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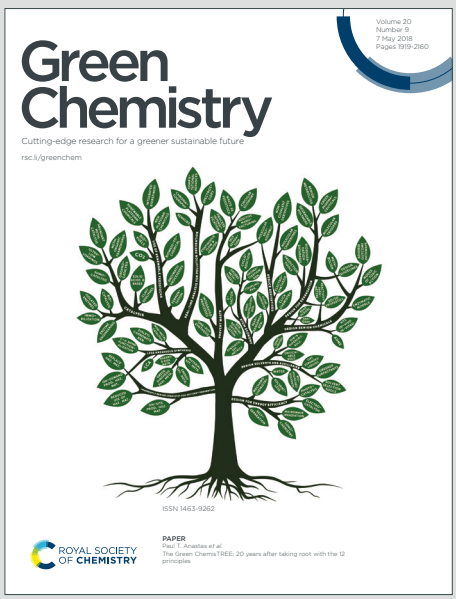

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Green Chemistry

ARTICLE

Electroactivated Alkylation of Amines with Alcohols via Both Direct and Indirect Borrowing Hydrogen Mechanisms

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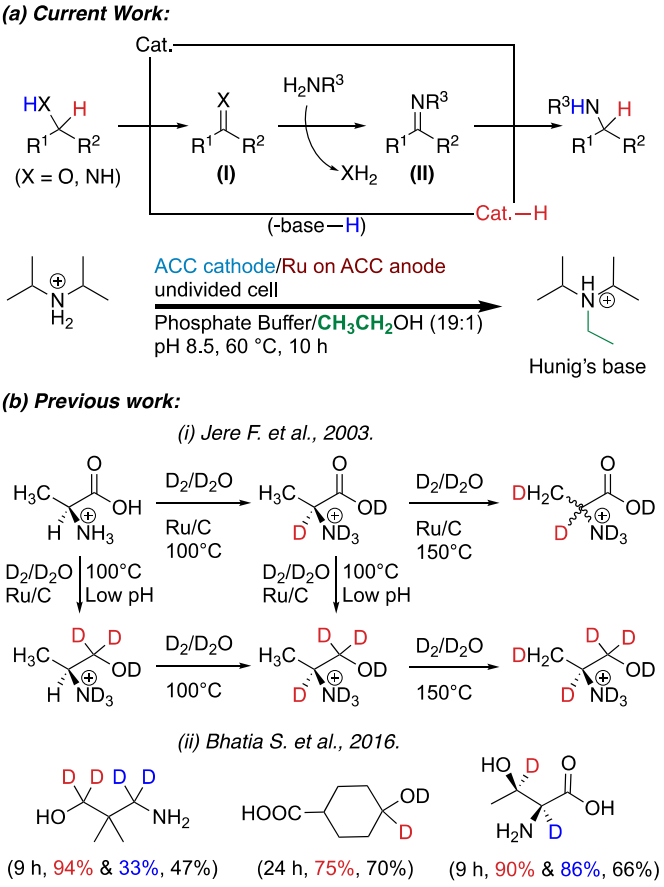
Benjamin Appiagyei, Souful Bhatia, Gabriela L. Keeney, Troy Dolmetsch, and James E. Jackson*

A green, efficient *N*-alkylation of amines with simple alcohols has been achieved in aqueous solution via an electrochemical version of the so-called "borrowing hydrogen methodology". Catalyzed by Ru on activated carbon cloth (Ru/ACC), the reaction works well with methanol, and with primary and secondary alcohols. Alkylation can be accomplished by either of two different electrocatalytic processes: (1) In an undivided cell, alcohol (present in excess) is oxidized at the Ru/ACC anode; the aldehyde or ketone product condenses with the amine; and the resulting imine is reduced at an ACC cathode, combining with protons released by the oxidation. This process consumes stoichiometric quantities of current. (2) In a membrane-divided cell, the current-activated Ru/ACC *cathode* effects direct C-H activation of the alcohol; the resulting carbonyl species, either free or still surface-adsorbed, condenses with amine to form imine and is reduced as in (1). These alcohol activation processes can alkylate primary and secondary aliphatic amines, as well as ammonia itself at 25-70 ℃ and ambient pressure.

Introduction

Amines play essential roles in industry, medicine, and the life sciences;[1–3] they are the building blocks of proteins, while various cofactors, vitamins, neurotransmitters, and alkaloids, not to mention the nucleic acids, bear alkylated amino moieties. Amines are classically synthesized via amide or nitrile reduction, by S_N2 alkylation with alkyl halides or their analogues, or via reductive alkylation with carbonyl species.[4–7] However, these methods may suffer from various disadvantages: (a) reducing agents such as $LiAlH_4$ and alkylating agents such as alkyl halides typically generate by-product salts, raising material and disposal costs; and (b) strong alkylating agents often over-alkylate to form quaternary ammonium ions. We describe here two modes of heterogeneous electrocatalytic amine alkylation with low cost, readily available alcohols: direct and indirect "borrowing hydrogen" paths. In this reaction (Scheme 1a), an alcohol undergoes temporary hydrogen removal to give an aldehyde or ketone (I). Condensation with an amine forms an imine (II) or iminium intermediate which is then reduced to the alkylated amine product, replacing the hydrogen "borrowed" in the alcohol oxidation. This path avoids the low electrophilicity of alcohols and the poor atom economy of classical alcohol activation methods, with their stoichiometric waste streams. For instance, Hünig's base (diisopropylethylamine) is made by reacting diisopropylamine with diethyl sulfate, a toxic, alcohol-derived alkylating agent.[8] The atom economy of the reaction is low (50%) due to the bulky ethylsulfate byproduct. Our net use of aqueous alcohol as alkylating agent forms water as the only by-product, making this process "green" and atom efficient.



Dept of Chemistry, Michigan State University, East Lansing, MI 48824, USA.
E-mail: jackson@chemistry.msu.edu
†Electronic Supplementary Information (ESI) available: SEM of electrodes, and structural and stereochemical product analyses. See DOI: 10.1039/x0xx00000x

Scheme 1. a) Mechanistic pathway of hydrogen auto-transfer ("borrowing hydrogen") process with amines and alcohols. b) (i) Stereoretentive C–H bond activation in the aqueous phase catalytic hydrogenation of amino acids to amino alcohols (ii) Stereoretentive H/D exchange at *sp*^{3} sites bearing alcohols and amines.

