Electrocatalytic redox neutral [3 + 2] annulation of N-cyclopropylanilines and alkenes†

Qi Wang, a Qile Wang, b Yuexiang Zhang, c Yasmine M. Mohamed, a Carlos Pacheco, id a Nan Zheng, id *b Richard N. Zare id *d and Hao Chen id *a

Although synthetic organic electrochemistry (EC) has advanced significantly, net redox neutral electrosynthesis is quite rare. Two approaches have been employed to achieve this type of electrosynthesis. One relies on turnover of the product by the reactant in a chain mechanism. The other involves both oxidation on the anode and reduction on the cathode in which the radical cation or the radical anion of the product has to migrate between two electrodes. Herein, a home-built electrochemistry/mass spectrometry (EC/MS) platform was used to generate an N-cyclopropylaniline radical cation electrochemically and to monitor its reactivity toward alkenes by mass spectrometry (MS), which led to the discovery of a new redox neutral reaction of intermolecular [3 + 2] annulation of N-cyclopropylanilines and alkenes to provide an aniline-substituted 5-membered carbocycle via direct electrolysis (yield up to 81%). A chain mechanism, involving the regeneration of the substrate radical cation and the formation of the neutral product, is shown to be responsible for promoting such a redox neutral annulation reaction, as supported by experimental evidence of EC/MS.

Introduction

Mass spectrometry (MS) has become a powerful technique for studying reaction mechanisms since the advent of soft ionization methods such as electrospray ionization (ESI).1–12 The combination of electrochemistry (EC) with MS, EC/MS, can be applied to produce drugs in vivo metabolites, or cleave proteins/peptides followed by MS analysis.13–17 It can also be used to reduce disulfide bonds to facilitate MS sequencing of proteins/peptides,18–20 oxidize tyrosine to perform absolute MS quantitation,21 and oxidize lipids to determine double bond locations of unsaturated lipids.22–23 It has also been used to capture elusive reaction intermediates24–26 and to screen electrosynthetic reactions.27 The advantages of EC/MS for reaction screening are multiple. It is very sensitive and uses a tiny amount of reactants (nmoles to pmoles). It allows the monitoring of the reactivity of electrochemically generated short-lived reactive species by online MS detection. In spite of these advantages, the integrated online EC/MS platform has not been extensively used to screen electrosynthetic reactions.

Recently, synthetic organic electrochemistry has achieved a dramatic uptick in popularity.28–51 Electrosynthesis uses a pair of electrodes to add or subtract electrons to or from the substrate, which triggers the formation of the target product.52–63 Compared with non-electrochemical synthesis, electrosynthesis has the advantages of offering more selective, safer, and less energy consumption approaches.64–74 One of the more challenging and thus elusive electrosyntheses that attracts much attention75–79 is net redox neutral reactions, in which both oxidation and reduction steps are involved to achieve overall redox neutrality. Initial anode oxidation or cathode reduction of the substrate to form a product radical cation or anion is usually paired with an opposite single-electron transfer (SET) event to furnish a neutral product.

Two possible conditions can trigger the occurrence of redox neutral electrochemical reactions. One involves the product radical cation or anion being stable enough to migrate to the cathode or anode so that a SET reduction or oxidation occurs to yield the final neutral product.77–80 The other requires the product radical cation or anion to undergo a SET oxidation or reduction with the starting material in a chain mechanism. The former is more arduous to meet as a tandem oxidation/reduction has to occur on a macroscopically separated anode and cathode. Most of the reported redox-neutral electrochemical syntheses are centered on the latter condition. Notable examples include [2 + 2] cycloaddition81–84 and [4 + 2] Diels-Alder reactions mediated by anodically...
produced radical cations of dienes or dienophiles. Chiba raised the importance of a redox tag on the chain event of these reactions. Radical anions of activated alkenes generated by cathodic reduction are equally capable of promoting these two classes of cycloaddition reactions. Xu developed a redox-neutral method for intramolecular hydroamination of alkenes without relying on a chain event. The hydroamination was achieved by an intramolecular addition of an amidyl radical generated via ferrocene as the redox catalyst to an alkene. The resulting carbon radical then abstracted a hydrogen atom from 1,4-cyclohexadiene (1,4-CHD) to complete the redox neutral process. For a handful of examples invoking a chain mechanism, catalytic current efficiency was usually used as the primary evidence, and limited kinetic studies were sometimes reported to strengthen the argument. Ambiguity about the chain event often remains.

