

Cite this: *Chem. Sci.*, 2021, 12, 969

All publication charges for this article have been paid for by the Royal Society of Chemistry

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

Qi Wang,<sup>a</sup> Qile Wang,<sup>b</sup> Yuexiang Zhang,<sup>c</sup> Yasmine M. Mohamed,<sup>a</sup> Carlos Pacheco,<sup>ib</sup><sup>a</sup> Nan Zheng,<sup>ib</sup><sup>\*b</sup> Richard N. Zare<sup>ib</sup><sup>\*d</sup> and Hao Chen<sup>ib</sup><sup>\*a</sup>

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.

Received 14th October 2020  
Accepted 6th November 2020

DOI: 10.1039/d0sc05665k

rsc.li/chemical-science

## 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).<sup>1–12</sup> 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.<sup>13–17</sup> It can also be used to reduce disulfide bonds to facilitate MS sequencing of proteins/peptides,<sup>18–20</sup> oxidize tyrosine to perform absolute MS quantitation,<sup>21</sup> and oxidize lipids to determine double bond locations of unsaturated lipids.<sup>22,23</sup> It has also been used to capture elusive reaction intermediates<sup>24–33</sup> and to screen electro-synthetic reactions.<sup>34</sup> 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.<sup>35–51</sup> Electrosynthesis uses a pair of electrodes to add or subtract electrons to or from the substrate, which triggers the formation of the target product.<sup>37,52–63</sup> Compared with non-electrochemical synthesis, electrosynthesis has the advantages of offering more selective, safer, and less energy consumption approaches.<sup>64–74</sup> One of the more challenging and thus elusive electrosyntheses that attracts much attention<sup>75–79</sup> 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.<sup>77–80</sup> 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] cycloaddition<sup>81–84</sup> and [4 + 2] Diels–Alder<sup>85–88</sup> cycloaddition reactions mediated by anodically

<sup>a</sup>Department of Chemistry & Environmental Science, New Jersey Institute of Technology, Newark, New Jersey, 07102, USA. E-mail: hao.chen.2@njit.edu

<sup>b</sup>Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, Arkansas 72701, USA. E-mail: nzhang@uark.edu

<sup>c</sup>Department of Chemistry and Biochemistry, Ohio University, Athens, Ohio, 45701, USA

<sup>d</sup>Department of Chemistry, Stanford University, Stanford, California 94305-5080, USA. E-mail: zare@stanford.edu

† Electronic supplementary information (ESI) available: General considerations, general procedures, and compound characterization. See DOI: 10.1039/d0sc05665k

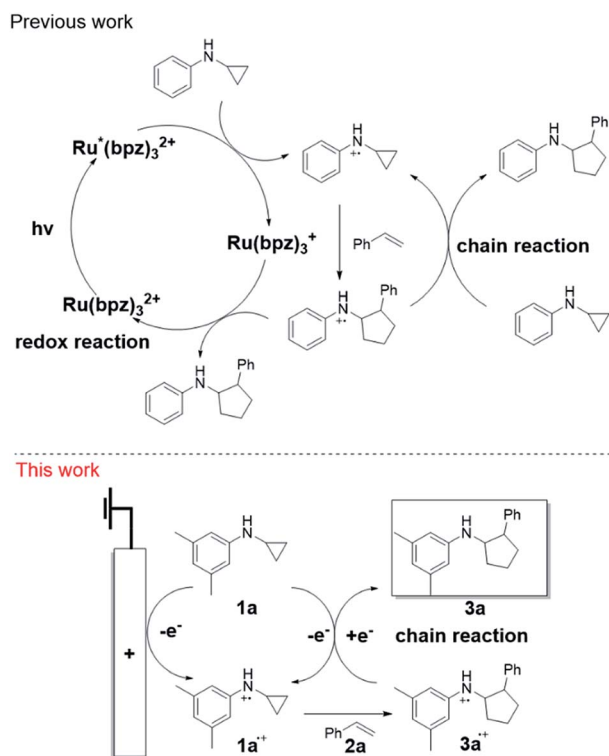
produced radical cations of dienes or dienophiles. Chiba<sup>40</sup> raised the importance of a redox tag on the chain event of these reactions. Radical anions of activated alkenes generated by cathodic reduction are equally capable of promoting these two classes of cycloaddition reactions. Xu<sup>89</sup> developed a redox-neutral method for intramolecular hydroamidation of alkenes without relying on a chain event. The hydroamidation 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,<sup>81,90</sup> and limited kinetic studies were sometimes reported to strengthen the argument.<sup>91</sup> Ambiguity about the chain event often remains.

