

Chemoselective, Metal-free, (Hetero)Arene Electroreduction Enabled by Rapid Alternating Polarity

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ABSTRACT:

Arene semi-reduction remains a challenge when multiple reductively labile functional groups are present or when using heteroarene substrates. Conventional chemical and even electrochemical Birch-type reductions suffer from a lack of chemoselectivity due to a reliance on alkali metals or harshly reducing conditions. This study reveals that a simpler avenue is available for such reductions by simply altering the waveform of current delivery, namely rapid alternating polarity (rAP). The developed method, which proceeds in protic solvent and can be easily scaled up, does not require any metal additives or stringently anhydrous conditions. The scope of this dearomatization is broad, tolerating numerous functional groups and providing rapid access to previously challenging molecules. While the mechanism has not been fully deciphered, the key feature of the rAP reduction is that the main competing process, namely proton reduction, can be suppressed. As such, unique arene reductions can be accomplished even outside solvent electrochemical window or in the presence of Brønsted acids.

MAIN TEXT:

The addition of hydrogen to an aromatic nucleus represents a widely used strategy for rapidly introducing complexity in synthesis.¹ As such, the impact of the Birch reduction and related dearomatization strategies in organic synthesis cannot be overemphasized.²⁻⁵ This foundational reaction of organic chemistry, taught at the undergraduate level, is also notorious for its harsh reaction conditions: liquid ammonia, elemental alkali metal (Li, Na, K), and a judiciously chosen proton source (Figure 1A).² Owing to the hazardous nature of these conditions, the search for more practical variants is still an active research topic in modern organic synthesis 70+ years following its original disclosure. These efforts can be placed into two categories: (1) conditions that ablate inherent safety hazards (elemental alkali metal and liquid ammonia) and (2) improving the chemoselectivity and scope. Within the former category, various solid-supported reagent systems⁶⁻⁸ have been disclosed as well as mineral oil dispersions with crown-ether additives.⁹ In 2019 a practical electrochemical Birch variant inspired by Li-ion batteries was developed for ammonia and elemental Li-free arene reduction (Li-ion electroreduction, LER).¹⁰ Photochemical variants have also been described, although the scope and reaction times required for those systems are suboptimal.^{11,12} Recently the Koide group demonstrated that ammonia could be replaced by ethylene diamine (e.g. Benkesser modification¹³⁻¹⁵) to further enhance practicality.¹⁶ Although some of these studies enabled practical and scalable Birch reduction, the chemoselectivity was revealed to be analogous to

conventional Birch reduction. To improve chemoselectivity, the procedure employing LiDBB reported by Donohoe and co-workers is notable since it is widely used for reduction of electron-deficient heteroarenes with good tolerance of esters, which seldom survives during Birch reduction.¹⁷ This Communication discloses the finding that simply modifying the waveform of electrolysis (rapid alternating polarity, rAP) can lead to a new level of chemoselectivity for arene and heteroarene reduction. This operationally simple protocol proceeds at ambient temperature in protic solvent, does not require sacrificial electrodes, or even any metal source, and tolerates functional groups that are notoriously challenging to accommodate such as ester, nitrile, epoxide and even alkyl chloride.

