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Cu/Nitroxyl-Catalyzed Aerobic Oxidation of Primary Amines into Nitriles at Room Temperature

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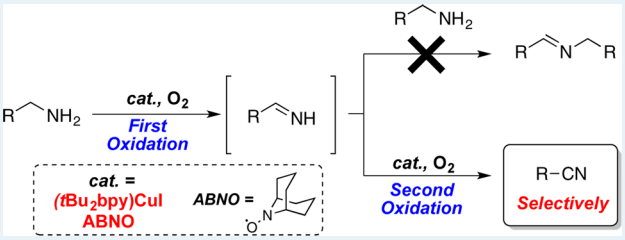
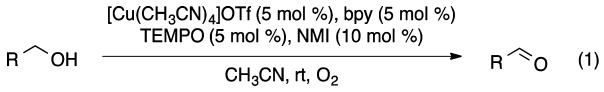
Supporting Information

ABSTRACT: An efficient catalytic method has been developed for aerobic oxidation of primary amines to the corresponding nitriles. The reactions proceed at room temperature and employ a catalyst consisting of (4,4′-^{t}Bu$_2$bpy)CuI/ABNO (ABNO = 9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl). The reactions exhibit excellent functional group compatibility and substrate scope and are effective with benzylic, allylic, and aliphatic amines. Preliminary mechanistic studies suggest that aerobic oxidation of the Cu catalyst is the turnover-limiting step of the reaction.



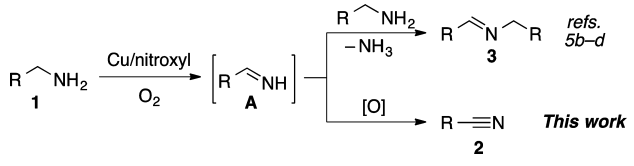
KEYWORDS: *aerobic oxidation, copper, nitroxyl, nitrile, amine oxidation*

Homogeneous (bpy)Cu/TEMPO and related catalyst systems have emerged as some of the most effective catalysts for aerobic oxidation of alcohols and amines.[1,2] Catalyst systems of this type can be traced to the 1960s,[3] but they have become the focus of extensive investigation and development in recent years.[4−6] In 2011, we reported a (bpy)Cu^I/TEMPO catalyst system that mediates efficient aerobic oxidation of primary alcohols to aldehydes (eq 1).[4i,j]



The reactions exhibit broad substrate scope and are compatible with benzylic, allylic, and aliphatic alcohols bearing diverse functional groups. We envisioned that amine oxidation (i.e., C−N dehydrogenation) could be achieved using a similar Cu/nitroxyl-based catalyst system. Several other groups recently reported important progress in this area. For example, Kerton,[5b] Kanai,[5c] and Xu[5d] demonstrated that various Cu/nitroxyl catalyst systems promote aerobic oxidation of primary amines to the corresponding homocoupled imines **3** (Scheme 1).[7] The production of homocoupled imines suggests that condensation of a second amine with the primary imine intermediate **A** is more facile than oxidation of **A** to the corresponding nitrile **2**. Here, we report a Cu/nitroxyl system that enables selective formation of nitriles from diverse primary amines. The room temperature reaction conditions are very convenient and much more mild than other catalytic methods for oxidation of primary amines to nitriles,[8,9] and the results highlight the ability to tune product selectivity by variation of the catalyst components. Preliminary mechanistic studies provide insights into the catalytic reactions.

Scheme 1. The Selectivity of Cu/Nitroxyl Catalyzed Primary Amine Oxidation



We initiated the present study with 4-methoxybenzylamine as a model substrate using 5 mol % of Cu and a nitroxyl radical source in acetonitrile (Table 1). Our previously reported alcohol oxidation conditions gave only 25% of nitrile **2a** with 50% of homocoupled imine **3a** (entry 1). Use of CuI led to better selectivity for **2a** (entry 2), albeit with lower yield. Replacement of TEMPO with the sterically less hindered nitroxyl species, such as ABNO and AZADO, resulted in a significantly improved yield and selectivity of the nitrile **2a** (entries 3 and 4).[10] Use of ketoABNO, which is a stronger oxidant but sterically the same as ABNO, led to inferior results (entry 5). Extensive screening of ligands and bases was carried out (Table 1, entries 6−9; for full screening data, see Supporting Information Table S2), and the best yield and selectivity for **2a** was achieved with reactions containing 4,4′-^{t}Bu$_2$bpy (4,4′-di-*tert*-butyl-2,2′-bipyridyl) and DMAP (4-dimethylaminopyridine) (entry 9). This optimized catalyst system was evaluated in solvents other than acetonitrile. Good substrate conversion was observed in THF, dioxane, DMF, and toluene; however, the selectivity for nitrile **2a** was significantly lower (Supporting Information Table S1). Use of air as the oxidant led to lower yield and selectivity (entry 10).

