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Copper-Catalyzed Aerobic Aliphatic C−H Oxygenation Directed by an Amidine Moiety

Yi-Feng Wang,[†] Hui Chen,[†] Xu Zhu, and Shunsuke Chiba*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: A method for the oxygenation of tertiary C−H bonds of *N*-alkylamidines and *N*-(2-alkylaryl)-amidines is described that utilizes the $CuBr{\cdot}SMe_2$/2,2′-bipyridine catalytic system under an O_2 atmosphere and provides dihydrooxazoles and 4*H*-1,3-benzoxazines. The oxygen atom is incorporated from atmospheric molecular oxygen during the present process.

Aliphatic C−H bonds are omnipresent functions in organic molecules, and those without activation by the adjacent functional groups (e.g., carbonyl groups) are extremely stable and inert even under strongly acidic and basic reaction conditions. Although various approaches for oxidative functionalization of unactivated aliphatic C−H bonds with transition-metal catalysts have recently been developed,[1,2] exploitation of the catalytic reaction that enables the realization of oxidative C−H functionalization in a predictable chemo- and regioselective manner is still one of the most challenging issues in organic synthesis. Especially, catalytic systems capable of performing selective C−H oxidation in substrates bearing electron-rich nitrogen functional groups are extremely scarce. Herein we report a copper-catalyzed aerobic C−H oxygenation of aliphatic C−H bonds (resulting in C−O bond formation) directed by an amidine moiety that is easily installed on primary amines.[3]

We have been interested in copper-mediated oxidative functionalization of carbon−carbon unsaturated bonds as well as C−H bonds under aerobic conditions,[4,5] and we recently reported the intramolecular [3 + 2] annulation reaction of *N*-pentenylamidines to give bi- and tricyclic amidines (eq 1).[4a] The reaction mechanism includes putative nitrene intermediate **B** (with its resonance form **C**), which might be formed by stepwise single-electron oxidation and deprotonation via 1,3-diazaallyl radical **A**. Stimulated by this discovery, we then became interested in the chemical reactivity of aliphatic C−H bonds toward the amidine moiety under Cu-catalyzed aerobic conditions, envisioning C−H radical abstraction (i.e., a 1,5-hydrogen radical shift)[6] via 1,3-diazaallyl radical **A** and C−H amination[7] via nitrene species **B** as possible reaction pathways (eq 2). In fact, we have found that the reactions proceed exclusively via the 1,5-hydrogen radical shift from 1,3-diazaallyl radical **A** to give C−H oxygenation products.

We began our investigation with the copper-catalyzed aerobic reactions of *N*-(2,2-diphenylethyl)benzimidamide (**1a**) (Table 1). Interestingly, when **1a** was treated with CuI (20 mol %) and 2,2′-bipyridine (bpy) (20 mol %) in dimethyl sulfoxide (DMSO) at 100 °C under an O_2 atmosphere, a C−H oxygenation product, dihydrooxazole **2a**, was isolated in 67% yield (entry 1). An isotope-labeling experiment using an $^{18}O_2$ atmosphere revealed that the oxygen atom in the resulting C−O bond was derived from atmospheric O_2 (see entry 11), which is particularly rare in the literature precedents for catalytic C−H oxygenation.[8,9] This unprecedented aerobic C−H oxygenation reaction to form dihydrooxazole **2a** prompted us to optimize the reaction conditions. Other Cu sources showed the catalytic activity regardless of their oxidation state (either I or II) (entries 2−5), and the highest yield was provided by $CuBr{\cdot}SMe_2$ (entry 2). Switching the solvent to *N*,*N*-dimethylformamide (DMF) decreased the yield of **2a** (entry

