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Chemoselective (Hetero)Arene Electroreduction Enabled by Rapid Alternating Polarity

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Abstract

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 solves these issues, proceeding in a protic solvent, and can be easily scaled up without any metal additives or stringently anhydrous conditions.

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 judicially 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

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Supporting Information
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Experimental procedures, additional experimental data, NMR characterization data, X-ray and cyclic voltammogram. (PDF)

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CCDC 2122303 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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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 systems[6–8] 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 are suboptimal.[11,12] Recently the Koide group demonstrated that ammonia could be replaced by ethylenediamine (e.g., Benkesser modification[13–15]) 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. Regarding chemoselectivity, the procedure employing LiDBB is notable, since it is widely used for reduction of electron-deficient heteroarenes with good tolerance of esters.[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 (hetero)arene reduction. This operationally simple protocol proceeds at ambient temperature in protic solvent without the need of sacrificial anode or metal additives, and tolerates functional groups that are notoriously challenging to accommodate by conventional methods.

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 because Birch reduction of thiophenecarboxylic acid poses an issue of ring fragmentation.[18] The ester functionality could cause a chemoselectivity issue such as overreduction. 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 conditions[5] (entry 1) resulted in complete decomposition of the starting material. The most recent modification[16] (entry 2) showed attenuated reactivity, yet extensive decomposition was still observed. Although Donohoe's LiDBB method[20] (entry 3) afforded the product in 39% yield, the highly sensitive nature of DBB (necessitating stringent degassing) and its removal are problematic. Additionally, in this particular case the cost of DBB ($915/mol, TCI) surpasses the cost of the starting material itself ($571/mol, TCI). Regarding the electrochemical conditions, LER[10] (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). Sinusoidal waveform was found to be less effective than rAP (see Supporting Information (SI)).

Subsequent 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 to be critical to achieve good reactivity (Table 1, Panel B and C). In particular, the combination of RVC electrodes with tetraalkylammonium salts exhibited superior reactivity among various conditions screened. As demonstrated in our previous rAP study,[21] 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[22] gave a similar product distribution to constant current rAP. Since a slight warming of the reaction was noted (from 23 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. 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 constant current as well as constant potential experiments at −2.3 V (see SI for cyclic voltammogram of **3**) afforded a small amount of **4** in some cases, the yield and the extent of carbonyl reduction were by no means similar to the case of the rAP-based method. These results are supportive of the documented fundamental reactivity difference between rAP and DC in other studies.[23,24]

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 ($E_{\mathrm{red,arene}} > E_{\mathrm{red,FG}}$). 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-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 to be challenging under conventional Birch reduction conditions as a mixture of products was obtained even if the two arenes are most electronically differentiated (Table 2A, chemical Birch for obtaining **18**). Nonconjugated 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 $E_{\mathrm{red,arene}}$ is close to $E_{\mathrm{red,FG}}$, 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, a collection of readily available heteroarenes **36–38** were enlisted for accessing partially desaturated heterocycles (Table 2B). Subsequent alkylation could also be a useful derivatization as exemplified in **42** (Table 2C). Throughout **39–42**, previous syntheses necessitate 4–6 steps involving denovo ring construction;[19,25–27] this method subverts conventional multistep 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. Although detailed mechanistic study is beyond the scope of this communication, several pieces of empirical evidence are presented in Figure 2 that help to rationalize the differences in bulk reactivity.[28] For instance, the reduction potential of **43** (<–3 V)[29] resides far outside the solvent electrochemical window (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, together with the observation of active gas evolution from the cathode. This gas evolution was also noted at the working electrode after measuring the 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).[30] 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. The extent of proton reduction could also be reflected to the basicity of the reaction medium; transesterification product **46** was observed under DC conditions, whereas no such product was observed under rAP conditions when the reduction of **1** was interrupted. Consistent with these findings are literature reports of CO_2 or CO reduction using pulsed potential instead of DC that produces less H_2.[31–36] Collectively, these experiments support the mechanism summarized in Figure 2C. During the cathodic phase, (hetero)arene reduction is taking place through direct SET, leading to the same regioselectivity outcome as conventional Birch reduction. Chemoselectivity follows the reduction potential of the (hetero)arene and those of existing functionalities. Proton reduction, a pathway that normally competes to diminish reactivity toward arene reduction, is largely suppressed by applying 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 an α-ethoxy derivative. Analogous species **47** was detected in GC analysis of crude reaction mixture when heavier Et_2S was used instead of DMS. A small amount of solvent oxidation may also take place during the anodic phase.