We previously developed a [3 + 2] annulation of *N*-cyclopropylanilines (CPA) with alkenes by photoredox catalysis<sup>92</sup> and subsequently investigated its mechanism.<sup>93</sup> As shown in Scheme 1 (top panel), upon irradiation, Ru(II)(bpz)<sub>3</sub><sup>2+</sup> is promoted to the excited triplet state Ru(II)\* (bpz)<sub>3</sub><sup>2+</sup>, 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

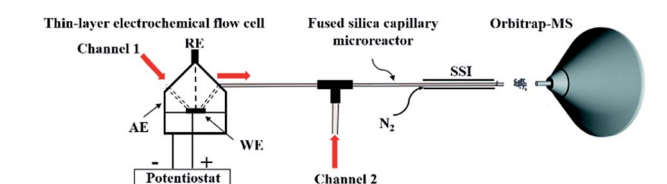
presumably *via* the chain process completely. However, converting the photoredox catalysis to electrochemistry for this annulation reaction was nontrivial, as net redox neutral reactions are known to be problematic for electrochemistry but facile by photoredox catalysis. Herein, we report our studies 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 *via* channel 1 and another reactant introduced for reaction *via* channel 2. 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  $\mu\text{L min}^{-1}$  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**<sup>+</sup> 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]<sup>+</sup> (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

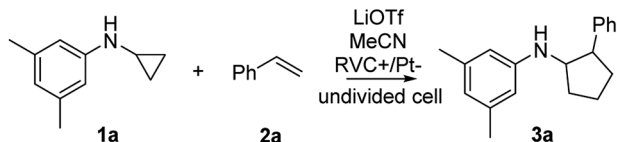


**Scheme 1** Proposed mechanism for the [3 + 2] annulation reaction of *N*-cyclopropylanilines and styrene (top panel illustrates the reaction catalyzed with a photocatalyst; bottom panel displays the reaction triggered electrochemically without using a catalyst).



**Scheme 2** Home-built electrochemistry/mass spectrometry (EC/MS) setup.





Scheme 3 Intermolecular [3 + 2] annulation of *N*-cyclopropyl-3,5-dimethylaniline (CPDA) **1a** and styrene **2a** by electrolysis.

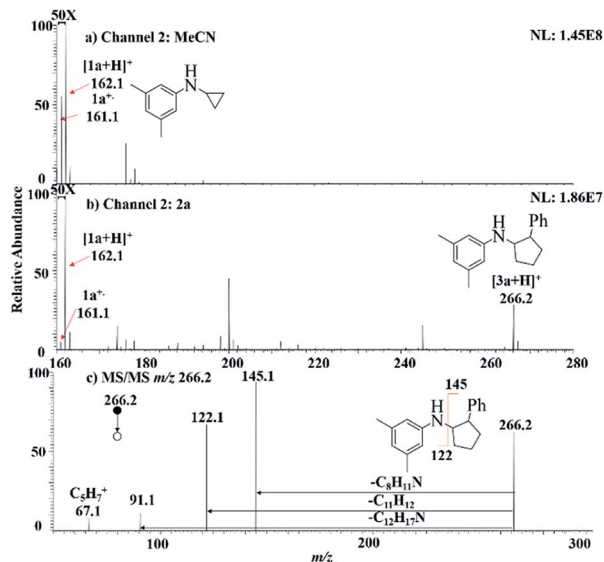


Fig. 1 MS spectra showing (a) the formation of radical cation **1a**<sup>•+</sup> when the cell was turned on with **1a** being introduced into the flow cell via channel 1 and MeCN being introduced via channel 2; (b) the product ion [**3a** + H]<sup>+</sup> was observed when the cell was turned on with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