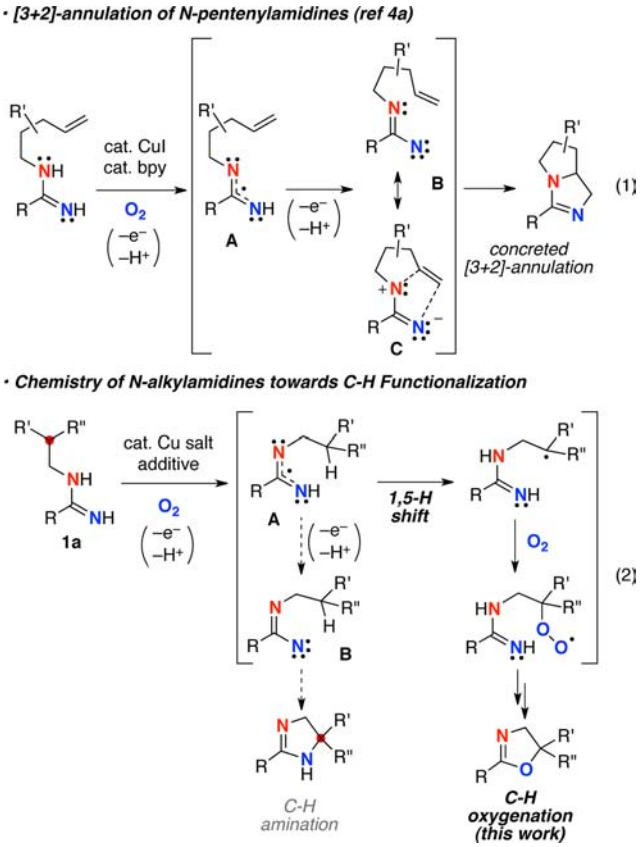

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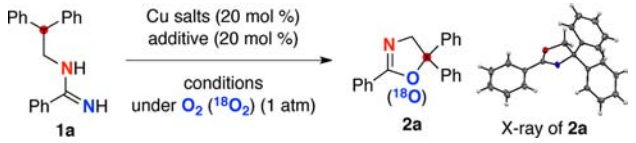
Table 1. Optimization of the Reaction Conditions[a]



entry	Cu salt	additive	solvent	temp (°C)	time (h)	yield (%)[b]
1	CuI	bpy	DMSO	100	5	67
2	CuBr·SMe$_2$	bpy	DMSO	100	3	70
3	CuCl	bpy	DMSO	10	5	56
4	CuBr$_2$	bpy	DMSO	100	4	62[c]
5	Cu(OAc)$_2$	bpy	DMSO	100	4	37[c]
6	CuBr·SMe$_2$	bpy	DMF	100	2	57
7	CuBr·SMe$_2$	DABCO	DMSO	100	2	53[c]
8	CuBr·SMe$_2$	phen	DMSO	100	2	70
9	CuBr·SMe$_2$	bpy	DMSO	80	24	77
10[d]	CuBr·SMe$_2$	bpy	DMSO	80	24	75
11	CuBr·SMe$_2$	bpy	DMSO/PhCF$_3$[e]	80	24	79 (76[f])
12[g]	CuBr·SMe$_2$	bpy	DMSO/PhCF$_3$[e]	80	40	0

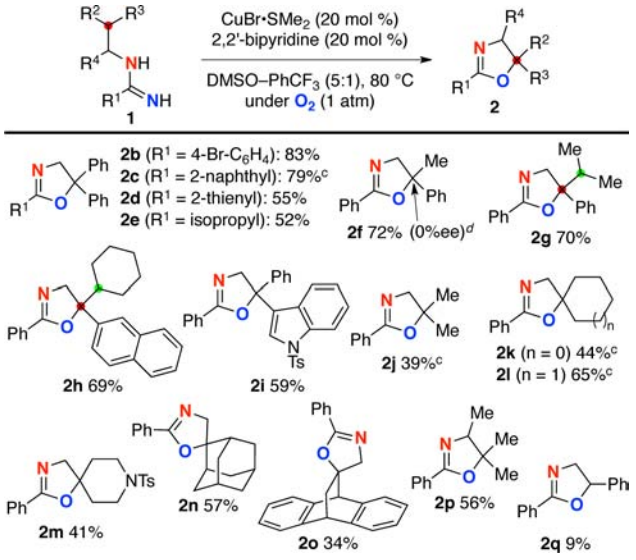
[a]Unless otherwise noted, the reactions were carried out using 0.3 mmol of amidine **1a** in solvent (0.05 M) at 60 °C under an O_2 atmosphere. [b]Isolated yields. [c]^{1}H NMR yield. [d]The reaction was carried out under an air atmosphere. [e]DMSO/PhCF$_3$ = 5:1. [f]Yield of **2a**-^{18}**O** when the reaction was carried out under an $^{18}O_2$ atmosphere. [g]The reaction was carried out under a N_2 atmosphere.

