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Ligand-Accelerated, Copper-Catalyzed Aerobic Oxidative Dehydrogenation of Primary Amines to Nitriles

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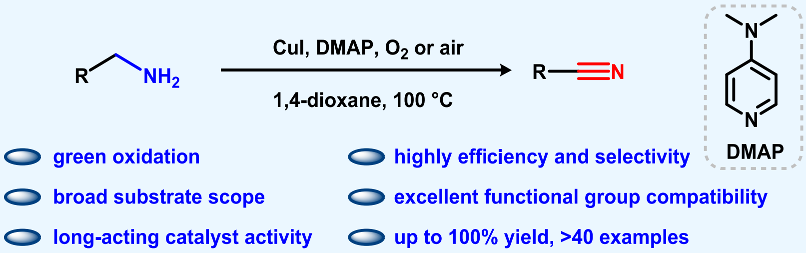

ABSTRACT: A highly efficient copper-catalyzed oxidative dehydrogenation of primary amines to access nitriles has been developed. We found that DMAP was an efficient ligand for copper-catalyzed oxidation and molecular oxygen was a green oxidizing agent. This reaction exhibited excellent functional group compatibility and a broad substrate scope. Various benzylic, allylic, and aliphatic amines were selectively and effectively oxidized to the corresponding nitriles in high yields (up to 100%). The ligand DMAP not only accelerated the reaction rate but also enhanced the stability of the catalyst. The practicality of the reaction was illustrated on a gram scale, even at a lower catalyst loading and/or under bubble air conditions.

■ INTRODUCTION

The nitrile moiety is a significant and abundant building block in pharmaceuticals, natural products, and functional materials as well as in many fine chemicals.[1] Nitriles are also important precursors in the synthesis of amides, carboxylic acids, amines, and numerous heterocycle compounds through multicomponent reactions.[2] Hence, the synthesis of nitrile has been of long-term interest to synthetic chemists, and numerous methods have been reported in the literature. Conventional approaches to access nitriles in the laboratory include the Schmidt reaction,[3] the Sandmeyer reaction,[4] the Rosenmund−von Braun reaction,[5] and the transition-metal-catalyzed cyanation.[6] However, these protocols suffer from poor atom economy and require stoichiometric oxidants or hazardous and explosive azides. Additionally, harsh reaction conditions limit functional group compatibility and selectivity.

Recently, a novel protocol for nitrile synthesis involves the oxidative dehydrogenation of primary amines (Scheme 1a). While stoichiometric amounts of oxidants such as $K_2S_2O_8$,[7] I_2,[8] Dess−Martin periodinane,[9] chlorinating reagents,[10] and TBHP are usually used.[11] Moreover, the aerobic oxidation protocols have emerged as mild and green catalytic methods with high synthetic potential because oxygen is an abundant, low-cost, and environmentally benign oxidant using ruthenium,[12] cobalt,[13] nickel,[14] iron,[15] manganese complexes,[16] and copper salts as catalysts.[17] Among them, copper catalyst systems attracted more and more researchers' interest because copper is a cheap, versatile, and powerful catalyst for many aerobic oxidative reactions.

The oxidation process involves the sequential oxidative dehydrogenation of amine (I) and the intermediate (imine, II). While imine (II) can easily hydrolyze to form the aldehyde (IV) or undergo nucleophilic attack by amines (I), followed by deamination to give symmetrical imines (V). To prevent the formation of these by-products and enhance the catalytic activity, stoichiometric copper salts and/or molecular sieves were usually used.[18] In 2013, Stahl's group reported an effective but somewhat complex oxidation system for converting primary amines to nitriles through catalysis by (4,4′-tBu_2bpy)CuI/ABNO.[19] In 2016, Lumb and Arndtsen revealed that counterions control the copper-catalyzed oxidation pathway, with $CuPF_6$ for imines and CuI for nitriles, while the catalyst is easily deactivated.[20] Ligands play an increasingly important role in organic reactions (Scheme 1b). Gu's group reported Cu(0)-catalyzed stoichiometric isoquinoline as a ligand for nitrile syntheses.[21] Furthermore, Xie's group reported *N*-methyl imidazole as a ligand for the $CuBr_2$-catalyzed aerobic oxidation of benzylic amines to aryl nitriles.[22] A CuCl/TEMPO-co-catalyzed aerobic oxidation of primary amines to nitriles using DMEDA as a ligand has been reported

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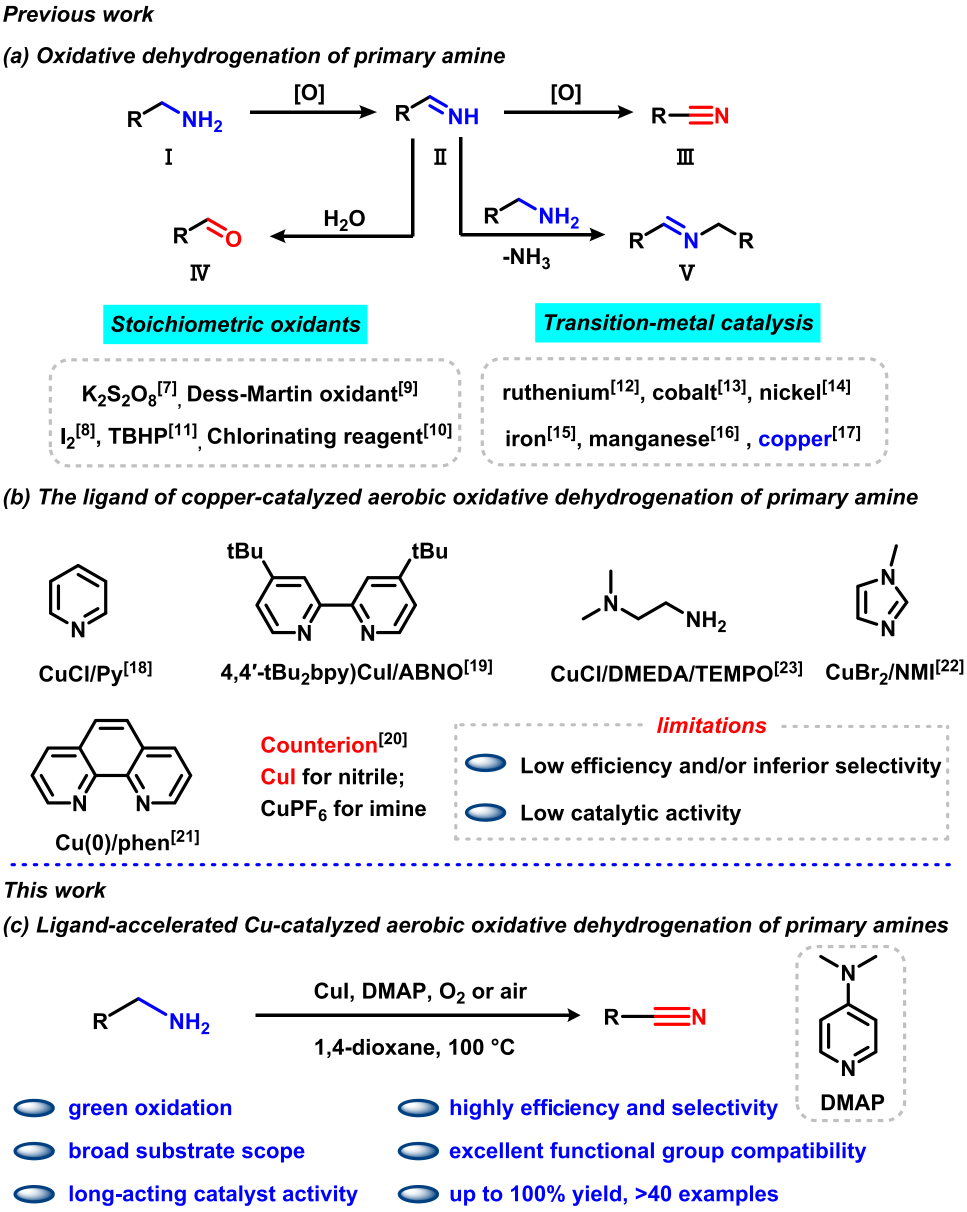
Scheme 1. Synthetic Approaches of the Oxidative Dehydrogenation of Primary Amines to Nitriles