The optimized reaction conditions (Table 1, entry 9) were applied to diverse substrates to assess the reaction scope and

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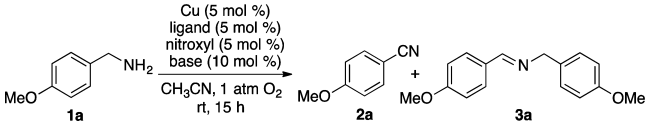
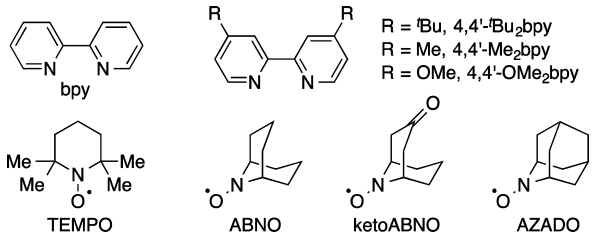
Table 1. Optimization of Cu/Nitroxyl Catalyzed Aerobic Oxidation of Primary Amine to Nitrile[a]



					yield (%)[b]	
entry	Cu	ligand	nitroxyl	base	**2a**	**3a**
1	CuOTf	bpy	TEMPO	NMI	25	50
2	CuI	bpy	TEMPO	NMI	27	34
3	CuI	bpy	ABNO	NMI	78	22
4	CuI	bpy	AZADO	NMI	77	23
5	CuI	bpy	ketoABNO	NMI	53	46
6	CuI	4,4′-^{t}Bu$_2$bpy	ABNO	NMI	87	13
7	CuI	4,4′-Me$_2$bpy	ABNO	NMI	80	14
8	CuI	4,4′-OMe$_2$bpy	ABNO	NMI	74	26
9	**CuI**	**4,4′-^{t}Bu$_2$bpy**	**ABNO**	**DMAP**	**90**	**4**
10[c]	CuI	4,4′-^{t}Bu$_2$bpy	ABNO	DMAP	75	24

[a]Conditions: **1a** (0.5 mmol), Cu, ligand, nitroxyl, and base in CH_3CN (2.0 mL) under O_2 balloon at room temperature for 15 h. [b]Yield determined by ^{1}H NMR (internal standard: 1,1,2,2-tetrachloroethane). [c]Carried out under air.



limitations (Table 2). Primary benzylic amines with a variety of substituents (**1a**−**1o**) reacted to afford the corresponding nitriles in good to excellent yields. Electron-donating and electron-withdrawing groups, ranging from −OMe to −CF_3 and −NO_2 groups, were all well tolerated in the reactions, and the method was compatible with aryl chlorides, bromides, and iodides that can be used in subsequent coupling reactions. Polycyclic or heteroaromatic methylamines, such as 1-naphthylmethylamine (**1m**) and 2-furyl-methylamine (**1n**), underwent effective conversion into the nitriles, and oxidation of *m*-xylenediamine (**1o**) afforded 1,3-dicyanobenzene in high yield. The allylic amines, cinnamylamine (**1p**) and geranylamine (**1q**), afforded *α*,*β*-unsaturated nitriles in good yields. As has been observed in alcohol oxidation reactions, aliphatic substrates were less reactive, but good yields of the corresponding nitriles (**2r**−**2v**) were obtained by increasing the CuI/ABNO catalyst loading to 10 mol %. A reduced yield of the nitrile was observed from oxidation of tetrahydrofurfurylamine (**1w**), possibly reflecting inhibition by chelation of the adjacent ether group. This amine oxidation method was effective on a larger scale (eq 2): amine **1l** underwent efficient oxidation on a 10 mmol scale, resulting in a 70% yield of the nitrile, even with decreased catalyst loading (3 mol %).