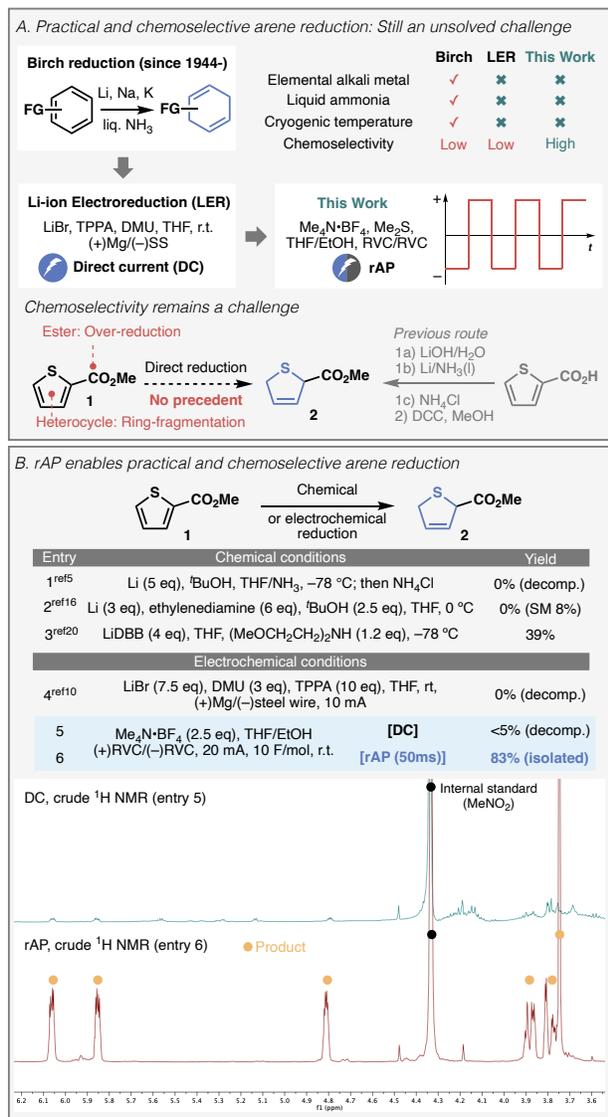


Figure 1. Background of arene reduction and discovery of efficient electroreductive dearomatization by rAP. (A) Practical and chemoselective arene reduction is an unsolved challenge in organic synthesis. (B) Case study with challenging chemoselectivity. rAP gave clean arene reduction without necessitating special additives, whereas DC electrolysis under the identical conditions resulted in decomposition (Y-axis of the crude NMRs was adjusted to the same scaling).

The canonical Birch reduction is typically applicable to only a limited number of heterocycles. The lack of chemoselectivity of the process is evident in the *absence* of a literature precedent for reduction of a trivial heterocycle methyl 2-thiophenecarboxylate **1** (Figure 1A). This is understandable since Birch reduction of thiophenecarboxylic acid poses an issue of ring fragmentation.¹⁸ The ester functionality could cause more chemoselectivity issues such as overreduction or further facilitating C–S bond cleavage. Accordingly, the reduction product **2** was previously accessed by careful Birch reduction of thiophene-2-carboxylate Li salt, followed by mild esterification.¹⁹

Intrigued by the absence of such an example, several representative Birch reduction conditions were applied on this simple substrate **1** (Figure 1B). Not surprisingly, standard Birch conditions⁵ (entry 1) resulted in complete decomposition of the starting material. The most recent modification¹⁶ (entry 2) showed attenuated reactivity, yet extensive decomposition was still observed. Donohoe's LiDBB method²⁰ (entry 3) afforded the product in 39% yield, which is reasonable considering that this method is particularly suitable for electron-deficient heterocycles. Yet, concerns remain; LiDBB is highly sensitive (necessitating stringent degassing) and removal of large amount of DBB is problematic. Additionally, in this particular case the cost of DBB (\$915/mol, TCI) surpasses the cost of the starting material itself (\$571/mol, TCI). Turning to electrochemical conditions, LER¹⁰ (entry 4) also led to decomposition. Although simple electrolysis of **1** under DC current in THF/EtOH with RVC electrodes resulted in decomposition (entry 5), it actually showed some peaks in the crude NMR indicative of trace dearomatization products. In striking contrast, under otherwise identical conditions, simply changing the waveform to rapid alternating polarity (rAP, entry 6) afforded 83% of the desired product (crude NMR shown in Figure 1).

