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Copper N-Heterocyclic Carbene: A Catalyst for Aerobic Oxidation or Reduction Reactions

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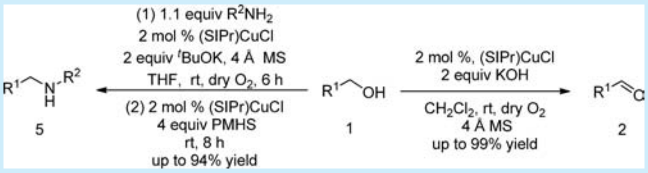
Supporting Information

ABSTRACT: Copper N-heterocyclic carbene complexes can be readily used as catalysts for both aerobic oxidation of alcohols to aldehydes and reduction of imines to amines. Our methodology is universal for aromatic substrates and shows versatile tolerance to potential cascade reactions. A one-pot tandem synthetic strategy could afford useful imines and secondary amines via an oxidation−reduction strategy.



The oxidation of alcohols to carbonyl compounds is one of the most common classes of oxidation reactions in organic chemistry. Widespread interest has been directed toward the development of catalytic aerobic oxidation methods.[1] Copper-catalyzed aerobic organic reactions have become a burgeoning field of research. Oxygen is a highly atom-economical, environmentally benign, and abundant oxidant. Since oxygen can serve as either a sink for electrons, a source of oxygen atoms that are incorporated into the product, or both, the chemistry of copper catalysis is increased exponentially when combined with molecular oxygen. Such oxidations using oxygen or air have been employed safely in numerous commodity chemical continuous and batch processes.[2] Similarly, significant advances have been made over the last two decades since the benefit of N-heterocyclic carbenes (NHCs) as ancillary ligands in organometallic catalysis has been realized.[3] Increasing experimental evidence clearly shows that metal−NHC catalysts can surpass their phosphine-based counterparts in both activity and scope,[4,5] and they are mainly known for their impact on palladium-,[6] ruthenium-,[7] silver-,[8,9] and gold-catalyzed[10] reactions. Copper is much cheaper than many transition metals that are commonly used in organometallic catalysis. In conjunction with copper, the strong electron-donating properties of NHCs yield catalysts that are often very robust, demonstrating air, moisture, and thermal stability.[5,11,12] In the past decade, NHC-ligated copper complexes (examples of which are shown in Figure 1) have been found to act as catalysts for functionalization of carbonyls, alkenes, and alkynes.[5]

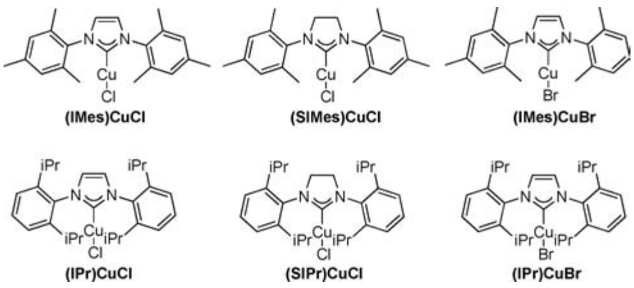


Figure 1. Selected Cu−NHC catalysts.

A remarkable number of transition-metal-catalyzed aerobic oxidations of alcohols have been well-established, including those using copper,[2] such as copper salts in combination with TEMPO and various N-ligands such as 2,2′-bipyridine, DABCO,[13] and TMDP. Recently, imidazolium salts bearing TEMPO groups were shown to react with copper powder to afford Cu−NHC−TEMPO complexes in situ as efficient catalysts for aerobic oxidation of primary alcohols to aldehydes at 80 °C.[14] In continuation of our interest in metal−NHC chemistry,[15] herein we report a Cu−NHC catalyst that was found to be competent for both aerobic oxidation of alcohols to aldehydes and reduction of imines to amines in excellent yields under mild conditions. The aerobic oxidation and reduction appear to be more advantageous and feasible methods because of the use of dry oxygen and polymethylhydrosiloxane (PMHS) as pollution-free reagents, safer and milder conditions, as well as fewer byproducts. We also explored a one-pot tandem synthetic strategy providing several greener and practical approaches for the preparation of aldehydes, ketones, imines, or secondary amines.