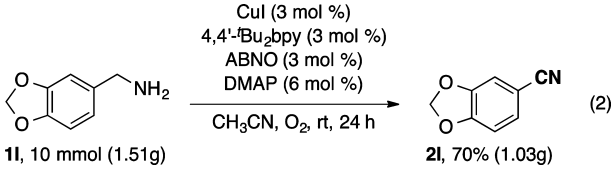
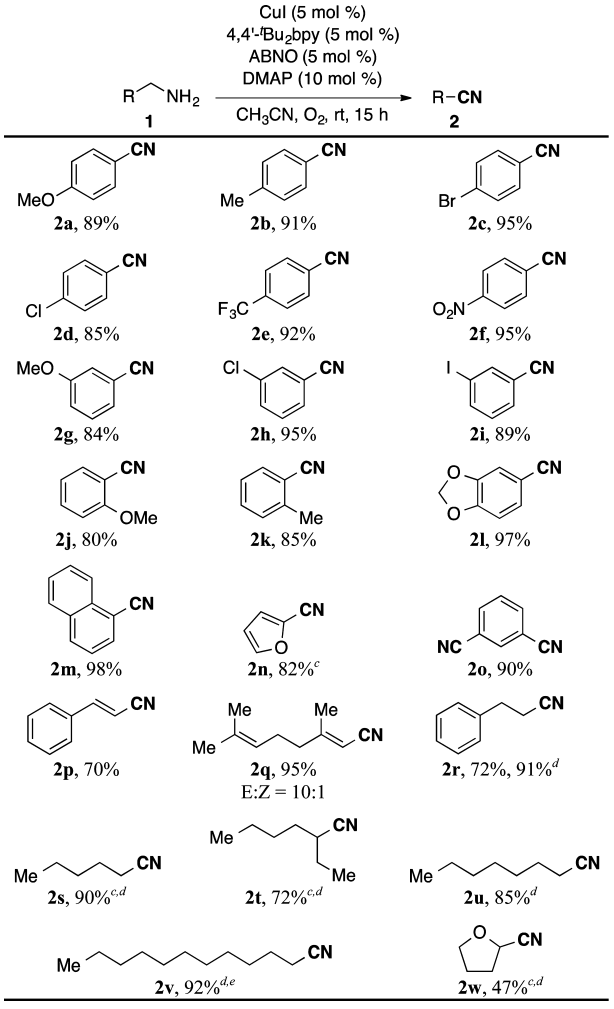


Table 2. Substrates Scope of CuI/ABNO Catalyzed Aerobic Oxidation of Primary Amine to Nitrile[a,b]



[a]Conditions: **1** (0.5 mmol), CuI, 4,4′-^{t}Bu$_2$bpy, ABNO, and DMAP in CH_3CN (2.0 mL) under O_2 (balloon) at room temperature for 15 h. [b]Isolated yield. [c]Yield determined by ^{1}H NMR spectroscopy. [d]10 mol % of CuI, 4,4′-^{t}Bu$_2$bpy, ABNO, and 20 mol % of DMAP were employed. [e]Carried out at 40 °C

Some limitations of substrate scope were observed in the oxidation of 4-bromophenethylamine, which formed a complex mixture of products, and 4-hydroxybenzylamine, which produced no 4-hydroxybenzonitrile (Figure 1). These

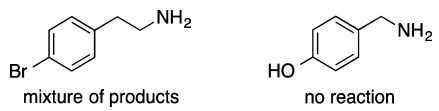


Figure 1. Problematic substrates for CuI/ABNO-catalyzed amine oxidation.

limitations resemble those of analogous alcohol oxidation reactions in which homobenzylic alcohols afford complex product mixtures and phenols inhibit catalytic turnover. Overall, these amine oxidation reactions exhibit a broad scope that closely resembles the alcohol oxidation reactions.

The reaction profile for the oxidation of *p*-methoxybenzyl amine, monitored by gas uptake methods and ^{1}H NMR analysis of the nitrile product, revealed an O_2/product stoichiometry of

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1:1 (Figure 2).[11] This ratio is consistent with that expected for four-electron oxidation of a primary amine to a nitrile with

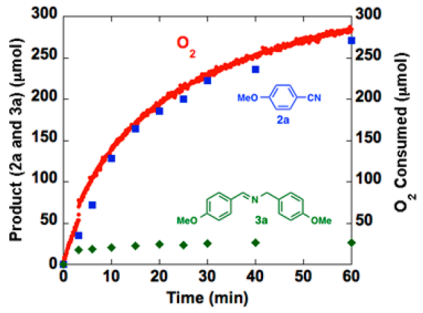


Figure 2. Reaction time course, monitored by gas uptake (O_2) and ^{1}H NMR analysis of the organic products (nitrile and imine), showing the 1:1 relationship between O_2 consumption and nitrile formed. See the Supporting Information for details.

concomitant four-electron reduction of O_2 to 2 equiv of water. Only a small amount of the homocoupled imine **3a** is detected, with the majority formed early in the reaction when the amine substrate concentration is highest.