With the above promising results in hand, optimization was pursued using a less reactive substrate **3** as shown in Table 1. In the initial attempt, a diminished yield (29%) was observed due to the higher aromaticity of this compound compared to **1**, along with the formation of benzyl alcohol (BnOH) presumably formed via carbonyl reduction. Standard Na or Li-based chemical conditions as well as LER on **3** did not afford any 1,4-diene product **4** (see SI). Instead, various over-reduced products and fragmentation-derived products predominated. A systematic study of chemical and electrochemical parameters revealed that dimethylsulfide (DMS) could be employed as a sacrificial electron-donor to improve the yield (Table 1, Panel A). Thus, the rest of the optimization was conducted using 3.0 equiv of DMS. Electrodes and electrolytes were found critical to achieve good reactivity (Table 1, Panel B). In particular, all electrodes examined resulted in little or no conversion with the exception of reticulated vitreous carbon (RVC) and boron-doped diamond (BDD). Due to the inexpensive nature of RVC, it was used exclusively in this study.²¹ A screening of electrolytes indicated that tetraalkyl ammonium salts were superior (except for the highly basic Me₄N•OH), while employing LiClO₄ reduced conversion (Table 1, Panel C). As demonstrated in our previous rAP study,²² the electrochemical driving force delivered is a function of both current and frequency (Table 1, Panel D). Thus, either decreasing pulse width (increasing frequency) or reducing current resulted in decreased conversion. Constant potential rAP (using the same terminal potential observed under constant current with 5 equiv. of Me₄N•BF₄ as electrolyte) gave a similar product distribution to constant current rAP. Since a slight warming of the reaction was noted (from 23 °C to 35 °C, see SI) submerging the reaction vessel in a 0 °C ice bath further increased the desired product yield to 59% (best yield) by suppressing BnOH formation originated from the carbonyl reduction. The nature of solvent and pH of the reaction (Table 1, Panel E) also affected the ratio of the arene reduction vs the carbonyl reduction. Lastly, several control experiments under direct current conditions were performed to provide a comparison with the rAP-based method (Table 1, Panel F). Although a small amount of the desired product was obtained at various current densities, the yield as well as the extent of carbonyl reduction were by no means similar to the rAP-based method. In an effort to mimic the unique reactivity of rAP, constant potential experiments were attempted. Thus, the reaction potential was set to -2.3 V (see SI for cyclic voltammogram of **3**) to achieve cleanest reduction possible. Despite this effort, the yield of **4** was still far below the rAP-based method, supportive of the documented fundamental reactivity difference between rAP and DC in other studies.²²⁻²⁴