In the Cu−NHC−TEMPO aerobic oxidation of alcohols reported by Chen,[14] addition of base (^{t}BuOK or Et$_3$N) resulted in an obvious decrease in yield, and the Cu−NHCs [(IMes)CuBr] and [(IPr)CuBr] became totally inactive. We reexamined the catalytic activities of Cu−NHCs for aerobic oxidation of alcohols and found that base is necessary for the aerobic oxidation. When the aerobic reaction was carried out with ^{t}BuOK in the presence of 4 Å molecular sieves (MS) in dichloromethane, high yields of aldehyde were obtained when

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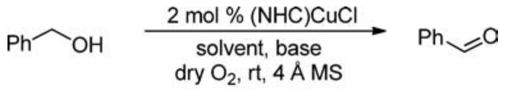
Table 1. Studies of Aerobic Oxidative Reaction Conditions[a]



1a **2a**

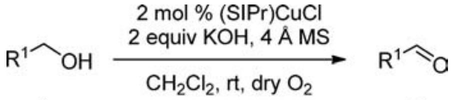
entry	catalyst	solvent	additive	time (h)	yield (%)[b]
1	(IMes)CuCl	CH_2Cl_2	^{t}BuOK (2 equiv)	24	35
2	(SIMes)CuCl	CH_2Cl_2	^{t}BuOK (2 equiv)	24	89
3	(IPr)CuCl	CH_2Cl_2	^{t}BuOK (2 equiv)	24	68
4	(SIPr)CuCl	CH_2Cl_2	^{t}BuOK (2 equiv)	24	95
5	(SIMes)CuCl	toluene	KOH (2 equiv)	12	92
6	(SIPr)CuCl	CH_2Cl_2	KOH (2 equiv)	12	99
7	(SIPr)CuCl	CH_2Cl_2	none	12	trace
8	(SIPr)CuCl	CH_2Cl_2	KOH (1 equiv)	12	58
9[c]	(SIPr)CuCl	CH_2Cl_2	KOH (2 equiv)	12	89
10[d]	(SIPr)CuCl	CH_2Cl_2	KOH (2 equiv)	12	NR

[a] Reaction conditions: the mixture of **1a**, Cu−NHC catalyst, base, and 4 Å MS was stirred at ambient temperature in a pure oxygen atmosphere. [b] Isolated yields. [c] The oxidation reaction was carried out in a dry air atmosphere. [d] The oxidation reaction was carried in an argon atmosphere.

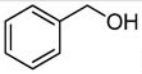
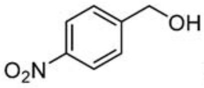
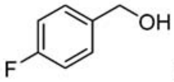
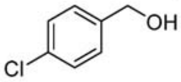
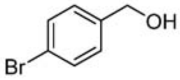
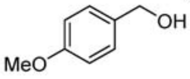
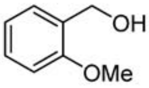
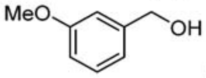
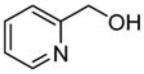
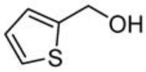
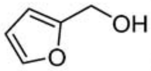
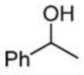
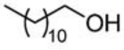
[(SIMes)CuCl] or [(SIPr)CuCl] was used as the catalyst (Table 1, entries 2 and 4), whereas [(IMes)CuCl] and [(IPr)CuCl] gave low yields (Table 1, entries 1 and 3), because the saturated NHC ligands are slightly less electron-donating than their unsaturated analogues.[16] Further screening of solvents and bases revealed that the reaction gave almost quantitative yield with KOH as the base in dichloromethane (Table 1, entries 5 and 6). When the amount of KOH was reduced to 1 equiv or none, the yield of the product was reduced to 58% or trace, respectively (Table 1, entries 7 and 8). Changing oxygen to air reduced the yield of the product to 89% (Table 1, entry 9). No product was detected when the reaction was carried out in an argon atmosphere (Table 1, entry 10).

