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A Biomimetic Electrocatalytic System for the Atom-Economical Chemoselective Synthesis of Secondary Amines

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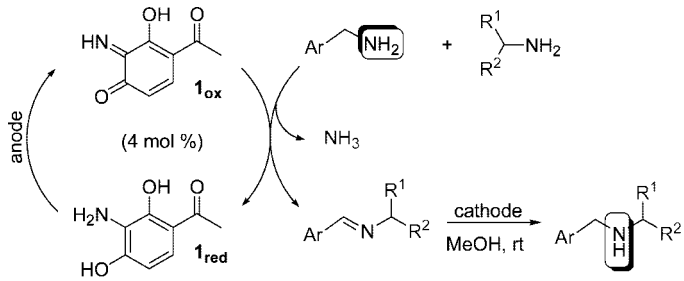
ABSTRACT



A facile one-pot oxidation−imine formation−reduction route to secondary amines can be achieved electrolytically from primary amines. This atom-economical 1_{ox}-mediated sequence, leaving ammonia as the sole byproduct, allows the rapid chemoselective synthesis of secondary amines, at both ambient temperature and pressure.

Secondary amines are highly versatile building blocks for various organic substrates and are essential pharmacophores in numerous biologically active compounds. Hence, the development of efficient methods for the synthesis of secondary amines has still been a challenging and active area of research. Conventional synthetic approaches from primary amines include reductive alkylation, protection−deprotection strategy, and direct N-alkylation. However, these methods suffer disadvantages such as low functional group tolerance, harsh reaction conditions, lengthy sequences, and overalkylation.[1]

To overcome these limitations, various efficient metal-catalyzed syntheses of secondary amines have been developed in the past decade. Although the hydroamination of alkenes or alkynes[2] and the amination of aryl halides[3] are most important, metal-catalyzed N-alkylation of primary amines with alcohols,[4] amines,[5] or nitriles[6] represents attractive approaches for the synthesis of secondary amines.

(1) For a review on the synthesis of secondary amines, see: Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811.

(2) For recent reviews on catalytic hydroamination of alkynes and alkenes, see: (a) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892.

(3) For recent reviews on metal-catalyzed amination of aryl halides, see: (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (b) Hartwig, J. F. *Nature* **2008**, *455*, 314–322. (c) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544.

(4) For selected recent examples see: (a) Fujita, K.-I.; Yamaguchi, R. *Synlett* **2005**, *4*, 560–571. (b) Tillack, D.; Hollmann, D.; Michalik, R.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8881–8885. (c) Hoolman, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. Asian J.* **2007**, *2*, 403–410. (d) Hamid, M. H. S. A.; Williams, M. J. *Chem. Commun.* **2007**, 725–727. (e) Nordstrom, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034–5036. (f) Fujita, K.-I.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943–1954. (g) Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K.-I. *Org. Lett.* **2008**, *10*, 181–184. (h) Pontes da Costa, A.; Viciano, M.; Sanau, M.; Merino, S.; Tejeda, J.; Peris, E.; Royo, B. *Organometallics* **2008**, *27*, 1305–1309.

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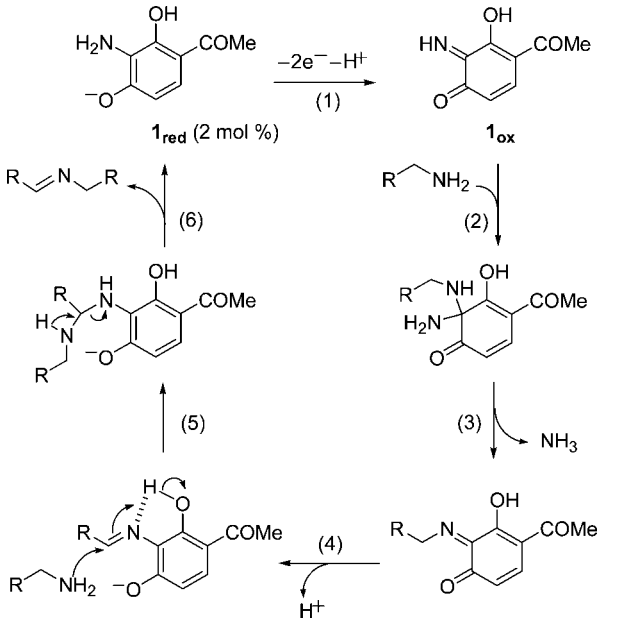
A noteworthy example is the selective ruthenium-catalyzed N-alkylation of aryl amines using aliphatic amines which produces the corresponding *N*-alkyl-aryl amines, in high yields, leaving ammonia as the only byproduct.[5a]

