**Electroredox Carbene Organocatalysis with iodine cocatalyst**

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Abstract

Oxidative carbene organocatalysis, inspired from Vitamin B1 catalyzed oxidative activation from pyruvate to acetyl coenzyme A, have been developed as a versatile synthetic method. To date, the $\alpha$, $\beta$, $\gamma$, $\delta$- and carbonyl carbons of (unsaturated)aldehydes have been successfully activated via oxidative N-heterocyclic carbene (NHC) organocatalysis. In comparison with chemical redox or photoredox methods, electroredox methods, although widely used in mechanistic study, were much less studied in NHC catalyzed organic synthesis. Herein, an electroredox NHC organocatalysis system with iodine cocatalyst was developed. With the help of non-uniform distribution of electrolysis system, NHC and iodine, which was normally not compatible in chemical reaction, cooperated well in the electrochemical system. This cocatalyst system provided general solutions for electrochemical single-electron-transfer (SET) oxidation of Breslow intermediate towards versatile transformations. Radical clock experiment and cyclic voltammetry results suggested an anodic radical coupling pathway.

Main Text

Oxidative activation is a general activation mode which widely existed not only in the biological system, but also in synthetic chemistry. As an important transformation, in mitochondria, oxidative activation from pyruvate to acetyl coenzyme A (CoA) have been discovered since 1937 (Fig. 1a). In this transformation, pyruvate was believed to be firstly reacted with thiamine pyrophosphate (TPP, Vitamin B1, VB1) to form a Breslow intermediate after decarboxylation, and followed by oxidation with pyruvate ferredoxin oxidoreductase (PFOR) (with two SET processes) towards an acyl azolium intermediate, which underwent thioesterification to give acetyl-CoA. In synthetic chemistry, besides 2-oxocarboxylic acids, aldehydes were also efficient substrate for this transformation. In 1968, Corey and coworkers developed an oxidative esterification of aldehydes using cyanide as catalyst and MnO$_2$ as oxidant. Since 1977, different types oxidative esterification transformations were developed, using thiazolium, imidazolium or triazolium NHC catalysts with various types of oxidants. Among them, tetra-tert-butyl diphenoquinone (DQ), pioneered by Studer, was eventually developed as the most popular oxidant in NHC organocatalysis. After Studer’s pioneer work of $\beta$-LUMO activation with oxidative NHC organocatalysis in 2010, the remote activation modes involving $\alpha$, $\gamma$, $\delta$- carbon functionalization were rapidly developed in the later several years. Recently, SET redox activation mode was developed in NHC organocatalysis, with chemical redox or photoredox methods.

With anodic electron transfer as green oxidant, electrochemical oxidation is one of the perfect choices in oxidation activation. Inspired by the biomimic electrochemical oxidation of pyruvate, Boydston and coworkers developed a pioneer work of electrochemical oxidative carbene organocatalysis in 2013. With thiazolium NHC catalyst, different aldehydes were smoothly oxidized to generate corresponding esters or thioesters in undivided cells with constant voltage direct current (DC). However, this system was limited to the (thio)esterification with thiazolium NHC catalyst, and with no further development in the later decade. The wonderful world of oxidative carbene organocatalysis with...
different NHC catalysts (imidazolium, triazolium NHCs), different activation modes (α-, β-, γ-, or δ-carbon functionalization) and enantioselective transformations were still waiting for a general and efficient electrochemical oxidation system.

Inspired by the proposed concept of coupled electrolysis in Lin’s work in 2018, herein we developed a general electrochemical catalytic system for oxidative carbene organocatalysis. As shown in Fig. 1b, Breslow intermediate was anodic oxidized to radical cation intermediate\[51, 52\] \(\text{I}\) (Fig. 1b, anodic event A), while iodine radical\[53\] was also generated on anode (Fig. 1b, anodic event B). The coupling of these two radicals gave intermediate \(\text{II}\), which further affording acyl azolium intermediate after an eliminative regeneration of iodine anion. It is worth to note that iodine can poison carbene catalyst\[54, 55\] (Fig. 1c) and was never applied as oxidant in NHC organocatalysis. However, with the help of non-uniform distribution of electrolysis system\[56\], the generation of iodine radical was well kinetically controlled to undergo radical coupling with NHC attached radical intermediate \(\text{I}\) near anode, without poisoning NHC. This cocatalyst strategy provide new possibility for electrochemical reaction to use the cocatalyst systems which are not compatible in normal chemical reactions. The radical clock experiment of \(\text{cis}\)-2-phenylcyclopropane-1-carbaldehyde gave difference results with traditional chemical oxidant DQ or our electrochemical cocatalytic oxidation system. Radical intermediate in our system was believed to undergo a reversible ring-opening of cyclopropane, to give the \(\text{trans}\)-ester product (Fig. 1d).