91 by losses of C<sub>8</sub>H<sub>11</sub>N, C<sub>11</sub>H<sub>12</sub>, and C<sub>12</sub>H<sub>17</sub>N, respectively, consistent with its assigned structure (Fig. 1c). At the same time, the intensity of the **1a**<sup>•+</sup> decreased from 1.6 × 10<sup>6</sup> (Fig. 1a) to 1.9 × 10<sup>4</sup> (Fig. 1b), indicating that **1a**<sup>•+</sup> did react with **2a** to produce the [3 + 2] annulation product. The +1 ion of **3a** instead of **3a**<sup>•+</sup> was observed probably due to the charge transfer between **3a**<sup>•+</sup> 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**<sup>•+</sup> 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 μL min<sup>-1</sup>. A voltage of +3.0 V was applied to the flow cell to trigger the oxidation of **3a**. The expected radical cation **3a**<sup>•+</sup> was detected (Fig. 2b, black line, theoretical 265.18250, measured 265.18234, mass error 0.60 ppm). When the solvent (MeCN) was replaced by **1a** (0.1 mM in MeCN) in channel 2, the intensity of **3a**<sup>•+</sup> decreased (Fig. 2b, red line), indicating the consumption of **3a**<sup>•+</sup> by **1a**. At the same time, radical cation **1a**<sup>•+</sup> was detected

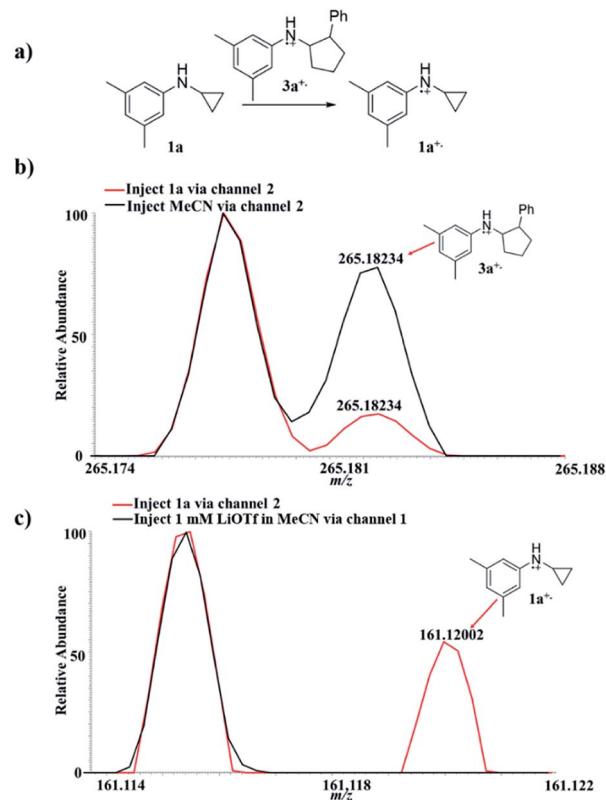


Fig. 2 Online MS monitoring of the oxidation of **1a** by **3a**<sup>•+</sup>: (a) chemical equation showing the reaction between **1a** and **3a**<sup>•+</sup>; (b) MS spectra showing the formation of the radical cation **3a**<sup>•+</sup> when the oxidation potential was applied to the cell. The signal of **3a**<sup>•+</sup> was lower when the solution injected via channel 2 changed from MeCN (black line) to **1a** (red line). (c) MS spectra showing the formation of radical cation **1a**<sup>•+</sup> (red line) when the cell was turned on with **3a** being introduced into the flow cell via channel 1 and **1a** being introduced via channel 2. No formation of radical cation **1a**<sup>•+</sup> was observed (black line) when the cell was turned on with 1 mM LiOTf in MeCN being introduced into the flow cell via channel 1 and **1a** being introduced via channel 2.

(Fig. 2c, red line, theoretical 161.11990, measured 161.12002, mass error 0.74 ppm). To confirm that the observed **1a**<sup>•+</sup> 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**<sup>•+</sup> was generated (Fig. 2c, black line). This set of data confirms that the oxidation of **1a** by the annulation product radical cation **3a**<sup>•+</sup> (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