In previous work, we discovered stereoretentive H/D exchange via chemical (2003)[9] and electrochemical (2016)[10] heterogeneous ruthenium activation at sp^3 C-H sites bearing amine or alcohol moieties. There we envisaged oxidative insertion of Ru at the sp^3 C-H geminal to the alcohol -OH, to form a surface-bound sp^2 intermediate which is then back reduced by surface-bound deuterium formed from D_2O (Scheme 1b). Building on these findings, in this manuscript, we exploit the electrophilicity of the sp^2 carbon intermediate to *N*-alkylate amines.

Ammonia alkylation by alcohols is thermodynamically favored, largely due to the exothermicity of water loss. Scheme 2 shows the uniformly favorable energetics for stepwise conversion of ammonia and ethanol to triethylamine and water.

								Energy Changes Gas Phase[a] and (aqueous phase)[b] (kcal/mol)
	NH_3	+	EtOH	⟶	$EtNH_2$	+	H_2O	
ΔH_f	-11.0		-55.9		-13.8		-57.6	-4.5
$+\Delta G_{hyd}$	(-15.3)		(-60.9)		(-18.3)		(-63.9)	(-6.0)
	$EtNH_2$	+	EtOH	⟶	Et_2NH	+	H_2O	
ΔH_f	-13.8		-55.9		-23.9		-57.6	-11.8
$+\Delta G_{hyd}$	(-18.3)		(-60.9)		(-28.0)		(-63.9)	(-12.7)
	Et_2NH	+	EtOH	⟶	Et_3N	+	H_2O	
ΔH_f	-23.9		-55.9		-34.2		-57.6	-12.0
$+\Delta G_{hyd}$	(-28.0)		(-60.9)		(-37.4)		(-63.9)	(-12.4)

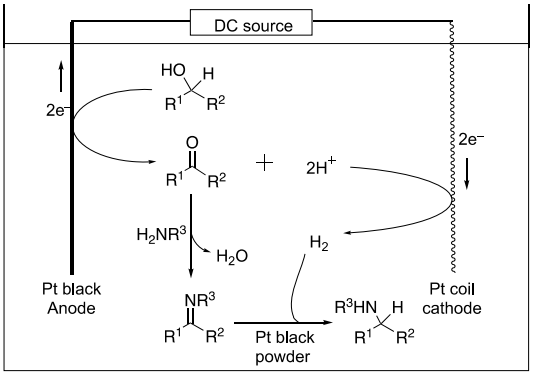
Scheme 2. Energy changes for stepwise ammonia ethylation to form triethylamine. [a]Data from NIST Webbook[11]; [b]Aqueous phase energies = $\Delta H_f + \Delta G_{hyd}$.[12]

N-alkylation of amines with alcohols was first reported by J.U. Nef in 1901. Achieved simply with sodium ethoxide at high temperature, this work showed that a transition metal catalyst was not necessary.[13] Homogenous catalysis of such processes was first reported in 1981 by Grigg *et al*.[14] who used rhodium, ruthenium and iridium catalysts to achieve selective mono *N*-alkylation of pyrrolidine with primary and secondary alcohols, and formed heterocyclic rings via inter- and intramolecular *N*-alkylations. In similar work, Watanabe *et al*. used the ruthenium complexes $[RuCl_2(PPh_3)_3]$ at 150-200 °C to N-alkylate aminopyridines with primary alcohols.[15] In 2009, William *et al*. alkylated various amines regioselectively with 1° and 2° alcohols using $[Ru(p\text{-cymene})Cl_2]_2$ and the bidentate phosphines dppf or DPEphos. In refluxing toluene for 24 h, this approach converted primary to secondary and secondary to tertiary amines. It was then used to synthesize Piribedil and Tripelennamine, anti-Parkinsonism and antihistamine drugs.[16] The team's 2011 microwave-promoted solvent-free update achieved similar *N*-alkylations of 1° and 2° amines with 1° and 2° alcohols.[17] In 2016, Takacs *et al.* demonstrated regioselective mono and sequential amination of diols with several ruthenium (II) complexes via a bifunctional borrowing hydrogen mechanism.[18]

Direct synthesis of alkyl amines from ammonia and alcohols is also a growing field. The water-soluble $[Cp^*Ir(NH_3)_3][I_2]_2$ catalyst of Yamaguchi *et al*. enabled reaction of 1° and 2° alcohols such as *n*-hexanol and cyclohexanol in aqueous ammonia to yield trihexylamine (96%) and dicyclohexylamine (84%) respectively. The size of the alcohol controlled the selectivity of the reaction to the 2° or the 3° amines.[19] Deutsch *et al*. also reported a new homogeneous catalyst, $[Ru(CO)ClH(PPh_3)_3]$, which enables mono-alkylation of NH_3 with secondary alcohols in toluene.[20] Overall, Ruthenium- and Iridium-based homogeneous catalysts appear most effective in *N*-alkylation of amines with alcohols.

Heterogenous catalysis for alcohol amination has been known since 1924, when Brown and Reid demonstrated the use of silica gel as an effective catalyst for *N*-alkylation of aniline with methyl, ethyl, *n*-propyl and *n*-butyl alcohols over a temperature range of 300-500 °C.[21] In recent studies Shi and Deng have used an iron oxide immobilized palladium catalyst under base and solvent free conditions to achieve *N*-alkylation of aniline with several primary alcohols to ca. 99% yield.[22] Also, Jaenicke *et al*. found Ag/Al_2O_3 promoted with Cs_2CO_3 or K_3PO_4 to be active and selective catalysts for *N*-alkylation or acylation of amines with several primary alcohols at 120 °C in xylene.[23] Thus, with secondary amines, piperidine and pyrrolidine, the hemiaminal intermediate underwent dehydrogenation as well as dehydration/rehydrogenation to give amides and amines, respectively. Mizuno *et al*. have developed heterogeneous Ru[24] and Cu[25] catalysts for polyalkylation of aqueous ammonia (or urea) by alcohols to form secondary and tertiary amines. The same group have also used ruthenium hydroxide to heterogeneously catalyze *N*-alkylation of various aromatic and heteroaromatic amines, forming secondary amines in moderate to excellent yields without need for co-catalysts or promoters.[26] Both homogeneous and heterogeneous catalysis of hydrogen autotransfer processes have recently been extensively reviewed.[27–30]

Most directly relevant to the work herein, electrocatalytic *N*-alkylation of amines with alcohols was reported by Kagiya in 1986.[31] Using Pt as electrodes and lithium nitrate as electrolyte with Pt black powder stirring in neat alcohol, aromatic amines and aniline were alkylated with methanol and ethanol with 65% current efficiency at ambient temperatures. Here, the platinum black was the key to the high current efficiency in reducing the Schiff base with the generated free hydrogen, which was soluble in the alcohol electrolyte. (Scheme 3).



