Angewandte
International Edition Chemie

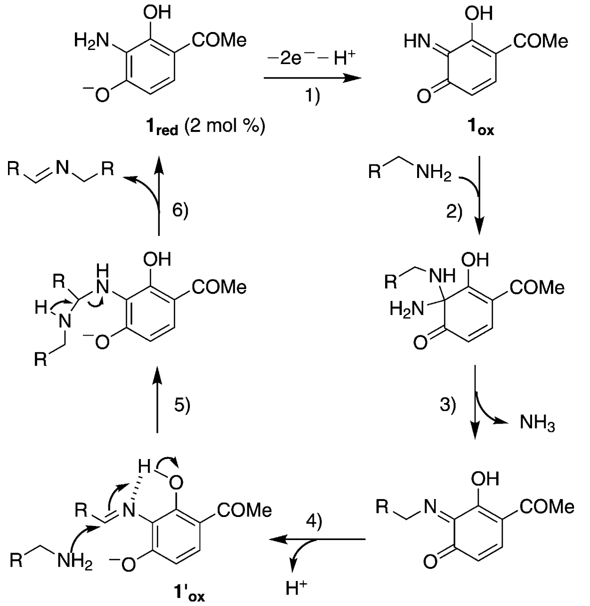
Homogeneous Catalysis

DOI: 10.1002/anie.201200587

A Biologically Inspired Cu^I/Topaquinone-Like Co-Catalytic System for the Highly Atom-Economical Aerobic Oxidation of Primary Amines to Imines

Martine Largeron and Maurice-Bernard Fleury*

Imines are versatile synthetic intermediates in a variety of organic transformations and are essential pharmacophores in numerous biologically active compounds.[1] Great progress has been made in the past decade for the synthesis of imines, including oxidation of secondary amines,[2] oxidative self- or cross-coupling of primary amines,[3] and direct synthesis from amines and alcohols in the presence of a catalyst.[4] However, most of the methods have some limitations, such as prolonged reaction times, high reaction temperatures, environmentally unfriendly oxidants, or low selectivity. Furthermore, metal-catalyzed oxidation reactions often utilize expensive and limited available precious metals such as palladium, ruthenium, gold, iridium, and vanadium. Consequently, the development of new efficient environmentally benign procedures for the synthesis of imines continues to be a challenging and active area of research.[5]



Scheme 1. Ionic transamination mechanism of the catalytic oxidation of primary amines to imines mediated by electrogenerated *o*-iminoquinone $\mathbf{1}_{ox}$, which mimics the cofactor of amine-oxidases.

Simulation of the functions of amine oxidase enzymes that govern the metabolism of amines may also lead to the development of methods for the biomimetic catalytic oxidation of amines to imines under mild conditions.[6] In this respect, we recently found that the electrogenerated *o*-iminoquinone species $\mathbf{1}_{ox}$ (step 1, Scheme 1) was able to replicate the activity and specificity of copper-containing amine oxidases (CuAOs) toward primary amines.[7] The catalytic cycle produced *N*-alkylidenealkylamine as the product of amine oxidation through the ionic pyridoxal-like transamination process reported for CuAO cofactors (Scheme 1). The rate-limiting step involves α-proton abstraction and the subsequent electron flow from the α-carbon atom to the *o*-iminoquinone moiety, which aromatizes to the highly reactive Schiff base cyclic transition state $\mathbf{1'}_{ox}$ (step 4, Scheme 1), thus allowing the activation of the imine function for further nucleophilic attack by the amine (step 5, Scheme 1).[7b] This $\mathbf{1}_{ox}$-mediated electrocatalytic oxidation of primary amines allowed the generation of unstable imines (step 6, Scheme 1) under metal-free conditions, without any stoichiometric reagents, at ambient atmosphere. These conditions are particularly favorable for using the imine in situ for further reactions. For example, we have recently developed a facile one-pot metal-free $\mathbf{1}_{ox}$-mediated oxidation/imine formation/reduction sequence for the atom-economical chemoselective N-alkylation of benzylic primary amines with amines; this sequence allows the synthesis of benzylic secondary amines, under mild conditions.[8]