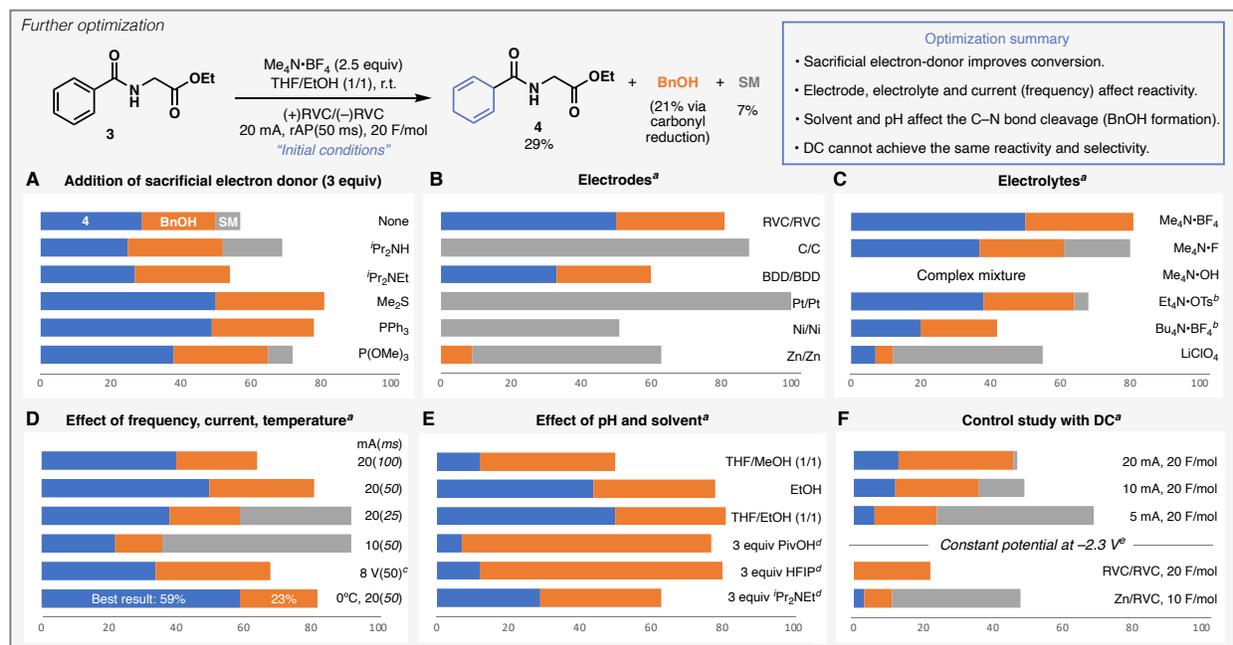


Table 1. Optimization study. All the reactions were performed on 0.1 mmol scale under the initial conditions with a deviation indicated. Product distribution was analyzed by ¹H NMR. ^aReactions were performed with 3 equiv of Me₂S. ^b1 equiv of electrolyte was used. ^c5 equiv of Me₄N•BF₄ was used. ^dIndicated additive was added to THF/EtOH (1/1). ^eBu₄N•BF₄ (0.2 M) was used as an electrolyte.

Table 2 demonstrates the reaction generality. Various (hetero)arenes can be reduced chemoselectively under operationally simple conditions without the need for any expensive reagents or additives (Table 2A). Complementary to standard Birch reduction, rAP reduction is most suitable for electron-deficient (hetero)arenes. The success of the reaction is predictable based on the reduction potential of an arene and a functional group that can be easily measured using CV (empirical guidance for FG tolerance is summarized in Table 2A). Thus, synthetically useful yields are obtained when a target arene has a more positive reduction potential than those of other functional groups ($E_{\text{red,arene}} > E_{\text{red,FG}}$). As such, electron-deficient heteroarenes exhibit the broadest functional group tolerance with ester (**5-10**, **12**, **14-16**), nitrile (**7**), allyl group (**11**), epoxide (**8**) and even alkyl chloride (**13**). Electron-deficient arenes are slightly less reducible than electron-deficient heterocycles, and the functional group compatibility of this class is more limited. Nevertheless, synthetically useful handles such as allyl (**21**), alkyne (**22**), ester (**23**, **24**, **27**), boronate ester (**25**), alkyl chloride (**26**) and nitrile (**27**, **28**) were well-