Scheme 3. Electrolytic *N*-alkylation of amines with alcohol by Kagiya *et al*.

Though the methods above did achieve alcohol amination with attractive yields, many used conditions of high temperature and pressure, organic (non-green) solvents, or costly homogeneous catalysts requiring later separation. Here, we describe two different mechanisms for net electrocatalytic alkylation of ammonia and other amines, in water at temperatures below the boiling point over an easily prepared and mechanically removable catalyst of ruthenium on activated carbon cloth.

Catalyst Preparation

An electrodeposited Ru/ACC catalyst was developed and optimized[32] based on the activated carbon cloth (Zorflex® ACC FM100) used in our earlier studies on electrocatalytic reduction by Li *et al.*[33] and H/D isotopic exchange by Bhatia *et al.*[10] The ACC (3 cm x 1.5 cm) was initially washed in de-ionized (DI) water and then allowed to dry in an oven overnight at 105 °C. It was then soaked in a solution of Ru $(NH_3)_6Cl_3$ (1.0089 g) dissolved in ammonium hydroxide (1.98 mL) and water (13.02 mL). The damp ACC was dried on the laboratory bench for 24 h, then under vacuum at room temperature. The Ru-impregnated ACC was then electrochemically reduced in an H-cell with 0.2 M HCl as electrolyte at a constant current of 150 mA for 30 mins (about 3 times the quantity of charge required). This catalyst showed similar reactivity to the H_2 reduced counterpart described by Li *et al.* and Bhatia *et al.* Figure 1 (I & II) shows the SEM images of the Ru/ACC before and after electrochemical reduction.

Reaction Optimization

The reaction was initially performed in a divided two-chamber (2-C) electrochemical cell with Ru/ACC as cathode and Pt as anode, separated by a Nafion®117 membrane. Preliminary investigations examined methylation of the secondary amine pyrrolidine with methanol. Conversion of 20 mM of pyrrolidine to 3° amine (1-methylpyrrolidine) would theoretically require only 20 mM of methanol, but at this low alcohol concentration, conversion was negligible at 33.3 mA/cm² over 6 hours.

Alcohol Concentration: Optimizing alcohol concentration to achieve practical reaction times, we studied a range from 1% v/v (250 mM) to 30% v/v (7.25 M) methanol in 0.01 M phosphate buffer at pH 7; rates rose with methanol concentration up to a saturation point at 20% v/v (Figure 1a).

Current Density: Using 20% v/v alcohol, we then studied the effect of varying current density on the rate of the reaction, exploring values ranging from 0.4 mA/cm² to 44.4 mA/cm² (Figure 1b). Initially, we hypothesized that the reaction would follow the borrowing hydrogen process at the cathode where Ru/ACC would catalyze C-H activation of alcohol to form a surface-bound aldehyde or ketone. This carbonyl species would condense with amine to generate surface imine or iminium species which would in turn undergo back reduction to amine. The current in this scenario should only be that needed for the electroactivation of Ru, ≥ 2.2 mA/cm², as seen in our earlier H/D exchange studies. But the alkylation rate showed a direct relationship to current density, reaching a maximum at 44.4 mA/cm², indicative of a true oxidation/reduction process. Further optimization studies used currents of 33.3 mA/cm².

Temperature: As expected, increasing temperature accelerated the reaction. However, at temperatures as low as 36 °C, alkylation still proceeded at useful rates, demonstrating the reaction's mildness (Figure 1c).

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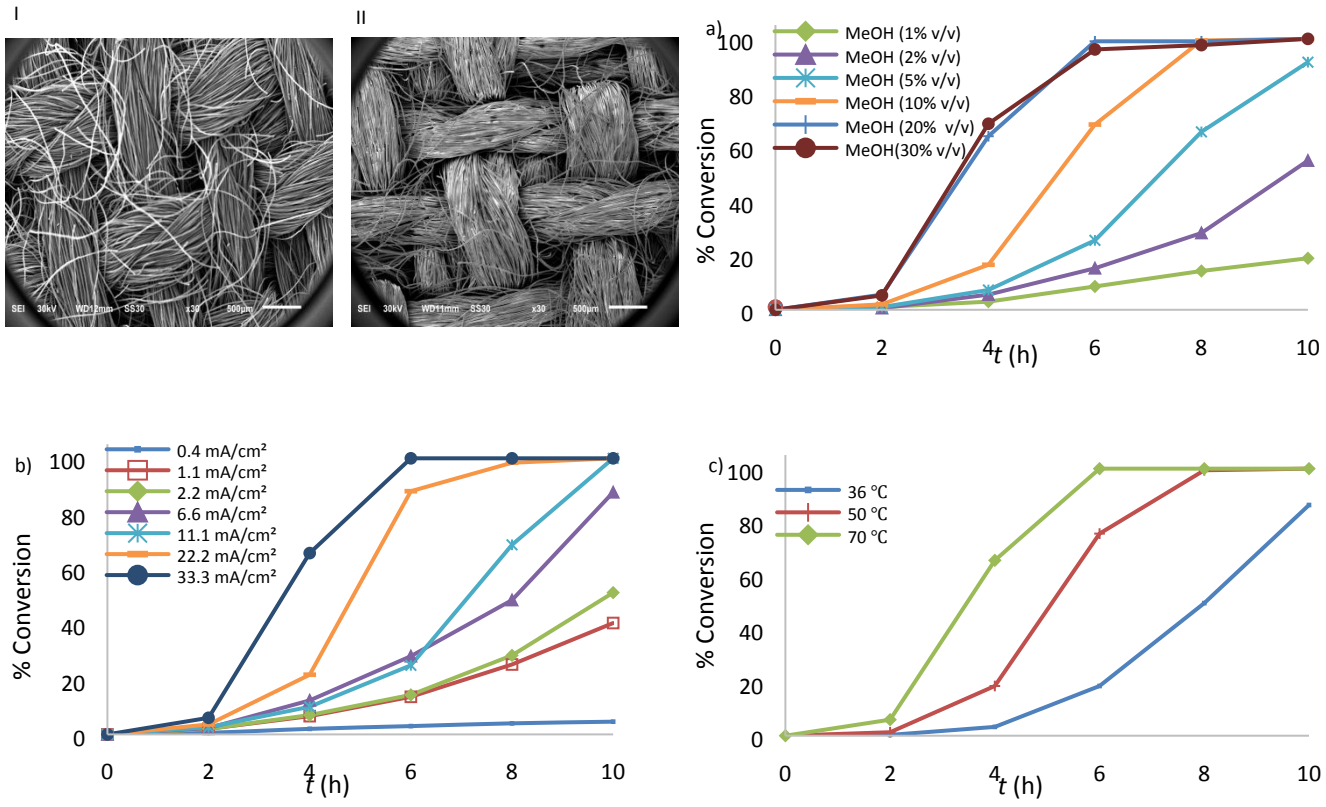

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Figure 1. SEM images of (I) ACC and (II) electrochemically reduced Ru/ACC in a divided H-cell. The white coating represents the reduced Ru as revealed by EDX in SI. (a) effect of alcohol concentration; (b) effect of current density and (c) effect of temperature. Conditions: Pyrrolidine (20 mM in 20 mL) with alcohol added to the cathodic chamber. Standard conditions when not varied: 20% v/v methanol; 33.3 mA/cm^2; 70 °C.