**Table 1 | Effect of Reaction Parameters\[8\].**

![Chemical Structure](image_url)
| Entry | variations                              | Yield (%)<sup>b</sup> | ee (%)<sup>c</sup> |
|-------|----------------------------------------|------------------------|-------------------|
| 1     | None                                   | 79                     | 97                |
| 2     | No NHC A                               | 0                      | -                 |
| 3     | No electricity                         | n.r.                   | -                 |
| 4     | DCE as solvent                         | 60                     | 95                |
| 5     | THF as solvent                         | 64                     | 96                |
| 6     | CH<sub>3</sub>CN as solvent            | 30                     | 93                |
| 7     | n-Bu<sub>4</sub>NBF<sub>4</sub> as electrolyte | trace              | -                 |
| 8     | n-Bu<sub>4</sub>NBr as electrolyte     | 30                     | 95                |
| 9     | Et<sub>4</sub>NI as electrolyte        | 68                     | 95                |
| 10    | Cs<sub>2</sub>CO<sub>3</sub> as base    | 29                     | 90                |
| 11    | DBU as base                            | 29                     | 31                |
| 12    | Graphite as anode                      | 62                     | 97                |

<sup>a</sup> Standard conditions: Pt anode, Pt cathode, 1a (0.15 mmol), 2a (0.1 mmol), NHC A (20%), K<sub>2</sub>CO<sub>3</sub> (150%), n-Bu<sub>4</sub>NI (1.0 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (3 mL), at a constant current of 1.0 mA for 6 h (2.24 F·mol<sup>-1</sup>) in IKA ElectraSyn 2.0 at room temperature.

<sup>b</sup> Yield of the isolated product.

<sup>c</sup> The enantiomeric ratio (ee) was determined by chiral stationary HPLC. DCE = 1,2-dichloroethane. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Results And Discussion

**Reaction optimization.** We started our investigation by choosing the formal [4+2] annulation of enal 1a and hydrazone 2a as the model reaction<sup>57, 58</sup> of NHC organocatalyzed oxidative γ-activation. In a constant current (1 mA) electrochemical system with platinum as both anode and cathode material, in the presence of 150% K<sub>2</sub>CO<sub>3</sub> and 1.0 equiv. n-Bu<sub>4</sub>NI in CH<sub>2</sub>Cl<sub>2</sub>, NHC precatalyst A<sup>59</sup> successfully catalyzed the reaction of enal 1a and hydrazone 2a, giving the desired product 3a in 79% isolated yield with 97% ee. Control experiments were conducted to indicate that both NHC catalyst and electricity were essential for this reaction. (Table 1, entries 2 and 3). Using other solvents (such as DCE, THF and CH<sub>3</sub>CN) instead of CH<sub>2</sub>Cl<sub>2</sub> all led to decreased product yield (Table 1, entries 4-6). Changing the anion of electrolyte to Br<sup>-</sup> or BF<sub>4</sub><sup>-</sup> lead to a sharp decline in yield (Table 1, entry 7-8), indicating that direct anodic
oxidation from Breslow intermediate (Fig. 1, intermediate I) to acyl azolium intermediate (Fig. 1, intermediate IV) was inefficient in this system and the strategy of anodic coupled electrolysis was necessary. In comparison, changing the cation of electrolyte to Et₄N⁺ only afford a slightly lower yield and ee (Table 1, entry 9). The effect of base was also investigated, K₂CO₃ showed better performance than other base such as Cs₂CO₃ or DBU (Table 1, entries 10-11). Platinum showed better performance than graphite as anode material (Table 1, entries 1 and 12).