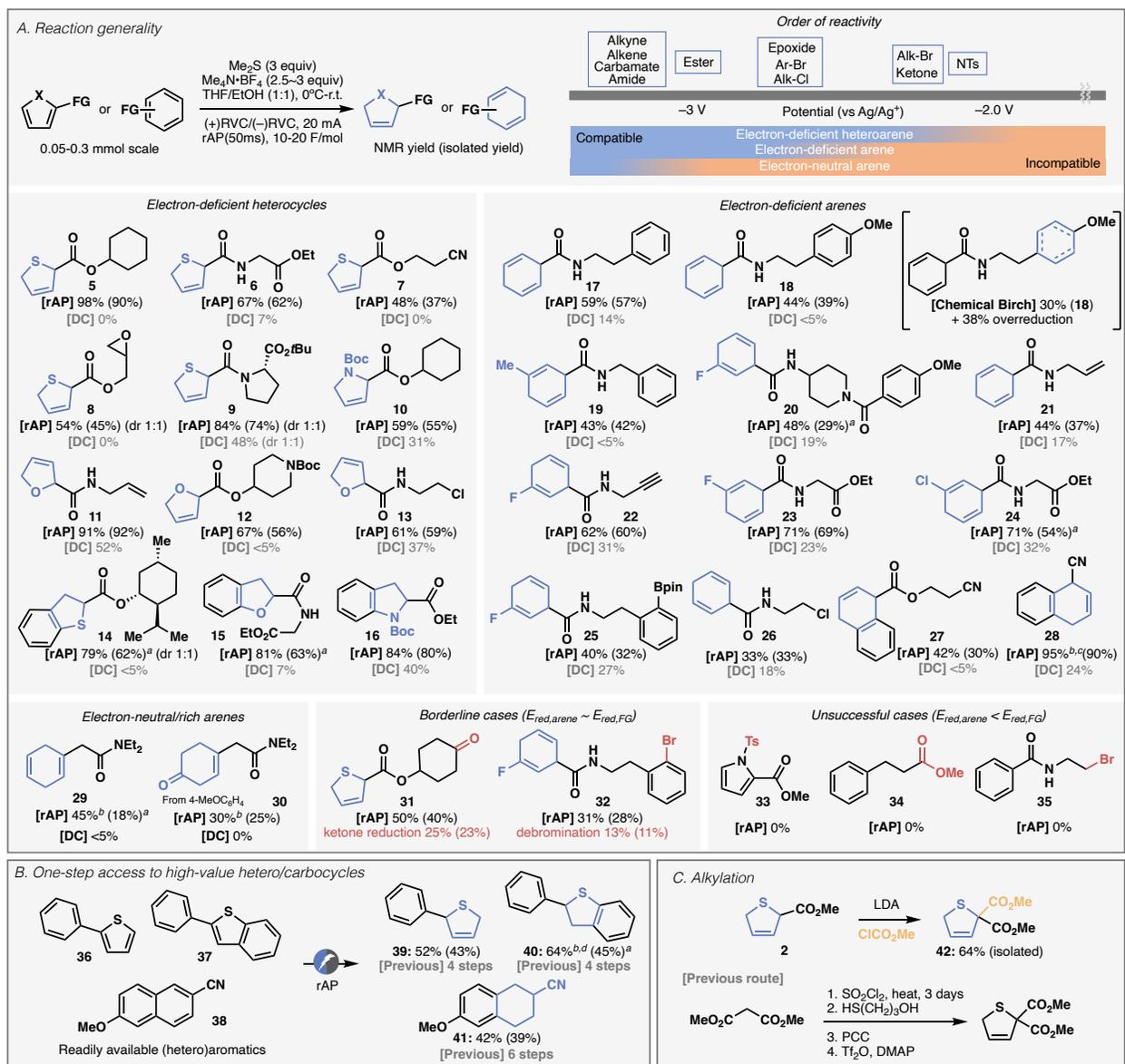


Table 2. Chemoselective reduction of (hetero)arenes by rAP. (A) Reaction generality and empirical guide for functional group tolerance. (B) Access to high-value (hetero)cyclic systems from readily available (hetero)arenes. See SI for individual reaction conditions. (C) Concise access to dihydrothiophene **42** via alkylation of **2**. ^aLarge drop of isolated yield was due to purification loss. ^b100 ms pulse was used instead of 50 ms. ^cThe reaction was performed in MeOH with PivOH as an additive. ^dAmount of Me₂S was 10 equiv.

tolerated. A halogen atom directly connected to an arene was also tolerated (**20**, **22-25**). Notably, differentiation of two arenes was possible as exemplified in **17-20** and **25**. Achieving such chemoselectivity was found challenging under conventional Birch reduction conditions as mixture of products was obtained even if the two arenes are most electronically differentiated (Table 2A, chemical Birch for obtaining **18**). Non-conjugated arenes can be reduced to afford **29** and **30** in this method, though the yields were moderate due to the low reactivity. Borderline cases also exist when $E_{\text{red,arene}}$ is close to $E_{\text{red,FG}}$, and such cases were exemplified in the reduction of **31** and **32**. In accord with this simple rubric, when a functional group is more easily reducible, the method is unable to favor the reduction of (hetero)arenes (**33-35**).

