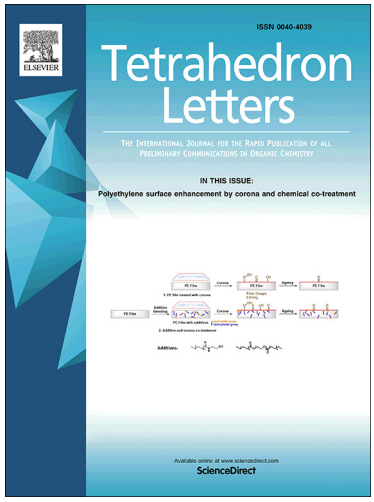

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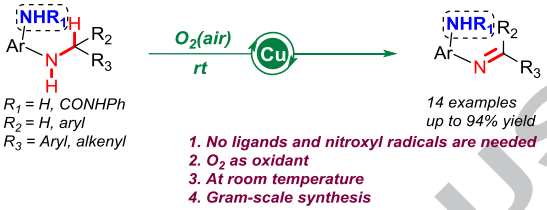

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Chemoselective aerobic oxidation of 2-amino-*N*-benzylanilines into *N*-(2-aminophenyl)imines via a nitroxide-free copper catalysis

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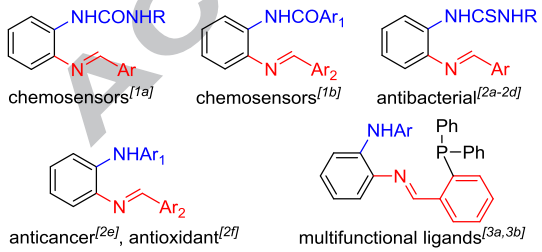
ABSTRACT

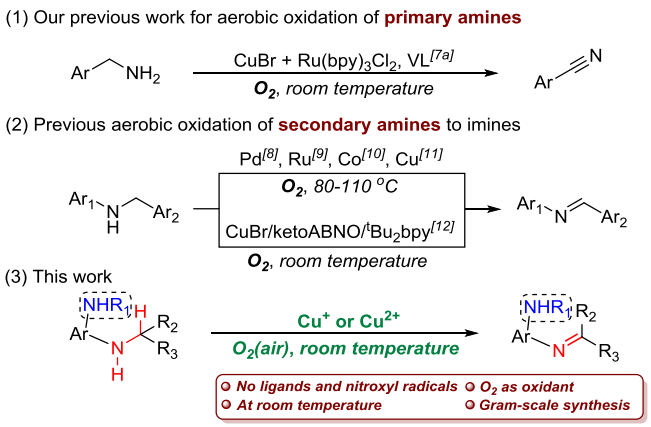
Chemoselective oxidative synthesis of *N*-(2-aminophenyl)imines from 2-amino-*N*-benzylanilines was accomplished through combined use of O_2(air) and copper salt. This transformation was performed at room temperature, and the mild oxidation was efficient and chemoselective without using nitroxyl radicals and ligands.

N-(2-aminophenyl)imines are not only valuable structural motifs in a variety of chemosensors [1] and bioactive molecules [2], but also serve as building blocks to produce multidentate ligands which were extensively studied in the transition metal catalysis (Scheme 1) [3]. Development of new methods for the synthesis of *N*-(2-aminophenyl)imines is of significant interest. Recently, great progress has been made in oxidative dehydrogenation of amines to synthesize imines [4]. Nevertheless, oxidative synthesis of the *N*-(2-aminophenyl)imines from corresponding amines is more challenging since oxidation of the amino is generally more facile than oxidation of the carbon atom, and amines tend to deactivate metal catalysis.



Scheme 1. Selected important compounds containing the *N*-(2-aminophenyl)imine core.

Oxidation of organic compounds with O_2 as a sole oxidant has remarkable advantages, including its abundance, low cost, and benign by-products (usually H_2O). For this reason, considerable efforts have been devoted in recent years to develop transition-metal-catalyzed aerobic oxidation reactions [5, 6]. One such example is aerobic oxidation of amines to afford imines or nitriles. Our group [7a] and others [7b, 7c] have developed copper catalyst systems to directly convert benzylic amines into aryl nitriles or imines (Scheme 2). When referred to secondary amines, homogeneous catalysts for aerobic oxidative synthesis of imines have been studied using Pd [8], Ru [9], Co [10] and Cu [11]. These reactions represented major advances in the imine synthesis, but usually were carried out at 80–100°C. Recently, Oisaki and Kanai reported an efficient copper catalyst system for aerobic oxidation of secondary amines to imines at room temperature. Nitroxyl radical compound ketoABNO (9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl) and ligand $^tBu_2$bpy were critical for the transformation (Scheme 2) [12].