A kinetic isotope effect (KIE) was obtained for oxidation of *p*-methoxybenzylamine by comparing the rate of the protio substrate with that of the deuterated derivative (Figure 3A).

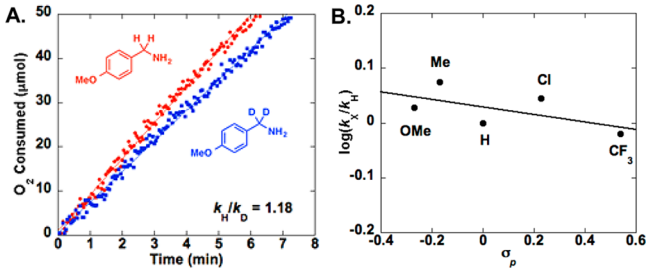


Figure 3. Isotope effect (A) and Hammett (B) data from CuI/ABNO-catalyzed aerobic oxidation of *p*-methoxybenzylamine to *p*-methoxybenzonitrile.

The small observed KIE, k_H/k_D = 1.18 ± 0.02, indicates that C−H bond cleavage is not turnover-limiting in this present reaction. Similarly, a Hammett study with different *p*-substituted benzylamines reveals the absence of a significant electronic effect on the reaction rate (ρ = −0.07; Figure 3B). On the other hand, the reaction rate exhibits a first-order dependence on the oxygen pressure (Figure 4 and Supporting Information Figure S3). These observations, together with insights from our recently reported mechanistic study of Cu/

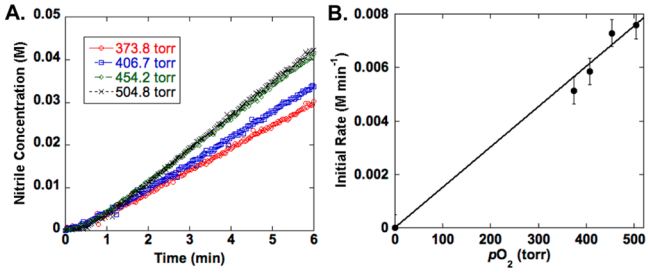
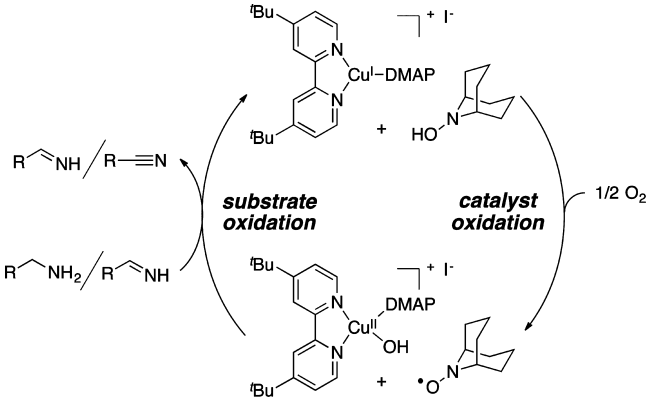


Figure 4. O_2-dependence kinetic data from CuI/ABNO-catalyzed aerobic oxidation of *p*-methoxybenzylamine to *p*-methoxybenzonitrile.

TEMPO-catalyzed alcohol oxidation,[12] are consistent with a two-stage catalytic mechanism consisting of (i) aerobic oxidation of the reduced catalyst, (^{t}Bu$_2$bpy)Cu^I and ABNO−H, and (ii) dehydrogenation of the amine substrate by (^{t}Bu$_2$bpy)Cu^{II} species and ABNO (Scheme 2). Both the

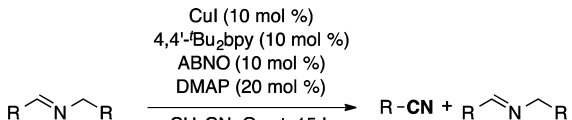
Scheme 2. Simplified Catalytic Cycle for (^{t}Bu$_2$bpy)Cu^I/-ABNO-Catalyzed Aerobic Amine Oxidation



primary amine and the primary imine can serve as substrates in the second stage of the reaction. The kinetic data suggest that catalyst oxidation by O_2, not substrate dehydrogenation, is turnover-limiting. These preliminary results, together with our previous study of Cu/TEMPO-catalyzed alcohol oxidation,[12] provide a foundation for a more thorough comparison of the relative reactivity of alcohols and amines and similarities and differences between the reaction mechanisms.