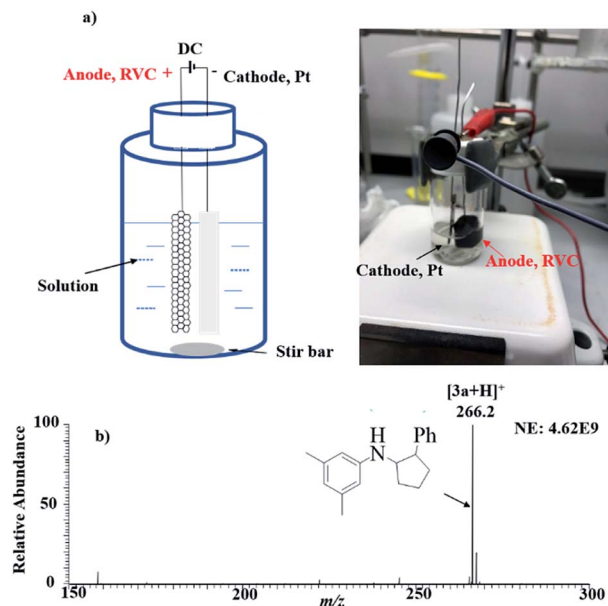


Fig. 3 Large-scale electrolysis: (a) setup and actual apparatus picture, and (b) MS spectrum showing the formation of the product **3a** by electrolysis.

(Fig. 3a, more details are shown in General procedure 2 of the ESI†). After 9 h at 1 mA direct current provided by a direct current (DC) power supply, the protonated  $[3 + 2]$  annulation 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  $C_8H_{11}N$ ,  $C_{11}H_{12}$ , and  $C_{12}H_{17}N$ , 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  $[3 + 2]$  annulation reaction worked.

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 led to a lower yield (entry 4). Compared with the constant voltage mode, the constant current was preferred because it gave the same yield (NMR yield) in a shorter reaction time (75%, 9 h for entry 1 vs. 75%, 12 h for entry 3). Switching the anode from porous RVC to planar Pt furnished the product in a lower yield (entry 5), probably because the porous RVC electrode provided a large electrode surface area to react with reactants. Doubling the amount of LiOTf (entry 6) or replacing LiOTf with other electrolytes (entries 7 and 8) all resulted in lower yields. The yield was also reduced when the amount of styrene was doubled (entries 9), probably caused by the side effect from styrene polymerization on the electrode. Likewise, halving the amount of LiOTf or styrene resulted in lower yields with more unreacted *N*-cyclopropylaniline. Finally, the addition

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.

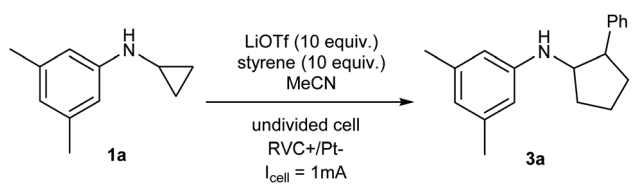
After optimizing the reaction conditions, a variety of *N*-cyclopropylamines and alkenes were investigated, and good isolation yields were obtained (Scheme 4). An aryl group on *N*-cyclopropylamines could promote the initial oxidation to occur as it decreased the redox potential of *N*-cyclopropylamines.<sup>94</sup> Substituents such as methyl and chlorine on the aromatic ring of cyclopropylamine were tolerated (**3a** and **4a**). *N*-Cyclopropylamines substituted with other arenes 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 annulation products (**3b**, **4b**, **5c**, and **6b**). The diastereoselectivity for the annulation 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**).

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  $[3 + 2]$  annulation product  $[3a + H]^+$  (theoretical  $m/z$ : 266.19033, measured  $m/z$ : 266.18938, mass error  $-3.57$  ppm) was detected from the anode side chamber by MS (Fig. S2,† the NMR yield was 23%). In contrast, no product or reactant was detected in the cathode side chamber, indicating that no product or reactant could pass through the frit membrane. The formation of **3a** in the divided cell suggested that the reduction of the **3a** radical cation was caused by the starting reactant **1a** with simultaneous formation of the **1a** radical cation *via* the chain mechanism rather than caused by the cathode reduction. The yield was lower than in the un-divided cell. Presumably because the membrane increased the resistance, a higher voltage was needed to apply to the cell to maintain a constant current (5.0–6.5 V for 1 mA electrolysis). As shown in Table 1 (entry 4), a higher voltage harmed the annulation reaction.