Scheme 2. Homogeneous transition-metal-catalyzed aerobic oxidation of amines.

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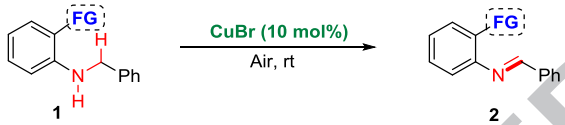
As part of our ongoing efforts to develop aerobic oxidation of amines [7a], herein, we disclose a homogeneous copper catalysis to accomplish efficient conversion secondary amines into the corresponding aldimines and ketimines at room temperature (Scheme 2). Without the need of nitroxyl radical and ligands, the reaction occurred effectively at room temperature. This new approach is versatile for various 2-amino group, including $–NH_2$, –NHCOR and –NHCONHPh, to yield the important framework of *N*-(2-aminophenyl)imines. Moreover, the catalytic system expands the toolbox for synthesis of imines through aerobic oxidation of amines at room temperature.

Initially, we attempted to perform the reaction by treating secondary amine (**1a**) with O_2(air) as the oxidant at room temperature. As shown in Table 1, with CuBr as the catalyst, aerobic oxidation of amine (**1a**) was unsuccessful (entry 1), and no imine product was detected. Then, we systematically evaluated different amino groups at 2-position of *N*-benzylaniline. Successfully, dramatic improvement was observed when 2-amino-*N*-benzylaniline (**1b**) was chosen as substrate, and 87% yield of *N*-(2-aminophenyl)imines (**2b**) was isolated (entry 2). The reaction exhibited high chemoselectivity between the amino and carbon atom. Changing the amino into (4-methylphenyl)sulfonamido failed to oxidize the amine (entry 3). After screening other amino group, we found benzamido and (tert-butoxycarbonyl)amino groups gave moderate yields (entries 4–5). Delightfully, when 2-(3-phenylureido)-*N*-benzylaniline (**1f**) was selected as starting material, the yield of oxidation product (**2f**) was up to 94% (entry 6).

Table 1. Screening the amino groups for copper-catalyzed aerobic oxidation of secondary amines to imines [a]



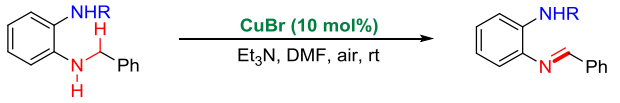
1 2

Entry	Amine **1**	-FG	Imine **2**	Yield [b]/%
1	**1a**	–H	**2a**	0
2	**1b**	$–NH_2$	**2b**	87
3	**1c**	–NHTs	**2c**	0
4	**1d**	–NHCOPh	**2d**	57
5	**1e**	–NHBoc	**2e**	54
6	**1f**	–NHCONHPh	**2f**	94

[a] Reaction conditions: 0.2 mmol amine **1**, 10 mol% CuBr, 0.8 mmol Et_3N, 0.5 mL DMF, room temperature (22-25 °C), air, 5 h. [b] The yields are isolated yields.

Next, we evaluated the reaction parameters in the copper-catalyzed aerobic oxidation of secondary amines to imines (Table 2). Initially, we assessed the reaction conditions for 2-amino-*N*-benzylaniline (**1b**). Cuprous and cupric salts gave high yields in the aerobic oxidation of secondary amines to imines (entries 1–3). For 2-(3-phenylureido)-*N*-benzylaniline (**1f**), various copper salts were evaluated in the atmosphere at room temperature. It was found that the copper sources with different valences all gave excellent yields (entries 4–9) and the yield was up to 94% with CuBr (entry 4). Using CuBr as a catalyst at room temperature, the solvents were screened (entries 10–13). It was found that good yields of the desired products were obtained in MeOH (entry 10) and DCM (entry 11), and moderate yields were obtained in THF (entry 12) and Toluene (entry 13). When we replaced the additive triethylamine with pyridine, the yield of imine decreased, which may be related to the decrease of alkalinity (entry 14). We tried to reduce the amount of the trimethylamine, however, the yield of imine was decreased (entry 15).