**Substrate scope.** With optimized conditions in hand, the substrate scope of the model reaction was investigated (Fig. 2). Functional groups in the aromatic ring of the hydrazones such as fluoro, methoxy and bromo substituents worked well (3a-3d). 3-pyridyl and 2-furyl substituents in the hydrazone substrates were also tolerated (3e and 3f). Various aryl substituents of the α,β-unsaturated aldehydes were all suitable for this transformation, giving the desired products in good yields with excellent ee (3g-3j). Substrates with different ester substituents were also tolerated, affording the corresponding products with good results (3k and 3l).

Encouraged by the success of electrochemical oxidative reaction on enal γ-carbon, we next evaluated the electrochemical approach for the oxidative β-carbon reaction of enal. As exemplified in Fig. 3, in the model reaction of formal [3+3] annulation of enals (4) and 1,3-dicarbonyls (5), both imidazolium catalyst B and triazolium catalysy C were applicable in our anodic coupled electrolysis system (The optimized condition with two catalyst was slightly different in base and solvent, see Supplementary Information for details). Reactions of different 1,3-dicarbonyl compounds with cinnamaldehyde gave the lactone products effectively (6a-6e). Reactions of 2,4-pentandione and enals with different aromatic substituents also successfully afford the corresponding products in moderate yield (6f-6i).

The electrocatalytic protocol for oxidative enal α-carbon atom functionalization was also studied. The formal [2+4] annulation of aliphatic aldehydes 7 and α,β-unsaturated ketones 8 was chosen as a model reaction and the results were shown in Fig. 4 (see Supplementary Information for details of condition optimization). Different aliphatic aldehydes reacted with chalcone smoothly, and gave the lactone products in good yield with excellent enantioselectivity (9a-9d). Variation in the chalcone skeleton with different aromatic substituents had little influence on the of this reaction, and a broad range of groups, such as fluoro, chloro, methyl, methoxy and furyl groups were viable to get excellent ee (9e-9i).

For oxidative functionalization of aldehyde carbonyl carbon, an NHC-catalyzed dynamic kinetic resolution of hemiacetal was selected as a model reaction and the results were shown in Fig. 5 (see Supplementary Information for details of condition optimization). One of the biggest challenge of this reaction was to prevent the anodic oxidation of hemiacetal towards phthalic anhydride. Fortunately, the anodic coupled electrolysis system was well kinetically controlled. The oxidation of Breslow intermediate was prior to that of hemiacetal, no phthalic anhydride byproduct was observed. Different aromatic aldehydes were appliable in the reaction, giving chiral acetal product 12a-12d with excellent ee.
Miscellaneous reactions and gram-scale synthesis. To further investigate the generality of our catalytic system, additional examples of different model reactions were tried and the results were summarized in Fig. 6. To our delight, the anodic couple electrolysis system was quite general for different reactions, including δ-carbon functionalization of enal 13 towards multisubstituted benzene 14 (Fig. 6a), β-carbon functionalization of enal 4a towards chiral lactam 16 (Fig. 6b) and γ-carbon functionalization of enal 1a towards multicyclic product 18 (Fig. 6c). Brief screening of solvent could find acceptable condition for these reactions (see Supplementary Information for details). The corresponding products were obtained in moderate yield with excellent ee. An initial test towards scale-up synthesis was also studied. As shown in Fig. 6d, the reaction of 1a and 2a on a 5 mmol scale underwent smoothly for 83.5 hours, giving the desired product 3a 62% yield with 96% ee. In comparison, the traditional chemical oxidant strategy of this reaction may need at least 3 gram of oxidant DQ and will generate the same amount of reductive byproduct (diphenyl diphenone). These results further demonstrate the generality and efficiency of the electrochemical oxidation system.