The performance of a metal-free in situ oxidation−imine formation−reduction sequence, using manganese dioxide in combination with sodium borohydride or polymer-supported cyanoborohydride, has also been reported for the conversion of activated alcohols into secondary amines.[7]

Related routes to secondary amines could also be achieved electrolytically from primary amines, but the fact these are oxidized at relatively high anodic potentials (> + 1.5 V vs SCE), and give rise to unstable cation radicals that rapidly deprotonate and attach to the electrode surface, does not make it possible directly.[8]

Recently, we reported that electrogenerated *o*-iminoquinone $\mathbf{1_{ox}}$ acted as an effective biomimetic catalyst for the chemoselective oxidation of primary aliphatic amines, under metal-free conditions. The mechanism was very close to the ionic pyridoxal-like transamination process reported for amine oxidase cofactors (Scheme 1).[9] The formation of a

Scheme 1. Ionic Transamination Mechanism of Catalytic Oxidation of Primary Aliphatic Amines Mediated by Electrogenerated *o*-Iminoquinone Amine Oxidase Mimic $\mathbf{1_{ox}}$



highly reactive Schiff base cyclic transition state (eq 4, Scheme 1), which allowed the activation of the imine function for further nucleophilic attack by the amine, constituted the driving force for the overall ionic mechanism.[9b] The catalytic cycle produced the reduced catalyst $\mathbf{1_{red}}$ and an unstable alkylimine as the product of amine oxidation, at room temperature, leaving ammonia as the sole byproduct. These conditions were particularly favorable for using the imine in situ for further reactions. Accordingly, we recently described the utilization of the tautomeric enamine form of certain in situ generated alkylimines as the cycloaddition partner in cascade reactions leading to potent neuroprotective 1,4-benzoxazine derivatives.[10]

Next, we decided to investigate the utility of the electrocatalyst $\mathbf{1_{ox}}$ for the synthesis of secondary amines through the $\mathbf{1_{ox}}$-mediated catalytic process followed by an electrochemical reduction of the extruded alkylimine. However, the yield of the produced secondary amine could not exceed 50%, because two molecules of primary amine (eqs 2 and 5, Scheme 1) are required to produce one molecule of alkylimine (eq 6, Scheme 1). Furthermore, secondary amines possessing different substituents on both sides of the nitrogen atom could not be prepared by this way.

Thus, we envisioned some modifications of our electrocatalytic procedure, and we report herein a facile one-pot metal-free $\mathbf{1_{ox}}$-mediated oxidation−imine formation−reduction sequence for the atom-economical chemoselective N-alkylation of activated primary amines with amines, under mild conditions.

As a starting point of our investigations, we chose to perform the $\mathbf{1_{ox}}$-mediated catalytic oxidation of an activated primary amine such as benzylamine, in the presence of a nonactivated primary amine such as aminomethylcyclopropane, which should serve as the alkylating agent. Upon optimization, we found that a combination of 2.50 mmol of benzylamine with 3.75 mmol of aminomethylcyclopropane and 0.10 mmol of $\mathbf{1_{red}}$ which corresponds to 4 mol % (relative to benzylamine) of the electrocatalyst $\mathbf{1_{ox}}$, gave the best results. Then, the $\mathbf{1_{ox}}$-mediated catalytic oxidation step was realized under the previously reported conditions, which required a platinum anode and methanol as the solvent.[9b] When the controlled potential of the Pt anode was fixed at + 0.6 V vs SCE, which is at a potential for which $\mathbf{1_{red}}$ could be oxidized to the iminoquinone form $\mathbf{1_{ox}}$, the anodic current remained constant for a long time, and the current efficiency obtained by electrolysis for 3 h was 100%, indicating that no side reaction took place under the experimental conditions used. These results confirmed that the $\mathbf{1_{ox}}$/$\mathbf{1_{red}}$ system behaved as a redox mediator for the indirect electrochemical oxidation

(5) (a) Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8291–8294. (b) Hollmann, D.; Bähn, S.; Tillack, A.; Beller, M. *Chem. Commun.* **2008**, 3199–3201. (c) Hollmann, D.; Bähn, S.; Tillack, A.; Parton, R.; Altink, R.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 5742–5745.