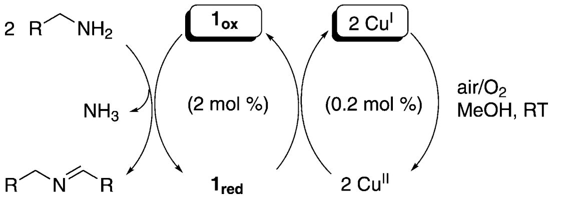
Nevertheless, it seemed doubtful that our electrochemical procedure[7] will ever be able to compete with more conventional chemical approaches at a large preparative scale. In contrast, the process would be most attractive if $\mathbf{1}_{ox}$ could be generated through aerobic oxidation of $\mathbf{1}_{red}$. So, inspired by the enzymatic reaction of CuAOs[9] and by recent breakthroughs on the aerobic oxidation of amines to imines,[5,6] we demonstrate herein that a synergistic combination of copper and organocatalyst $\mathbf{1}_{ox}$ constitutes a novel approach to imines from primary amines, under very mild conditions, which include dioxygen in air as the oxidant together with ambient temperature and pressure.

Based on the efficient reactivity between electrocatalyst $\mathbf{1}_{ox}$ and various amines,[7] we hypothesized that the oxidation process started with atmospheric oxygen, as shown in Scheme 2, and continued in a cascade-like manner by passing the oxidation potential of oxygen through copper salt to the organic *o*-iminoquinone mediator $\mathbf{1}_{ox}$, which finally oxidized the amine substrate after forming the Schiff base cyclic transition state $\mathbf{1'}_{ox}$ (step 4, Scheme 1). To evaluate the validity

---

[*] Dr. M. Largeron, Prof. Dr. M.-B. Fleury
Université Paris Descartes, UMR CNRS 8638
4, avenue de l'Observatoire, 75270 Paris Cedex 06 (France)
E-mail: martine.largeron@parisdescartes.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201200587.

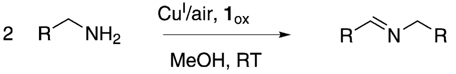


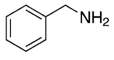
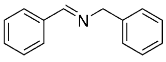
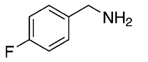
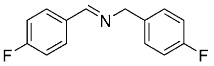
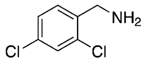
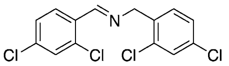
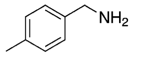
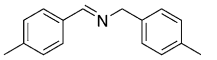
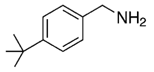
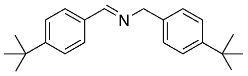
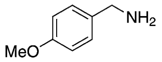
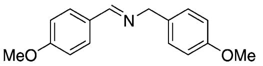
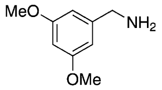
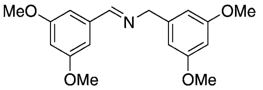
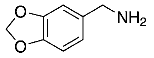
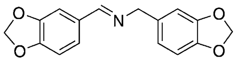
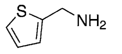
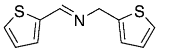
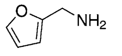
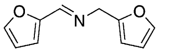
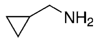
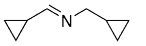
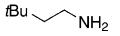
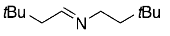
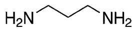
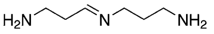
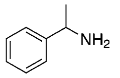
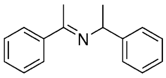
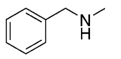
Scheme 2. Aerobic oxidation of primary amines to imines catalyzed by Cu^I/*o*-iminoquinone $\mathbf{1}_{ox}$.

