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Tunable System for Electrochemical Reduction of Ketones and Phthalimides

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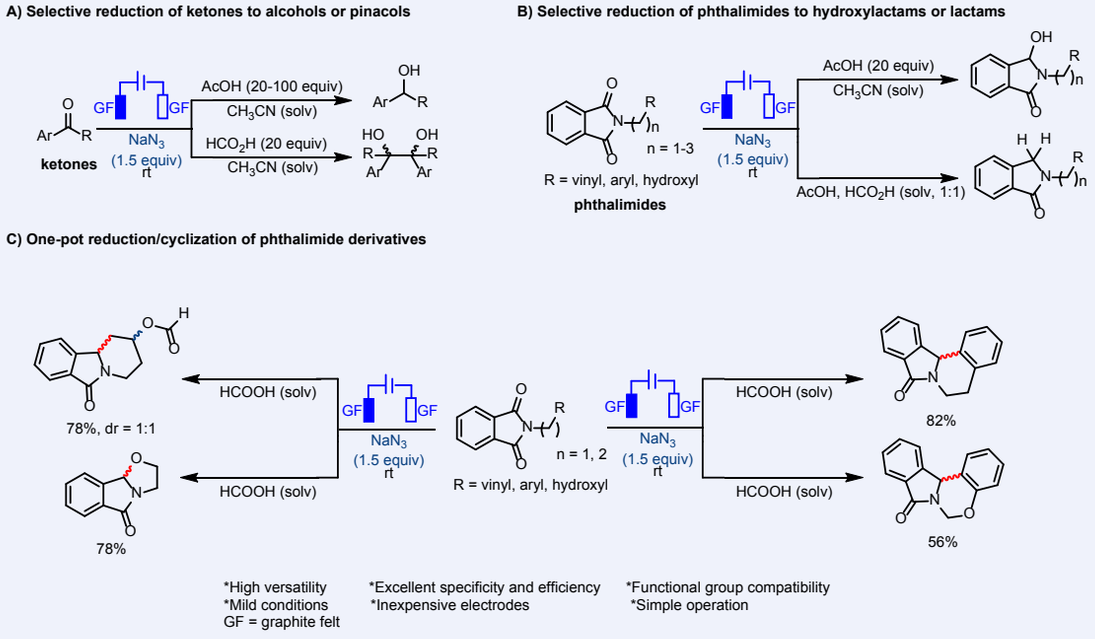
Keywords

Electrochemistry | Reduction | Ketones | Phthalimides | Indolizidine

Main observation and conclusion

Herein we report an efficient, tunable system for electrochemical reduction of ketones and phthalimides at room temperature without the need for stoichiometric external reductants. By utilizing NaN_3 as the electrolyte and graphite felt as both the cathode and the anode, we were able to selectively reduce the carbonyl groups of the substrates to alcohols, pinacols, or methylene groups by judiciously choosing the solvent and an acidic additive. The reaction conditions were compatible with a diverse array of functional groups, and phthalimides could undergo one-pot reductive cyclization to afford products with indolizidine scaffolds. Mechanistic studies showed that the reactions involved electron, proton, and hydrogen atom transfers. Importantly, an N_3·/HN_3 cycle operated as a hydrogen atom shuttle, which was critical for reduction of the carbonyl groups to methylene groups.