The suppression of proton reduction may enable new types of chemoselective (hetero)arene reduction by running reactions deliberately *under acidic conditions* (Figure 2D), which is challenging under conventional DC electrolysis or Birch reduction. An interesting case was indeed found in the reduction of **48**. Standard rAP reduction furnished debrominated dihydropyrolidine **49** in 40% yield via dissociative electron transfer, a 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 usef ul 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** with incomplete conversion. Another dramatic benefit for suppressing proton reduction was found during scale-up efforts (Figure 2E). After introducing several modifications to be more process-friendly (see SI for reoptimization), 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.[37] 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 not only for chemoselective reductions of organic compounds in protic media but also for electrochemical CO_2 reduction as well as nitrogen fixation in which proton reduction often competes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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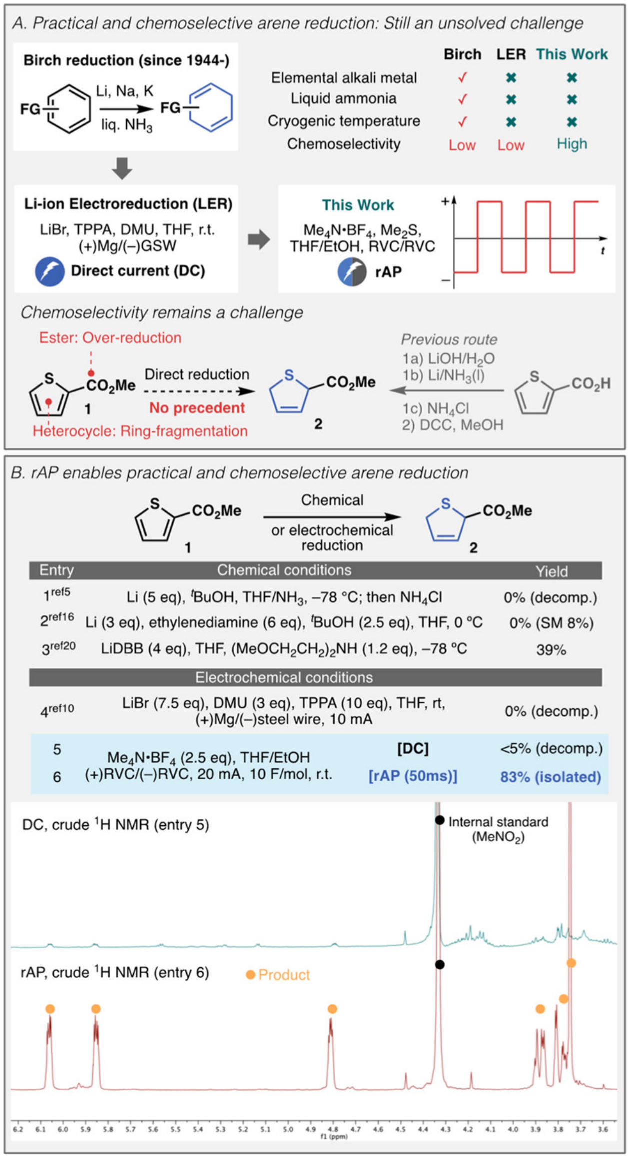