Mechanistic studies. Some controlled experiments were carried out for mechanistic study, the results were summarized in Fig. 7. In the presence of 50 mol% I2, the [4+2] annulation of enal 1a and hydrazone 2a was fully suppressed (Fig. 7a). When 10 mol% I2 was subjected to the optimized reaction conditions (20 mol% NHC), half of the NHC catalyst A were believed to be poisoned and the result was nearly the same with the reaction with 10% NHC catalyst A (Fig. 7b). This result told us that the poisoned catalyst was probably inert in the reaction. The poisoned catalyst iodination poisoned effect of NHC catalyst was irreversible. Another possible pathway involving iodination of enal substrate was also excluded by the iodination control test (Fig. 7d). To further confirm the existence of key radical intermediate (Fig. 1, intermediate II) from anodic SET oxidation of Breslow intermediate, a radical clock experiment was carried out (Fig. 7e). Aldehyde cis-20 with cyclopropyl group was conducted in the anodic coupled electrolysis system to undergo a NHC catalyzed oxidative esterification reaction. As we expected, due to the radical isomerization towards a more thermal dynamically stabled trans- structure (Fig. 7e), ester product trans-21 was obtained as main product. In comparison, cis-20 did not isomerize to trans-20 in the reaction system. And the reaction with traditional chemical oxidant strategy only gave non-isomerized product cis-21. These results clearly showed that the SET oxidation of Breslow intermediate in our anodic coupled electrolysis system is completely different from the traditional electron paired oxidation with chemical oxidant DQ.

The electrochemical properties of different reactants and reagents were investigated in cyclic voltammetry experiments (Fig. 8). Direct electrochemical oxidation of enal 1a required high potential (about 2.75 V vs. Ag/AgCl, green line). After the addition of NHC A and DBU, the formation of Breslow intermediate lead to a dramatically decline in oxidation potential to 0.24 V (red line). The onset oxidation of iodine anion to iodine radical resulted in a feature from 0.25 V to 0.64V (blue line). The similar oxidation potential of Breslow intermediate and iodine anion probably leads to an efficient anodic radical coupling of NHC-attached radical intermediate (Fig. 1, intermediate II) and iodine radical. The slightly lower oxidation potential of Breslow intermediate also ensure the sufficient capture of iodine.
radical and prevent its catalyst poison effect. Cyclic voltammetry experiments involving other model reactions were also carried out, and all of them gave similar results that the oxidation potential of corresponding Breslow intermediate was slightly lower than iodine anion (see Supplementary Information for details).

In summary, we have developed a modular method of anodic coupled electrolysis system in which NHC catalysis is merged with cooperative iodine anion and electrocatalysis. With the help of non-uniform distribution of electrolysis system, NHC and iodine, which was normally not compatible in chemical reaction, cooperated well in the electrochemical cocatalyst system. This electrochemistry incorporated cocatalyst strategy allow new possibilities for recently non-compatible catalysts. Besides, this coupled electrolysis system successfully avoided the usage of big amount of chemical oxidant in oxidative NHC organocatalysis. The green reaction system was readily available for different activation modes (α-, β-, γ-, δ- or carbonyl carbon functionalization), different reaction types (cyclization, benzannulation, dynamic kinetic resolution, etc.) and scale up productions. Mechanism studies involving controlled test, radical clock experiments and cyclic voltammetry measurements provided solid evidence to support our proposal of anodic oxidation induced radical coupling, which differs with chemical oxidative approach. Learning from the wonderful features of oxidative NHC organocatalysis (two-electron oxidation or SET oxidation), we believed the electrosynthesis method would not only provide more feasibility for large-scale applications, but also open new avenues in the area of NHC-catalyzed radical reactions.

**Methods**

**General produce for electrochemical [4+2] annulation of 1 with 2 by the catalysis of NHC A.** The ElectraSyn vial (5 mL) with a stir bar was charged with β-methyl enals 1 (0.15 mmol, 1.5 equiv.), NHC A (0.02 mmol, 20%), K₂CO₃ (0.15 mmol, 1.5 equiv.), n-Bu₄NI (0.1 mmol, 1.0 equiv.) and hydrazones 2 (0.1 mmol, 1.0 equiv.) followed by anhydrous CH₂Cl₂ (3.0 mL). The ElectraSyn vial cap equipped with anode (Pt) and cathode (Pt) were inserted into the mixture. After pre-stirring for 2 minutes, the Electrasyn vial was connected to the Electrasyn 2.0 and the reaction mixture was electrolyzed under a constant current of 1.0 mA for a total reaction time of 6 hours accompanied by magnetic stirring. The ElectraSyn vial cap was removed, and electrodes were rinsed with EtOAc, which was combined with the crude mixture. After concentrated under reduced pressure, the crude residue was purified via flash column chromatography to afford the desired product 3