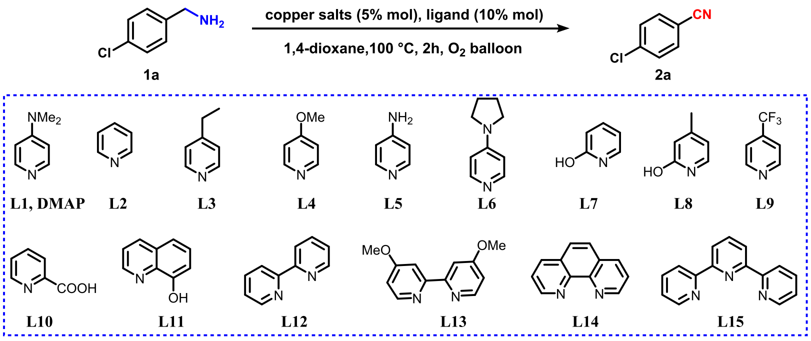
by Xu's group.[23] However, these catalytic systems exhibited low efficiency and/or inferior selectivity toward aliphatic primary amines.[21−23]

Our group is devoted to developing a sustainable oxidation method utilizing dioxygen or hydrogen peroxide as the green oxidant.[24] In our previous investigation of the oxidative dehydrogenative coupling of 1,1′-biphenyl-2,2′-diamine to access benzo[*c*]cinnolines, we identified an extremely effective copper-catalyzed oxidation monodentate ligand, 4-dimethylaminopyridine (DMAP), which can efficiently accelerate the oxidative dehydrogenation process.[24a] To further improve the oxidative efficiency and broaden the substrate scope of the primary amines. Herein, we reported a readily available and effectively copper-catalyzed system for the aerobic oxidation of primary amines to nitriles using dioxygen or air as an oxidant, with DMAP as a highly effective ligand under mild conditions (Scheme 1c).

■ RESULTS AND DISCUSSION

Oxygen has attracted significant interest as a green oxidant. Initially, we screened different copper salt catalysts using 4-chlorobenzylamine as a template substrate, DMAP as a ligand, and 1,4-dioxane as a solvent under an oxygen atmosphere. Preliminary experiment results indicated that Cu(I) catalyzed more effectively than Cu(II) (Table 1, entries 1 and 2, and Table S1). Among the Cu(I) catalysts, CuI performed the best for nitrile synthesis because it gave the highest yield (99%). CuCl was a better effective catalyst, with a yield of 78%, while CuBr was the least effective, with a yield of 75%. The conversion rate of these catalysts was consistently 100% (Table 1, entries 3−5, and Table S1). Attempts to use other copper catalysts, such as Cu_2O, Cu(0), and $Cu(acac)_2$, were unsuccessful, while $Cu(OAc)_2$ yielded 81% (Table S1). These results also indicate that the copper source or the counterion of the copper salts is significant in the reaction. Subsequently, the influence of the solvent and reaction temperature was investigated (Table S2). The polar aprotic

Table 1. Copper-Catalyzed Oxidative Dehydrogenation of Primary Amines 1a under an Oxygen Atmosphere[a]



entry	catalyst	ligand	yield[b] (%)
1	$CuCl_2$	L1	6
2	$CuBr_2$	L1	31
3	CuBr	L1	75
4	CuCl	L1	78
5	**CuI**	**L1**	**99**
6	CuI	L2	58
7	CuI	L3	58
8	CuI	L4	78
9	CuI	L5	95
10	CuI	L6	71
11	CuI	L7	17
12	CuI	L8	5
13	CuI	L9	63
14	CuI	L10	58
15	CuI	L11	NR
16	CuI	L12	39
17	CuI	L13	53
18	CuI	L14	56
19	CuI	L15	56

[a] Reaction conditions: **1a** (1 mmol), CuI (5 mol %), and DMAP (10 mol %) were stirred in 1,4-dioxane (5 mL) at 100 °C under an oxygen atmosphere for a reaction time of 2 h. The bold data is the optimal reaction condition. [b] Yield determined by GC. NR, no reaction.