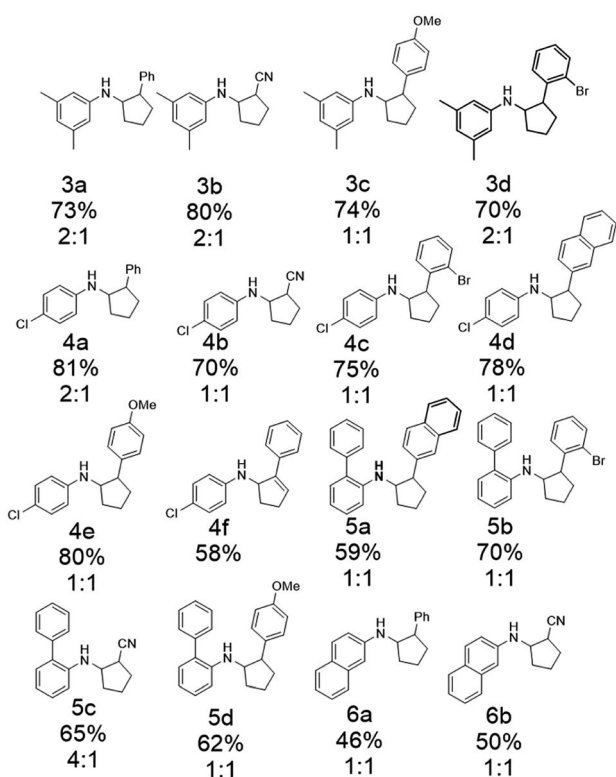
A comparison between the total charge required for the reaction and the electrical input could also help to clarify if the reaction involves the chain reaction mechanism.<sup>81</sup> According to Faraday's law, the total electric charge ( $Q$ ) responsible for



Table 1 Reaction optimization

				
Entry	Variation from standard condition	Reaction yield <sup>a</sup>	Reactant leftover (Y/N)	Reaction time
1	None	75%	N	9 h
2	$I_{\text{cell}} = 4 \text{ mA}$	No product	N	9 h
3	$E_{\text{cell}} = 3.5 \text{ V}$	75%	N	12 h
4	$E_{\text{cell}} = 4.5 \text{ V}$	42%	N	12 h
5	$\text{Pt}^+/\text{Pt}^-$ , $E_{\text{cell}} = 3.5 \text{ V}$	40%	Y	12 h
6	LiOTf (20 equiv.)	65%	N	9 h
7	Electrolyte $\text{LiClO}_4$	15%	Y	9 h
8	Electrolyte $\text{Me}_4\text{NOAc}$	42%	Y	9 h
9	Styrene (20 equiv.)	20%	Y	9 h
10	Solvent MeCN/ $\text{H}_2\text{O}$ 9 : 1	No product	Y	9 h
11	Solvent MeOH	35%	Y	9 h

<sup>a</sup> NMR yield with dibromomethane used as the reference.



Scheme 4 The substrate scope of intermolecular [3 + 2] annulation by the electrochemical approach (percentages show the isolation yields). The ratios for *cis/trans* product isomers are also listed.

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 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  $Q = it$ , 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.

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



## Acknowledgements

This work was supported by NSF (CHE-1915878) and NIH (1R15GM137311-01).