Mechanistic investigation and the role of the catalyst

To explore the importance of current density, an experiment using Ru/ACC (cathode) and Pt (anode), was run with pyrrolidine and methanol added to the cathodic chamber. Though the Ru/ACC electrode was activated by passing current prior to addition of the organics, no current was passed afterward. No alkylated product was formed, confirming the need for current to enable the reaction. Most importantly, simple ACC without Ru as the cathode gave alkylation results and rates similar to those with Ru/ACC. To confirm that this finding did not arise via reductive deposition of catalytic metal contaminants on the cathode, we conducted two experiments: (a) the divided H-cell was rinsed with aqua regia for 96 h, and (b) a brand-new H-cell was used to eliminate the possibility of the presence of even minute amounts of remaining Ru that could catalyze the reaction. Both scenarios yielded alkylated product. Together with the above current requirement, these results pointed to simple anodic oxidation, imine formation, and reduction at the ACC cathode. Even higher alkylation rates were seen if the carbonyl species was supplied directly. Thus, with a Ru/ACC cathode and a Pt anode at 33.3 mA/cm^2, we found 92% alkylation of pyrrolidine to 1-isopropyl pyrrolidine in the presence of 20% v/v acetone over 4 h as compared to 62% in the same period with isopropyl alcohol (figure 2).

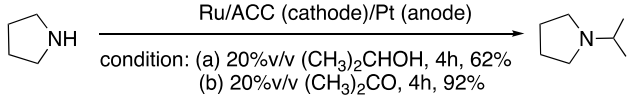
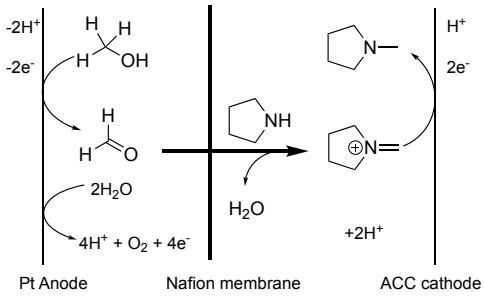


Figure 2. Comparison of reactions of pyrrolidine with isopropyl alcohol *vs* acetone, confirming the corresponding carbonyl species as an intermediate.

The above findings implied that methanol had permeated through the Nafion®117 membrane to the Pt anode, gotten oxidized to formaldehyde, permeated back to the cathodic chamber, condensed with pyrrolidine to form iminium, and undergone reduction on the ACC. To test this hypothesis, a cell with ACC (cathode) and Pt (anode) was charged with amine (pyrrolidine) and methanol respectively in the cathodic and anodic chambers. If methanol was indeed oxidized by the Pt anode, amine methylation should be, and indeed was, faster than the case with methanol on the cathode side (Figure 3b, green line). Thus, Ru was unnecessary for the alcohol activation in this case (Figure 3b, red line). This finding also explained the observed 2 h induction periods seen in our initial studies, which we had earlier attributed to electroactivation of ruthenium.[10]

a)



b)

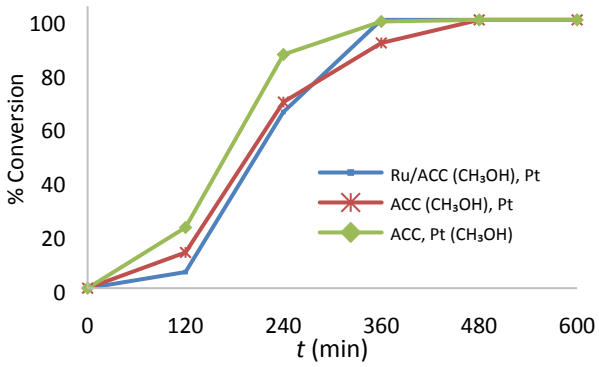


Figure 3. (a) Pyrrolidine methylation with methanol in the anode chamber. (b) Alkylation with varied electrode (cathode, anode) pairs with methanol. In the case of the (—blue line) and (—red line) runs, methanol was added to the cathodic side with pyrrolidine. In the last (—green line) example, methanol was added to the Pt anode side. Conditions: Pyrrolidine (20 mM in 20 mL) and 20% v/v methanol in a divided cell with 33.3 mA/cm^2 at 70 °C.

Substrate scope in divided 2-chamber (2-C) cell

Using ACC as cathode and Pt as anode at 33.3 mA/cm^2 and 70 °C, we explored the reaction's substrate scope by methylating additional secondary amines to give 1,4-dimethylpiperazine, 1-methylmorpholine, 1-methyldicyclohexylamine, and 1-methyl-piperidine-4-carboxylic acid. Except for morpholine, these 8 h runs, with methanol in the cathode chamber, gave relatively low yields but did demonstrate the ability of the 2-C cell to effect alkylation with more diverse substrates (Figure 4).

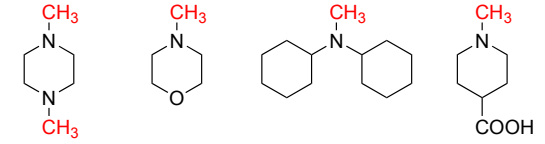


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Figure 4. Methylation products from alkylation with ACC/Pt in 2-C Cell. Conditions: Substrate (20 mM in 20 mL), 33.3 mA/cm^2, 70 °C & CH_3OH (20% v/v added to anodic chamber).