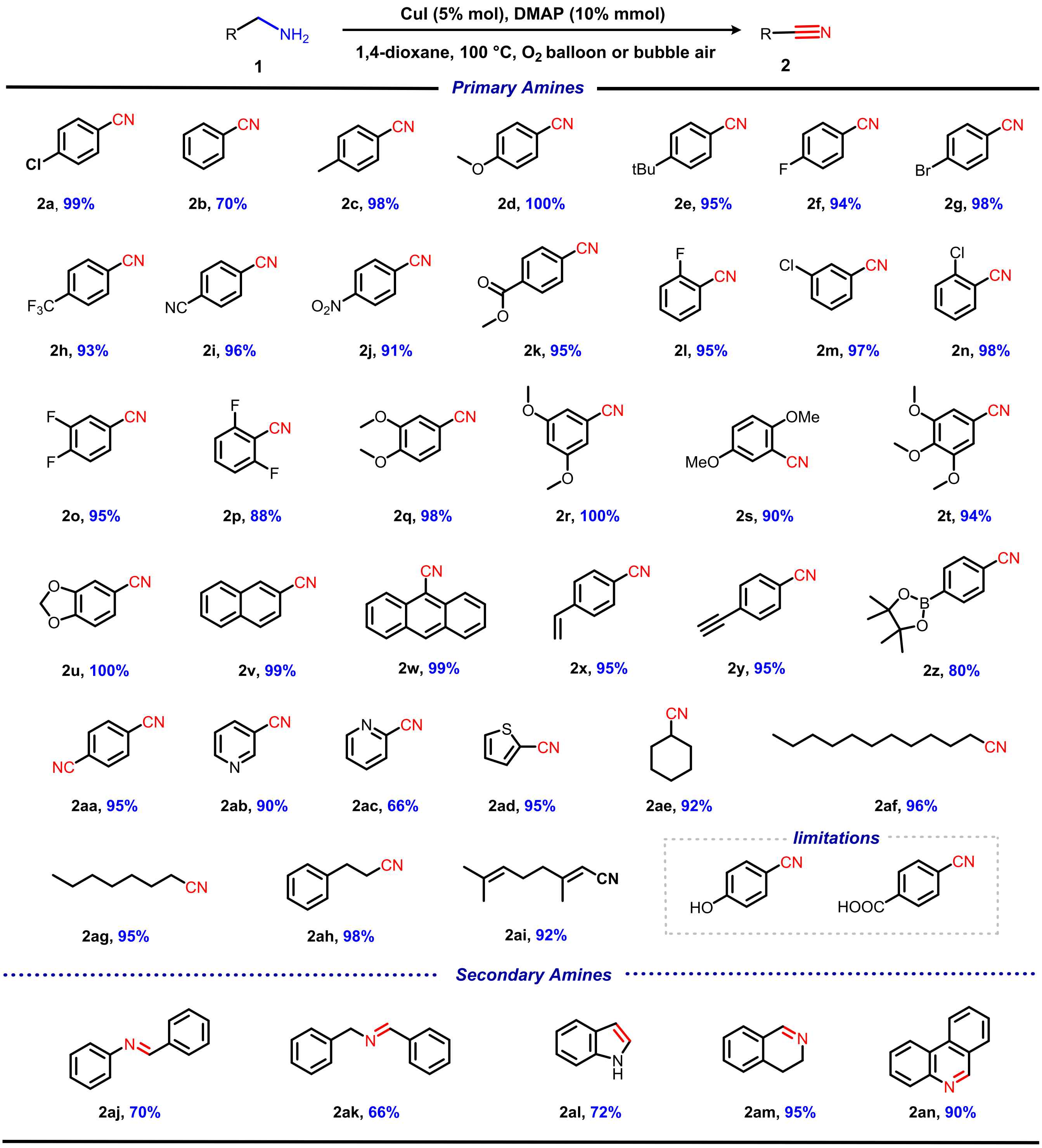
solvents 1,4-dioxane, dichloroethane (DCE), and ethyl acetate (EA) exhibited favorable reactivity. While the reactions gave lower yields and selectivity in dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN), and tetrahydrofuran (THF), respectively. 1,4-Dioxane was selected as the reaction solvent due to its low cost and simplicity of post-treatment. The reaction can also be converted at lower temperatures but with diminished selectivity.

The latest research suggests that pyridine ligands are the optimal ligands for copper-catalyzed oxidative process.[24] Therefore, further screening of the pyridine ligands was conducted. The substituting pyridine generally improves reaction efficiency, and electron-donating substituents at the 4-position significantly enhance the reaction yield (Table 1, entries 6−13), among which the yield of 4-aminopyridine was 95%. Further investigation was conducted into bidentate or tridentate pyridine ligands; however, the yield of the reaction also decreased (Table 1, entries 14−19). Interesting, the *N*,*O*-bidentate ligands **L11** did not react at all, maybe the exposed hydroxyl group inactivated the catalyst (Table 1, entry 15). The copper catalyst−ligand complexes have a flexible structure that facilitates dissociation from the ligands and binding to the reactants.[25] Compared with the copper/pyridine (**L4**) complex, the copper/bipyridine (**L13**) complex is less flexible; as a result, the copper/bipyridine catalysis system gave a poor yield (Table 1, entries 8 and 17).

Therefore, the small size of the ligands is favorable for coordination, so their volume should not be too large.

With the optimal conditions in hand, the scope of primary amines was investigated in this copper-catalyzed aerobic oxidation method (Scheme 2). Like the model reaction (**2a**), both benzylamines bearing electron-donating group (methyl, methoxy, *tert*-butyl) and electron-withdrawing group (fluoro, chloro, bromo, trifluoromethyl, cyano, nitro, and ester) at the *para*-position could be smoothly oxidized under the standard conditions to give the desired aryl nitriles **2b**−**2k** in excellent yields (up to 100%). Monosubstituted benzylamines at the *ortho*- or *meta*-position such as 2-fluorobenzylamine, 2-chlorobenzylamine, and 3-chlorobenzylamine also afforded the corresponding aryl nitriles (**2l**−**2n**) in high yields (yield up to 98%). In addition, substrates bearing multiple electron-donating groups and electron-withdrawing groups also afforded the corresponding aryl nitriles (**2o**−**2t**) in excellent yields (>90%), regardless of the position of the substituent. Surprisingly, bearing a bulky steric substrate such as 2,6-difluorobenzylamine can also efficiently synthesize the corresponding 2,6-difluorobenzonitrile (**2p**). Polycyclic methylamines, such as piperonylamine (**1u**), 2-naphthylmethylamine (**1v**), and anthracene-9-methylamine (**1w**), underwent effective conversion into the nitriles (**2u**−**2w**). This reaction was also compatible with a variety of active functional groups, including alkene, alkyne, and boronic acid ester **2x**−**2z**.