**General produce for electrochemical [3+3] annulation of 4 with 5 by the catalysis of NHC B.** The ElectraSyn vial (5 mL) with a stir bar was charged with α,β-unsaturated aldehydes 4 (0.1 mmol, 1.0 equiv.), NHC B (0.03 mmol, 30%), Cs₂CO₃ (0.03 mmol, 30%), n-Bu₄NI (0.1 mmol, 1.0 equiv.) and 1,3-dicarbonyl derivatives 5 (0.2 mmol, 2.0 equiv.) followed by anhydrous CH₂Cl₂ (2.0 mL) and t-BuOH (1.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (Pt) were inserted into the mixture. After pre-stirring for 2 minutes, the Electrasyn vial was connected to the Electrasyn 2.0 and the reaction mixture was electrolyzed under a constant current of 1.0 mA for a total reaction time of 6 hours accompanied by magnetic stirring. The ElectraSyn vial cap was removed, and electrodes were rinsed with
EtOAc, which was combined with the crude mixture. After concentrated under reduced pressure, the crude residue was purified via flash column chromatography to afford the desired product 6.

**General produce for electrochemical [3+3] annulation of 4 with 5 by the catalysis of NHC C.** The ElectraSyn vial (5 mL) with a stir bar was charged with α,β-unsaturated aldehydes 4 (0.1 mmol, 1.0 equiv.), NHC C (0.02 mmol, 20%), K$_2$CO$_3$ (0.02 mmol, 20%), n-Bu$_4$NI (0.1 mmol, 1.0 equiv.) and 1,3-dicarbonyl derivatives 5 (0.2 mmol, 2.0 equiv.) followed by anhydrous CH$_3$CN (1.5 mL) and t-BuOH (1.5 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (Pt) were inserted into the mixture. After pre-stirring for 2 minutes, the Electrasyn vial was connected to the Electrasyn 2.0 and the reaction mixture was electrolyzed under a constant current of 0.8 mA for a total reaction time of 10 hours accompanied by magnetic stirring. The ElectraSyn vial cap was removed, and electrodes were rinsed with EtOAc, which was combined with the crude mixture. After concentrated under reduced pressure, the crude residue was purified via flash column chromatography to afford the desired product 6.

**General produce for electrochemical [2+4] annulation of 7 with 8 by the catalysis of NHC A.** The ElectraSyn vial (5 mL) with a stir bar was charged with enones 8 (0.1 mmol, 1.0 equiv.), NHC A (0.03 mmol, 30%), Cs$_2$CO$_3$ (0.03 mmol, 30%), n-Bu$_4$NI (0.1 mmol, 1.0 equiv.) and aldehydes 7 (0.25 mmol, 2.5 equiv.) followed by anhydrous DMF (2.0 mL) and DCE (1.0 mL). The ElectraSyn vial cap equipped with anode (Pt) and cathode (Pt) were inserted into the mixture. After pre-stirring for 2 minutes, the Electrasyn vial was connected to the Electrasyn 2.0 and the reaction mixture was electrolyzed under a constant current of 0.8 mA for a total reaction time of 9 hours accompanied by magnetic stirring. The ElectraSyn vial cap was removed, and electrodes were rinsed with EtOAc, which was combined with the crude mixture. After concentrated under reduced pressure, the crude residue was purified via flash column chromatography to afford the desired product 9.