Comprehensive Graphic Content



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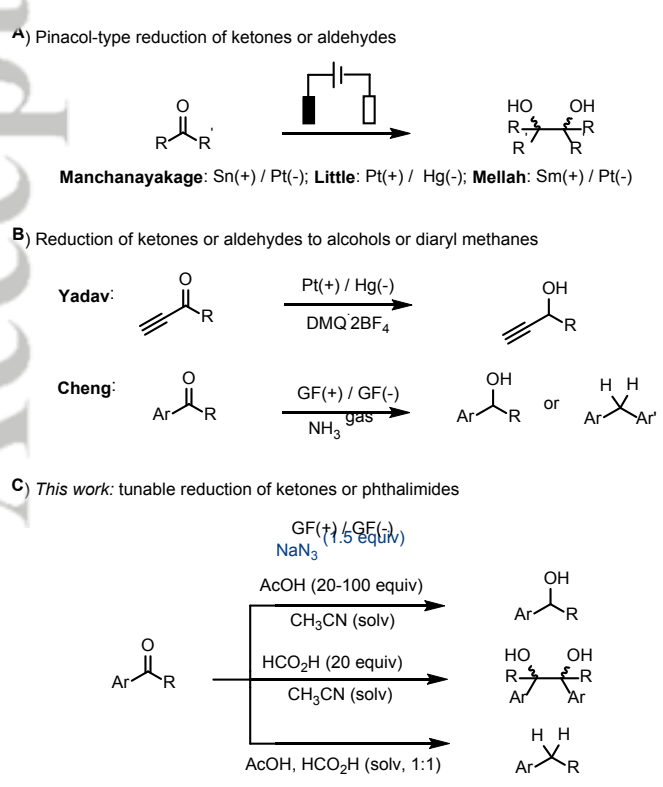
Background and Originality Content

The reduction of carbonyl groups is undoubtedly one of the most central organic transformations, and alcohols, pinacols, and alkanes generated by these reactions are essential building blocks for the synthesis of drugs and other biologically active molecules.[1] Carbonyl groups are generally reduced with hydrogen gas, metal hydrides, or other strongly reducing reactive metals.[2, 3] Despite the benefits of these well-established methods, some of them require stoichiometric flammable reagents, special equipment, or complicated work-up procedures, features that limit their substrate scope and their utility for large-scale applications.[1–4] Therefore, new methods that are versatile and environmentally and user friendly are in demand.

Recently, electrochemical methods have emerged as an attractive option for organic synthesis because they are operationally safe, do not require stoichiometric external reductants or oxidants, and are highly atom economical.[5, 6] Direct reduction of carbonyl compounds via electrolysis in the absence of stoichiometric reductants has been reported,[7–9] however, most of transformations in these reports involve metal electrodes, which usually serve as sacrificial anodes (Scheme 1A). In 2019, Cheng and co-workers developed a method for electrochemical hydrogenation of ketones to afford alcohols or diaryl methanes by using reductive gas ammonia as the hydrogen source with graphite felt electrodes; the anodic reaction involves oxidation of an amide anion (Scheme 1B).[10] Herein we present our investigation of electrochemical reduction of carbonyl compounds with graphite felt electrodes and NaN_3 as an electrolyte. We discovered that carbonyl reduction, in a certain degree, could be chemoselectively controlled to generate alcohols, pinacols, or methylene groups by adjustment of the solvent and acidic additives without any reductive gases such as ammonia and hydrogen (Scheme 1C).

Scheme 1 Electrochemical reduction of carbonyl compounds.



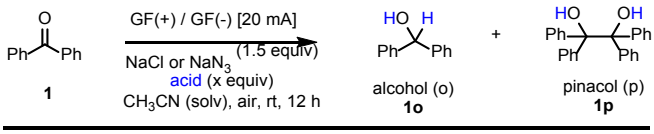
*DMQ·$2BF_4$ = dimethylquininium tetrafluoroborate; GF= graphite felt.