6). Reactions with other types of nitrogen ligands, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,10-phenanthroline (phen), also gave moderate to good yields of **2a** (entries 7 and 8). It was found that lowering the reaction temperature to 80 °C increased the reaction time but resulted in a better yield of **2a** (entry 9). Reduction of the oxygen partial pressure by using an air atmosphere (P_{O_2} = 0.21 atm) did not affect the product yield of **2a** (entry 10). It was found that the cosolvent system of 5:1 DMSO/PhCF$_3$ delivered a slightly better yield of **2a** (entry 11). Under a N_2 atmosphere, no reaction was observed even after 40 h, and **1a** was completely recovered (entry 12).

Using the CuBr·SMe$_2$/2,2′-bipyridine catalytic system in 5:1 DMSO/PhCF$_3$ solvent (Table 1, entry 11), we examined the generality of this C−H oxygenation of *N*-alkylamidines **1** for the synthesis of dihydrooxazoles **2** (Chart 1). Variation of the R^1 substituent of **1** showed that various aromatic rings, including bromophenyl, naphthyl, and thienyl groups (for **2b**−**d**), were tolerated and that an isopropyl substituent could be introduced (**2e**). Starting from optically active amidine **1f** bearing a chiral tertiary carbon center,[10] racemic dihydrooxazole **2f** was formed in 72% yield, suggesting that the present process indeed involves a carbon radical intermediate.[11] Amidines **1g** and **1h** with two successive tertiary carbons at the 5- and 6-positions (marked in red and green, respectively) relative to the amidine nitrogen at the 1-position (marked in blue) selectively provided the corresponding dihydrooxazoles **2g** and **2h**. The reaction allowed the installation of an indole motif (**2i**). 5,5-Dialkyloxazoles, including several spirocyclic compounds, could be constructed in good to moderate yields (**2j**−**o**). Introduction of a methyl group at R^4 did not affect the reaction (**2p**), while oxygenation of the secondary C−H bond resulted in a low yield (**2q**).

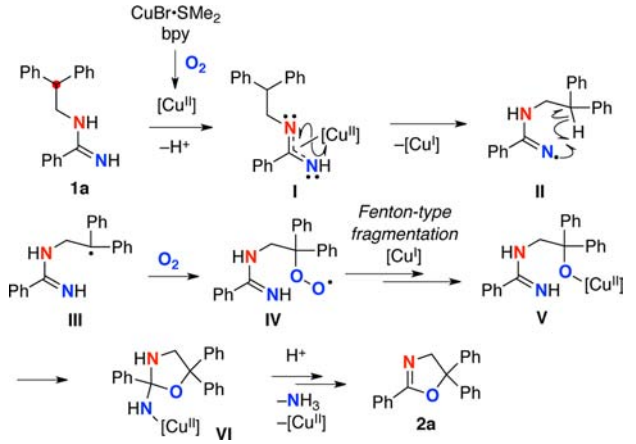
On the basis of these results, a possible mechanism is proposed in Scheme 1. In this scenario, one-electron oxidation

Chart 1. C−H Oxygenation of *N*-Alkylamidines[a,b]



[a]Unless otherwise noted, the reactions were carried out using 0.3 mmol of amidine **1** with 20 mol % CuBr·SMe$_2$ and 20 mol % 2,2′-bipyridine in 5:1 DMSO/CF$_3$Ph at 80 °C under an O_2 atmosphere. [b]Isolated yields are shown. [c]The reaction was run at 100 °C. [d]Optically active **1f** was used for the reaction and gave racemic **2f**.