**General produce for electrochemical asymmetric acylation of hydroxyphthalide by carbene-catalyzed dynamic kinetic resolution.** The ElectraSyn vial (5 mL) with a stir bar was charged with aldehydes 10 (0.18 mmol, 1.8 equiv.), NHC A (0.02 mmol, 20%), DIEA (0.1 mmol, 100%), n-Bu$_4$NI (0.1 mmol, 1.0 equiv.) and hydroxyphthalide 11 (0.1 mmol, 1.0 equiv.) followed by anhydrous THF (3.0 mL). The ElectraSyn vial cap equipped with anode (Pt) and cathode (Pt) were inserted into the mixture. After pre-stirring for 2 minutes, the Electrasyn vial was connected to the Electrasyn 2.0 and the reaction mixture was electrolyzed under a constant current of 1 mA for a total reaction time of 6 hours accompanied by magnetic stirring. The ElectraSyn vial cap was removed, and electrodes were rinsed with EtOAc, which was combined with the crude mixture. After concentrated under reduced pressure, the crude residue was purified via flash column chromatography to afford the desired product 12.

**Declarations**

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Author contributions

P.Z. conducted most of the experiments; P.Z. and W.L. prepared substrates for the reaction scope evaluation; P.Z. and J.L. analyzed the data. T.Z. conceptualized and directed the project, and drafted the manuscript with the assistance from all co-authors. All authors contributed to discussions.

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**Figures**
Figure 1

**Electroredox Carbene Organocatalysis with iodine as cocatalyst.** (a) The developing history of redox carbene organocatalysis. (b) This work: electroredox single-electron-transfer (SET) with NHC/iodine cocatalyst. (c) The challenge of the cocatalyst system: catalyst poisoning effect with carbene and iodine. (d) Different results of radical clock experiment with traditional DET models and our SET models.
**Figure 2**

γ-carbon atom reaction: Scope of the reaction of enals with hydrazones. Reaction conditions: Pt anode, Pt cathode, 1 (0.15 mmol), 2 (0.1 mmol), NHC A (20%), K₂CO₃ (150%), n-Bu₄NI (1.0 equiv.), CH₂Cl₂ (3 mL), at a constant current of 1 mA for 6 h (2.24 F·mol⁻¹) in IKA ElectraSyn 2.0 at room temperature. The ee was determined by chiral stationary HPLC.

**Figure 3**

β-carbon atom reaction: Scope of the reaction of enals with 1,3-dicarbonyls. Conditions B: graphite anode, Pt cathode, 4 (0.1 mmol), 5 (0.2 mmol), NHC B (30%), Cs₂CO₃ (30%), n-Bu₄NI (1.0 equiv.), CH₂Cl₂/t-BuOH (2 mL/ 1 mL), at a constant current of 1 mA for 6 h (2.24 F·mol⁻¹) in IKA ElectraSyn 2.0 at room temperature. Conditions C: graphite anode, Pt cathode, 4 (0.1 mmol), 5 (0.2 mmol), NHC C (20%), K₂CO₃ (20%), n-Bu₄NI (1.0 equiv.), CH₃CN/t-BuOH (1.5 mL/ 1.5 mL), at a constant current of 0.8 mA for 10 h (2.98 F·mol⁻¹) in IKA ElectraSyn 2.0 at room temperature.
**α-carbon atom reaction: Scope of the reaction of aldehydes with chalcone enones.** Reaction conditions: Pt anode, Pt cathode, 7 (0.25 mmol), 8 (0.1 mmol), NHC A (30%), Cs$_2$CO$_3$ (30%), $n$-Bu$_4$NI (1.0 equiv.), DMF/DCE (2 mL/ 1 mL), at a constant current of 0.8 mA for 9 h (2.68 F·mol$^{-1}$) in IKA ElectraSyn 2.0 at room temperature. The diastereomeric ratio (dr) was determined by $^1$H NMR analysis of the crude products. The ee was determined by chiral stationary HPLC.
Figure 5

The enantioselective of hydroxyphthalide acylation by carbene-catalyzed dynamic kinetic resolution.

Reaction conditions: Pt anode, Pt cathode, 10 (0.18 mmol), 11 (0.1 mmol), NHC A (20%), DIEA (100%), n-Bu$_4$NI (1.0 equiv.), THF (3 mL), at a constant current of 1 mA for 6 h (2.24 F·mol$^{-1}$) in IKA ElectraSyn 2.0 at room temperature. The ee was determined by chiral stationary HPLC.
Figure 6

Miscellaneous reactions and gram-scale synthesis.

Figure 7
Mechanistic studies.

Figure 8

Cyclic voltammograms recorded in CH$_2$Cl$_2$.

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