The undivided 1-chamber (1-C) cell

Noting that the above alkylations entailed alcohol oxidation at the Pt anode rather than hydrogen auto-transfer at a Ru/ACC cathode, the process was reoptimized in a 1-chamber (1-C) cell with ACC cathode and Pt anode. This new context enabled reaction at lower current density (2.2 mA/cm^2), alcohol concentration (5% v/v), and temperature (60 °C) values, substantially improving over the 2-C conditions. Based on a flow of 2e- per molecule to oxidize methanol to formaldehyde, and to reduce the iminium species, the optimized current efficiency (CE%, defined in equation 1) for 1-C pyrrolidine methylation was 22%, ignoring any losses due to adsorption of organic substrates into the ACC cloth electrode.

$$CE\% = \frac{(Mol_{prod} \times n \times F)}{C_{total}} \times 100\% \quad (1)$$

where Mol_{Prod} = moles of products formed, F = faraday's constant, 96,485 C mol^{-1}, n = number of electrons per reaction, and C_{total} = total charge passed in coulombs.

Several cathode-anode catalyst combinations (Figure 5) were explored in the 1-C context, again using pyrrolidine methylation as the test reaction. Use of ACC as cathode but replacing Pt with Ru/ACC at the anode gave improved conversion (98.3% vs. 83.3% in 6 h) and CE% (30% vs. 22%). Use of Ru/ACC for both electrodes yielded similar results.

Importantly, no reaction was observed when ACC was used as both cathode and anode (Figure 5). As a check, the inability of the ACC to activate alcohols was further explored via experiments in D_2O with ACC as both anode and cathode electrodes; no C-H exchange was seen. Literature confirms the inertness of carbon electrodes for alcohol oxidation. For instance, glassy carbon (not competent) has been studied with boron-doped diamond (BDD) (competent) for the oxidation of methanol and benzyl alcohol.[30] The inertness of common carbon electrode materials makes them ideal as catalyst and electrocatalyst supports. Examples include ultrathin Co_3O_4 supported on carbon paper and carbon cloth for ethanol oxidation,[31] platinum on graphite for benzyl alcohol oxidation,[32] and indium tin oxide (ITO) on reticulated vitreous carbon[34] electrodes for ethanol oxidation.

Most intriguing was the case with Ru/ACC as the cathode and ACC as the anode, where methylation still occurred, albeit slowly, even with an anode unable to oxidize alcohol. This observation indicates that the electroactivated Ru/ACC cathode is capable of alkylation via actual hydrogen auto-transfer, the classic "borrowing hydrogen" mechanism.

For the two-electrode process, substrate scope was explored with the ACC cathode and Ru/ACC anode combination in a 1-C cell (Figure 5). Reaction of pyrrolidine in 5% methanol at 60 °C gave a 98% yield of 1-methylpyrrolidine in 6 h at pH 7.5. Though the ACC-Pt combination had given only modest yields (≤ 30%) upon pyrrolidine alkylation with ethanol and 2-propanol, at pH 8.5 these substrates, as well as cyclohexanol and benzyl alcohol, now yielded 1-ethylpyrrolidine (99%), 1-isopropylpyrrolidine (92%), 1-cyclohexylpyrrolidine (20%), and 1-benzylpyrrolidine (30%) respectively (Table 1). The slightly alkaline pH increases the free amine concentration, presumably accelerating imine formation. Pyrrolidine alkylations with two alcohols incapable of oxidation to carbonyl species, phenol and *t*-butanol, were also attempted, but as expected, they yielded no alkylation products, consistent with the borrowing hydrogen mechanism.

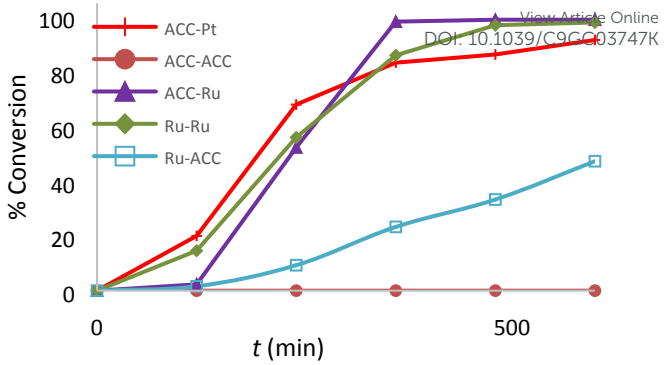
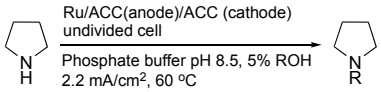
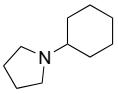
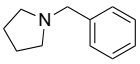


Figure 5. Pyrrolidine methylation in 1-chamber cell (1-C, open cell) with various cathode-anode electrode combinations. Conditions: Pyrrolidine (20 mM in 20mL), 2.2 mA/cm^2, 60 °C and CH_3OH (5% v/v).

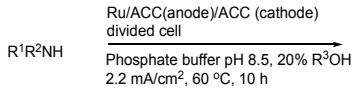
Table 1. Alkylation of pyrrolidine with 1° and 2° alcohols

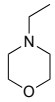
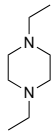
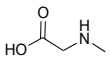
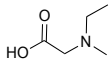
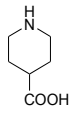
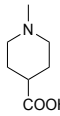
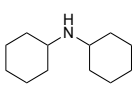
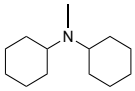


Entry	Alcohol	product	Conversion %	Yield %	C.E %
1	CH_3OH		99 (100)	42 (98)[a]	18
2	HO		99 (100)	49 (99)[a]	18
3	HO		96 (98)	39 (92)[a]	16
4	HO		55 (65)	8 (20)[b]	4
5	HO		90	30[b]	8

C.E % = current efficiency, [a] yield at 6 hours, [b] yield at 10 h. Values in parentheses includes species in solution and extracted from the electrodes using 5 mL *t*-BuOH. Conversion values are based on pyrrolidine.

Table 2. Alkylation of 2° amines with methanol and ethanol



Entry	Alcohol	R_2NH	Product	Conversion %	Yield %
1	CH_3OH			86	46
2				91	59
3	CH_3OH			71	55
4				67	47
5				48	17
6	CH_3OH			68	33
7	CH_3OH			58	34

Extending the amine substrate scope led to yields of 4-methylmorpholine (46%) and 1-methylpiperidine (55%) respectively after 10 h reactions with methanol at pH 7.5. These efforts were extended to ethanol at pH 8.5, yielding 4-ethylmorpholine (69%) and 1,6-diethylpiperazine (47%) respectively (Table 3). Methylations worked best at pH 7.5 whereas the 1° and 2° alcohols gave excellent results at pH 8.5. Traces of hydrocarbon-range resonances in the ^{1}H-NMR are attributed to the possible formation of branched Guerbet alcohols[35] (See SI).