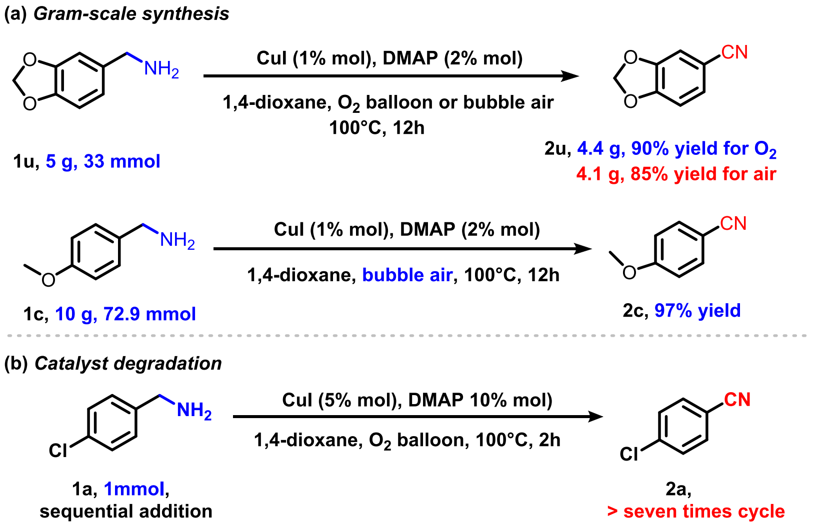
Scheme 2. Substrate Scope of CuI/DMAP-Catalyzed Aerobic Oxidative Dehydrogenation of Primary Amines and Secondary Amines[a]



[a] Reaction condition: **1** (1 mmol), CuI (5 mol %), and DMAP (10 mol %) were stirred in 1,4-dioxane (5 mL) at 100 °C under an oxygen atmosphere for 2−10 h with isolated yields.

Interestingly, the oxidation of *p*-xylenediamine (**1aa**) afforded 1,4-dicyanobenzene (**2aa**) in 95% yield. A heterocycle substrate bearing pyridine (**1ab**, **1ac**) and thiophene (**1ad**) moieties were also suitable for this transformation with moderate to high yields (66−100%). Although aliphatic substrates were less reactive, excellent yields (96−99%) of the corresponding nitriles (**2ae**−**2ah**) were obtained in this method. The aerobic oxidation of allyl amines (**1ai**) afforded the corresponding *α*,*β*-unsaturated nitriles in high yields. However, limitations of the current protocol include substrates with hydroxyl and carboxyl groups, which provided products in less than 5% yield; this may be because the phenol group is oxidized to benzoquinone and the carboxylic acid group deactivates the catalyst.

Scheme 3. Gram-Scale Synthesis and Catalyst Cycle Experiment



The oxidative dehydrogenation of partial secondary amines was also evaluated. Interestingly, the secondary amines such as *N*-benzylaniline and dibenzylamine can be successfully oxidized to the corresponding imines (**2aj**, **2ak**) in moderate yields. Moreover, cyclic secondary amines such as indoline and tetrahydroisoquinoline were efficiently converted into indole (**2al**) and 3,4-dihydroisoquinoline (**2am**) in 72 and 95% yields, respectively, while 3,4-dihydroisoquinoline does not undergo further oxidative dehydrogenation to produce isoquinoline under this condition. Furthermore, 5,6-dihydrophenanthridine (**1an**) can be rapidly oxidized to phenanthridine (**2an**) with a 90% yield.

Next, we tried to explore the synthetic utility of the CuI/DMAP-catalyzed aerobic oxidative dehydrogenation of primary amines for the synthesis of nitriles (Scheme 3a). We performed a gram-scale oxidative reaction of piperamine (**1u**, 5 g, 33 mmol) to access piperitrile (**2u**) in an excellent yield (90%) under an oxygen atmosphere, even at a lower catalyst loading (1%). Interestingly, piperonitrile can also be efficiently obtained (85% yield) under bubble air conditions. Similarly, 4-methoxybenzonitrile (**2c**) can also be scaled up under bubble air conditions (97% yield). The activity of the catalyst is essential for the reaction, but it will gradually decrease as the reaction progresses. To investigate the catalyst efficiency, we performed a sequential addition of **1a** after 2 h under the optimal reaction conditions (Scheme 3b). Gratifyingly, the CuI/DMAP catalyst system could undergo at least seven consecutive reaction cycles without any significant loss of activity (Figure 1). In contrast, the CuI catalytic system reported by Arndtsen was quickly deactivated, and the decrease in catalytic activity might be due to the lack of the ligand.[20] These results indicate that our catalyst system has potential for industrial-scale production.

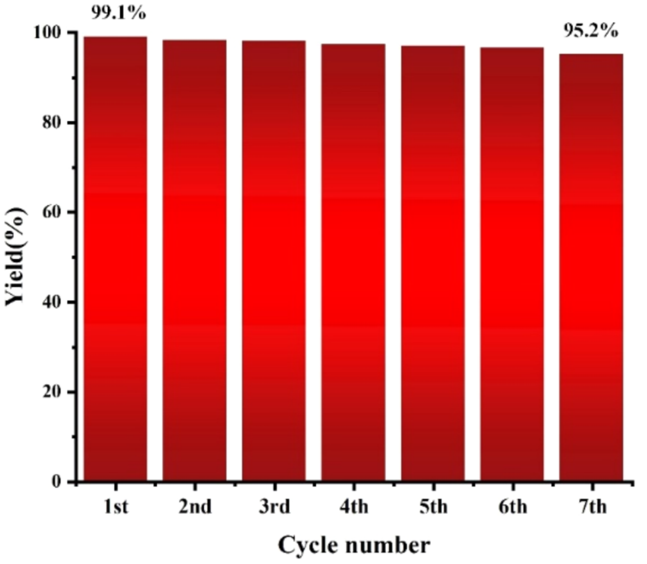
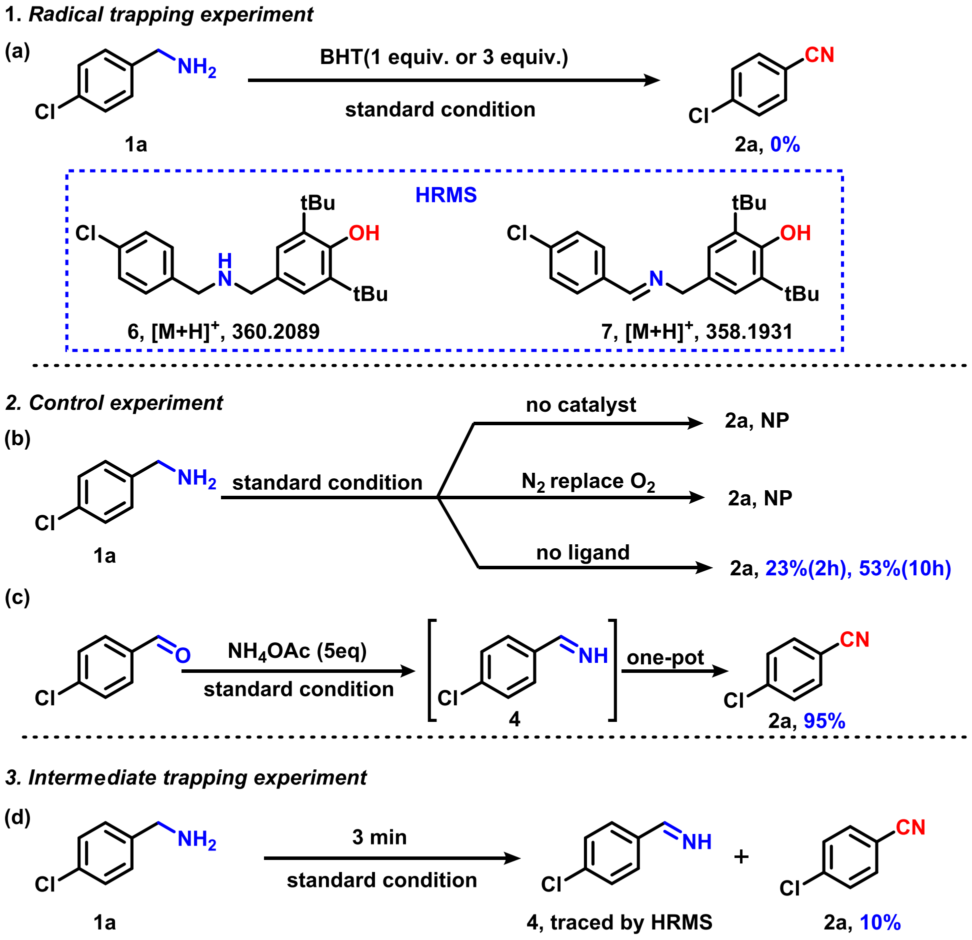