Results and Discussion

Results

We began our studies with diphenyl methanone (**1**) as a model substrate with graphite felt as electrodes in an undivided cell (Table 1). For our initial attempts, we tested the inexpensive and readily available electrolyte NaCl, which functioned both to conduct electric current and to finish the anodic oxidation; in addition, we used acetic acid (AcOH) to increase the reactivity of the carbonyl group. Preliminary results indicated that constant-current electrolysis (20 mA) of **1** for 12 h with 1.5 equiv. of NaCl and 20 equiv. of AcOH in CH_3CN and H_2O gave a 53% yield of alcohol **1o**, along with a small amount of pinacol **1p** (entry 1). Encouraged by this result, we set about to optimize the reaction conditions. First, screening of different sodium salt electrolytes revealed that NaN_3 had better solubility than other sodium salts and gave the highest yield of **1o**.[11] Next, we investigated the influence of protic acids on the reaction outcome. Interestingly, increasing the amount of AcOH increased both the overall yield and the **1o**/**1p** ratio (entries 2–6); specifically, the use of 100 equiv. of AcOH resulted in a 70% isolated yield of **1o** (78% by NMR spectroscopy) (entry 6). Other carboxylic acids were much less effective (entries 7 and 8), and mineral acids provided low yields of both reduction products (entry 9).

Table 1 Optimization of conditions for reduction of ketone **1**.



Entry	Electrolyte / Acid (equiv.)	Yield of **1o** (%)[a]	Yield of **1p** (%)[a]
1[b]	NaCl / AcOH (20)	53	13
2	NaN_3 / AcOH (20)	56	12
3	NaN_3 / AcOH (40)	57	12
4	NaN_3 / AcOH (60)	64	10
5	NaN_3 / AcOH (80)	69	10
6	NaN_3 / AcOH (100)	78 (70[c])	<10
7	NaN_3 / *t*-$BuCO_2H$ (20)	23	6
8	NaN_3 / *i*-$PrCO_2H$ (20)	26	15
9[d]	NaN_3 / aq. H_2SO_4 or HCl (20)	<10	<10
10	NaN_3 / HCO_2H (20)	<10	93 (86[b])
11	NaN_3, no acid	<10	<10
12	AcOH (100), no NaN_3	no electric current	
13	NaN_3 / AcOH (100), GF(+) / GF(−) were replaced with Pt(+) / Pt(−)	28	<10

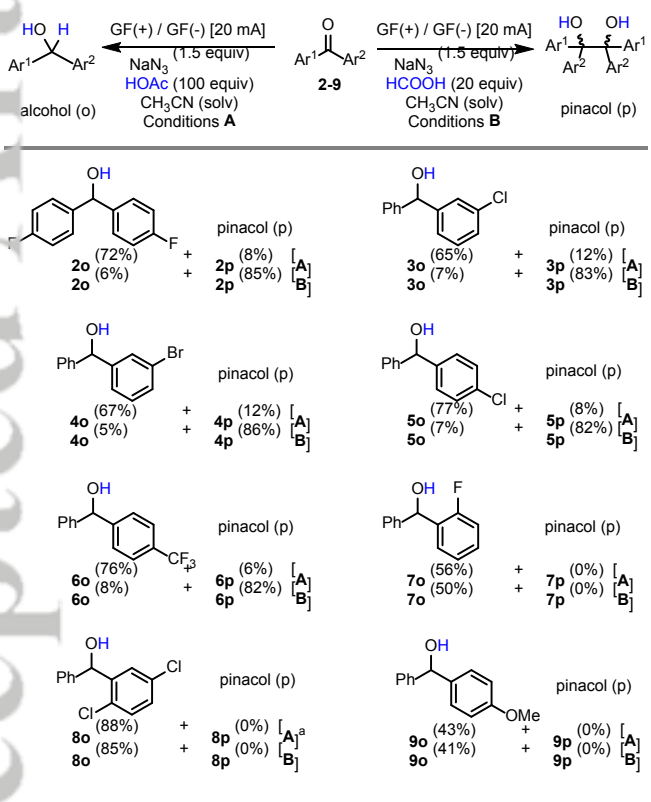
[a] Reactions were carried out on a 0.5 mmol scale at room temperature (25 °C), and yields were determined from the ^1H NMR spectra of the reaction mixtures. GF = graphite felt. [b] 0.5 mL H_2O was added to dissolve NaCl. [c] Isolated yield. [d] The concentration of H_2SO_4 is 18.4 mol/L and the concentration of HCl is 12 mol/L.