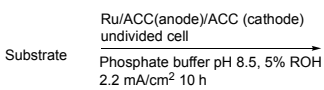
As seen in Table 2, the system tolerated the carboxylic functional groups in isonipeconic acid (4-carboxypiperazine) and sarcosine (*N*-methylglycine). Though slow, methylation of the strongly sterically hindered 2° amine dicyclohexylamine gave (34%) 1-methyldicyclohexylamine. Turning to aniline as the simplest aromatic amine, we attempted ethylation, but even after substantial optimization efforts, lowering the pH to 3 to minimize aniline oxidation, we still only obtained small amounts of the monosubstituted *N*-ethylaniline.

Alkylation of Ammonia

Attempting direct alkylation of ammonia with ethanol (Table 3), a 9% yield of triethylamine was obtained in 10 hours at 60 °C. This low yield was attributed to loss of ammonia by evaporation. We then studied the reaction at room temperature (25 °C) and observed a decreased yield to 7% but still suspected loss of ammonia by evaporation. Use of ammonium acetate[36] (to provide aqueous ammonia *in situ*) at 60 °C with a Teflon cap to partially seal the electrochemical cell yielded 36% triethylamine. Reaction progress, monitored by 1H NMR, showed the formation of ethylamine (b.p. = 16 °C) and diethylamine (b.p. = 55 °C) in small quantities, supporting the expected stepwise formation of triethylamine. To explore the possibility of intermediate disproportionation to mono and triethylated products, diethylamine was subjected to the reaction with ethanol, yielding 92% triethylamine; ethylamine was not observed, indicating no disproportionation as expected from the thermodynamic data in Scheme 2. Two different paths to diethylbutylamine were explored: (1) a 1° amine (*n*-butylamine) and 5% ethanol and (2) a 2° amine (diethylamine) and 5% *n*-butanol, with yields of 32% to 52% respectively. As expected, the reaction requiring two sequential alkylations gave the lower yield. The low solubility of *n*-butanol (8% v/v in H_2O)[37] compared to ethanol (fully miscible with H_2O) could also have contributed to its lower yield.

With isopropyl alcohol, only diisopropylamine was formed, regardless of reaction time. Consistent with the literature report on cyclohexylation,[19] this result is presumably due to the bulky isopropyl groups hindering the formation of the final imine intermediate. However, alkylation of diisopropylamine with ethanol, a primary alcohol, did give a 28% yield of Hünigs base (Table 3).

Table 3. Synthesis of triethylamine and diisopropylamine



Entry	Alcohol	substrate	product	Temp. °C	Yield %
1		NH_3		60	9
2		NH_3		r.t	7
3		NH_4OAc		60	36
4				60	39
5				60	26
6		NH_3		60	20
7[a]				34	30
8				34	28
9				70	32
10				34	19

Single-electrode Alkylation

Returning to the relatively slow amine alkylation achieved on the cathode alone, a new mechanism must be considered. Here no free carbonyl species is seen or expected. Our previously reported finding of stereoretentive C-H activation and H/D exchange in alcohols and amines on the Ru/ACC cathode suggested that in the amine alkylation reactions, the stereochemistry of the original alcohol might be carried over to the resulting amine. We explored the stereochemical outcome of the single-electrode alkylation with the *cis*/*trans* isomers of 4-methylcyclohexanol and with 4-methylcyclohexanone reacting with pyrrolidine. Using *t*-butanol as co-solvent to improve the solubility of the cyclohexyl systems, reactions were conducted in a series of membrane-separated and open electrochemical systems, with

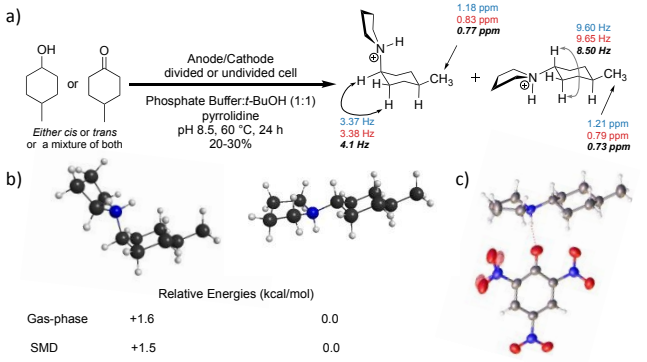


Figure 6. (a) Reactions of pyrrolidine with *cis*-4-methylcyclohexanol, *trans*-4-methylcyclohexanol, a mixture of *cis/trans*-4-methylcyclohexanol or 4-methylcyclohexanone. (b) Relative energies of the most stable conformers and coupling constants of (left) *cis*-4-methylcyclohexylpyrrolidine and (right) *trans*-4-methylcyclohexylpyrrolidine computed with Gaussian16 at the b3lyp[43]/6-31G(d,p)[44] level. For NMR chemical shift and coupling constant calculations, the GIAO method in Gaussian16 was used with the above geometries at the mpw1pw91[45]/6-311+g(2d,p)[46] level of theory, with chemical shifts referenced against tetramethylsilane (TMS) calculated at the same level of theory. Coupling constant values shown are experimental (blue) and computed "aqueous phase (SMD)" (red) and "gas phase" (black). (c) Crystal structure of the picrate salt of *trans*-4-methylcyclohexylpyrrolidine (m.p = 189-191 °C) obtained from amination of 4-methylcyclohexanol. [38]

yields and product stereochemistry evaluated.

Stereochemistry of One- and Two-electrode Alkylation

As seen in Table 4 (entries 1, 2), no alkylation product was observed with ACC for the two electrodes, with or without a membrane divider. This finding is consistent with the earlier noted inability of ACC alone to oxidize alcohols to the corresponding carbonyl compounds; as expected, no direct reaction is seen between alcohol and pyrrolidine. On the other hand, with cyclohexanone, regardless of membrane, the expected alkylation did occur. The resulting 1:1 ratio of cis and trans pyrrolidinyl cyclohexanes was essentially like that seen from classical sodium borohydride reduction (entry 5). As expected with the ketone substrate, the nature of the anode was unimportant (entries 6, 7). Significantly, with an oxidation-competent Ru/ACC anode, reaction with the cis isomer of the alcohol did yield the same 1:1 amination ratio, consistent with formation of ketone at the anode (entry 8), enabling the 2-electrode amination process.

