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The merger of electro-reduction and hydrogen bonding activation for a radical Smiles rearrangement†

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The reductive activation of chemical bonds at less negative potentials provides a foundation for high functional group tolerance and selectivity, and it is one of the central topics in organic electrosynthesis. Along this line, we report the design of a dual-activation mode by merging electro-reduction with hydrogen bonding activation. As a proof of principle, the reduction potential of *N*-phenylpropiolamide was shifted positively by 218 mV. Enabled by this strategy, the radical Smiles rearrangement of *N*-arylpropiolamides without external radical precursors and prefunctionalization steps was accomplished. [DBU][HOAc], a readily accessible ionic liquid, was exploited for the first time both as a hydrogen bonding donor and as a supporting electrolyte.

Introduction

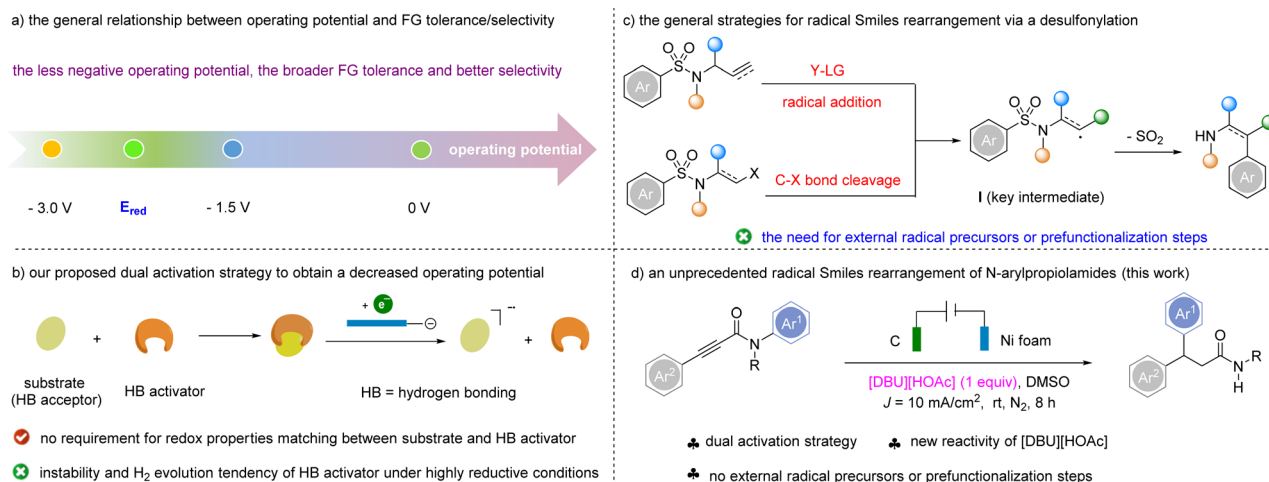
Organic electrosynthesis provides a simple and sustainable way to alter the redox-states of organic molecules, and it has merged as an increasingly viable platform in modern organic synthesis.¹ While selectivity and functional group tolerance are deciding factors in how useful a methodology may ultimately be, the electro-activation of chemical bonds under low operating potentials (absolute value) to fulfill the criteria of good selectivity and broad functional group tolerance is a sought-after goal in organic electrosynthesis.² In the context of electro-reduction, the reduction of functionalities at less negative potentials is much appreciated (Scheme 1a). To meet this requirement, the concept of mediated cathodic reduction has shown great promise for reducing functionalities at lower operating potentials.³ However, this strategy loses its utility when functionalities possessing high reduction potentials are used, considering the limited availability of strongly reducing mediators. Against this background, the merger of electro-reduction and photoredox catalysis to generate strongly reducing species at less negative potentials has been developed in recent years.⁴ Another conceptually appealing activation mode is the strategic exploitation of the collaboration between electro-reduction and hydrogen bonding (Scheme 1b). Hydrogen bonding, a classical noncovalent interaction, has wide applications in organic synthesis due to its high directionality.⁵ In this sense, the synergism of electro-reduction with hydrogen bonding activation would, in principle, decrease the

activation potentials of hydrogen bonding acceptors, thus providing valuable advantages in terms of functional group tolerance, as well as selectivity. Although voltammetric studies have shown that electro-reduction could be enhanced by hydrogen bonding,⁶ the application of this noncovalent interaction in reductive bulk electrolysis is still in its infancy, mainly due to the fact that hydrogen bonding donors are susceptible to H₂ evolution under highly reductive conditions. As such, overcoming this synthetic challenge requires the identification of an electro-reductively stable hydrogen bonding donor.