(6) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977–4980.

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(8) For recent papers, see: (a) Adenier, A.; Chehimi, M. M.; Gallardo, I.; Pinson, J.; Vilà, N. *Langmuir* **2004**, *20*, 8243–8253. (b) Gallardo, I.; Pinson, J.; Vilà, N. *J. Phys. Chem. B* **2006**, *110*, 19521–19529. (c) Bourdelande, J. L.; Gallardo, I.; Guirado, G. *J. Am. Chem. Soc.* **2007**, *129*, 2817–2821.

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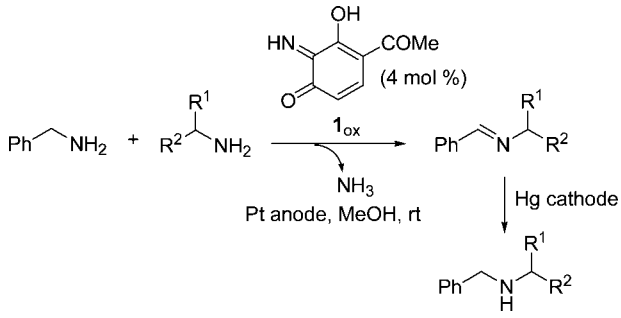
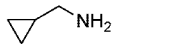
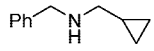
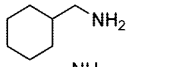
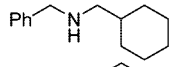
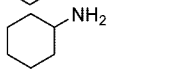
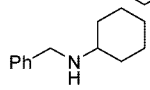
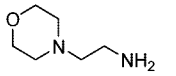
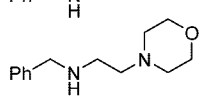
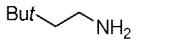
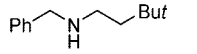
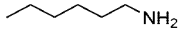
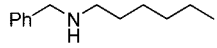
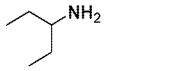
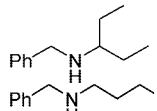
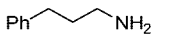
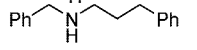
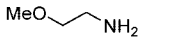
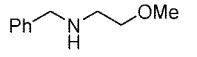
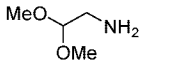
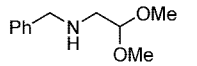
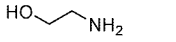
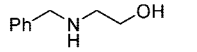
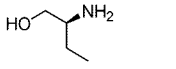
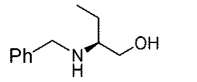
(10) (a) Largeron, M.; Neudörffer, A.; Vuilhorgne, M.; Blattes, E.; Fleury, M.-B. *Angew. Chem., Int. Ed.* **2002**, *41*, 824–827. (b) Blattes, E.; Fleury, M.-B.; Largeron, M. *J. Org. Chem.* **2004**, *69*, 882–890. (c) Blattes, E.; Lockhart, B.; Lestage, P.; Schwendimann, L.; Gressens, P.; Fleury, M.-B.; Largeron, M. *J. Med. Chem.* **2005**, *48*, 1282–1286. (d) Xu, D.; Chiaroni, A.; Fleury, M.-B.; Largeron, M. *J. Org. Chem.* **2006**, *71*, 6374–6381.

of benzylamine to the corresponding *N*-benzylidenealkylamine (see the equation in Table 1). The in situ presence of *N*-benzylidenealkylamine could be evidenced through the UV−vis absorption changes observed in the course of the catalytic anodic process (see Figure 1(a) in the Supporting Information). Effectively, a UV absorption band at 250 nm developed which was close to that recorded from a solution of commercially available related *N*-benzylidenemethylamine in methanol. In a control experiment, the chemoselectivity of the oxidation−imine formation reaction was verified by converting the unstable in situ generated imine to the 2,4-dinitrophenylhydrazone (DNPH) by aqueous acidic workup of the oxidized solution with 2,4-dinitrophenylhydrazine.[9b] As expected, only benzaldehyde DNPH was isolated, indicating that no alkylidenealkylamine was formed in the course of the catalytic anodic process.

