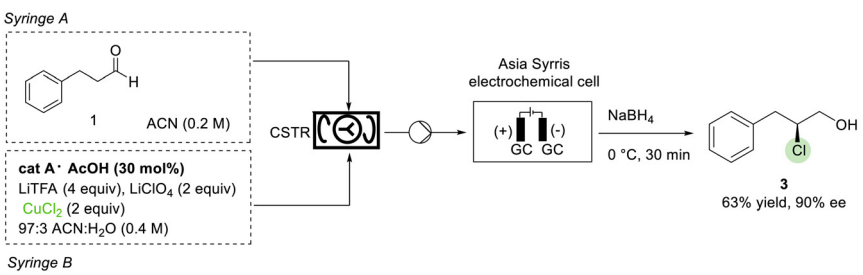
The setup employed a 225 μL reactor cell; the crude reaction mixture at the output of the reactor was then subjected to reduction with $NaBH_4$ under batch conditions (see the SI). Different flow rates were investigated employing glassy carbon electrodes as both anode and cathode, under potentiostatic conditions with a cell potential of 1 V (Table 5).

When operating at room temperature with a flow rate of 130 μL min^{-1} (entry 4), compound **3** was isolated in 85% yield and 91% ee after only 1.73 minutes of residence time. This significant reduction in reaction time compared to the batch process highlights the efficiency of the flow system approach. Attempts to further decrease the reaction time led to lower yields (entries 5–7). However, when using the same fluidic setup without applying electricity, compound **3** was isolated in very low yield (23%) with 89% ee, demonstrating that the activity of the *in situ* generated $Cu(TFA)_2$ is less efficient in promoting the transformation under such short reaction times. The comparison of the productivity and the space time yield between the batch and flow processes is reported in Table 6.

Based on the experimental results, it is noteworthy that the same amount of product obtained in a batch process over 16 hours could be produced in a flow process in only 77 minutes, with comparable levels of enantioselectivity. To further confirm the process intensification positive features of the in-flow protocol, a gram-scale in-flow synthesis was performed (Scheme 6). Starting from 8.9 mmol of aldehyde **1** (1.2 g), in the presence of 30 mol% of cat **A**, 0.960 g of compound **3** was isolated with 63% yield and 90% ee in 11 hours.

Conclusions

In conclusion, the enantioselective α-chlorination of aldehydes using electrochemistry to activate the enamine through SOMO activation was investigated. From these studies, it was found



Scheme 6 Gram-scale synthesis of compound **3** performed under continuous flow conditions using the Asia Syrris system.

that under galvanostatic conditions, without the presence of a metal species, α-chloroalcohols can be obtained in modest yields with low enantioselectivities. This limited success led us to further investigate the underlying reaction mechanisms and, by cyclic voltammetry studies, to identify $CuCl_2$ as the paramagnetic species involved in the reaction with the enamine radical cation. This interaction plays a crucial role in enabling the transfer of a chlorine atom, thereby promoting the formation of enantioenriched α-chlorinated aldehydes with high stereocontrol.

This insight enabled the development of a modified protocol that directly reacts copper chloride(II) with an aldehyde under potentiostatic conditions of 1 V, using glassy-carbon electrodes in a 0.2 M solution of $LiClO_4$, in the presence of an imidazolidinone as an organocatalyst. High yields and enantioselectivities (up to 97% ee) were achieved and, thanks to the electrochemical approach, stoichiometric amounts of $Na_2S_2O_8$ were successfully replaced by electrons, enabling a more efficient and sustainable reaction process. Another significant improvement compared to the known procedures comes with the switching from batch to flow chemistry:[19] the productivity of the process was notably enhanced, and the reaction time was reduced to only 1.73 min.

Author contributions

M. B. conceived the project. S. A. and M. B. designed the research. S. A. and F. M. carried out the experiments. S. A., F. M., S. R. and A. P. analysed the results. M. B., S. A. and S. R. wrote, edited and completed the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). The Supporting Information provides detailed experimental procedures, including the synthesis of starting materials and derivatives, representative protocols for key reactions, and characterization data. Additional analytical results, such as NMR spectra, HPLC traces, and cyclic voltammetry measurements, are also included. Supplementary information is available. See DOI: **https://doi.org/10.1039/d5qo01249j**.

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