This latter result may be attributable to the evolution of hydrogen, which is kinetically favored under strongly acidic conditions. Unexpectedly, when 20 equiv. of formic acid (HCO_2H) was used, the

product selectivity was reversed; that is, the pinacol product was favored over the alcohol (entry 10). A series of control experiments proved that both the acidic additive and NaN_3 were necessary (entries 11 and 12). Platinum electrodes were evaluated and found to give a low yield of the desired alcohol (entry 13).

Substrate Scope.

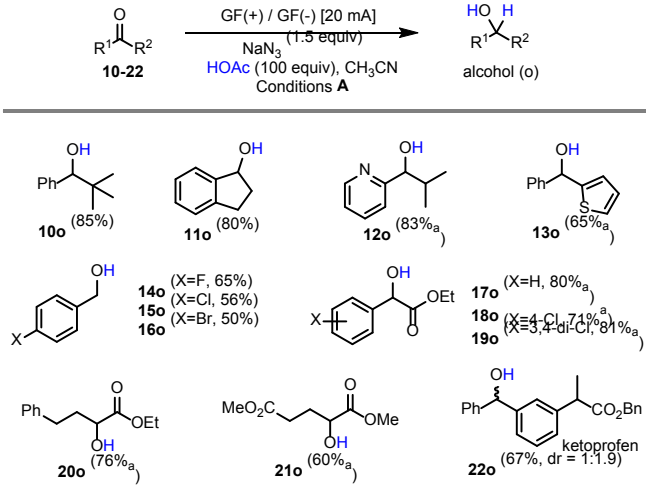
Selective reduction of diaryl ketones to alcohols or pinacols. We explored the scope of the reaction by testing some diaryl ketones under conditions A (for alcohols) or B (for pinacols) (Figure 1). In general, *para*- and *meta*-substituted diaryl ketones (**2–6**) could be selectively reduced to alcohols or pinacols in high yields under the corresponding reaction conditions. However, coupling of ketyl radicals derived from *ortho*-substituted diaryl ketones was hindered by the steric bulk of the substituents, and thus only direct reduction products (alcohols) were obtained (**7o** and **8o**). A reaction of (4-methoxyphenyl)(phenyl)methanone gave only alcohol **9o** in moderate yield, an outcome that may be attributable to oxidation of the methoxyphenyl group.



Reactions were conducted on a 0.5 mmol scale at room temperature under air. [a] 20 equiv. of AcOH was used.

Figure 1. Reduction of diaryl ketones to alcohols or pinacols.

Selective reduction of other carbonyl compounds to alcohols. Additionally, various aryl alkyl ketones (**10** and **11**), heteroaryl aryl ketones (**12** and **13**), aryl aldehydes (**14–16**), and α-ketoesters (**17–21**) were smoothly reduced to the corresponding alcohols under conditions A (Figure 2). Pyridine and thiophene rings, a benzyl group, halogen atoms, and esters were tolerated. Moreover, we were delighted to find that benzyl-protected ketoprofen (**22**) could also be reduced efficiently to the corresponding alcohol (**22o**). Interestingly, even when NaN_3 was replaced with NaCl in these reactions, the alcohol products were obtained in similar yields.

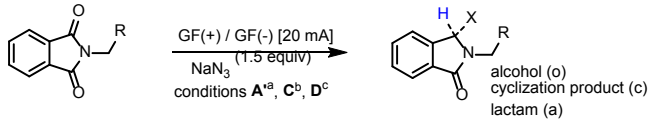


Reactions were conducted on a 0.5 mmol scale at room temperature under air. [a] 20 equiv. of AcOH was used.

Figure 2. Selective reduction of other carbonyl compounds to alcohols.