To implement this dual activation strategy, the electro-chemical radical Smiles rearrangement of *N*-arylpropiolamides possessing high reduction potentials was investigated. Radical Smiles rearrangement offers a powerful approach to arylation *via ipso* substitution, thus leading to an increased interest from the synthetic community in recent years.⁷ Taking the widely studied desulfonylative variant for example (Scheme 1c), the radical Smiles rearrangement was often triggered by the generation of a key carbon-centered radical (intermediate **I**) either by an intermolecular radical addition⁸ or by an intramolecularly reductive C–X bond cleavage.⁹ In contrast, the generation of intermediate **I** that relied on Mn(III)-catalyzed hydrogen atom transfer or Fe(III)-mediated alkene oxidation has been developed by Shenvi and Studer groups, respectively.¹⁰ Encouraged by the recent achievements in electro-reductive synthesis,^{11,12} we envisioned that the electro-reduction of *N*-arylpropiolamides would generate the corresponding vinyl radicals to trigger the following radical Smiles rearrangement. Considering that *N*-arylpropiolamides are difficult to be reduced, the introduction of hydrogen bonding activation would decrease their reduction potentials to provide broader functional group tolerance and improved selectivity. Herein, we report a dual-activation strategy integrating electro-reduction

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Scheme 1 The collaboration between electro-reduction and hydrogen bonding and the reported strategies to radical Smiles rearrangement.

and hydrogen bonding activation to shift the reduction potential of *N*-phenylpropiolamide positively by 218 mV (Scheme 1d). [DBU][HOAc], a typical ionic liquid,¹³ was exploited for the first time both as a hydrogen bonding donor and as a supporting electrolyte. Taking advantage of this strategy, the radical Smiles rearrangement of *N*-arylpropiolamides was realized, providing a rapid access to diarylpropanamides that widely exist in biologically relevant molecules.¹⁴ Distinct from prior-art on radical Smiles rearrangements, this electro-reductive variant obviates the use of external radical precursors, prefunctionalization steps to install C–X bonds, and transition metal catalysts.