Figure 1. Yields of **2a** in seven sequential additions.

To investigate the mechanism of this conversion, radical trapping experiments were initially conducted. When the radical trapping agent 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction system, none of the nitrile **2a** was formed (Scheme 4a). Additionally, two intermediates, **6** and **7**, were captured by HRMS, suggesting that the reaction proceeded via a radical mechanism (Figures S1 and S2). A controlled experiment was then conducted, revealing that the reaction did not proceed in the absence of a catalyst or oxygen was replaced by nitrogen. Furthermore, the efficiency of the reaction is significantly decreased without ligand (Scheme 4b). It is concluded that molecule oxygen serves as both an oxidant and a radical initiator, driving the reaction. Meanwhile, ligands play a vital role in maintaining the catalyst activity and accelerating the reaction rate. It is noteworthy that 4-chlorobenzaldehyde and ammonium acetate smoothly produced 4-chlorobenzonitrile (**2a**) in a one-pot manner under the standard conditions (Scheme 4c). The time-course profile of this reaction is detected by GC (Figure 2), with no imine **4** detected. Therefore, the intermediate trapping experiment of **1a** was conducted within 3 min using GCMS. Interestingly, imine **4** was captured by HRMS (Scheme 4d and Figure S3, details see in the Supporting Information). These results indicated that imine **4** was the intermediate of the reaction, and the oxidative dehydrogenation of imine to nitrile was not the rate-determining step.

Additionally, a Hammett study (Figure 3, details see in the Supporting Information) was carried out using various *para*-substituted benzylamines, revealing a significant electronic

Scheme 4. Mechanistic Studies



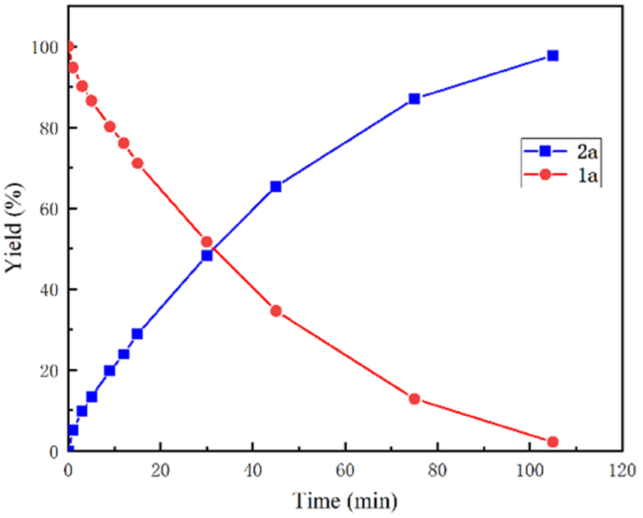


Figure 2. Time-course profile of the oxidative dehydrogenation of **1a**.

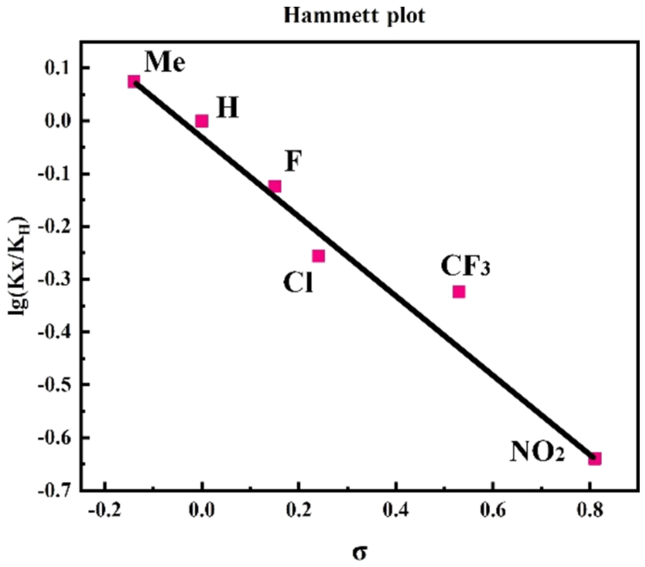
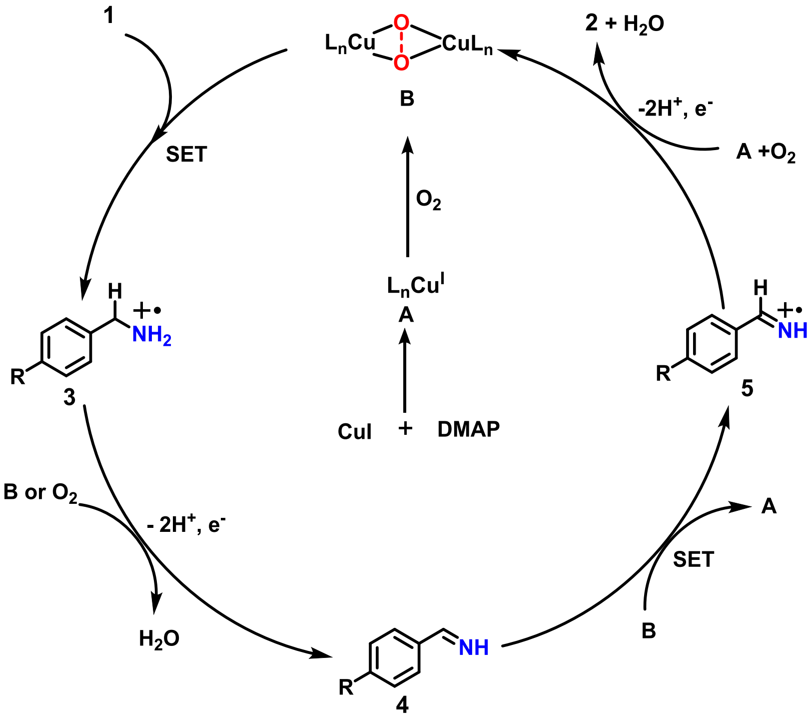