To demonstrate the utility of this method for accessing partially saturated heterocycles, a collection of readily available heteroarenes **36-38** were enlisted (Table 2B). Subsequent alkylation could also be used to install additional complexity to an arene reduction product, which was demonstrated in the synthesis of **42** (Table 2C). The preparation of partially saturated heterocycles such as those exemplified above are often cumbersome since de-novo ring constructions are needed (**39-42**, previously required 4-6 step preparations).^{19,25-27} Chemoselective rAP-based arene reduction subverts conventional multi-step ring construction by repurposing existing, readily available heteroarenes.

The mechanistic details of this reaction are of great interest due to the notable reactivity difference observed between DC and rAP. A truly authoritative and complete understanding of this phenomenon would likely entail the use of various electroanalytical methods involving microelectrodes as well as rotating disc electrodes to dissect fast electron transfer kinetics under stationary and non-stationary electrolysis conditions.²⁸ Such detailed studies are beyond the scope of this Communication, and will form the basis of a separate endeavor. For the time being, several pieces of empirical evidence are presented in Figure 2 that help to rationalize the differences in bulk reactivity. For instance, a large reactivity difference was observed in the reduction of compound **43** between DC and rAP. Remarkably, the reduction potential of this compound ($<-3\text{V}$)²⁹ resides far outside the reduction potential of the reaction solvent (Figure 2A, solvent CV), yet rAP delivered the product in 45% NMR yield. In contrast, under otherwise identical conditions employing a standard DC waveform resulted in mostly recovered starting material. The most notable visual difference between these two reactions was gas evolution. With DC, gas evolution was clearly visible from the cathode, whereas this phenomenon was not apparent in the rAP experiment. Consistent with this observation, gas evolution from the working electrode was also confirmed after measuring CV of the solvent. We hypothesized that hydrogen gas was being formed on the cathode (reductive) in the protic medium. To prove the existence of H_2 qualitatively, simple hydrogenation experiments were performed; namely, either DC or rAP was applied to the reaction solvent including cyclooctene in the presence of Pd/C catalyst (Figure 2B). To be sure, cyclooctene is unreactive under the arene reduction conditions, and redox perturbation of Pd/C catalyst by electrodes is unlikely since Pd/C does not dissolve in the solvent. A considerable quantity of hydrogenated product **45** was observed in the DC electrolysis, while **45** was below the GC/MS detection limit in the rAP experiment, suggesting that H_2 gas was not generated to an appreciable extent. As another proof of H_2 evolution, the basicity of the reaction was probed; if proton reduction took place, a basic environment would result and facilitate base-mediated side reactions. The reduction of **1** was therefore interrupted to study a possible side reaction occurring on base-sensitive methyl ester. Indeed, transesterification product **46** was observed under DC conditions, whereas no such product was observed under rAP conditions. Consistent with these findings are literature reports of CO_2 or CO reduction using pulsed potential instead of DC that produce less H_2 .³⁰⁻³⁵ Collectively, these experiments support the mechanism summarized in Figure 2C. During the cathodic phase, (hetero)arene reduction is taking place through direct SET. This mechanism is supported by the fact that the regioselectivity of 1,4-diene products corresponds to those in conventional Birch reduction products. Regarding chemoselectivity, it follows the reduction potential of the (hetero)arene and those of existing functionalities. Proton reduction, a pathway that normally competes to diminish reactivity towards arene reduction, is largely suppressed by applying rAP. In other words, cathodic limit of solvent electrochemical window is kinetically expanded by rAP. This effect also explains improved chemoselectivity under rAP conditions by removing side reactions promoted under a highly basic environment. During the anodic phase, DMS is presumably oxidized to generate α -ethoxy derivative. Analogous species **47** was detected in GC analysis

of crude reaction mixture when heavier Et₂S was used instead of DMS. A small amount of solvent oxidation may also take place during the anodic phase.