Results and discussion

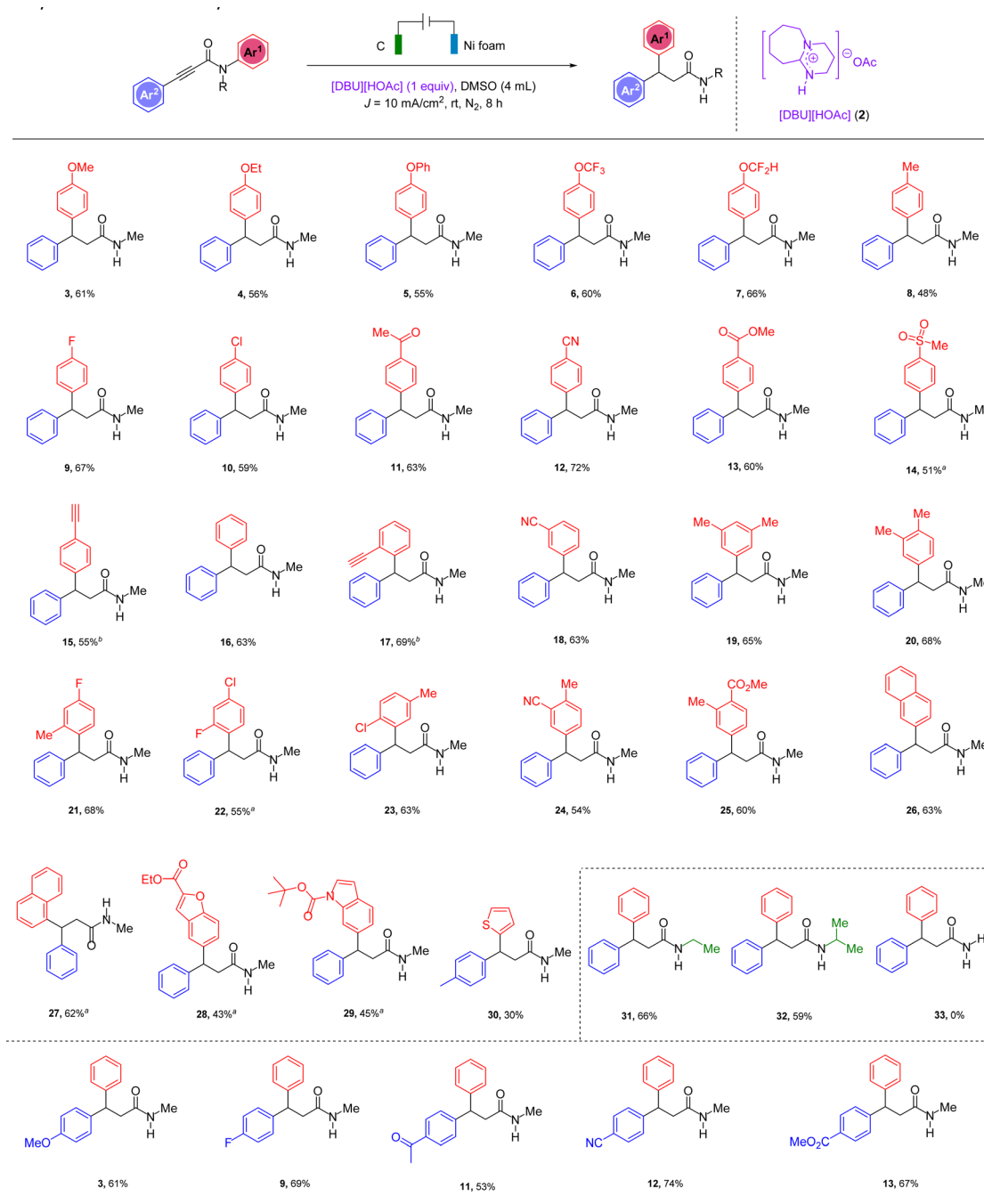
We began our study with the electrochemical rearrangement of **1a** as the model reaction for reaction condition optimization (Table 1). When the Smiles rearrangement was carried out in an undivided cell with [DBU][HOAc] (**2**) as the additive under constant current conditions, the desired product **3** was obtained in 61% yield (entry 1). Replacing [DBU][HOAc] with [DBU][TFA] or [DBU][MSA] afforded **3** in 52% and 50% yields, respectively (entries 2 and 3), while [DBU][PhCO₂H] as the additive gave **3** in the highest yield of 68% (entry 4). However, [DBU][HOAc] was selected as the

Table 1 Reaction condition optimization^a

Entry	Deviation from standard conditions	Yield (%)
1	None	61
2	[DBU][TFA] instead of 2	52
3	[DBU][MSA] instead of 2	50
4	[DBU][PhCO ₂ H] instead of 2	68
5	Pt plate or graphite as the cathode	44 or 47
6	CH ₃ CN instead of DMSO	32
7	DMA instead of DMSO	Trace
8	DMF instead of DMSO	Trace
9	<i>n</i> -Bu ₄ NPF ₆ (0.05 M) as the supporting electrolyte	44
10	<i>n</i> -Bu ₄ NClO ₄ (0.05 M) as the supporting electrolyte	46
11	LiClO ₄ (0.05 M) as the supporting electrolyte	Trace
12	<i>n</i> -Bu ₄ NBF ₄ (0.05 M) as the supporting electrolyte	58
13	6 mA cm ⁻² or 8 mA cm ⁻²	41 or 57
14	No N ₂	54
15	No 2 , <i>n</i> -Bu ₄ NBF ₄ (0.05 M) as the supporting electrolyte	Trace
16	No electrolysis	0

^a Reaction conditions: **1a** (0.3 mmol), **2** (0.3 mmol), DMSO (4 mL), graphite anode (1 cm × 1 cm × 0.2 cm), foamed nickel cathode (1 cm × 1 cm × 0.2 cm), J = 10 mA cm⁻², N₂, rt, 8 h; isolated yield; TFA = trifluoroacetic acid, MSA = methanesulfonic acid.