The Cu−NHC-catalyzed aerobic oxidation was then extended to various alcohol substrates (Table 2). It seemed that this method not only was suitable for benzylic alcohols bearing electron-withdrawing groups (Table 2, entries 2−5) but also afforded benzaldehydes substituted with electron-donating groups in excellent yields (Table 2, entries 6−8). Our mild oxidation strategy was also tolerant of heterocyclic substrates such as pyridine- (**1i**) and thiophene-derived (**1j**) alcohols, which are especially advantageous compared with their furan counterpart (**1k**), which is sensitive to heat (Table 2, entries 9−11). Besides, we have extended our alcohol substrates to cinnamyl alcohol (**1l**) (Table 2, entry 12), and aromatic ketone **2m** was also obtained in excellent yield (Table 2, entry 13). For an aliphatic alcohol, we detected the aldehyde in only 9% GC−MS yield (Table 2, entry 14).

Table 2. Study of Aerobic Oxidation of Alcohols to Aldehydes[a]

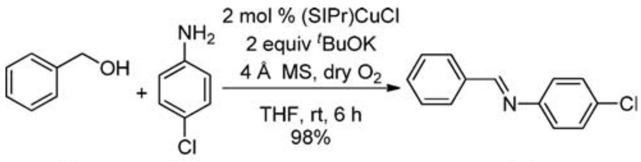


1 **2**

entry	substrate	yield/% (product)[b]
1	 (**1a**)	99 (**2a**)
2	 (**1b**)	98 (**2b**)
3	 (**1c**)	95 (**2c**)
4	 (**1d**)	99 (**2d**)
5	 (**1e**)	97 (**2e**)
6	 (**1f**)	99 (**2f**)
7	 (**1g**)	95 (**2g**)
8	 (**1h**)	93 (**2h**)
9	 (**1i**)	87 (**2i**)
10	 (**1j**)	94 (**2j**)
11	 (**1k**)	89 (**2k**)
12	 (**1l**)	90 (**2l**)
13	 (**1m**)	95 (**2m**)
14[c]	 (**1n**)	9 (**2n**)

[a] Reaction conditions: the mixture of **1** (1 mmol), (SIPr)CuCl catalyst (0.02 mmol, 2 mol %), KOH (2 mmol), 4 Å MS, and CH_2Cl_2 (10 mL) was stirred at ambient temperature in a pure oxygen atmosphere for 12 h. [b] Isolated yields. [c] Reaction conditions: the mixture of **1n** (1 mmol), (SIPr)CuCl catalyst (0.02 mmol, 2 mol %), KOH (2 mmol), 4 Å MS, and THF (10 mL) was stirred at 60 °C in a pure oxygen atmosphere for 12 h, and the yield was determined by GC−MS.

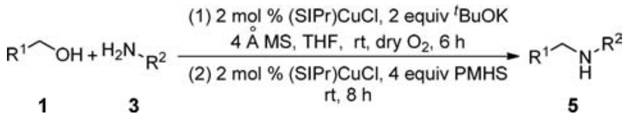
Scheme 1. Tandem Attempt To Afford Imine 4a

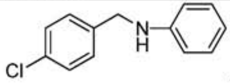
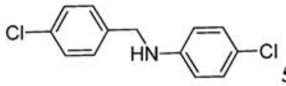
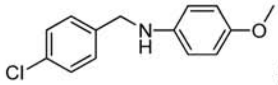
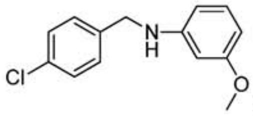
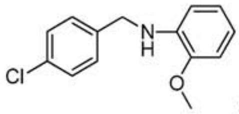
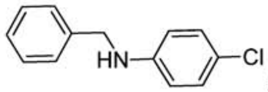
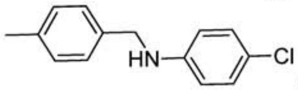
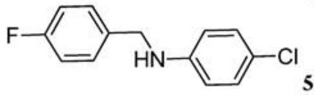
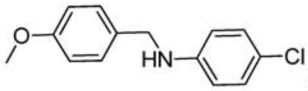
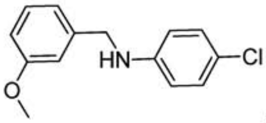
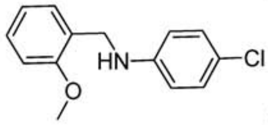
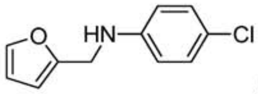
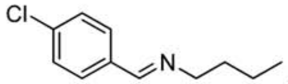