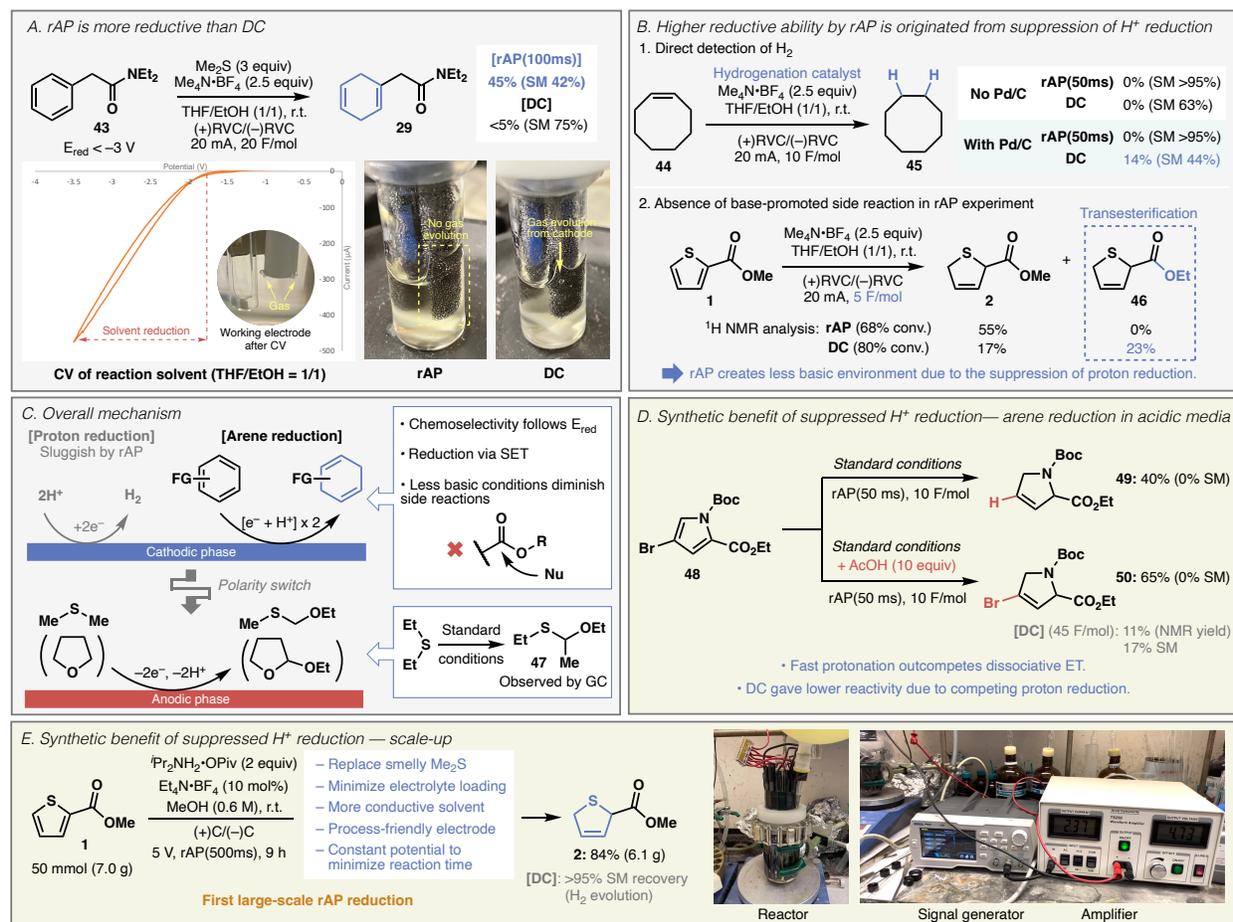


Figure 2. Mechanistic studies and synthetic advantage of outcompeting proton reduction. (A) Gas evolution was notable during DC electrolysis (including CV), whereas little gas evolution was observed with rAP. (B) Direct detection of H₂ gas and resulting pH change in the reaction probed by transesterification. (C) Overview of cathodic and anodic reactions. (D) rAP enables efficient arene reduction in the presence of acid with unique chemoselectivity, whereas DC electrolysis suffers proton reduction. (E) First example of large-scale electrolysis with rAP. Corresponding DC reduction resulted in complete recovery of the starting material due to the competing H₂ evolution.

The suppression of proton reduction can enable new types of chemoselective (hetero)arene reduction by running reactions deliberately *under acidic conditions* (Figure 2D). This is challenging for DC electrolysis since proton reduction is more pronounced under acidic conditions, and not advisable for chemical arene reduction owing to dangerously aggressive reactions of alkali metals with acids. As a proof of concept for this interesting possibility, standard rAP reduction of **48** furnished debrominated dihydropyrrolidine **49** in 40% yield via dissociative electron-transfer, common phenomenon during single-electron reduction of halogenated arenes. In striking contrast, running the same reaction in the presence of 10 equiv of AcOH furnished dihydropyrrolidine **50** in 65% yield, *maintaining the useful C–Br bond*. As expected, the corresponding DC electrolysis under identical conditions required a much longer reaction time (6 h, 45 “equiv” of electrons) due to the competing proton reduction, and only delivered 11% of **50** along with 17% recovered **48**. Another dramatic benefit for suppressing proton reduction was found during scale-up efforts (Figure 2E). Thus, optimized conditions for small scale could be modified to realize the reaction under more process-friendly conditions. Key modifications included replacing the sacrificial electron-donor DMS to ⁱPr₂NH (buffered with pivalic acid) as well as switching solvents from THF/EtOH to more conductive MeOH. In addition, RVC electrodes were replaced with graphite electrodes due