Scheme 1. Proposed Reaction Mechanism for the C−H Oxygenation



of amidine **1** by higher-oxidation-state Cu^{II} species (described as [Cu^{II}]) generated from Cu^{I}Br with molecular oxygen[12] would provide 1,3-diazaallyl radical **II**, which may undergo a 1,5-H radical shift to afford tertiary carbon radical **III**. Subsequently, **III** would react with molecular oxygen to give superoxo radical **IV**, further Fenton-type fragmentation of which would deliver Cu(II) alkoxide **V**.[13] Finally, intramolecular nucleophilic attack of alkoxide **V** onto the amidine moiety followed by elimination of ammonia would lead to the formation of dihydrooxazole **2**.[14]

Next, the reactivity of *N*-(2-isopropylphenyl)amidines **3** for the present C−H oxygenation was examined (Scheme 2). In this case, 4*H*-1,3-benzoxazines **4** were obtained via a 1,6-H radical shift followed by oxygenation and cyclization. Brasche and Buchwald[15] reported the reaction of *N*-arylamidines in the presence of 15 mol % Cu(OAc)$_2$ and 5 equiv of AcOH in DMSO at 100 °C under an O_2 atmosphere, which provided benzimidazoles via aromatic C−H amination, while the present

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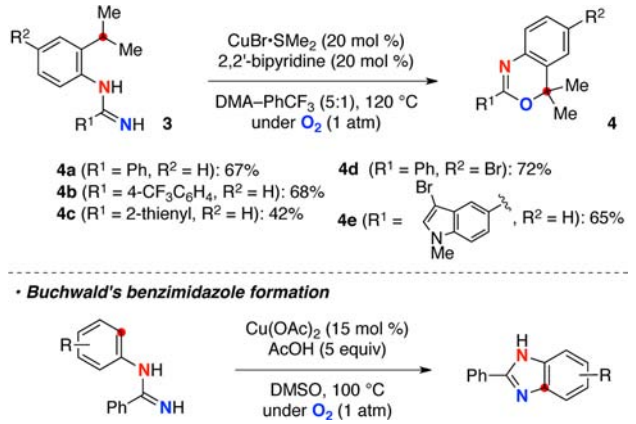
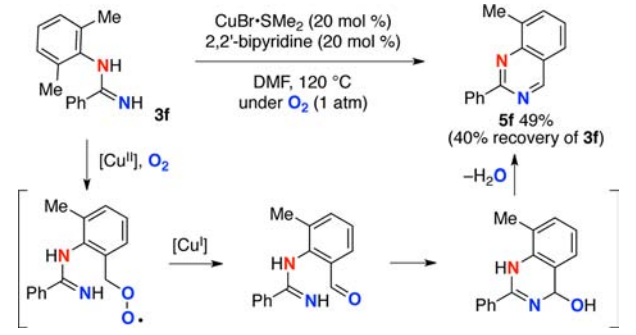
Scheme 2. C−H Oxygenation of *N*-(2-Isopropylphenyl)amidines



system interestingly afforded 4*H*-1,3-benzoxazines exclusively via sp^3 C−H oxygenation.

When *N*-(2,6-dimethylphenyl)amidine **3f** was subjected to the present reaction conditions, quinazoline **5f** was formed in 49% yield via formal C−H amination, which could be achieved in a stepwise manner through oxygenative C═O bond formation on one of the methyl groups and successive dehydrative cyclization of the amidine moiety with the carbonyl group (Scheme 3).