The time course in Figure 2 suggests that the homocoupled imine **3a** does not convert into the nitrile once it forms, and it is obtained in ∼5% yield after completion of the reaction. Control experiments were performed to assess the reversibility of imine formation under the reaction conditions. Imine **3a** was independently prepared and subjected to the typical reaction conditions. Some conversion of **3a** into nitrile **2a** could be achieved by adding ammonia to the reaction mixture (Scheme 3), and increasing the ammonia equivalents increases the nitrile

Scheme 3. Investigation of the Possiblities of Homocoupled Imine Intermediates



1) with 1 equiv of NH_3 (aq) (17μL)	39%	50%
2) with 3 equiv of NH_3 (aq) (51μL)	60%	30%

yield. Nevertheless, the relatively slow rate and the quantity of ammonia required to promote this reaction suggest that the homocoupled imine will, at best, convert slowly into nitrile under the amine oxidation reaction conditions. These observations further suggest that nitrile formation with this catalyst system primarily proceeds via direct oxidation of primary imine **A**, without diverting to the homocoupled imine.

The compatibility of this catalyst system with aqueous ammonia raised the possibility of converting alcohols to nitriles via oxidative coupling with ammonia (Scheme 4). Upon

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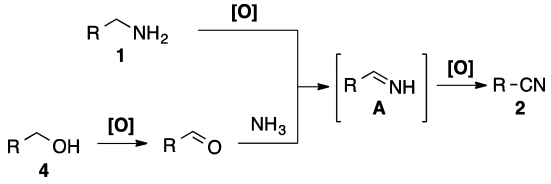
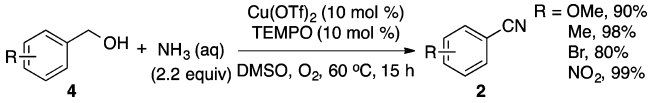
Scheme 4. Complementary Pathways for the Preparation of Nitriles from Primary Amines or Primary Alcohols/Ammonia



oxidation of the alcohol to the aldehyde, condensation with ammonia would afford the same primary imine intermediate (**A**) involved in amine oxidation reactions. In this case, the reaction would not be susceptible to formation of the homocoupled imine. Initial screening studies revealed that $Cu(OTf)_2$/TEMPO catalyzes efficient conversion of benzylic alcohols into nitriles in high yield with 2.2 equiv of aqueous ammonia in DMSO at 60 °C (Scheme 5; see Supporting Information for full details). While this effort was in progress, the groups of Huang,[6c] Tao,[6d] and Muldoon[6e] reported similar catalyst systems for this transformation. The work of Huang et al. is particularly noteworthy because their (bpy)CuI/TEMPO catalyst system enables conversion of a broad range of allylic, benzylic and aliphatic alcohols.

Scheme 5. Preliminary Results of Aerobic Oxidative Coupling of Alcohols and Ammonia to Form Nitriles



In conclusion, we have identified (^{t}Bu$_2$bpy)CuI/ABNO as an efficient catalyst system with broad substrate scope for oxidative dehydrogenation of primary amines to nitriles. The identity of the nitroxyl reagent and the solvent are key factors in achieving selectivity for nitrile rather than the homocoupled imine. Elucidation of the mechanistic origin of this nitroxyl-dependent selectivity, together with characterization of the mechanistic similarities and differences among reactions of alcohols and amines is an important focus of ongoing work.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, kinetic data, and additional experiment data are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ABNO, 9-azabicyclo [3.3.1] nonane *N*-oxyl; bpy, 2,2′-bipyridyl; DMAP, 4-dimethylaminopyridine; DTBNO, di-*tert*-butylnitroxide; ketoABNO, 9-azabicyclo[3.3.1]nonan-3-one-*N*-oxyl; NMI, *N*-methylimidazole; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxyl

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