of this concept, we began our investigations with benzylamine as the amine substrate. If our hypothesis is right, part of the optimum conditions should be identical to that required for the electrochemical process. Accordingly, MeOH was preferred over other solvents, such as THF, MeCN, or $CHCl_3$, because strong solvation of the *o*-iminoquinone $\mathbf{1}_{ox}$ by MeOH was necessary to enhance the electrophilicity of its quinonoid moiety, thereby favoring the nucleophilic attack (step 2, Scheme 1) of the amine. Likewise, a combination of one equivalent of amine with 0.02 equivalent of $\mathbf{1}_{red}$,[10] which corresponds to 2 mol % of organocatalyst $\mathbf{1}_{ox}$, was found to be ideal for the reaction.[7b] In the absence of copper catalyst, the reaction proceeded very slowly, and the conversion of benzylamine into *N*-benzylidenebenzylamine reached 66 % in seven days, owing to the slow spontaneous aerobic oxidation of $\mathbf{1}_{red}$. When, in turn, 0.2 mol % of copper(I) 3-methylsalicylate (CuMeSal) was added as the co-catalyst (0.002 equiv), only ten hours were needed for full conversion of benzylamine (85 % conversion after three hours). Then, *N*-benzylidenebenzylamine was isolated in 96 % yield as the sole product (as observed by ^{1}H NMR spectroscopy) after evaporation of the solvent at ambient temperature. No improvements were observed when Cu^I loading was increased. Different copper catalysts such as CuI and $Cu(OAc)_2$ were also screened. All the copper salts catalyzed the reaction, but a reduction of reaction time was observed with CuMeSal. In a separate control experiment, $\mathbf{1}_{red}$ was fully omitted from the reaction mixture. Then, no reaction occurred at room temperature when copper was used as the sole catalyst.[5a,d] Interestingly, when monitoring the progress of the synergistic catalytic process in MeOD by ^{1}H NMR spectroscopy, we found that only *N*-benzylidenebenzylamine was formed, with no evidence for the formation of benzaldehyde; this result is in agreement with the formation of the Schiff base intermediate $\mathbf{1'}_{ox}$ as shown in Scheme 1 (step 4).

Next, the scope of the biomimetic $Cu^I/\mathbf{1}_{ox}$ co-catalytic system was examined with regard to a range of structurally diverse primary amines. High catalytic activity was found for the conversion of benzylic amines (Table 1, entries 1–8), and the imine product yield did not markedly depend on the substitution of the phenyl ring. In particular, halo-substituted benzylamines (Table 1, entries 2 and 3) performed well and lead to halo-substituted imines, which could be used for further transformations along with the imine functionality. It should be noted that this approach was also applicable to heteroatom-containing amine substrates, such as thiophene (Table 1, entry 9) and furan (entry 10), the imine products of which are usually inaccessible by transition-metal-complex catalysis because of deactivation of the catalysts, which is caused by the strong coordination of these amines to the metal center. The synthesis of aliphatic imines is inherently more challenging because of their instability and difficult isolation. Therefore, the possibility of expanding the scope of this novel method to the synthesis of aliphatic imines was also explored (Table 1, entries 11–13). Although *N*-alkylidenealkylamine could be observed during the first hours of the reaction through monitoring the ^{1}H NMR spectrum (see the Supporting Information), its instability did not permit to isolate it as such. Consequently, the yield was obtained by conversion to the 2,4-dinitrophenylhydrazone (DNPH) by aqueous acidic work-up of the reaction mixture with 2,4-dinitrophenylhydrazine.[7b] Interestingly, as for the CuAOs, α-branched amines (Table 1, entry 14) were found to be inferior

Table 1: Aerobic $Cu^I/\mathbf{1}_{ox}$-catalyzed oxidation of different amines.[a]



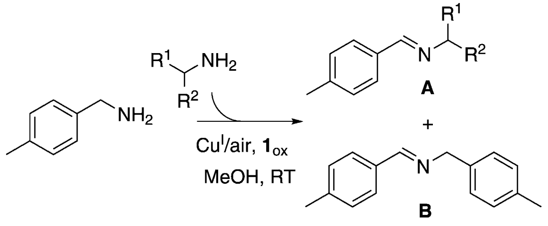
Entry	Substrate	Product	Yield[b] [%]
1			96
2			93
3			90[c]
4			97
5			96
6			95
7			85
8			88[c]
9			88
10			78
11			40[d]
12			50[d]
13			55[d]
14			25[d]
15		–	0