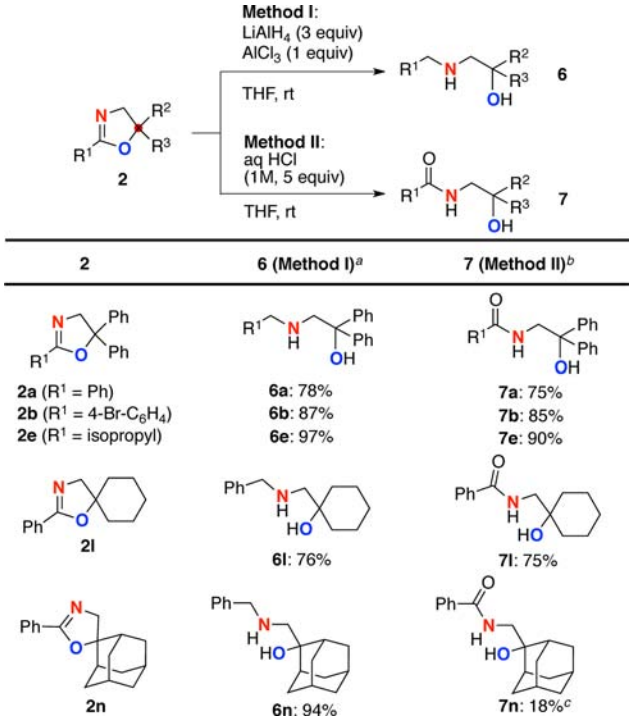
Scheme 3. Formation of a Quinazoline via C−H Amination



Vicinal amino alcohol functionalities are privileged as the structural elements in biologically active molecules as well as ligands for transition-metal catalysts.[16] Having developed a method for the preparation of dihydrooxazoles **2** through the present aerobic C−H oxygenation, we finally explored their concise transformation into vicinal amino alcohols (Chart 2). It was found that reduction of **2** by aluminum hydride (AlH_3, prepared in situ from $LiAlH_4$ and $AlCl_3$)[4a,17] proceeded smoothly to give *N*-benzylamino alcohols **6** (the reduction of **2e** provided *N*-isobutylamino alcohol **6e**). On the other hand, acid-mediated hydrolysis[18] of **2** provided *N*-acylamino alcohols **7**, although the hydrolysis of **2n** was very sluggish, probably because of steric hindrance by the adamantyl moiety. Taking advantage of the ready accessibility of amidines **1** from the corresponding primary amines allows the overall transformation to be summarized as *β*-C−H hydroxylation of primary amines, where the amidine moiety plays the role of a directing group for C−O bond formation as well as a potential protecting group for the amine.

In summary, amidine-directed C−H oxygenation of aliphatic C−H bonds under copper-catalyzed aerobic reaction conditions has been exploited for the synthesis of dihydrooxazoles and 4*H*-1,3-benzoxazines. The dihydrooxazoles could be further converted into *N*-benzyl- and *N*-acylamino alcohols by treatment with AlH_3 and aqueous HCl, respectively. We are currently engaged in further synthetic applications of the amidine moiety as a potential directing group for other types of C−H oxidation reactions.

Chart 2. Transformation of 2 into Amino Alcohols



2	6 (Method I)[a]	7 (Method II)[b]

[a]Method I: the reaction was carried out by initial treatment of $AlCl_3$ (1 equiv) in tetrahydrofuran (THF) with $LiAlH_4$ (3 equiv) at 0 °C followed by addition of dihydrooxazole **2** and stirring at room temperature. [b]Method II: unless otherwise noted, the reaction was carried out using 5 equiv of HCl (1 M) in THF at room temperature. See the Supporting Information for more details. [c]The reaction was carried out using method II with 10 equiv of HCl (1 M) at 65 °C. **2n** was recovered in 78% yield.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

shunsuke@ntu.edu.sg

Author Contributions

[†]Y.-F.W. and H.C. contributed equally.

Notes

The authors declare no competing financial interest.

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(10) Amidine **1f** was prepared from commercially available optically active (*R*)-(+)-β-methylphenethylamine (see the Supporting Information).

(11) The reaction of *N*-(2-cyclopropyl-3-phenylpropyl)benzimidamide **1r** (R^1 = Ph, R^2 = benzyl, R^3 = cyclopropyl, R^4 = H) was also tested to examine a radical clock, and it gave a complex mixture (see the Supporting Information).

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