1a **3a** **4a**

Amines are important compounds that are prominent in bioactive molecules and natural products and widely used in agrochemicals, chemical industries, and pharmaceuticals.[17,19] A classical method for preparing *N*-alkylamines is the reaction of an amine with an alkyl halide.[18] However, it is difficult to get the desired product as the reaction is prone to overalkylation.[19] As an environmentally benign approach for the synthesis of amines, widespread interest has been directed toward reductive amination with alcohols as alkylating agents based on the catalytic hydrogen transfer process.[20] A corresponding aldehyde or ketone is generated by this reaction sequence, which would

Table 3. Study of Cascade Oxidative and Reductive Reactions To Afford Secondary Amines[a]



entry	products	yield (%)[b]
1	 **5a**	93
2	 **5b**	94
3	 **5c**	90
4	 **5d**	78
5	 **5e**	76
6	 **5f**	92
7	 **5g**	91
8	 **5h**	75
9	 **5i**	97
10	 **5j**	92
11	 **5k**	89
12	 **5l**	87
13	 **4b**	90%

[a]Reaction conditions: the mixture of **1** (1 mmol), **3** (1.1 mmol), (SIPr)CuCl catalyst (0.02 mmol, 2 mol %), ᵗBuOK (2 mmol), THF (10 mL), and 4 Å MS was stirred at ambient temperature in pure oxygen for 6 h before the addition of PMHS (0.24 mL, 4 mmol) and (SIPr)CuCl catalyst (0.02 mmol, 2 mol %), after which the stirring was continued at ambient temperature for 8 h. [b]Isolated yields.

be kicked off by the dehydrogenation of an alcohol. Subsquently, dehydrative condensation would cause the formation of an imine intermediate, which would then be followed by transfer hydrogenation, affording the desired *N*-alkylamine.[21] Tandem catalysis that enables a one-pot multistep reaction shows great potential for increasing the efficiency of chemical synthesis.[15] Since mild conditions are used for the selective oxidation of alcohols, a cascade reaction was attempted for the one-pot oxidative tandem synthesis of imine **4a** from alcohol **1a** and amine **3a**, and we got the desired imine in high yield (Scheme 1).

Considering the catalytic activities in reduction reactions of Cu−NHCs,[22] we designed a one-pot process for the synthesis of important secondary amines from alcohols and primary amines via aerobic oxidation, amination, and reduction catalyzed by [(SIPr)CuCl]. The aerobic oxidation of alcohols by the [(SIPr)CuCl]/ᵗBuOK/4 Å MS catalyst system was performed, and the reaction was monitored by TLC. After consumption of the alcohol, PMHS and additional [(SIPr)-CuCl] catalyst (2 mol %) was added to the reaction mixture to reduce the imine to the secondary amine. Thus, the reaction of 4-chlorobenzyl alcohol and aniline for 6 h followed by the addition of PMHS and [(SIPr)CuCl] gave a high yield of **5a** (Table 3, entry 1).We found that no obvious electronic effect contributed to the yield of secondary amine (Table 3, entries 1−3) when para-substituted amines bearing electron-deficient or electron-rich groups were used as substrates. Comparative experiments on *p*-, *m*-, and *o*-methoxyaniline identified that steric hindrance influences the yield of the secondary amine (Table 3, entries 3−5). Amine **3a** likewise reacted with benzylic alcohols bearing electron-donating or electron-withdrawing substituents (Table 3, entries 2 and 6−9), and the comparative experiments on *p*-, *m*-, and *o*-methoxybenzyl alcohols identified that steric hindrance more or less influences the yield of the secondary amine (Table 3, entries 9−11). The mild conditions were also used for the furan counterpart, which is sensitive to heat (Table 3, entry 12). For the aliphatic amine, we obtained the imine in only 90% yield, and the amine reductive product could not be detected (Table 3, entry 13).

In conclusion, a robust and effective Cu−NHC for aerobic alcohol oxidation that is effective for a variety of alcohols was discovered and studied. When KOH is used in the presence of 4 Å molecular sieves, the oxidation can be carried out under an oxygen atmosphere to afford aldehydes and ketones selectively in excellent yields. In addition, the one-pot synthesis of imines from benzylic alcohols and primary amines was achieved using the Cu−NHC catalyst. The one-pot process for the synthesis of important secondary amines via aerobic oxidation, amination, and reduction catalyzed by [(SIPr)CuCl] was found to be high-yielding.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02756.

Full experimental details, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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