to unsatisfactory mechanical properties of RVC on scale. With these modifications, rAP-based conditions successfully afforded the product **2** in 84% isolated yield on 50 mmol scale, whereas DC electrolysis resulted in full recovery of **1** under identical reaction conditions.³⁶ Again, a large volume of gas evolution was observed during DC electrolysis, rendering the arene reduction unfavorable under such simple conditions.

This study demonstrates another compelling example of how the outcome of an electrochemical transformation can be completely altered simply by changing the waveform of current delivery. This time, chemoselective (hetero)arene reduction under rAP is shown to complement the scope of conventional chemical or electrochemical arene reductions. The enhanced reactivity as well as higher chemoselectivity can be explained by a suppression of competing proton reduction by the easily accessible rAP waveform. On preparative scales, no specialized equipment or engineering is required. On larger scales, a simple signal amplifier and signal generator can be employed (see SI). Although further in-depth analysis of the mechanism is necessary, the implications of this unique mode of reaction control may hold great promise for other types of chemoselective reductions of import to organic synthesis. Efficient reductive processes in protic media by rAP may also imply an interesting innovation opportunity in the areas of electrochemical CO₂ reduction as well as nitrogen fixation, where proton reduction often competes.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray, cyclic voltammogram and characterizations of compounds.

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Author Contributions

YK and PSB conceptualized the study, KH, YK, PSB designed experiments and KH, YK performed experiments. All the authors contributed to data analysis and manuscript preparation.

Notes

Authors declare no competing financial interest.

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