## Notes and references

- 1 A. A. Sabino, A. H. L. Machado, C. R. D. Correia and M. N. Eberlin, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 2514–2518.
- 2 D. Feichtinger and D. A. Plattner, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1718–1719.
- 3 D. J. Wilson and L. Konermann, *Anal. Chem.*, 2003, **75**, 6408–6414.
- 4 S. Fürmeier, J. Griep-Raming, A. Hayen and J. O. Metzger, *Chem.-Eur. J.*, 2005, **11**, 5545–5554.
- 5 M. M. Meyer, G. N. Khairallah, S. R. Kass and R. A. J. O'Hair, *Angew. Chem., Int. Ed. Engl.*, 2009, **48**, 2934–2936.
- 6 L. P. E. Yunker, R. L. Stoddard and J. S. McIndoe, *J. Mass Spectrom.*, 2014, **49**, 1–8.
- 7 S. Chen, Q. Wan and A. K. Badu-Tawiah, *Angew. Chem., Int. Ed. Engl.*, 2016, **55**, 9345–9349.
- 8 S. Fürmeier and J. O. Metzger, *J. Am. Chem. Soc.*, 2004, **126**, 14485–14492.
- 9 W. Ai, Y. Gao, J. Xue, X. Liu, H. Liu, J. Wang and Y. Bai, *Chem. Commun.*, 2020, **56**, 2163–2166.
- 10 T. Chen, Q. Yao, R. R. Nasaruddin and J. Xie, *Angew. Chem., Int. Ed. Engl.*, 2019, **58**, 11967–11977.
- 11 H. Zhang, X. Li, K. Yu, N. Li, J. He, H. You and J. Jiang, *Anal. Chim. Acta*, 2018, **1013**, 36–42.
- 12 M. Lu, Y. Su, P. Zhao, X. Ye, Y. Cai, X. Shi, E. Masson, F. Li, J. L. Campbell and H. Chen, *Chem.-Eur. J.*, 2018, **24**, 2144–2150.
- 13 S. Bruckenstein and R. R. Gadde, *J. Am. Chem. Soc.*, 1971, **93**, 793–794.
- 14 F. Zhou and G. J. Van Berkel, *Anal. Chem.*, 1995, **67**, 3643–3649.
- 15 G. Diehl and U. Karst, *Anal. Bioanal. Chem.*, 2002, **373**, 390–398.
- 16 H. P. Permentier, A. P. Bruins and R. Bischoff, *Mini-Rev. Med. Chem.*, 2008, **8**, 46–56.
- 17 M. C. S. Regino and A. Brajter-Toth, *Anal. Chem.*, 1997, **69**, 5067–5072.
- 18 Y. Zhang, W. Cui, H. Zhang, H. D. Dewald and H. Chen, *Anal. Chem.*, 2012, **84**, 3838–3842.
- 19 Y. Zhang, H. D. Dewald and H. Chen, *J. Proteome Res.*, 2011, **10**, 1293–1304.
- 20 J. Li, H. D. Dewald and H. Chen, *Anal. Chem.*, 2009, **81**, 9716–9722.
- 21 P. Zhao, Q. Wang, M. Kaur, Y.-I. Kim, H. D. Dewald, O. Mozziconacci, Y. Liu and H. Chen, *Anal. Chem.*, 2020, **92**, 7877–7883.
- 22 S. Tang, H. Cheng and X. Yan, *Angew. Chem., Int. Ed. Engl.*, 2020, **59**, 209–214.
- 23 K. Chintalapudi and A. K. Badu-Tawiah, *Chem. Sci.*, 2020, **11**, 9891–9897.
- 24 J. Hu, N. Zhang, P.-K. Zhang, Y. Chen, X.-H. Xia, H.-Y. Chen and J.-J. Xu, *Angew. Chem., Int. Ed. Engl.*, 2020, **59**, 209–214.
- 25 T. A. Brown, H. Chen and R. N. Zare, *J. Am. Chem. Soc.*, 2015, **137**, 7274–7277.