Figure 3. Hammett study of the copper-catalyzed oxidation of *para*-substituted benzylamine.

effect on the reaction rate (Figure S4). A good linear correlation between the values of $\log(k_X/k_H)$ and substituent constant (σ) was obtained, $R^2 = 0.964$. The negative slope $\rho = -0.721$ indicates that a carbocation-type intermediate is involved in the oxidation process, and the reaction rate of the electron-donating group is faster than that of the electron-withdrawing group.

Therefore, based on the above studies, a plausible mechanism for the oxidative dehydrogenative of primary amine to form nitrile is illustrated in Scheme 5. First, CuI coordinates with DMAP to form a chelate (**A**, $\mathrm{Cu^I}$),[26] which subsequently binds with oxygen to form the more active (μ-η^2:η^2-peroxo) dicopper(II) complex (**B**, $\mathrm{Cu^{II}}$); at this stage,

Scheme 5. Plausible Reaction Mechanism



molecular oxygen is activated and the dicopper complex is considered a key catalyst for amine oxidation.[26] The primary amine (**1**) undergoes a single-electron oxidation by the dicopper(II) complex (**B**) to form Cu(I) and an aminium radical (**3**). The α-proton is released from the aminium radical (**3**) and one electron and another proton are rapidly oxidized by dioxygen, followed by the removal of a water molecule to generate an imine (**4**). Then, **4** undergoes a single-electron oxidation again to form iminium cation (**5**), which is further rapidly oxidized through dehydrogenation by the dicopper(II) complex (**B**) or dioxygen to form the corresponding nitriles (**2**).[27]

CONCLUSIONS

In conclusion, a convenient and efficient copper-catalyzed aerobic oxidative dehydrogenation of primary amines to synthesize nitriles has been developed under mild reaction conditions, utilizing dioxygen or air as a green oxidant and DMAP as an extremely efficient ligand. The method can generate excellent yields of nitriles (up to 100%) compatible with multiple functional groups. The mechanism of the reaction was clearly investigated, and the reaction intermediates were captured by HRMS. DMAP as the ligand not only accelerated the reaction rate but also enhanced the stability of the catalyst. This method supports the preparation of nitriles on a gram scale with a lower catalyst loading and under bubble air conditions. Therefore, the catalysis system has the potential for large-scale industrial production. Further applications of copper-catalyzed aerobic oxidation reactions are still ongoing in our group.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c11496.

General remarks; experimental procedures; mechanism study; reference; and NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Pollak, G.; Romeder, F.; Hagedorn, H. P. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2012. (b) Fatiadi, A. J. Preparation and Synthetic Applications of Cyano Compounds. In *Triple-Bonded Functional Groups*; Patai, S.; Rappaport, Z., Eds.; Wiley: New York, 1983; pp 1057−1303. (c) Miller, J. S.; Manson, J. L. Designer magnets containing cyanides and nitriles. *Acc. Chem. Res.* **2001**, *34*, 563−570.

(2) (a) Yamaguchi, K.; Matsushita, M.; Mizuno, N. Efficient hydration of nitriles to amides in water, catalyzed by ruthenium hydroxide supported on alumina. *Angew. Chem., Int. Ed.* **2004**, *43*, 1576−1580. (b) Moorthy, J. N.; Singhal, N. Facile and highly selective conversion of nitriles to amides via indirect acid-catalyzed hydration using TFA or AcOH-H2SO4. *J. Org. Chem.* **2005**, *70*, 1926−1929. (c) Jnaneshwara, G. K.; Deshpande, V. H.; Lalithambika, M.; Ravindranathan, T.; Bedekar, A. V. Natural Kaolinitic clay catalyzed conversion of nitriles to 2- oxazolines. *Tetrahedron Lett.* **1998**, *39*, 459−462. (d) Chen, H.; Dai, W.; Chen, Y.; et al. Efficient and selective nitrile hydration reaction in water catalyzed by unexpected dimethylsulfinyl anion generated in situ from CsOH and DMSO. *Green Chem.* **2014**, *16*, 2136−2141. (e) Li, Y.; Chen, H.; Liu, J.; Wan, X.; Xu, Q. Clean synthesis of primary to tertiary carboxamides by CsOH-catalyzed aminolysis of nitriles in water. *Green Chem.* **2016**, *18*, 4865−4870.