Selective reduction of phthalimides. Phthalimides with a variety of functional groups also efficiently underwent selective reduction under conditions A' to afford hydroxylactams **23o**, **24o**, **27o**, and **28o**. These results prompted us to evaluate the possibility of C–C bond formation via an acyl-iminium ion (Figure 3). We discovered that by changing the reaction medium from CH_3CN/AcOH to HCO_2H, we could obtain various pharmaceutically important indolizidine scaffolds by means of a one-pot reduction/cyclization of phthalimide derivatives with a tethered nucleophile (vinyl, aryl, or hydroxyl) (**23c–26c**)[12, 13].

Moreover, we were pleased to find that when 1:1 (v/v) HCO_2H/AcOH was used as solvent, reactions of imides gave lactams[12]. Specifically, electrochemical reactions of various imides with 1.5 equiv. of NaN_3 gave the corresponding lactams (**23a**, **24a**, **27a**, and **28a**) in moderate to good yields (Figure 3). The phthalimide tether profoundly influenced the yield, with longer tethers favoring the lactam products (compare the yields of **27a** and **28a**).

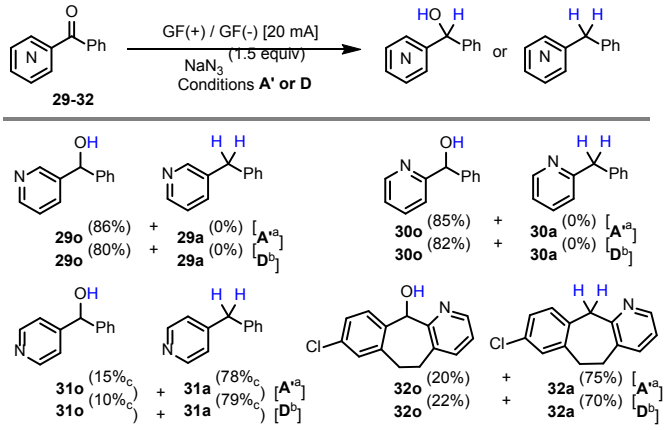


substrate	Conditions **A'**[a] HOAc (20 equiv) CH_3CN (solv)	Conditions **C**[b] HCO_2H (solv)	Conditions **D**[c] HCO_2H/HOAc (solv, 1:1)
PhthN (**23**)	**23o** (87%)	**23c** (78%, dr = 1:1)	**23a** (70%) & [**23o** (17%)]
Ph, PhthN (**24**)	**24o** (85%)	**24c** (82%)	**24a** (50%) & [**24o** (30%)]
Ph, O, PhthN (**25**)		**25c** (56%)	
HO, PhthN (**26**)		**26c** (78%)	
Ph, PhthN (**27**)	**27o** (85%)		**27a** (73%) & [**27o** (15%)]
Ph, PhthN (**28**)	**28o** (80%)		**28a** (30%) & [**28o** (60%)]

0.5 mmol of substrate. [a] Conditions A': 20 equiv. of AcOH, CH_3CN (4.5 mL). [b] Conditions C: HCO_2H (5.0 mL). [c] Conditions D: HCO_2H (4.0 mL), AcOH (4.0 mL).

Figure 3. Selective reduction of phthalimides.

Reduction of pyridyl aryl ketones. Interestingly, in reactions of phenyl pyridinyl ketones (Figure 4), the location of the nitrogen atom played a substantial role in the outcome of the reduction. Under conditions A' and D, phenyl(pyridin-4-yl)methanone mainly gave the corresponding diaryl methanes, whereas phenyl(pyridin-2-yl)methanone and phenyl(pyridin-3-yl)methanone gave the corresponding alcohols; these results indicate that product selectivity was controlled by the substrate itself rather than by the reaction conditions. Finally, we found that the reduction of phenyl(pyridin-2-yl)methanone to alcohol could easily be carried out on a gram scale.[11]



0.5 mmol of substrate, 1.5 equiv. [a] Reaction conditions A': 20 equiv. of AcOH, CH_3CN (4.5 mL). [b] Reaction conditions D: HCO_2H (4.0 mL), AcOH (4.0 mL). [c] Crude ^{1}H-NMR yield.