Table 2. Optimizing the reaction conditions for copper-catalyzed aerobic oxidation of secondary amines to imines [a]



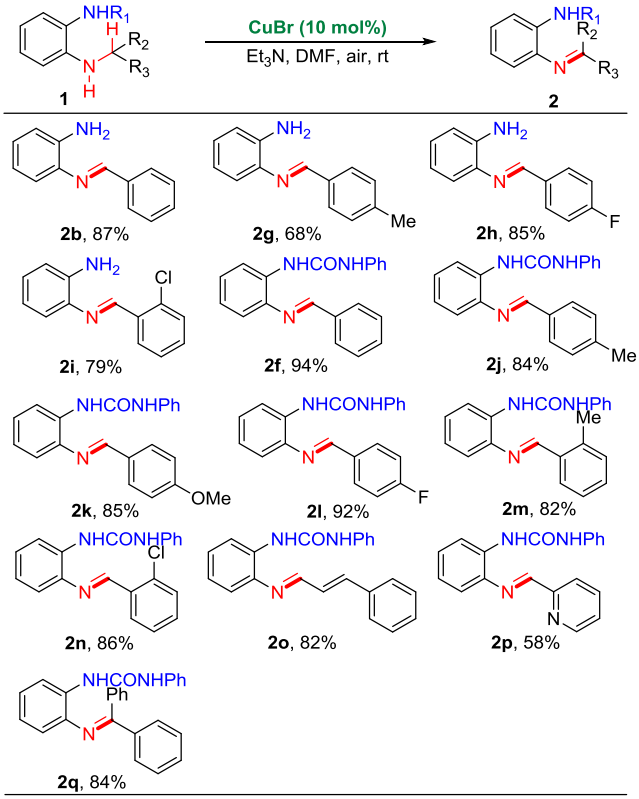
1b, *R = H* **2b**
1f, *R = CONHPh* **2f**

Entry	**1**	Change from optimal conditions	**2**	Yield[b]/%
1	**1b**	none	**2b**	**87**
2	**1b**	CuCl instead of CuBr	**2b**	75
3	**1b**	$Cu(OAc)_2$ instead of CuBr	**2b**	80
4	**1f**	none	**2f**	**94**
5	**1f**	CuCl instead of CuBr	**2f**	84
6	**1f**	$CuBr_2$ instead of CuBr	**2f**	82
7	**1f**	$CuCl_2$ instead of CuBr	**2f**	82
8	**1f**	$Cu(OAc)_2$ instead of CuBr	**2f**	77
9	**1f**	$Cu(NO_3)_2$ instead of CuBr	**2f**	67
10	**1f**	MeOH instead of DMF	**2f**	71
11	**1f**	CH_2Cl_2 instead of DMF	**2f**	77
12	**1f**	THF instead of DMF	**2f**	50
13	**1f**	Toluene instead of DMF	**2f**	48
14	**1f**	Py instead of Et_3N	**2f**	28
15	**1f**	Amount of Et_3N is 2 eq.	**2f**	82

[a] Reaction conditions: 0.2 mmol amine **1**, 10 mol% catalyst loading, 0.8 mmol additive, 0.5 mL solvent, room temperature (22-25 °C), air, 5h. [b] The yields are isolated yields.

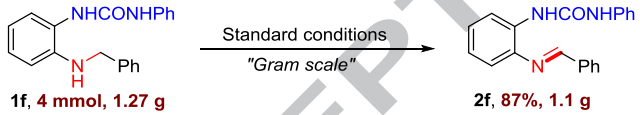
The above results show that CuBr/Et_3N/DMF is an efficient combination for the aerobic synthesis of *N*-(2-aminophenyl)benzaldimines from amines. Using the optimized conditions, we next explored the scope and generality of the process (Table 3). The reaction was proven to be effective for 2-amino-*N*-benzylaniline carrying electron-donating and electron-withdrawing groups on benzyl scaffold. The good to excellent isolated yields of aldimines were obtained (68–87%, **2b, 2g**–**2i**), and the group $–NH_2$ was well tolerated in the oxidation reactions. It was found that benzyl scaffolds of 2-(3-phenylureido)-*N*-benzylicanilines carrying electron-donating and electron-withdrawing groups could be smoothly converted into the imines with good to excellent isolated yields (up to 94%, **2f, 2j**–**2l**). The substrates carrying an ortho-substituent on the benzyl group were also found to readily participate in the reaction (82–86%, **2m**, **2n**). When 2-(3-phenylureido)-*N*-cinnamylaniline was used as substrate, the reaction gave 82% yield of the corresponding imine (**2o**). The catalysis was also tolerant of heteroaryl group, and pyridyl-containing aniline reacted smoothly to afford the corresponding aldimine in moderate yield (58%, **2p**). In addition, *N*-benzhydrylaniline also could be converted into ketimine under the standard conditions, and excellent yield was obtained (84%, **2q**).