A different pattern emerged with ACC anodes and Ru/ACC cathodes. Here the amination must have occurred only at the activated ruthenium cathode, as the ACC anode is not able to oxidize the alcohol. With or without membrane present, this one-electrode process effects amination of the ketone or either of the 4-methylcyclohexanol isomers with a 2:1 cis:trans ratio of aminated cyclohexane. Disappointingly, no direct reflection of the initial alcohol's stereochemistry is seen in the product ratio, but the Ru/ACC reduction does have a different stereochemical selectivity than reduction by ACC alone. Evidently the alcohol undergoes C-H activation at the cathode (a process known to retain stereochemistry) but undergoes release at some point in the process of forming the imine intermediate and undergoing the final reduction. In sum, the Ru/ACC cathode does activate and aminate alcohols but is not able to retain a trace of their original stereochemistry under the present reaction conditions.

Table 4. Stereochemical outcome by electrode pairing in 1-C and 2-C reactor configurations

Exp.	Cathode	Membrane	Anode	Alcohol	Product; Cis/trans-Selectivity
1	ACC	Yes	ACC	Alcohol[a,b] (cis/trans)	No Reaction
2	ACC	No	ACC	Alcohol[a] (cis/trans)	No Reaction
3	ACC	No	ACC	Ketone[c]	1:1
4	ACC	Yes	ACC	Ketone[b,c]	1:1
5	$NaBH_4$/TFE/ 40 °C	N/A	N/A	Ketone[c]	1:1
6	ACC	Yes	Ru/ACC	Ketone[b,c]	1:1
7	ACC	No	Ru/ACC	Ketone[c]	1:1
8	ACC	No	Ru/ACC	Alcohol[a] (cis)	1:1
9	Ru/ACC	No	ACC	Alcohol[a] (cis)	2:1
10	Ru/ACC	Yes	ACC	Alcohol[a,b] (trans)	2:1
11	Ru/ACC	Yes	ACC	Alcohol[a,b] (cis/trans)	2:1
12	Ru/ACC	Yes	ACC	Ketone[b,c]	2:1

[a]Alcohol = 4-methylcyclohexanol; [b]Substrate placed in cathode compartment; [c]Ketone = 4-methylcyclohexanone.

Notably, no re-equilibration of the above cis/trans ratios was observed after amination. Product mixtures with the 1:1 ratio obtained from the ACC reductive amination reactions remained the same when re-exposed to any of the electrode

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combinations. Products were identified by melting point,[38] GC/MS and 2D-NMR, but most significantly confirmed by the X-ray structure of the *trans*-N-(4-methylcyclohexyl)pyrrolidine, which we obtained in the form of the picrate salt (Figure 6). This isolated material enabled unambiguous assignments of the NMR spectra, enabling easy analysis of product mixtures. To estimate the energetics of the cis and trans aminated isomers, we also ran b3lyp/6-31G(d,p) calculations in gas and simulated aqueous[39] phases on both neutral and protonated forms of the 4-methylcyclohexyl pyrrolidine. For the latter, which are expected to dominate at a pH of 8.5, the *trans* isomer was calculated to be 1.5 kcal/mol lower in free energy than the *cis* isomer, when solvation and vibrational analyses are included. However, it was the cis product that dominated in the Ru/ACC-reduced product mixtures. This apparent deviation from the purely thermochemical ratio presumably reflects imine adsorption on the catalyst surface and hydrogen delivery to the less sterically hindered face of the cyclohexane ring, opposite to the methyl substituent.

For product analysis, fortunately, the chemical shifts of the methine hydrogens on the carbon bearing the nitrogen were distinct in the experimental ^{1}H-NMR with coupling constants of 8.50 Hz for the *trans*-isomer and 4.10 Hz for *cis*. The calculated NMR coupling constants in gas-phase/simulated solvent were 9.60 Hz/9.65 Hz and 3.37/3.38 Hz respectively (figure 6). Also, the 4-methyl protons were distinctly separated in the experimental NMR. Computing the theoretical NMR chemical shifts (CS) of the 4-methyl groups in the two isomers relative to that of TMS,[40,41] our results were consistent with experimental data, finding the 4-methyl group of the trans isomer to be upfield from that of the cis by 0.3 (gas phase), 0.3 (SMD[42], water) and 0.4 (experimental) ppm (see SI).

Conclusions and Outlook

In conclusion, we have developed an electrocatalytic system that achieves amine alkylation with alcohols via two differing "hydrogen borrowing" pathways: an indirect, two-electrode path in which the hydrogen "borrowed" at the anode is returned via regeneration from H^+ and e^- at the cathode; and a direct C-H activation, condensation, and re-reduction scheme taking place at the cathode alone. We have found that for imine reduction to N-(4-methylcyclohexyl)pyrrolidine, the Ru/ACC cathode has a (*trans/cis)* selectivity of 1:2 whereas the plain ACC cathode forms a 1:1 product ratio, essentially the same as the classical reductive amination with $NaBH_4$. Investigating the use of various cathode-anode pairings, we have found Ru/ACC as anode and ACC as cathode to be the optimal system for amine alkylation via electrocatalytic oxidation at the anode and reduction at the cathode in an undivided one-chamber H-cell (open cell). The reaction is most readily accomplished using smaller primary and secondary alcohols, but bulkier alcohols such as benzyl alcohol and cyclohexanol can also be used successfully. The chemistry has been applied to synthesis of laboratory reagents such as triethylamine, diethylbutylamine and *N,N*-diisopropylamine (Hünig's base) in good yields. Looking ahead, we continue to pursue more effective ways to alkylate aromatic amines, and to extend these electrocatalytic strategies to the classes of C-C bond forming reactions observed in more conventional catalytic settings.[27–29]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 B. S. Sekhon, *J. Pharm. Technol. Res. Manag.*, 2013, **1**, 43–68.

2 J. Genovino, S. Lütz, D. Sames and B. B. Touré, *J. Am. Chem. Soc.*, 2013, **135**, 12346–12352.

3 R. Yadav, M. Ahmed, A. K. Singh and A. Sakthivel, *Sci. Rep.*, 2016, **6**, 1–9.

4 M. B. Smith and J. March, *March's advanced organic chemistry*, Wiley & Sons, New York, 5th edn., 2001.

5 M. Lersch and M. Tilset, *Chem. Rev.*, 2005, **105**, 2471–2526.

6 D. S. Surry and S. L. Buchwald, *Angew. Chemie - Int. Ed.*, 2008, **47**, 6338–6361.

7 C. A. Olsen, M. Witt, J. W. Jaroszewski and H. Franzyk, *Synlett*, 2004, **3**, 473–476.

8 S. Hünig and M. Kiessel, *Chem. Ber.*, 1958, **91**, 380–392.

9 F. T. Jere, D. J. Miller and J. E. Jackson, *Org. Lett.*, 2003, **5**, 527–530.

10 S. Bhatia, G. Spahlinger, N. Boukhumseen, Q. Boll, Z. Li and J. E. Jackson, *European J. Org. Chem.*, 2016, **2016**, 4230–4235.