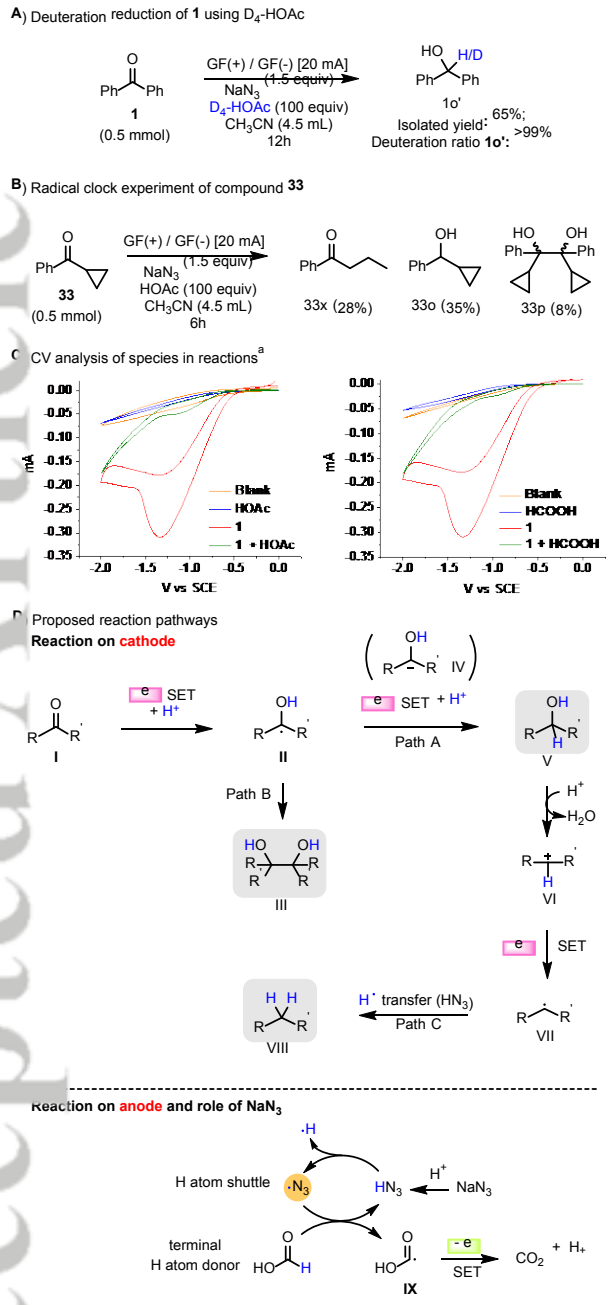
Figure 4. Reduction of pyridyl aryl ketones.

Mechanistic Studies.

To determine the mechanism of these reduction reactions, we carried out a series of control experiments (Scheme 2). First, when reduction of diphenyl ketone **1** was conducted with deuterated acetic acid (D_4-HOAc), alcohol **1o'** (99% deuterium incorporation) was isolated in 65% yield (Scheme 2A),[14] indicating that AcOH was the hydrogen source. Moreover, reaction of radical clock substrate **33** gave ring-opening product **33x** in 28% isolated yield, suggesting that a benzyl radical was involved in the reaction (Scheme 2B). In addition, cathodic cyclic voltammetry analysis of a mixture of **1** and AcOH or HCO_2H revealed that the absolute value of the reduction potential of the diphenyl ketone was lower under weakly acidic conditions than in CH_3CN alone; the reduction peak of **1** was observed at −1.3 V in CH_3CN (*vs* SCE [saturated calomel electrode]), whereas the reduction peak in CH_3CN/AcOH was at −1.1 V and that in CH_3CN/HCO_2H) was at −1.0 V (Scheme 2C).[14]