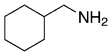
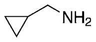
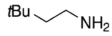
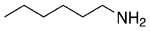
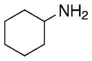
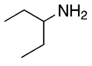
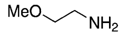
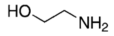
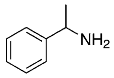
[a] Reagents and conditions: amine substrate (20 mм); $\mathbf{1}_{ox}$ (0.4 mм; 2 mol % relative to amine); Cu^I: CuMeSal (0.04 mм; 0.2 mol % relative to amine); MeOH (10 mL), 10 h, RT. [b] Yields of the imine refer to the isolated unpurified product, which, unless otherwise stated, was pure by ^{1}H NMR spectroscopy (see the Supporting Information). [c] Imine product directly precipitated in the bulk solution. [d] Yields obtained by conversion to the corresponding DNPH by aqueous acidic work-up of the reaction mixture with 2,4-dinitrophenylhydrazine.

substrates for the biomimetic $Cu^I/\mathbf{1}_{ox}$ co-catalytic system, whereas secondary amines were not reactive at all (entry 15).

In subsequent studies, we attempted the synthesis of cross-coupling products **A** by reacting 4-methylbenzylamine in the presence of different primary amines (Table 2). The real-time monitoring of the reaction between 4-methylbenzylamine and aminomethylcyclohexane (equimolar amounts) by ^1H NMR spectroscopy indicated that both self-coupling product **B** (singlet around $\delta = 8.40$ ppm) and cross-coupling product **A** (singlet around $\delta = 8.20$ ppm) were initially formed, with a preference for homo-coupling product **B** (see Figure 1 in the Supporting Information, spectra a and b). However, after 30 min, imine **B** gradually turned to cross-coupling product **A**, which finally became the major product after ten hours (spectra c and d, Figure 1 in the Supporting Information). From these results, we envision two different pathways. First, homo-coupling product **B** is extruded as the sole imine product through the reaction shown in Scheme 1 and further N-alkylated by the second primary amine. In this case, copper could promote reaction of the homo-coupling product **B** with the alkylating primary amine through an addition–elimination mechanism leading to the cross-coupling product **A**. Second, both homo- and cross-coupling products are produced competitively through the reaction shown in Scheme 1 (steps 5 and 6). At this point, it seems that the formation of the cross-coupling product **A** would preferably result from the nucleophilic attack by the alkylating aliphatic primary amine on the Schiff base intermediate $\mathbf{1'}_{ox}$ (step 5, Scheme 1). Accordingly, the presence of an excess of the alkylating primary amine (2 equiv) did not increase the amount of cross-coupling product **A** versus that of homo-coupling product **B**, and 4-methylbenzaldehyde has never been observed during the catalytic process. As shown in Table 2, a good imine selectivity was observed in all cases. Note that the $Cu^I/\mathbf{1}_{ox}$-catalyzed aerobic oxidative imination of 4-methylbenzylamine by ethanolamine showed good tolerance of an alcohol group (Table 2, entry 8).

Table 2: Aerobic $Cu^I/\mathbf{1}_{ox}$-catalyzed oxidative cross-coupling of amines.[a]



Entry	Alkylating amine	Imine selectivity A:B[b]
1		85:15
2		83:17
3		70:30
4		81:19
5		79:21
6		95:5
7		76:24
8		80:20
9		98:2

[a] Reagents and conditions: 4-methylbenzylamine (10 mM), alkylating amine (10 mM), $\mathbf{1}_{ox}$ (0.4 mM; 4 mol% relative to amine), Cu^I: CuMeSal (0.04 mM; 0.4 mol% relative to amine), MeOH (10 mL), 10 h, RT; the conversion of 4-methylbenzylamine was roughly quantitative in all cases. [b] Molar ratio based on the ^1H NMR spectrum of the crude product.