We previously developed a [3 + 2] annulation of N-cyclopropylanilines (CPA) with alkenes by photoredox catalysis and subsequently investigated its mechanism. As shown in Scheme 1 (top panel), upon irradiation, Ru(bpz)$_3^{2+}$ is promoted to the excited triplet state Ru(bpz)$_3^{*+}$, which oxidizes CPA to the radical cation. The radical cation subsequently undergoes ring opening, and then adds to styrene to produce the [3 + 2] annulation product radical cation. Finally, the radical cation is reduced via two mechanisms: a photoredox reaction and a chain reaction. We questioned whether we could achieve the annulation reaction by direct electrolysis presumably via the chain process completely. However, converting the photoredox catalysis to electrochemistry for this annulation reaction was nontrivial, as net redox neutral reactions are known to be problematic for electrochemistry but facile by photoredox catalysis. Herein, we report our studies in developing the electrocatalytic redox neutral [3 + 2] annulation of N-cyclopropylanilines and alkenes by the chain mechanism (Scheme 1, bottom panel). We took full advantage of the capabilities of the integrated online EC/MS platform as a screening tool to expedite the discovery. As evidenced by net redox neutral reactions, photochemistry and electrochemistry complement each other. This study overcame the inherent limitation of net redox neutral reactions in electrochemistry and used it as a template to address other types of challenging electro-synthetic reactions.

### Results and discussion

We started our investigation using a home-built electrochemistry/mass spectrometry (EC/MS) platform (Scheme 2). It consisted of an electrochemical thin-layer flow cell, a short piece of a fused silica capillary as a microreactor and an online MS detector, with one reactant fused into the flow cell and another reactant introduced for reaction. The flow cell was equipped with a glassy carbon disc (i.d., 6 mm) as the working electrode (WE), Ag/AgCl (3 M NaCl) as the reference electrode (RE), and the cell stainless steel body serving as a counter electrode (CE). The solution flowing out of the capillary microreactor was soft ionized by sonic spray ionization (SSI). To prove that the electrochemical method can be used to generate the [3 + 2] annulation reaction product, N-cyclopropyl-3,5-dimethylaniline (CPDA, 1a), and styrene (2a) were first chosen as reactants (Scheme 3). A small-scale test was performed using an electrochemical thin-layer flow cell along with online MS monitoring. A solution of 1a (1 mM) and lithium triflate (LiOTf, 1 mM) in MeCN was infused into the cell via channel 1 and MeCN was infused via channel 2 (flow rate: 50 µL min$^{-1}$ for each channel). When a potential of +3.0 V was applied to the WE, as shown in the recorded SSI-MS spectrum (Fig. 1a), the 1a$^+$ of m/z 161 (theoretical m/z 161.11990, measured m/z: 161.12017, mass error 1.68 ppm) was detected, indicating the occurrence of the electro-oxidation of 1a. When 2a was introduced to replace MeCN via channel 2, indeed, the protonated [3 + 2] annulation product [3a + H]$^+$ (theoretical m/z 266.19033, measured m/z: 266.18972, mass error 2.29 ppm) was observed (Fig. 1b). Upon collision induced dissociation (CID), the ion of m/z 266 gave rise to fragment ions of m/z 145, 122, and

![Scheme 1](image1.png)

Proposed mechanism for the [3 + 2] annulation reaction of N-cyclopropylanilines and styrene (top panel illustrates the reaction catalyzed with a photocatalyst; bottom panel displays the reaction triggered electrochemically without using a catalyst).

![Scheme 2](image2.png)

Home-built electrochemistry/mass spectrometry (EC/MS) setup.
Intermolecular [3 + 2] annulation of N-cyclopropyl-3,5-dimethylaniline (CPDA) 1a and styrene 2a by electrolysis.