Table 3. The scope and generality of copper-catalyzed aerobic oxidation of secondary amines to imines [a,b]



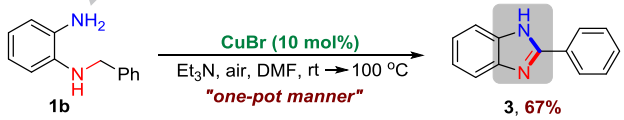
[a] Reaction conditions: 0.4 mmol amine **1**, 10 mol% CuBr, 1.6 mmol triethylamine, 0.5 mL DMF, room temperature (22-25 °C), air, 5 h. [b] The yields are isolated yields.

To showcase the scalability of this process, a gram-scale reaction was performed with 2-(3-phenylureido)-*N*-benzylaniline (**1f**). Gratifyingly, secondary amine (**1f**) underwent efficient oxidation on gram-scale (4 mmol/1.27 g) resulting in an 87% isolated yield of the imine (**2f**, 1.1g) without modification of the optimized conditions (Scheme 3).



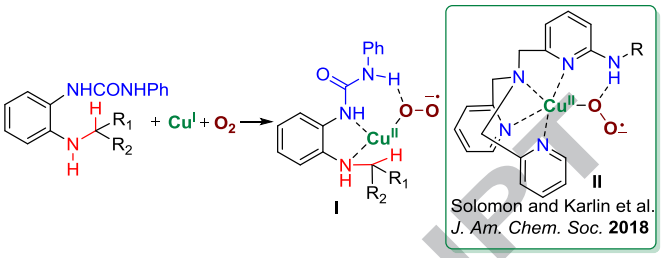
Scheme 3. Gram-scale aerobic oxidative synthesis of imine.

To further demonstrate the synthetic utility and compatibility of this process, sequential aerobic oxidation/cyclization/aerobic oxidation reactions were performed with 2-amino-*N*-benzylaniline (**1b**) as starting material. 2-Substituent benzoimidazole (**3**, 67%) was successfully obtained in one-pot manner, which is important compound in organic chemistry and medicinal chemistry (Scheme 4).



Scheme 4. Synthetic utilities of the aerobic oxidation of 2-amino-*N*-benzylaniline.

As to the mechanism of copper-catalyzed aerobic oxidation of 2-amino-*N*-benzylanilines to *N*-(2-aminophenyl)imines, we have to point out the special effect of amino group on the 2-position of *N*-benzylanilines. We hypothesized that the amino group may chelate the copper catalyst and facilitate its aerobic oxidation. Besides, the intramolecular hydrogen bonding could stabilize the intermediate **I** (Scheme 5). Interestingly, this hypothesis had some literature support, since Solomon et al. reported in 2018 a very interesting finding that intramolecular hydrogen bonding enhanced stability and reactivity of mononuclear cupric superoxide complexes (**II**) [13].



Scheme 5. The postulated mechanism for the copper-catalyzed aerobic oxidation of 2-amino-*N*-benzylanilines.

In summary, we have developed an aerobic oxidative synthesis of imines from secondary amines. With copper as catalyst, the conversion of 2-amino-*N*-benzylanilines into aldimines and ketimines were realized with O_2(air) as the oxidant. This new protocol combined copper in a single reaction system and showed great substrate tolerance providing efficient access to a variety of imines in a highly concise fashion. Further studies on the mechanism of this process is underway. Given the fact that *N*-(2-aminophenyl)imines play an important role in chemosensors and bioactive molecules, we anticipate this method will find practical applications in various synthesis of relevant imines.

Acknowledgments

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Highlights

- Copper as catalyst, without nitroxyl radicals and ligands
- Molecular oxygen as the sole oxidant at room temperature.
- Gram-scale synthesis