- 26 T. A. Brown, H. Chen and R. N. Zare, *Angew. Chem., Int. Ed. Engl.*, 2015, **54**, 11183–11185.
- 27 R. Qiu, X. Zhang, H. Luo and Y. Shao, *Chem. Sci.*, 2016, **7**, 6684–6688.
- 28 H. Cheng, X. Yan and R. N. Zare, *Anal. Chem.*, 2017, **89**, 3191–3198.
- 29 J. Yu, Y. Zhou, X. Hua, S. Liu, Z. Zhu and X.-Y. Yu, *Chem. Commun.*, 2016, **52**, 10952–10955.
- 30 F. T. G. van den Brink, L. Büter, M. Odijk, W. Olthuis, U. Karst and A. van den Berg, *Anal. Chem.*, 2015, **87**, 1527–1535.
- 31 Z. Wang, Y. Zhang, B. Liu, K. Wu, S. Thevuthasan, D. R. Baer, Z. Zhu, X.-Y. Yu and F. Wang, *Anal. Chem.*, 2017, **89**, 960–965.
- 32 E. L. Clark and A. T. Bell, *J. Am. Chem. Soc.*, 2018, **140**, 7012–7020.
- 33 P. Khanipour, M. Löffler, A. M. Reichert, F. T. Haase, K. J. J. Mayrhofer and I. Katsounaros, *Angew. Chem., Int. Ed. Engl.*, 2019, **58**, 7145.
- 34 Q. Wan, S. Chen and A. K. Badu-Tawiah, *Chem. Sci.*, 2018, **9**, 5724–5729.
- 35 E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate and P. S. Baran, *Nature*, 2016, **533**, 77–81.
- 36 A. Badalyan and S. S. Stahl, *Nature*, 2016, **535**, 406–410.
- 37 A. Wiebe, D. Schollmeyer, K. M. Dyballa, R. Franke and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 2016, **55**, 11801–11805.
- 38 L. Schulz, M. Enders, B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 2017, **56**, 4877–4881.
- 39 M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230–13319.
- 40 Y. Okada and K. Chiba, *Chem. Rev.*, 2018, **118**, 4592–4630.
- 41 W. Zhang, K. L. Carpenter and S. Lin, *Angew. Chem., Int. Ed. Engl.*, 2020, **59**, 409–417.
- 42 K. D. Moeller, *Chem. Rev.*, 2018, **118**, 4817–4833.
- 43 R. Francke and R. D. Little, *Chem. Soc. Rev.*, 2014, **43**, 2492–2521.
- 44 N. Fu, G. S. Sauer and S. Lin, *Nat. Protoc.*, 2018, **13**, 1725–1743.
- 45 W. R. Leow, Y. Lum, A. Ozden, Y. Wang, D.-H. Nam, B. Chen, J. Wicks, T.-T. Zhuang, F. Li, D. Sinton and E. H. Sargent, *Science*, 2020, **368**, 1228.
- 46 X. Hu, L. Nie, G. Zhang and A. Lei, *Angew. Chem., Int. Ed. Engl.*, 2020, **59**, 15238–15243.
- 47 E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. DiRocco, I. W. Davies, S. L. Buchwald and D. W. C. MacMillan, *Science*, 2016, **353**, 279–283.
- 48 J. J. Murphy and P. Melchiorre, *Nature*, 2015, **524**, 297–298.
- 49 J. L. Jeffrey, J. A. Terrett and D. W. C. MacMillan, *Science*, 2015, **349**, 1532–1536.
- 50 Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle and D. W. C. MacMillan, *Science*, 2014, **345**, 437–440.
- 51 L. Shi and W. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687–7697.