(3) (a) Han, M.; Yang, M.; Wu, R.; Li, Y.; Jia, T.; Gao, Y.; Ni, H. L.; Hu, P.; Wang, B. Q.; Cao, P. Highly Enantioselective Iridium−Catalyzed Coupling Reaction of Vinyl Azides and Racemic Allylic Carbonates. *J. Am. Chem. Soc.* **2020**, *142*, 13398−13405. (b) Hyodo, K.; Togashi, K.; Oishi, N.; Hasegawa, G.; Uchida, K. Bronsted Acid Catalyzed Nitrile Synthesis from Aldehydes Using Oximes via Transoximation at Ambient Temperature. *Org. Lett.* **2017**, *19*, 3005−3008. (c) Liang, Y.; Liang, Y.-F.; Jiao, N. Cu−or Fe−catalyzed C−H/C−C bond nitrogenation reactions for the direct synthesis of N−containing compounds. *Org. Chem. Front.* **2015**, *2*, 403−415. (d) Wang, T.; Yin, H.; Jiao, N. Copper−Catalyzed Oxidative Transformation of Aryl Propargylic Azides to Aryl Propiolonitriles. *Adv. Synth. Catal.* **2013**, *355*, 1207−1210. (e) Xu, L.; Hu, Y.; Zhu, X.; He, L.; Wu, Q.; Li, C.; Xia, C.; Liu, C. Momentary click nitrile synthesis enabled by an aminoazanium reagent. *Org. Chem. Front.* **2022**, *9*, 3420−3427. (f) Zhan, W.; Tong, M.; Ji, L.; Zhang, H.; Ge, Z.; Wang, X.; Li, R. Continuous−flow synthesis of nitriles from aldehydes via Schmidt reaction. *Chin. Chem. Lett.* **2019**, *30*, 973−976.

(4) Sandmeyer, T. The Substitution of the Amine Group with Chlorine Atom in Aromatic Systems. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633−1635.

(5) Rosenmund, K. W.; Struck, E. Das am ringkohlenstoff gebundene halogen und sein ersatz durch andere substituenten. I. Mitteilung: Ersatz des halogens durch die carboxylgruppe. *Chem. Ber.* **1919**, *52*, 1749−1756.

(6) (a) Yan, G.; Zhang, Y.; Wang, J. Recent Advances in the Synthesis of Aryl Nitrile Compounds. *Adv. Synth. Catal.* **2017**, *359*, 4068−4105. (b) Anbarasan, P.; Schareina, T.; Beller, M. Recent Developments and Perspectives in Palladium-Catalyzed Cyanation of Aryl Halides: Synthesis of Benzonitriles. *Chem. Soc. Rev.* **2011**, *40*, 5049−5067.

(7) Biondini, D.; Brinchi, L.; Germani, R.; Goracci, L.; Savelli, G. Dehydrogenation of amines to nitriles in aqueous micelles. *Eur. J. Org. Chem.* **2005**, *2005*, 3060−3063.

(8) Iida, S.; Togo, H. Direct oxidative conversion of alcohols and amines to nitriles with molecular iodine and DIH in aq NH3. *Tetrahedron* **2007**, *63*, 8274.

(9) (a) Nicolaou, K. C.; Mathison, C. J. N. Synthesis of Imides, N-Acyl Vinylogous Carbamates and Ureas, and Nitriles by Oxidation of Amides and Amines with Dess−Martin Periodinane. *Angew. Chem., Int. Ed.* **2005**, *44*, 5992−5997. (b) Singh, K.; Kaur, A.; Mithu, V. S.; Sharma, S. Metal-Free Organocatalytic Oxidative Ugi Reaction Promoted by Hypervalent Iodine. *J. Org. Chem.* **2017**, *82*, 5285−5293.

(10) Gaspa, S.; Porcheddu, A.; Valentoni, A.; Garroni, S.; Enzo, S.; De Luca, L. A Mechanochemical-Assisted Oxidation of Amines to Carbonyl Compounds and Nitriles. *Eur. J. Org. Chem.* **2017**, *2017*, 5519−5526.

(11) (a) Zhang, J.; Wang, Z.; Wang, Y.; Wan, C.; Zheng, X.; Wang, Z. A metal-free catalytic system for the oxidation of benzylic methylenes and primary amines under solvent-free conditions. *Green Chem.* **2009**, *11*, 1973. (b) Gomes, S. Q.; Salles, A. G., Jr. A metal-free approach to access ketones, amides, and nitriles employing TBAI/TBHP oxidative system in water. *Synth. Commun.* **2019**, *49*, 3389−3399.

(12) (a) Ray, R.; Chandra, S.; Yadav, V.; Mondal, P.; Maiti, D.; Lahiri, G. K. Ligand controlled switchable selectivity in ruthenium catalyzed aerobic oxidation of primary amines. *Chem. Commun.* **2017**, *53*, 4006−4009. (b) Heydari, M.; Ganji, N.; Veisi, H. H.; Karimi, B.; Vali, H. Ru Nanoclusters Supported on a Bimodal N,S-Doped Mesoporous Carbon: An Efficient and Reusable Catalyst for Selective Aerobic Oxidation of Alcohols and Amines. *Catal. Sci. Technol.* **2024**, *14* (16), 4684−4696. (c) Pagliaro, M.; Campestrini, S.; Ciriminna, R. Ru-based oxidation catalysis. *Chem. Soc. Rev.* **2005**, *34*, 837. (d) Muthusamy, S.; Kumarswamyreddy, N.; Kesavan, V.; Chandrasekaran, S. Recent advances in aerobic oxidation with ruthenium catalysts. *Tetrahedron Lett.* **2016**, *57*, 5551. (e) Ray, R.; Hazari, A. S.; Lahiri, G. K.; Maiti, D. Ruthenium-Catalyzed Aerobic Oxidation of Amines. *Chem. − Asian J.* **2018**, *13*, 2138. (f) Yamaguchi, K.; Mizuno, N. Efficient Heterogeneous Aerobic Oxidation of Amines by a Supported Ruthenium Catalyst. *Angew. Chem., Int. Ed.* **2003**, *42*, 1479−1483.

(13) (a) Tian, H.; Ding, C.-Y.; Liao, R.-Z.; Li, M.; Tang, C. Cobalt-Catalyzed Acceptorless Dehydrogenation of Primary Amines to Nitriles. *J. Am. Chem. Soc.* **2024**, *146*, 11801−11810. (b) Natte, K.; Jagadeesh, R. V.; Sharif, M.; Neumann, H.; Beller, M. Synthesis of nitriles from amines using nanoscale Co_3O_4-based catalysts via sustainable aerobic oxidation. *Org. Biomol. Chem.* **2016**, *14*, 3356−3359.

(14) Guenani, N.; Solera-Rojas, J.; Carvajal, D.; Mejuto, C.; Mollar-Cuni, A.; Guerrero, A.; Fabregat-Santiago, F.; Mata, J. A.; Mas-Marzá, E. Room Temperature Hydrogen Production via Electro-Dehydrogenation of Amines into Nitriles: Advancements in Liquid Organic Hydrogen Carriers. *Green Chem.* **2024**, *26* (15), 8768−8776.