Scheme 2 The substrate scope. ^aReaction conditions: **1a** (0.3 mmol), **2** (0.3 mmol), DMSO (4 mL), graphite anode (1 cm × 1 cm × 0.2 cm), foamed nickel cathode (1 cm × 1 cm × 0.2 cm), $J = 10 \text{ mA cm}^{-2}$, N_2 , rt, 8 h; isolated yield. ^a $J = 8 \text{ mA cm}^{-2}$. ^b $J = 5 \text{ mA cm}^{-2}$.

optimal additive for further optimization due to its low cost and high atom economy. When the Pt plate or graphite was employed as the cathode instead of nickel foam, the product **3** was obtained in 44% and 47% yields, respectively (entry 5). The solvent screening showed that dimethyl sulfoxide (DMSO) was the optimal solvent, while other commonly used solvents such as CH_3CN , N,N -dimethylacetamide (DMA) and N,N -dimethylformamide (DMF) gave **3** in trace to low yields (entries 6–8). Next, the addition of external supporting electrolytes such as $n\text{-Bu}_4\text{NPF}_6$, $n\text{-Bu}_4\text{NClO}_4$,

LiClO_4 , and $n\text{-Bu}_4\text{NBF}_4$ failed to improve the yield of **3** (entries 9–12). Further optimization showed that 10 mA cm^{-2} was the optimal current density, while decreased current densities led to lower yields (entries 13). The yield of **3** decreased to 54% when the electrolysis was carried out in the absence of N_2 protection (entry 14). The control experiments revealed that a complex mixture involving a trace amount of **3** was generated in the absence of $[\text{DBU}][\text{HOAc}]$ with $n\text{-Bu}_4\text{NBF}_4$ as the supporting electrolyte (entry 15), while no reaction occurred without electrolysis (entry 16).



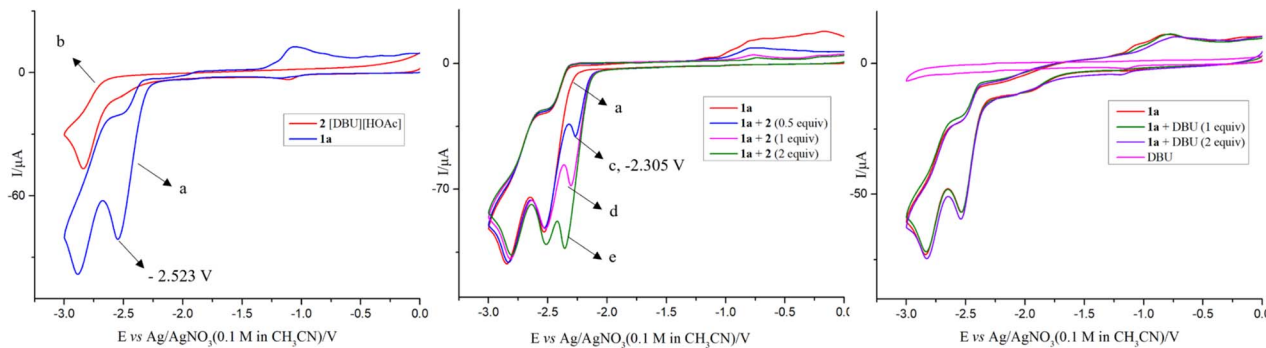
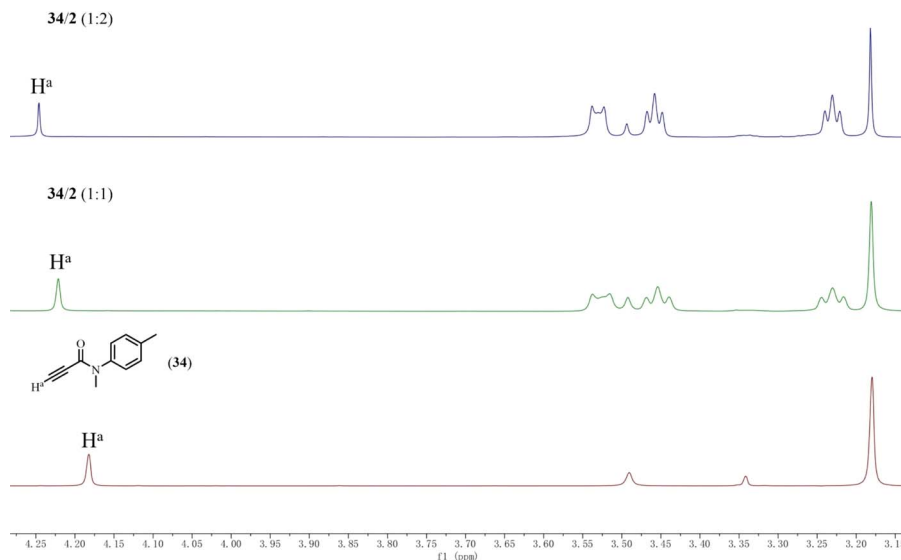