### Scheme 3

![Scheme 3](image)

Chemical Science

Fig. 1 MS spectra showing (a) the formation of radical cation 1a$$^+$$ when the cell was turned on with 1a being introduced into the flow cell via channel 1 and MeCN being introduced via channel 2; (b) the product ion [3a + H$$^+$$]$$^-$$ was observed when the cell was turned on with 2a being introduced via channel 2. (c) MS/MS spectrum of m/z 266.

91 by losses of C$_8$H$_{11}$N, C$_{11}$H$_{12}$, and C$_{12}$H$_{17}$N, respectively, consistent with its assigned structure (Fig. 1c). At the same time, the intensity of the 1a$$^+$$ decreased from 1.6 x 10$^6$ (Fig. 1a) to 1.9 x 10$^4$ (Fig. 1b), indicating that 1a$$^+$$ did react with 2a to produce the [3 + 2] annulation product. The +1 ion of 3a instead of 3a$$^+$$ was observed probably due to the charge transfer between 3a$$^+$$ and 1a to form 3a which was ionized as the +1 ion by SSI.

The EC/MS setup (Scheme 2) also allowed us to verify whether or not the charge transfer between 3a$$^+$$ and 1a could take place, a key step in the chain reaction mechanism (Fig. 2a), that would be needed to generate the neutral product 3a. Using the EC/MS setup, a solution of the annulation product 3a (1 mM) and LiOTf (1 mM) in MeCN was infused into the flow cell through channel 1, and MeCN was injected via channel 2. A potentiostat was used to supply the potential for electro-oxidation. The injection flow rate for both channels was 15 $\mu$L min$^{-1}$. A voltage of +3.0 V was applied to the flow cell to trigger the oxidation of 3a. The expected radical cation 3a$$^+$$ was detected (Fig. 2b, black line, theoretical 265.18250, measured 265.18234, mass error 0.60 ppm). When the solvent (MeCN) was detected (Fig. 2b, black line, theoretical 265.18250, measured 265.18234, mass error 0.60 ppm), LiOTf was replaced by 1a (0.1 mM in MeCN) in channel 2, the intensity of 3a$$^+$$ decreased (Fig. 2b, red line), indicating the consumption of 3a$$^+$$ by 1a. At the same time, radical cation 1a$$^+$$ was detected (Fig. 2c, red line, theoretical 161.11990, measured 161.12002, mass error 0.74 ppm). To confirm that the observed 1a$$^+$$ was not due to oxidation of 1a by other oxidative species from the cell, a control experiment was performed in which only LiOTf (1 mM) in MeCN (without 3a) was infused into the cell for oxidation under the same conditions and then mixed with 1a. In this control experiment, no 1a$$^+$$ was generated (Fig. 2c, black line). This set of data confirms that the oxidation of 1a by the anellation product radical cation 3a$$^+$$ (Fig. 2a) did occur, being the critical step responsible for completing the redox neutral reaction.

As encouraged by the success of observing individual key reaction steps that are needed for electrosynthesis of 3a from 1a and 2a, we attempted bulk solution electrolysis. A piece of Pt plate and reticulated vitreous carbon (RVC, a porous carbon electrode) were inserted into a 20 mL clear screw glass vial, serving as the cathode and anode, respectively. A solution of 1a (100 mM, 1 mmol), styrene 2a (1 M, 10 mmol), and LiOTf (1 M, 10 mmol) in 10 mL MeCN was added into the electrolysis cell.
We thus went ahead to optimize the electrolysis conditions, and again, 1a and 2a were chosen as the model substrates (Table 1). A constant current (entries 1 and 2) or a constant voltage (entries 3 and 4) was used for electrolysis. No product was observed using a higher current (entry 2) while a higher voltage (entries 3 and 4) was used for electrolysis. No product or reactant were observed for the two products, respectively, with the cis isomer as the major product). Phenylacetylene was shown to be a viable annulation partner (4f).