11 A. V. Naumkin, A. Kraut-Vass, C. J. Powell and S. . Gaarenstroom, NIST Standard Reference Database 20 version 4.1, http://srdata.nist.gov/xps.

12 R. C. Rizzo, T. Aynechi, D. A. Case and I. D. Kuntz, *J. Chem. Theory Comput.*, 2006, **2**, 128–139.

13 J. U. Nef, *Justus Liebig's Ann. der Chemie*, 1901, **318**, 137–230.

14 R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *J. Chem. Soc. Chem. Commun.*, 1981, 611–612.

15 Y. Watanabe, Y. Morisaki, T. Kondo and T. Mitsudo Ta, *J. Org. Chem.*, 1996, **61**, 4214–4218.

16 M. H. S. a Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. a Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766–1774.

17 A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *J. Org. Chem.*, 2011, **76**, 2328–2331.

18 K. O. Marichev and J. M. Takacs, *ACS Catal.*, 2016, **6**, 2205–2210.

19 R. Kawahara, K. Fujita, R. Yamaguchi and S. Kyoto, *J. Am. Chem. Soc.*, 2010, **3**, 15108–15111.

20 W. Baumann, A. Spannenberg, J. Pfeffer, T. Haas, A. Köckritz, A. Martin and J. Deutsch, *Chem. - A Eur. J.*, 2013, **19**, 17702–17706.

21 A. B. Brown and E. E. Reid, *J. Am. Chem. Soc.*, 1924, **46**, 1836–1839.

22 Y. Zhang, X. Qi, X. Cui, F. Shi and Y. Deng, *Tetrahedron Lett.*, 2011, **52**, 1334–1338.

23 H. Liu, G. K. Chuah and S. Jaenicke, *J. Catal.*, 2012, **292**, 130–137.

24 K. Yamaguchi, J. He, T. Oishi and N. Mizuno, *Chem. - A Eur. J.*, 2010, **16**, 7199–7207.

25 J. He, K. Yamaguchi and N. Mizuno, *Chem. Lett.*, 2010, **39**, 1182–1183.

26 J. Won, K. Yamaguchi and N. Mizuno, 2009, **263**, 205–208.

27 A. Corma, J. Navas and M. J. Sabater, *Chem. Rev.*, 2018, **118**, 1410–1459.

28 K. I. Shimizu, *Catal. Sci. Technol.*, 2015, **5**, 1412–1427.

View Article Online
DOI: 10.1039/C9GC03747K

29 M. A. R. Jamil, A. S. Touchy, M. N. Rashed, K. W. Ting, S. M. A. H. Siddiki, T. Toyao, Z. Maeno and K. ichi Shimizu, *J. Catal.*, 2019, **371**, 47–56.

30 B. G. Reed-Berendt, K. Polidano and L. C. Morrill, *Org. Biomol. Chem.*, 2019, **17**, 1595–1607.

31 B. Ohtani, K. Nakagawa, S. Nishimoto and T. Kagiya, *Chem. Soc. Japan*, 1986, 1917–1920.

32 M. Garedew, in *Ph.D. Dissertation, Michigan State University*, 2018, p. 69,94.

33 Z. Li, M. Garedew, C. H. Lam, J. E. Jackson, D. J. Miller and C. M. Saffron, *Green Chem.*, 2012, **14**, 2540.

34 M. A. Méndez, L. Alibabaei, J. J. Concepcion and T. J. Meyer, *ACS Catal.*, 2013, **3**, 1850–1854.

35 J. T. Kozlowski and R. J. Davis, *ACS Catal.*, 2013, **3**, 1588–1600.

36 R. Yamaguchi, S. Kawagoe, C. Asai and K. I. Fujita, *Org. Lett.*, 2008, **10**, 181–184.

37 A. Maczynski, D. G. Shaw, M. Goral and B. Wisniewska-Goclowska, *J. Phys. Chem. Ref. Data*, 2007, **36**, 59–132.

38 R. O. Hutchins, W. Y. Su, R. Sivakumar, F. Cistone and Y. P. Stercho, *J. Org. Chem.*, 1983, **48**, 3412–3422.

39 C. C. Chambers, G. D. Hawkins, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem.*, 1996, **100**, 16385–16398.

40 D. H. Barich, J. B. Nicholas and J. F. Haw, *J. Phys. Chem. A*, 2001, **105**, 4708–4715.

41 J. R. Cheeseman, G. W. Trucks, T. A. Keith and M. J. Frisch, *J. Chem. Phys.*, 1996, **104**, 5497–5509.

42 A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B*, 2009, **113**, 6378–6396.

43 P. J. Stephens, F. J. Devlin, C. F. Chabalowski and M. J. Frisch, *J. Phys. Chem.*, 1994, **98**, 11623–11627.

44 W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.*,

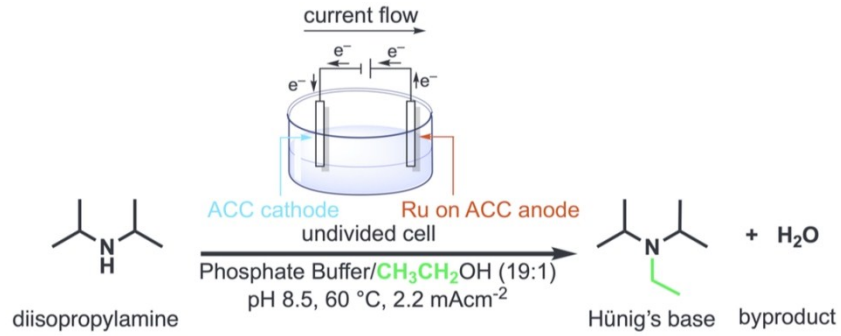
View Article Online
DOI: 10.1039/C9GC03747K

1972, **56**, 2257–2261.

45 C. Adamo and V. Barone, *J. Chem. Phys.*, 1998, **108**, 664–675.

46 R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys*, 1980, **72**, 650–654.

View Article Online
DOI: 10.1039/C9GC03747K



Aqueous electrocatalytic alkylation of amines with alcohol; water is the only byproduct

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