Entry	Chemical conditions		Yield
1[ref5]	Li (5 eq), ^{t}BuOH, THF/NH$_3$, –78 °C; then NH$_4$Cl		0% (decomp.)
2[ref16]	Li (3 eq), ethylenediamine (6 eq), ^{t}BuOH (2.5 eq), THF, 0 °C		0% (SM 8%)
3[ref20]	LiDBB (4 eq), THF, (MeOCH$_2$CH$_2$)$_2$NH (1.2 eq), –78 °C		39%
	Electrochemical conditions		
4[ref10]	LiBr (7.5 eq), DMU (3 eq), TPPA (10 eq), THF, rt, (+)Mg/(–)steel wire, 10 mA		0% (decomp.)
5	Me$_4$N•BF$_4$ (2.5 eq), THF/EtOH (+)RVC/(–)RVC, 20 mA, 10 F/mol, r.t.	[DC]	<5% (decomp.)
6		[rAP (50ms)]	83% (isolated)

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 neccesitating special additives, whereas DC electrolysis under the identical conditions resulted in decomposition (*Y*-axis of the crude NMRs was adjusted to the same scaling).

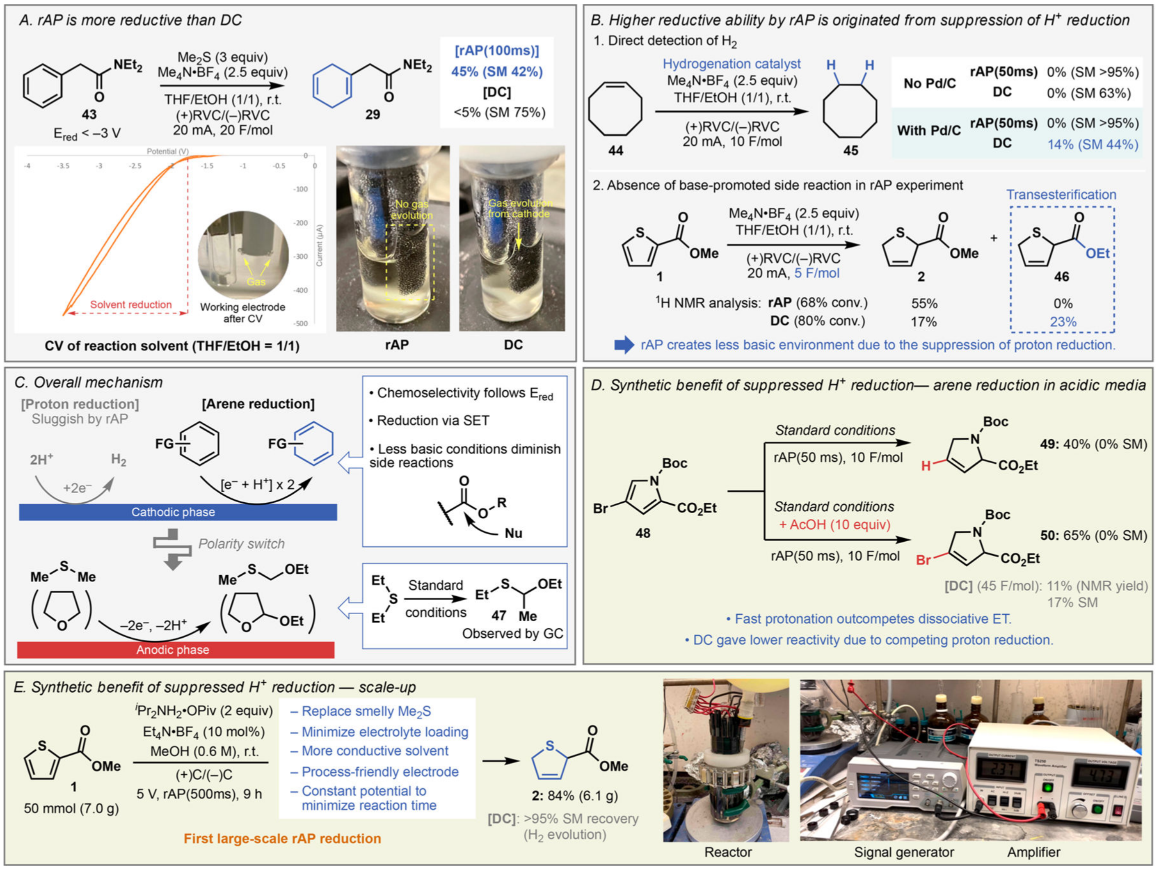
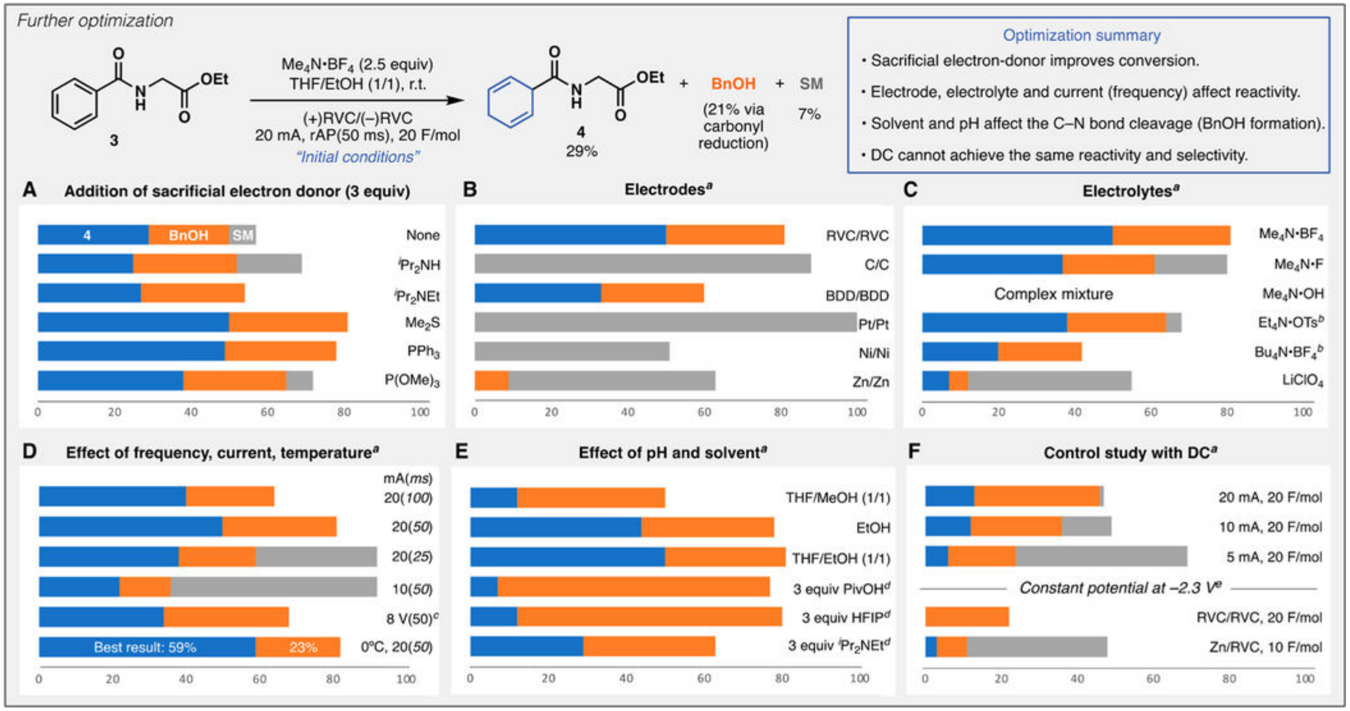