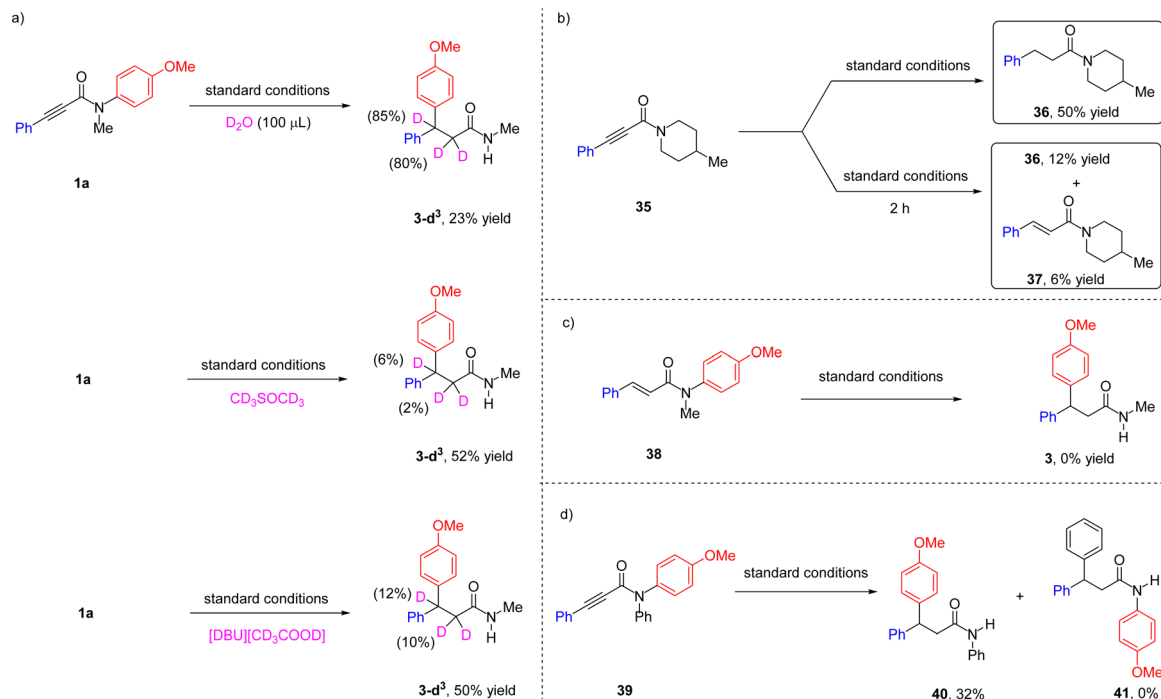
Fig. 1 CV experiments.

Having established the optimal conditions for this radical Smiles rearrangement, the substrate scope was then investigated (Scheme 2). For the mono-substituted Ar¹ moiety, both electron-donating and electron-withdrawing substituents were well tolerated to give the corresponding products **3–16** with up to 72% yield. When the substituent was shifted from the *para*-position to the *ortho*- or *meta*-position, the Smiles rearrangement also proceeded smoothly to afford the corresponding products **17–18** with up to 69% yield. For the di-substituted Ar¹ moiety, substituents can be located relative to each other in the *ortho*, *meta*, or *para* position, yielding diarylpropanamides **19–25** with up to 68% yield. In addition, both 1-naphthyl and 2-naphthyl substituted substrates proved to be efficient to generate diarylpropanamides **26–27** in 62–63% yields. Noteworthy, *N*-heteroaryl substituted propiolamides were also suitable substrates to afford products **28–30** in 30–45% yields. Altering the R group from the methyl group to the ethyl or isopropyl group led to a slightly decreased efficiency, delivering products **31–32** in 59–66% yields. Finally, the scope of the Ar² moiety was examined. It was found that both electron-rich and electron-deficient substituents attached on the Ar² moiety were