Mechanistically, after establishing the chain mechanism as a viable pathway to achieve the redox neutral reaction, we questioned the feasibility of the other conditions in which the product radical cations were reduced on the cathode. We carried out the reaction of 1a and 2a using an H-type divided cell with two compartments separated with a frit membrane. The two electrodes, RVC and Pt electrodes, were inserted into one chamber each separately (Fig. S1†). A solution of 1a (32 mM, 0.64 mmol), 2a (300 mM, 6 mmol), and LiOTf (300 mM) in 20 mL MeCN was added into one chamber of the electrolysis cell (the anode RVC side) and 20 mL of MeCN containing 300 mM LiOTf was added into the other chamber (the cathode Pt side). After 9 h of electrolysis with an applied 1 mA constant current across the two electrodes, interestingly, the protonated [3 + 2] annihilation product [3a + H]† (theoretical m/z: 266.19033, measured m/z: 266.19003, mass error −1.13 ppm) was detected by MS and appeared as the dominant peak in the MS spectrum (Fig. 3b), indicating a good yield of the reaction. Upon CID, the ion m/z 266 gave rise to fragment ions of m/z 145, 122, and 91 upon CID by losses of C₆H₁₁N, C₁₁H₁₂, and C₁₂H₁₇N, respectively, consistent with its assigned structure. Using dibromomethane as the internal standard, the NMR yield was measured to be 68%. This result showed that the scale-up electrolysis for intermolecular [3 + 2] annihilation reaction worked.

of water completely inhibited the product formation (entry 10) and replacing MeCN with MeOH led to a lower yield (entry 11). Thus entry 1 experimental conditions were adopted for electrolysis of different substrates.

After optimizing the reaction conditions, a variety of N-cyclopropylamines and alkenes were investigated, and good isolation yields were obtained (Scheme 4). An aryl group on N-cyclopropylamines could promote the initial oxidation to occur as it decreased the redox potential of N-cyclopropylamines.⁴ Substituents such as methyl and chlorine on the aromatic ring of cyclopropylamine were tolerated (3a and 4a). N-Cyclopropylamines substituted with other amines such as biphenyl and naphthalene also worked (5a and 6a). Substituents on the phenyl group of styrenes such as ortho-bromine and para-methoxy groups had little effect on the yields (3c, 3d, 4c, 4e, 5b, and 5d). Substitution of the phenyl group of styrene by a naphthyl group lowered the yield (4d). Other types of pi bonds were explored. Acrylonitrile gave acceptable to good yields of the annihilation products (3b, 4b, 5c, and 6b). The diastereoselectivity for the annihilation reaction was generally poor, as most of them gave a 1:1 mixture except 4a and 5c (2:1 and 4:1 were observed for the two products, respectively, with the cis isomer as the major product). Phenylacetylene was shown to be a viable annulation partner (4f).
oxidizing/reducing a reactant in a redox reaction, is directly proportional to the quantity of the oxidized/reduced substance: $Q = nzF$, where $n$ is the moles of the reactant, $z$ is the number of electrons transferred per molecule for the redox reaction ($z = 1$ for oxidation of 1a), and $F$ is the Faraday constant ($9.65 \times 10^4 \text{ C mol}^{-1}$). According to $Q = nzF$, $1 \times 10^{-3} \text{ mol} \times 1 \times 9.65 \times 10^4 \text{ C mol}^{-1} = 96.5 \text{ C}$ electricity would be needed for the complete oxidation of $1 \text{ mmol}$ 1a experimentally. As mentioned before, 1 mA was applied to the undivided electrolysis cell for 9 h to complete the electrolysis. The actual consumption of electricity was calculated to be $1 \times 10^{-3} \text{ A} \times 9 \times 3600 \text{ s} = 32.4 \text{ C}$ based on $Q = i t$, where $i$ was the applied current and $t$ was the reaction time. Therefore, the reaction was driven to completion with 0.34 equiv. of the current. The catalytic current used for the reaction also supported the chain reaction mechanism.

### Conclusions

A new type of challenging electrochemical redox neutral reaction was developed using our homemade online EC/MS platform. Without using any catalyst, the [3 + 2] annulation of $N$-cyclopropylamines and alkenes proceeded by direct electrolysis instead. Various mechanistic investigations including the use of a divided cell, measurements of the catalytic current, and online MS monitoring of the key electron transfer step between the product radical cation and the reactant supported that the reaction was completed via a chain reaction process. Considering that a chain reaction mechanism is often accompanied by a photoredox reaction in photocatalysis, we expect that electrolysis can be applied to many other visible-light-mediated reactions as an alternative catalyst-free approach.

### Conflicts of interest

There are no conflicts to declare.
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Notes and references