Figure 2.

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 H_2 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 H_2 evolution.

Table 1.

Optimization Study

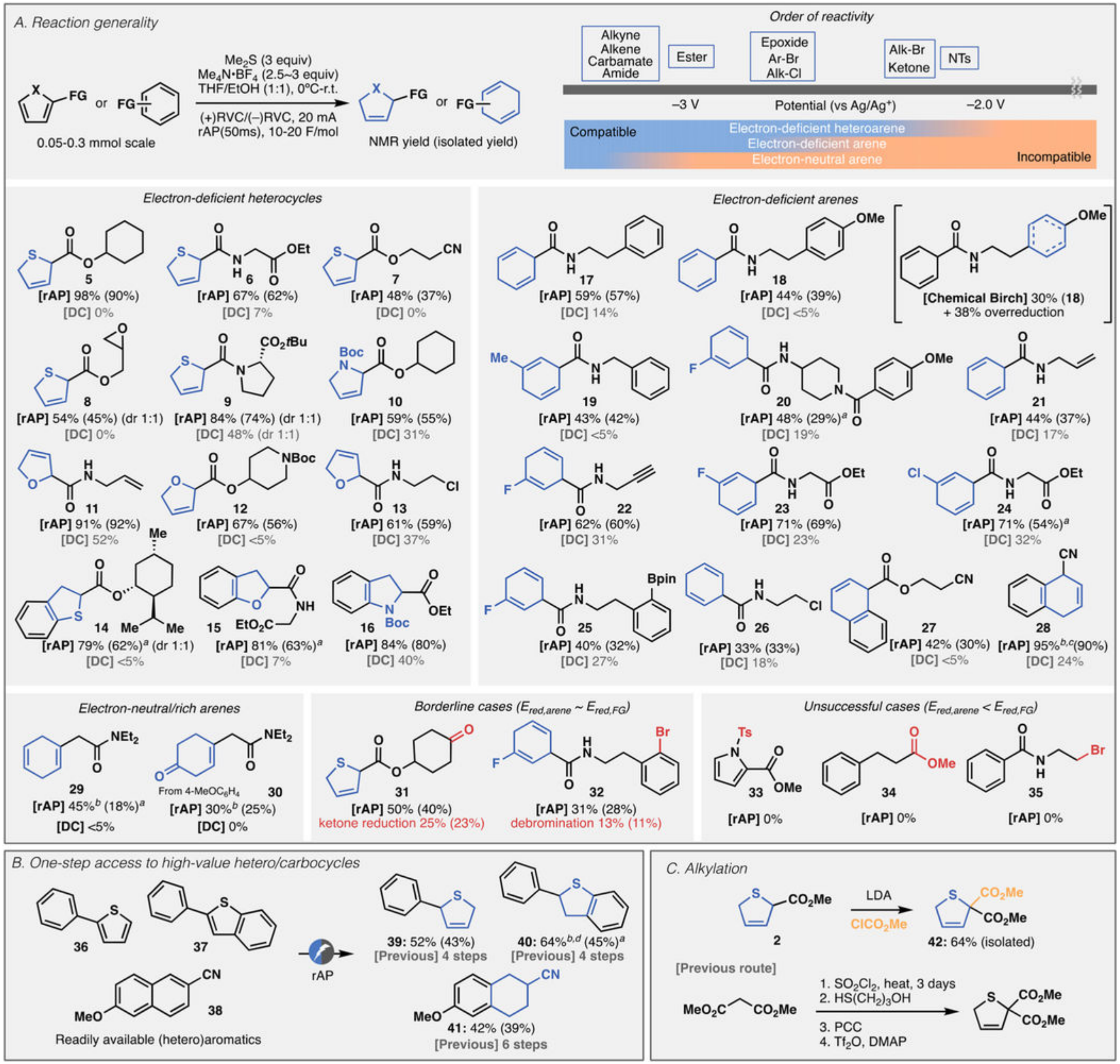


- Sacrificial electron-donor improves conversion.
- Electrode, electrolyte and current (frequency) affect reactivity.
- Solvent and pH affect the C–N bond cleavage (BnOH formation).
- DC cannot achieve the same reactivity and selectivity.

All the reactions were performed on 0.1 mmol scale under the initial conditions with a deviation indicated. Product distribution was analyzed by ^{1}H NMR. [a]Reactions were performed with 3 equiv of Me$_2$S. [b]1 equiv of electrolyte was used. [c]5 equiv of Me$_4$N·BF$_4$ was used. [d]Indicated additive was added to THF/EtOH (1/1). [e]Bu$_4$N·BF$_4$ (0.2 M) was used as an electrolyte.

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



[a] Large drop of isolated yield was due to purification loss. [b] 100 ms pulse was used instead of 50 ms. [c] The reaction was performed in MeOH with PivOH as an additive. [d] Amount of Me_2S was 10 equiv.