well tolerated to give **3, 9, 11, 12**, and **13** in 61–74% yields. The moderate yields result from the incomplete conversion of starting materials and the side reaction of alkyne hydrogenation. This electrochemical Smiles rearrangement features excellent functional group compatibility, as evidenced by the tolerance of various reducible functionalities such as carbonyl (**11**), cyan (**12, 18, 24**), ester (**13, 25, 28**), sulfonyl (**14**), alkynyl (**15, 17**), and amide (**29**). As a limitation, the reaction did not occur when the R group was replaced with hydrogen (**33**). In addition, the alkyl-substituted *N*-arylpropiolamides did not work under the optimal conditions.

First, cyclic voltammetry (CV) experiments were carried out to reveal the hydrogen bonding between **1a** and [DBU][HOAc] (**2**). As shown in Fig. 1, left, the CV of substrate **1a** showed an obvious reduction peak at -2.5 V vs. Ag/AgNO₃ (curve a), while **2** exhibited no obvious reduction behaviour within the range of 0 to -2.7 V (curve b). These results suggest that the electro-reduction of **1a** is much preferred to that of **2**. As shown in Fig. 1, middle, the CV of the mixture of **2** (0.5 equiv.) and **1a** showed the evolution of a new reduction peak at -2.3 V vs. Ag/AgNO₃ (curve c). Compared with curve b, the reduction

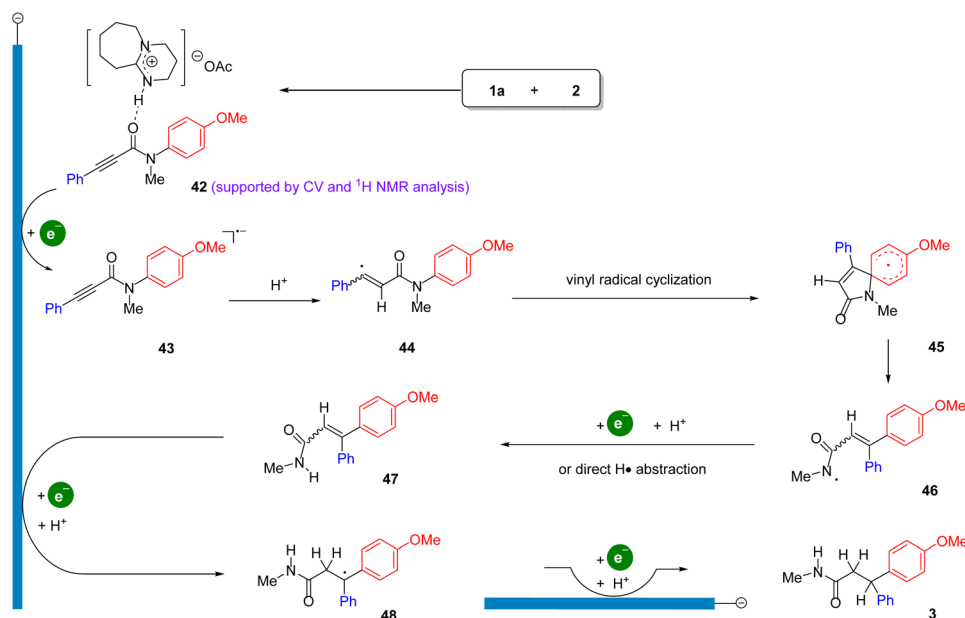
Fig. 2 ¹H NMR experiments.



Scheme 3 The control experiments.

potential of **1a** was shifted positively by 218 mV. Notably, the corresponding reduction current was enhanced upon gradually increasing the molar ratio of **2/1a** (curves d and e). However, DBU cannot shift the reduction potential of **1a** positively upon addition of DBU to the mixture of **1a**/DMSO (Fig. 1, right). Collectively, the CV analyses suggest the hydrogen bonding between **1a** and **2**.