Table 1. Electrocatalyzed N-Alkylation of Benzylamine with Different Primary Aliphatic Amines[a]



entry	alkylating amine	product	yield%[b]
1			80
2			60[c,d]
3			68[c]
4			66[c]
5			70[c]
6			57[c]
7			51[e]
8			64[c]
9			71[d]
10			60[d]
11			68[c]
12			70[c]

[a] Reagents and conditions: (**1**$_{ox}$) = 0.4 mM (4 mol % relative to benzylamine), (benzylamine) = 10 mM, (alkylating amine) = 15 mM, MeOH, rt. Oxidation−imine formation step: Pt anode (E = +0.6 V vs SCE), 3 h. Imine reduction step: Hg cathode (E = −1.6 V vs SCE), 1 h. [b] Yields refer to chromatographically pure isolated products and are relative to benzylamine. [c] Dibenzylamine was formed as a byproduct (5−10%). [d] Diamines were observed as byproduct (5−15%). [e] Diamine was isolated in 30% yield and was partly formed during workup.

After exhaustive anodic oxidation, the Pt anode was replaced by a mercury pool because *N*-benzylidenealkylamine could not be reduced at the platinum cathode in methanol. Obviously, the switch to a mercury cathode constitutes a relative weakness of the process from practical and environmental points of view. Replacing the Hg cathode by a graphite carbon cathode, the yield was roughly halved because of partial loss of the product on the porous graphite carbon material. Achieving both the oxidative amine alkylation and the imine reduction using a single anode/cathode couple would be a challenge for the future. When the potential of the mercury pool was fixed at −1.6 V vs SCE, which is at a potential for which *N*-benzylidenealkylamine could be reduced to the corresponding secondary amine, the UV absorption band at 250 nm disappeared in agreement with the formation of the secondary amine (see Figure 1(b) in the Supporting Information). Note the UV−vis absorption changes recorded in the course of the imine reduction reaction were almost superimposed with those observed during the oxidation−imine formation sequence. Accordingly, the two-electron reduction process led to *N*-benzyl-*N*-cyclopropylmethylamine in 80% yield (entry 1, Table 1).

In subsequent studies, we examined the scope of the process using different alkylating amines. The results are summarized in Table 1. Various aliphatic primary amines reacted with benzylamine to give the desired products in yields ranging from 51 to 80%. In several cases (entries 2−6, entry 8, entries 11, and 12, Table 1), dibenzylamine was formed as a byproduct. However, the formation of dibenzylamine could be limited to 5−10%, through the addition of an excess of alkylating amine (1.5 equiv).

In some cases (entries 2, 7, 9, and 10, Table 1), diamines arising from a one-electron reduction mechanism were also observed as a dimeric byproduct. To minimize the formation of these compounds, which were produced after a bimolecular dimerization reaction, benzylamine concentration did not exceed 10 mM. Furthermore, the application of a sufficiently negative cathodic potential (−1.6 V vs SCE) favored the electroreduction of the alkylimine intermediate to the desired secondary amine.[11]

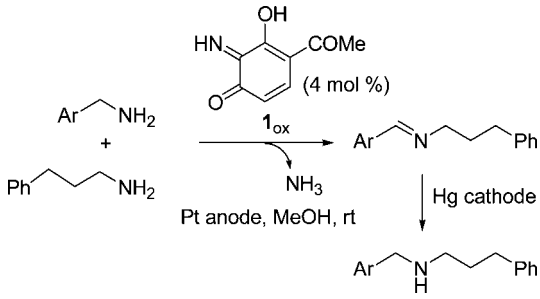
Interestingly, in the case of β-aminoalcohols (entries 11 and 12, Table 1), the presence of the alcohol group did not interfere with the catalytic anodic process indicating a good tolerance of this functional group. Furthermore, the use of (*R*)-(−)-2-amino-1-butanol gave the expected aminoalcohol with no loss of optical activity {$[\alpha]^{22}_{D}$ −22.0 (*c* 2.6, EtOH);

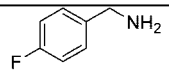
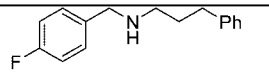
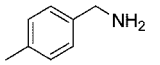
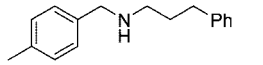
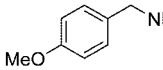
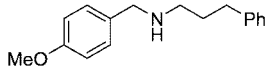
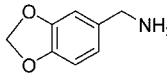
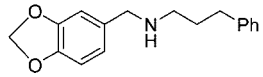
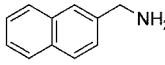
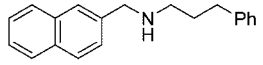
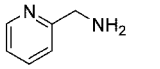
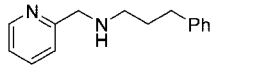
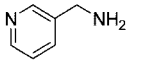
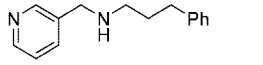
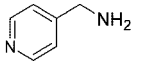
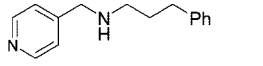
lit.[12] $[\alpha]^{20}_D$ −25.6 (*c* 0.08, EtOH)} as shown in entry 12. So, the synthesis of various *β*-aminoalcohols should be feasible through this one-pot oxidation−imine formation−reduction sequence.