(15) Jagadeesh, R. V.; Junge, H.; Beller, M. Nanorust"-catalyzed benign oxidation of amines for selective synthesis of nitriles. *ChemSusChem* **2015**, *8*, 92−96.

(16) Jia, X.; Ma, J.; Xia, F.; Gao, M.; Gao, J.; Xu, J. Switching acidity on manganese oxide catalyst with acetylacetones for selectivity-tunable amines oxidation. *Nat. Commun.* **2019**, *10*, No. 2338.

(17) (a) Damodara, D.; Arundhathi, R.; Likhar, P. R. Copper Nanoparticles from Copper Aluminum Hydrotalcite: An Efficient Catalyst for Acceptor- and Oxidant-Free Dehydrogenation of Amines and Alcohols. *Adv. Synth. Catal.* **2014**, *356*, 189−198. (b) Patil, R. D.; Gupta, M. K. Methods of Nitriles Synthesis from Amines through Oxidative Dehydrogenation. *Adv. Synth. Catal.* **2020**, *362* (19), 3987−4009.

(18) (a) Kametani, T.; Takahashi, K.; Ohsawa, T.; Ihara, M. Oxidation of Amines to Nitriles or Aldehydes using Copper(I) Chloride. *Synthesis* **1977**, *1977*, 245. (b) Capdevielle, P.; Lavigne, A.; Maumy, M. Simple and Efficient Copper-Catalyzed One-Pot Conversion of Aldehydes into Nitriles. *Synthesis* **1989**, *1989*, 453−454. (c) Maeda, Y.; Nishimura, T.; Uemura, S. Copper-Catalyzed

Oxidation of Amines with Molecular Oxygen. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399−2403.

(19) Kim, J.; Stahl, S. S. Cu/Nitroxyl-Catalyzed Aerobic Oxidation of Primary Amines into Nitriles at Room Temperature. *ACS Catal.* **2013**, *3*, 1652−1656.

(20) Xu, B.; Hartigan, E. M.; Feula, G.; Huang, Z.; Lumb, J.-P.; Arndtsen, B. A. Simple copper catalysts for the aerobic oxidation of amines: selectivity control by the counterion. *Angew. Chem., Int. Ed.* **2016**, *55*, 15802−15806.

(21) Wang, J. Q.; Lu, S. L.; Cao, X. Q.; Gu, H. W. Common Metal of Copper(0) as an Efficient Catalyst for Preparation of Nitriles and Imines by Controlling Additives. *Chem. Commun.* **2014**, *50*, 5637−5640.

(22) Shen, Y.; Zhou, Y.; Jiang, L.; Ding, G.; Luo, L.; Zhang, Z.; Xie, X. Selective aerobic oxidation of benzylic amines to aryl nitriles catalyzed by CuBr2/N-methyl imidazole. *Tetrahedron* **2018**, *74*, 4266−4271.

(23) Ma, X.-T.; Xu, H.; Xiao, Y.; Su, C.; Liu, J.; Xu, Q. Direct synthesis of nitriles by Cu/DMEDA/TEMPO-catalyzed aerobic oxidation of primary amines with air. *Chin. Chem. Lett.* **2017**, *28*, 1336.

(24) (a) Li, S.; An, Y.; Zhao, W.; Huang, J.; Wen, B.; Chen, X. Copper-catalyzed aerobic oxidative dehydrogenative coupling to access benzo[c]cinnolines. *Org. Lett.* **2024**, *26*, 6988. (b) Li, S.; Zhao, W.; Wang, L.; Jia, Y.; Cui, Q.; Wen, B.; Chen, X. Controllable Selective Oxidation of Anilines to Azoxybenzenes and Nitrobenzenes by Regulating the Base. *ACS Omega* **2024**, *9* (38), 39715−39723.

(25) Zhang, C.; Jiao, N. Copper-catalyzed aerobic oxidative dehydrogenative coupling of anilines leading to aromatic azo compounds using dioxygen as an oxidant. *Angew. Chem., Int. Ed.* **2010**, *49*, 6174.

(26) (a) Zhang, C. X.; Liang, H.-C.; Kim, E.; Shearer, J.; Helton, M. E.; Kim, E.; Kaderli, S.; Incarvito, C. D.; Zuberb_hler, A. D.; Rheingold, A. L.; Karlin, K. D. Tuning Copper− Dioxygen Reactivity and Exogenous Substrate Oxidations via Alterations in Ligand Electronics. *J. Am. Chem. Soc.* **2003**, *125*, 634. (b) Obias, H. V.; Lin, Y.; Murthy, N. N.; Pidcock, E.; Solomon, E. I.; Ralle, M.; Blackburn, N. J.; Neuhold, Y.-M.; Zuberb_hler, A. D.; Karlin, K. D. Peroxo-, oxo-, and hydroxo-bridged dicopper complexes: Observation of exogenous hydrocarbon substrate oxidation. *J. Am. Chem. Soc.* **1998**, *120*, 12960. (c) Itoh, S.; Taki, M.; Nakao, H.; Holland, P. L.; Tolman, W. B.; Que, L., Jr.; Fukuzumi, S. Aliphatic Hydroxylation by a Bis(μ-oxo)dicopper(III) Complex. *Angew. Chem., Int. Ed.* **2000**, *39*, 398. (d) Mahadevan, V.; Henson, M. J.; Solomon, E. I.; Stack, T. D. P. Differential Reactivity between Interconvertible Side-On Peroxo and Bis-μ-oxodicopper Isomers Using Peralkylated Diamine Ligands. *J. Am. Chem. Soc.* **2000**, *122*, 10249. (e) Kunishita, A.; Ishimaru, H.; Nakashima, S.; Ogura, T.; Itoh, S. Reactivity of mononuclear alkylperoxo copper (II) complex. O− O bond cleavage and C− H bond activation. *J. Am. Chem. Soc.* **2008**, *130*, 4244. (f) Taki, M.; Teramae, S.; Nagatomo, S.; Tachi, Y.; Kitagawa, T.; Itoh, S.; Fukuzumi, S. Fine-tuning of copper (I)-dioxygen reactivity by 2-(2-pyridyl) ethylamine bidentate ligands. *J. Am. Chem. Soc.* **2002**, *124*, 6367.

(27) Capdevielle, P.; Lavigne, A.; Sparfel, D.; Baranne-Lafont, J.; Cuong, N. K.; Maumy, M. Mechanism of primary aliphatic amines oxidation to nitriles by the cuprous chloride - dioxygen - pyridine system. *Tetrahedron Lett.* **1990**, *31*, 3305−3308.