- 52 T. Gieshoff, A. Kehl, D. Schollmeyer, K. D. Moeller and S. R. Waldvogel, *J. Am. Chem. Soc.*, 2017, **139**, 12317–12324.
- 53 R. Hayashi, A. Shimizu and J.-i. Yoshida, *J. Am. Chem. Soc.*, 2016, **138**, 8400–8403.
- 54 S. Lips, D. Schollmeyer, R. Franke and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 2018, **57**, 13325–13329.
- 55 S. Lips, B. A. Frontana-Urbe, M. Dörr, D. Schollmeyer, R. Franke and S. R. Waldvogel, *Chem.–Eur. J.*, 2018, **24**, 6057–6061.
- 56 A. Wiebe, S. Lips, D. Schollmeyer, R. Franke and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 2017, **56**, 14727–14731.
- 57 S. Lips, A. Wiebe, B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 2016, **55**, 10872–10876.
- 58 T. Wirtanen, E. Rodrigo and S. R. Waldvogel, *Chem.–Eur. J.*, 2020, **44**, 777–780.
- 59 K. Mahanty, D. Maiti and S. De Sarkar, *J. Org. Chem.*, 2020, **85**, 3699–3708.
- 60 X. Ye, P. Zhao, S. Zhang, Y. Zhang, Q. Wang, C. Shan, L. Wojtas, H. Guo, H. Chen and X. Shi, *Angew. Chem., Int. Ed. Engl.*, 2019, **58**, 17226–17230.
- 61 P. Xiong, H. Long, J. Song, Y. Wang, J.-F. Li and H.-C. Xu, *J. Am. Chem. Soc.*, 2018, **140**, 16387–16391.
- 62 A. J. J. Lennox, S. L. Goes, M. P. Webster, H. F. Koolman, S. W. Djuric and S. S. Stahl, *J. Am. Chem. Soc.*, 2018, **140**, 11227–11231.
- 63 Y. Liang, F. Lin, Y. Adeli, R. Jin and N. Jiao, *Angew. Chem., Int. Ed. Engl.*, 2019, **58**, 4566–4570.
- 64 Y. N. Ogibin, M. N. Elinson and G. I. Nikishin, *Russ. Chem. Rev.*, 2009, **78**, 89–140.
- 65 J. B. Sperry and D. L. Wright, *Chem. Soc. Rev.*, 2006, **35**, 605–621.
- 66 J.-i. Yoshida, K. Kataoka, R. Horcajada and A. Nagaki, *Chem. Rev.*, 2008, **108**, 2265–2299.
- 67 B. A. Frontana-Urbe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099–2119.
- 68 E. J. Horn, B. R. Rosen and P. S. Baran, *ACS Cent. Sci.*, 2016, **2**, 302–308.
- 69 Y. Jiang, K. Xu and C. Zeng, *Chem. Rev.*, 2018, **118**, 4485–4540.
- 70 Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 7448–7451.
- 71 S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 2018, **57**, 6018–6041.
- 72 A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 2018, **57**, 5594–5619.
- 73 A. S. S. Doobary and H. P. Caldora, *Angew. Chem., Int. Ed.*, 2020, **59**, 1155–1160.
- 74 A. J. J. Lennox, J. E. Nutting and S. S. Stahl, *Chem. Sci.*, 2018, **9**, 356–361.
- 75 H. Wang and H. Huang, *Chem. Rec.*, 2016, **16**, 1807–1818.
- 76 Q. Qin and S. Yu, *Org. Lett.*, 2014, **16**, 3504–3507.
- 77 K. D. Moeller, M. R. Marzabadi, D. G. New, M. Y. Chiang and S. Keith, *J. Am. Chem. Soc.*, 1990, **112**, 6123–6124.
- 78 K. D. Moeller and L. D. Rutledge, *J. Org. Chem.*, 1992, **57**, 6360–6363.
- 79 K. D. Moeller, P. W. Wang, S. Tarazi, M. R. Marzabadi and P. L. Wong, *J. Org. Chem.*, 1991, **56**, 1058–1067.
- 80 C. Zhu, H. Yue, P. Nikolaienko and M. Rueping, *CCS Chem.*, 2020, **2**, 179–190.
- 81 M. Arata, T. Miura and K. Chiba, *Org. Lett.*, 2007, **9**, 4347–4350.
- 82 K. Chiba, T. Miura, S. Kim, Y. Kitano and M. Tada, *J. Am. Chem. Soc.*, 2001, **123**, 11314–11315.
- 83 Y. Okada, A. Nishimoto, R. Akaba and K. Chiba, *J. Org. Chem.*, 2011, **76**, 3470–3476.
- 84 Y. Okada, R. Akaba and K. Chiba, *Org. Lett.*, 2009, **11**, 1033–1035.
- 85 Y. Imada, N. Shida, Y. Okada and K. Chiba, *Chin. J. Chem.*, 2019, **37**, 557–560.
- 86 K. Chiba and M. Tada, *J. Chem. Soc., Chem. Commun.*, 1994, 2485–2486.
- 87 Y. Okada, Y. Yamaguchi, A. Ozaki and K. Chiba, *Chem. Sci.*, 2016, **7**, 6387–6393.
- 88 A. Ozaki, Y. Yamaguchi, Y. Okada and K. Chiba, *ChemElectroChem*, 2017, **4**, 1852–1855.
- 89 L. Zhu, P. Xiong, Z.-Y. Mao, Y.-H. Wang, X. Yan, X. Lu and H.-C. Xu, *Angew. Chem., Int. Ed. Engl.*, 2016, **55**, 2226–2229.
- 90 Y. Imada, Y. Okada and K. Chiba, *Beilstein J. Org. Chem.*, 2018, **14**, 642–647.
- 91 K. T. Lorenz and N. L. Bauld, *J. Am. Chem. Soc.*, 1987, **109**, 1157–1160.
- 92 S. Maity, M. Zhu, R. S. Shinabery and N. Zheng, *Angew. Chem., Int. Ed. Engl.*, 2012, **51**, 222–226.
- 93 Y. Cai, J. Wang, Y. Zhang, Z. Li, D. Hu, N. Zheng and H. Chen, *J. Am. Chem. Soc.*, 2017, **139**, 12259–12266.
- 94 G. J. Kavarnos and N. J. Turro, *Chem. Rev.*, 1986, **86**, 401–449.