On the basis of the results of our mechanistic studies, we propose the mechanism outlined in Scheme 2D. First, the carbonyl group is protonated and then reduced by a single electron at the cathode to generate radical **II**. This species can either be further reduced to alcohol **V** (path A) or undergo radical dimerization to furnish pinacol product **III** (path B). In the presence of AcOH, the reduction of **II** occurs via either a proton/electron transfer sequence or by transfer of a hydrogen atom from HN_3 generated *in situ*.[15] Our initial screening of sodium salt electrolytes demonstrated that NaN_3 can be replaced with NaCl for the reduction of ketones to alcohols, indicating radical **II** is more likely to undergo proton/electron transfer to give alcohol **V** rather than hydrogen transfer with HN_3. When HCO_2H is present in the medium, it may serve as the more reactive reductant, preventing further reduction of **II**, thus resulting in the formation of dimerization products. For reduction to methylene compounds, we envisaged that at high proton concentrations, carbocation **VI** is generated by protonation and subsequent dehydration. Carbocation **VI** can be reduced by an electron from the cathode to produce radical **VII**, which may undergo a hydrogen atom transfer reaction with HN_3 to generate **VIII** and N_3·. N_3· Subsequent hydrogen abstraction from HCO_2H provides radical **IX**, which undergoes anodic oxidation to give CO_2 and a proton.[16] With HN_3 as a hydrogen atom donor and N_3· as a hydrogen atom abstractor, the N_3·/HN_3 cycle operates as a hydrogen atom shuttle,[15] while HCO_2H serves as the terminal oxidant. In this process, NaN_3 is a necessary reagent.

Scheme 2. Mechanistic studies.



[a] In the cyclic voltammetry experiment, the concentrations of **1** and the acid (AcOH or HCO_2H) were 0.02 M. SCE = saturated calomel electrode.

Conclusions

In summary, we have developed a system for electrochemical reduction of carbonyl compounds without the need for a catalyst or a stoichiometric external reductant. By using NaN_3 as an electrolyte and graphite felt as both the cathode and the anode, we successfully reduced various carbonyl compounds to the corresponding alcohols, pinacols, or methylene compounds by judiciously choosing the solvent and acidic additive. These reactions were efficient, chemoselective, and compatible with various functional groups. Moreover, one-pot reductive cyclization of phthalimide substrates provided a valuable tool for direct construction of indolizidine scaffolds, which are found in natural products and drug molecules. Further mechanism studies of this chemistry and exploration of its applications for pharmaceutical synthesis are ongoing in our laboratories.

Experimental

The flask was equipped with two rubber plugs, graphite felt (2 cm×1 cm×0.5 cm) as anode and cathode. Two electrodes were separated with a Teflon film. The graphite felt anode and cathode attached to a platinum wire. A Teflon wire tied around two electrodes. Substrate (0.5 mmol, 1.0 equiv) and acid (AcOH or HCOOH) (10.0 mmol, 20.0 equiv) were first dispersed CH_3CN (4.5 mL) stirred for 5 min at room temperature. NaN_3 (49.0 mg, 0.75 mmol, 1.5 equiv) was then added. The reaction mixture was stirred and electrolyzed with a constant current of 20 mA at room temperature (25 °C). After the reaction completed as monitored with TLC, the solvents were removed *in vacuo* and the residue was purified by silica gel flash chromatography to give the desired products.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

Acknowledgement

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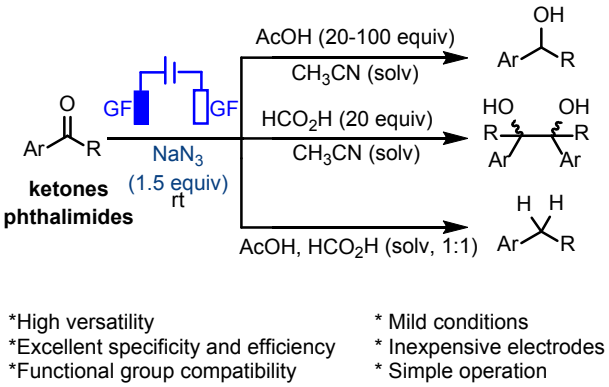

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