In conclusion, we have achieved chemoselective biologically inspired $Cu^I/\mathbf{1}_{ox}$-mediated aerobic oxidation of primary amines. Low catalytic amounts of biocompatible Cu^I metal catalyst (0.2 mol%) and organocatalyst $\mathbf{1}_{ox}$ (2 mol%) are sufficient to activate the α-C–H bond of primary amines which are converted into alkylated imines under ambient conditions. This atom-economical green process tolerates the presence of various reactive functional groups and is highly selective in the case of cross-coupling of two amines. Studies are underway to investigate further synthetic applications.

Experimental Section

N-Benzylidenebenzylamine.[11] Typical procedure: Benzylamine (5 mmol, 1 equiv), reduced organocatalyst $\mathbf{1}_{red}$ (0.1 mmol, 0.02 equiv),[10] and copper 3-methylsalicylate (0.01 mmol, 0.002 equiv) were mixed in MeOH (10 mL) in an air atmosphere. The reaction mixture was stirred at room temperature for ten hours. The progress of the reaction was monitored by ^1H NMR spectroscopy. After completion of the reaction, the solvent was evaporated at room temperature to give *N*-Benzylidenebenzylamine as an almost pure product, the identity and purity of which were confirmed by ^1H and ^{13}C NMR spectroscopy, after comparison with an authentic sample.

Received: January 20, 2012

Keywords: amines · chemoselectivity · imines · oxidation · homogeneous catalysis

---

[1] For a review on the synthesis of imines see: J. P. Adams, *J. Chem. Soc. Perkin Trans. 2* **2000**, 125–139.
[2] For selected recent examples, see: a) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *Angew. Chem.* **2003**, *115*, 4211–4216; *Angew. Chem. Int. Ed.* **2003**, *42*, 4077–4082; b) K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2003**, *115*, 1518–1521; *Angew. Chem. Int. Ed.* **2003**, *42*, 1480–1483; c) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5196–5201; d) J. W. Wang, Y. Fu, B.-B. Zhang, X. Cui, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2006**, *47*, 8293–8297; e) H. Choi, M. P. Doyle, *Chem. Commun.* **2007**, 745–747; f) N. Mizuno, K. Yamaguchi, *Catal. Today* **2008**, *132*, 18–26; g) G. Jiang, J. Chen, J.-S. Huang, C.-M. Che, *Org. Lett.* **2009**, *11*, 4568–4571; h) R. Yamaguchi, C. Ikeda, Y. Takahashi, K.-I. Fugita, *J. Am. Chem. Soc.* **2009**, *131*, 8410–8412.
[3] a) S. I. Murahashi, Y. Okano, H. Sato, T. Nakae, N. Komiya, *Synlett* **2007**, 1675–1678; b) B. Zhu, M. Lazar, B.-G. Trewyn, R.-J. Angelici, *J. Catal.* **2008**, *260*, 1–6; c) L. Aschwanden, T. Mallat, F. Krumeich, A. Baiker, *J. Mol. Catal. A* **2009**, *309*, 57–62; d) M.-H. So, Y. Liu, C.-M. Ho, C.-M. Che, *Chem. Asian J.* **2009**, *4*, 1551–1561; e) A. Dhakshinamoorthy, M. Alvaro, H. Garcia,

ChemCatChem **2010**, *2*, 1438 – 1443; f) S. Kodama, J. Yoshida, A. Nomoto, Y. Ueta, S. Yano, M. Ueshima, A. Ogawa, *Tetrahedron Lett.* **2010**, *51*, 2450 – 2452; g) W. He, L. Wang, C. Sun, K. Wu, S. He, J. Chen, P. Wu, Z. Yu, *Chem. Eur. J.* **2011**, *17*, 13308 – 13317.

[4] a) L. Blackburn, R. J. K. Taylor, *Org. Lett.* **2001**, *3*, 1637 – 1639; b) M. S. Kwon, S. Kim, S. Park, W. Bosco, R. K. Chidrala, J. Park, *J. Org. Chem.* **2009**, *74*, 2877 – 2879; c) J. W. Rigoli, S. A. Moyer, S. D. Pearce, J. M. Schomaker, *Org. Biomol. Chem.* **2012**, *10*, 1746 – 1749.