In a second series of experiments, we explored the electrocatalyzed N-alkylation of various activated amine substrates with phenylpropylamine chosen as the alkylating agent (Table 2). As expected, activated substituted benzylamines were good substrates for this reaction, and the product yield did not markedly depend on the substitution of the phenyl ring (entries 1−4, Table 2). However, in the case of 1-naphtalenemethylamine, the yield of the desired secondary amine decreased to 51%, while that of bisnaphtalen-2-yl-methylamine increased to 25% (entry 5, Table 2). Probably, the stability of the symmetrical imine species facilitated its extrusion during the $\mathbf{1_{ox}}$-mediated catalytic process at the expense of the unsymmetrical expected imine. Less activated pyridinemethanamines could be also N-alkylated with phenylpropylamine by the present biomimetic electrocatalytic system (entries 6−8, Table 2).

Finally, the possibility to apply our methodology to nonactivated primary amines was briefly examined using aminomethylcyclopropane as the amine substrate and phenylpropylamine as the alkylating agent (Scheme 2). The yield of isolated product (48%) was lower than that expected on the basis of the high current efficiency (95% for 3 h),[9b] probably as a result of the lower stability of the produced secondary alkylamine during workup. However, this moderate yield is redeemed by the simplicity and the rapidity of our approach which could be useful for the assembly of libraries.

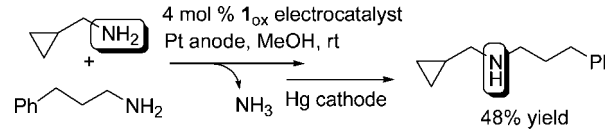
Table 2. Electrocatalyzed N-Alkylation of Different Activated Primary Amines with Phenylpropylamine[a]



entry	amine substrate	product	yield%[b]
1			68[c]
2			62[c]
3			65[c]
4			68[c]
5			51[d]
6			61[e]
7			56[e]
8			58[e]

[a] Reagents and conditions: (amine substrate) = 10 mM, (phenylpropylamine) = 15 mM, ($\mathbf{1_{ox}}$) = 0.4 mM (4 mol % relative to the amine substrate), MeOH, rt. Oxidation−imine formation step: Pt anode (E = +0.6 V vs SCE), 3 h. Reduction step: Hg cathode (E = −1.6 V vs SCE), 1 h. [b] Yields refer to chromatographically pure isolated products and are relative to the amine substrate. [c] Substituted dibenzylamine was formed as a byproduct (5−10%). [d] Bisnaphtalen-2-yl-methylamine was isolated as a byproduct in 25% yield. [e] *N*-(Pyridinylmethyl)pyridinemethanamine was formed as a byproduct: 4%, entry 6; 12%, entry 7; 11%, entry 8.

Scheme 2. Electrocatalyzed N-Alkylation of Nonactivated Aminomethylcyclopropane with Phenylpropylamine



Supporting Information Available:

Figure 1, general experimental procedure, high-field ^{1}H NMR spectra for known compounds as a criterion of purity, and characterization data for new secondary amines, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The formation of related diamines has already been observed from the one-electron cathodic reduction of aldimines. See, for example: (a) Tanaka, H.; Nakahara, T.; Dhimane, H.; Torii, S. *Synlett* **1989**, 51–52. (b) Largeron, M.; Fleury, M.-B. *J. Org. Chem.* **2000**, *65*, 8874–8881. (c) Siu, T.; Li, W.; Yudin, A. K. *J. Comb. Chem.* **2001**, *3*, 554–558.

(12) (a) Togrul, M.; Turgut, Y.; Hosgoren, H. *Chirality* **2004**, *16*, 351–355. (b) Togrul, M.; Askin, M.; Hosgoren, H. *Tetrahedron: Asymmetry* **2005**, *16*, 2771–2777.