To further demonstrate the proposed hydrogen bonding, ¹H NMR experiments were carried out (Fig. 2). However, considering that **1a** doesn't have alkyne protons and the signal of the NH proton in **2** can't be observed in d₆-DMSO (see the ESI† for details), an analog compound (**34**) was employed for ¹H NMR analysis. As shown in Fig. 2, the signal of the alkyne proton in **34** appeared at 4.18 ppm. Upon addition of **2** (1 equiv.) into the

Scheme 4 A plausible mechanism accounting for the generation of **3**.

mixture of **34**/d₆-DMSO, the chemical shift value of the alkyne proton shifted to down-field. This value shifted to down-field again when another portion of **2** was added. The ¹H NMR analyses in combination with CV experiments support the hydrogen bonding between **1a** and [DBU][HOAc] (**2**).

To gain more mechanistic insight into this electrochemical Smiles rearrangement, some control experiments were carried out (Scheme 3). When the electrochemical rearrangement was performed in the presence of D₂O, **3-d³** was obtained in 23% yield in which 85% and 80% deuterations were found at the two benzylic positions, respectively (Scheme 3a). In contrast, the deuteration ratios were very low when d₆-DMSO or [DBU][CD₃-COOD] was used as the deuterium source (Scheme 3a). These deuterium-labeling studies demonstrate that carbanions were generated at these two benzylic positions during the electrolysis. When 1-(4-methylpiperidin-1-yl)-3-phenylprop-2-yn-1-one (**35**) was electrolyzed under the standard conditions, the complete hydrogenation product **36** was obtained in 50% yield (Scheme 3b). However, the semi-reduction of alkyne (**37**), as well as the completely hydrogenated product (**36**), was observed when shortening the reaction time to 2 h (Scheme 3b). These results suggest that the electro-reduction of **35** proceeds *via* a stepwise electron transfer-proton transfer process. To demonstrate that the radical Smiles rearrangement was initiated by a transient vinyl radical instead of an alkyl radical, the electrolysis of **38** was performed (Scheme 3c). As expected, no Smiles rearrangement product **3** was observed. This result excludes the possibility that the Smiles rearrangement was triggered by an alkyl radical resulting from the SET reduction of **38**. The selectivity experiment suggests that the vinyl radical would more likely attack the electron-rich site of substrate **39** to yield **40** in 32% yield (Scheme 3d).

Based on the control experiments, CV and ¹H NMR analyses, the generation of **3** through the relay of electro-reduction of alkyne *via* a proton-coupled electron-transfer (PCET) process, radical Smiles rearrangement, and alkene hydrogenation was proposed (Scheme 4). Initially, the mixture of **1a** and [DBU][HOAc] (**2**) forms a complex of **42** through a hydrogen bonding interaction, which was supported by the CV analysis and ¹H NMR analyses. The hydrogen bonding enables the SET reduction of **42** at decreased potential to afford a radical anion **43**, which undergoes protonation to yield a transient vinyl radical **44**. Subsequently, radical **44** triggers a Smiles rearrangement *via* an unusual C–N cleavage to afford a postulated amidyl radical **46**. Upon hydrogen atom abstraction or SET reduction of **46** followed by protonation, intermediate **47** is generated. The cathodic reduction of **47** followed by protonation generates **48**, which proceeds *via* a radical-polar crossover (RPC)¹⁵ pathway to deliver product **3**. Simultaneously, the anodic oxidation of DMSO maintains the charge balance.

Conclusions

In conclusion, this work details the strategic integration of hydrogen bonding into electro-reduction to activate *N*-arylpropiolamides at less negative potentials, which in turn provides a basis for high selectivity and functional group compatibility.

This dual activation strategy led to a radical Smiles rearrangement of *N*-arylpropiolamides to deliver diarylpropanamides that are otherwise difficult to access. Distinct from prior-art on radical Smiles rearrangement, this electro-reductive variant obviates the use of external radical precursors or prefunctionalization steps, and features 100% atom efficiency. Uniquely, [DBU][HOAc] serves both as a hydrogen bonding donor and as a supporting electrolyte. The stable nature of [DBU][HOAc] under highly reductive conditions is the key to the success of this work. The proposed hydrogen bonding was supported by CV and ¹H NMR studies. We hope this dual activation strategy would offer new possibilities for reductive electrosynthesis.

Data availability

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

Author contributions

L. Y. L. performed the experiment and data analyses. K. X. conceived the idea and designed the research. K. X. drafted the manuscript; C. C. Z. helped supervise the project and revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

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