[5] For recent environmentally benign new methods, see: a) J. Srogl, S. Voltrova, *Org. Lett.* **2009**, *11*, 843 – 845; b) B. Gnanaprakasam, J. Zhang, D. Milstein, *Angew. Chem.* **2010**, *122*, 1510 – 1513; *Angew. Chem. Int. Ed.* **2010**, *49*, 1468 – 1471; c) G. Chu, C. Li, *Org. Biomol. Chem.* **2010**, *8*, 4716 – 4719; d) R. D. Patil, S. Adimurthy, *Adv. Synth. Catal.* **2011**, *353*, 1695 – 1700; e) L. Liu, S. Zhang, X. Fu, C.-H. Yan, *Chem. Commun.* **2011**, *47*, 10148 – 10150; f) X. Lang, H. Ji, C. Chen, W. Ma, J. Zhao, *Angew. Chem.* **2011**, *123*, 4020 – 4023; *Angew. Chem. Int. Ed.* **2011**, *50*, 3934 – 3937; g) L. Jiang, L. Jin, H. Tian, X. Yuan, X. Yu, Q. Xu, *Chem. Commun.* **2011**, *47*, 10833 – 10835; h) Y. Shiraishi, M. Ikeda, D. Tsukamoto, S. Tanaka, T. Hirai, *Chem. Commun.* **2011**, *47*, 4811 – 4813; i) Z. Hu, F. M. Kerton, *Org. Biomol. Chem.* **2012**, *10*, 1618 – 1624; j) X. Lang, W. Ma, Y. Zhao, C. Chen, H. Ji, J. Zhao, *Chem. Eur. J.* **2012**, *18*, 2624 – 2631.

[6] For recent reviews, see: a) M. Mure, *Acc. Chem. Res.* **2004**, *37*, 131 – 139; b) J. Piera, J. E. Bäckvall, *Angew. Chem.* **2008**, *120*, 3558 – 3576; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506 – 3523. See also: c) A. H. Éll, J. S. M. Samec, C. Brasse, J. E. Bäckvall, *Chem. Commun.* **2002**, 1144 – 1145; d) J. S. M. Samec, A. H. Ell, J. E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 2327 – 2334.

[7] a) M. Largeron, A. Neudörffer, M.-B. Fleury, *Angew. Chem.* **2003**, *115*, 1056 – 1059; *Angew. Chem. Int. Ed.* **2003**, *42*, 1026 – 1029; b) M. Largeron, A. Chiaroni, M.-B. Fleury, *Chem. Eur. J.* **2008**, *14*, 996 – 1003; c) M. Largeron, M.-B. Fleury, M. Strolin Benedetti, *Org. Biomol. Chem.* **2010**, *8*, 3796 – 3800.

[8] a) M. Largeron, M.-B. Fleury, *Org. Lett.* **2009**, *11*, 883 – 886; b) M. Largeron, *Electrochim. Acta* **2009**, *54*, 5109 – 5115.

[9] S. Suzuki, T. Okajima, K. Tanizawa, M. Mure in *Copper Amine Oxidases. Structures, Catalytic Mechanisms, and Role in Pathophysiology* (Eds.: G. Floris, B. Mondovi), CRC, Taylor and Francis Group Publishing, New York, **2009**, p. 19.

[10] Reduced catalyst $\mathbf{1}_{\mathbf{red}}$ can be easily prepared in two steps from commercially available 2-nitroresorcinol, according to our published procedure: D. Xu, A. Chiaroni, M.-B. Fleury, M. Largeron, *J. Org. Chem.* **2006**, *71*, 6374 – 6381 (See the Supporting Information).

[11] For the analytical data of *N*-benzylidenebenzylamine, see P. G. M. Wuts, Y.-W. Jung, *J. Org. Chem.* **1991**, *56*, 365 – 372.