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Copper-Catalyzed Aminooxygenation of *N*-Allylamidines with PhI(OAc)$_2$

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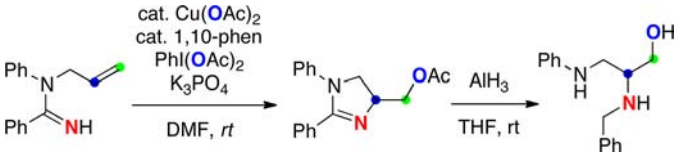
ABSTRACT



A Cu-catalyzed aminoacetoxylation of *N*-alkenylamidines has been achieved using PhI(OAc)$_2$ as an oxygen source for synthesis of 4-acetoxymethyl-4,5-dihydroimidazoles, which could be further converted into 2,3-diaminopropanol derivatives using AlH$_3$ as a reductant.

Oxidative functionalization of alkenes is one of the most fundamental and important processes in organic synthesis.[1] Among various types of the reactions, transition-metal-mediated/catalyzed aminooxygenation of alkenes has been studied extensively because the products, vicinal aminoalcohols, are privileged as the structural elements in biologically active molecules as well as ligands for transition metal catalysts.[2] Although diverse approaches have recently been developed for aminooxygenation of alkenes such as Chemler's copper-mediated/-catalyzed intramolecular aminooxygenation of alkenes with sulfonamide or aniline nitrogens[3] as well as others,[4,5] there remains a demand for exploitation of the catalytic aminooxygenation that enables realization of predictable chemo- and regioselectivity.

We have recently studied copper-catalyzed aerobic oxidative functionalization of aliphatic C−H bonds and C−C unsaturated bonds (alkene and alkyne) installed on amidine moieties such as C−H oxygenation,[6] diamination of alkenes,[7] and aminooxygenation of alkyne (Scheme 1 a−c).[8] These reactions of amidines have driven our continuous investigation to develop copper-catalyzed aminooxygenation of *N*-alkenylamidines. The group of Zhang and Zhu recently reported a copper-catalyzed aerobic reaction of *N*-allylamidines that affords formylimidazoles via the sequence of aminooxygenation of the alkene and aromatization

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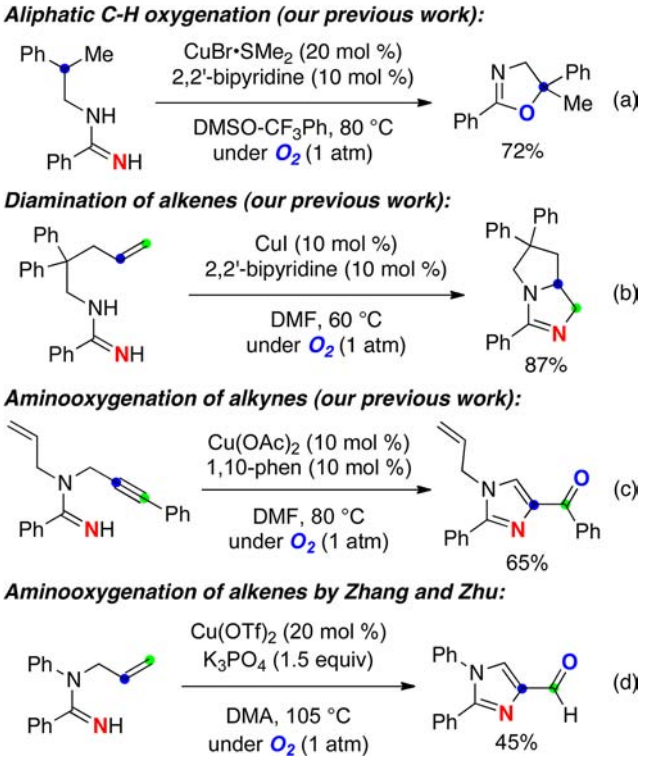
(Scheme 1d).[9] In this context, we have strived to develop aminooxygenation of alkenes with amidine moieties to target nonaromatized dihydroimidazole derivatives using alternative oxygen sources to molecular oxygen that can be achieved under milder reaction conditions.[10]

Scheme 1. Oxidative Functionalization of C−H Bonds, Alkenes, and Alkynes with an Amidine Moiety



Herein, we report copper-catalyzed aminoacetoxylation of *N*-allylamidines with $PhI(OAc)_2$ as the oxygen source and the reoxidant to maintain the catalytic turnover for synthesis of 4-acetoxymethyl-4,5-dihydroimidazoles, which could be further converted into 2,3-diamino-1-propanols by reduction with AlH_3. With the advantage of easy preparation of *N*-allylamidines by the Lewis acid mediated reaction of the corresponding allylamines and carbonitriles, the overall process could be regarded as regioselective aminohydroxylation of allylamines (Scheme 2).

Our study commenced with the reaction of *N*-allyl-*N*-phenylbenzamidine (**1a**) with 20 mol % of $Cu(OAc)_2$ and 1.2 equiv of $PhI(OAc)_2$ in DMF (Table 1, entry 1), which provided 5-*exo* cyclization product 4-acetoxymethyl-4,5-dihydroimidazole **2a** exclusively in 59% yield as the sole product even at *room temperature*. By screening nitrogen ligands as an additive (entries 2−4), 1,10-phenanthroline was found to improve the reaction yield to 71% yield (entry 4). Further optimization of the reaction conditions

(10) As a preliminary result, we have found aminooxygenation of *N*-allylamidines with TEMPO as an oxygen source, whereas the process needed a stoichiometric amount of $Cu(OAc)_2$ with a high reaction temperature (80 °C), giving dihydroimidazoles in moderate yields; see: Sanjaya, S.; Chua, S. H.; Chiba, S. *Synlett* **2012**, *23*, 1657.

Scheme 2. Synthesis of 4-Acetoxymethyl-4,5-dihydroimidazoles via Aminooxygenation of Alkenes and Their Conversion to 2,3-Diamino-1-propanols: Stepwise Strategy on Regioselective Aminohydroxylation of Allylamine (This Work)

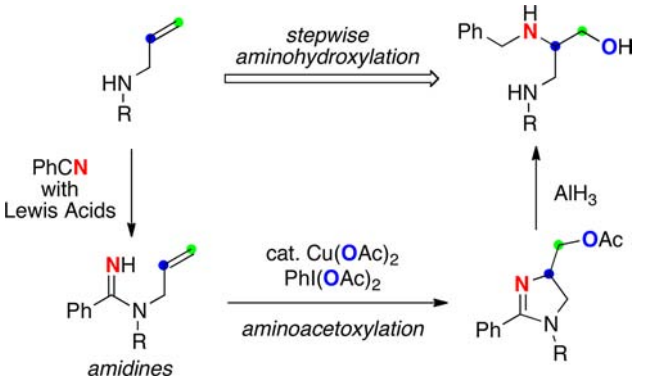
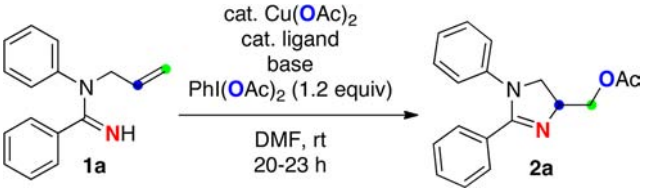


Table 1. Optimization of Reaction Conditions[a]

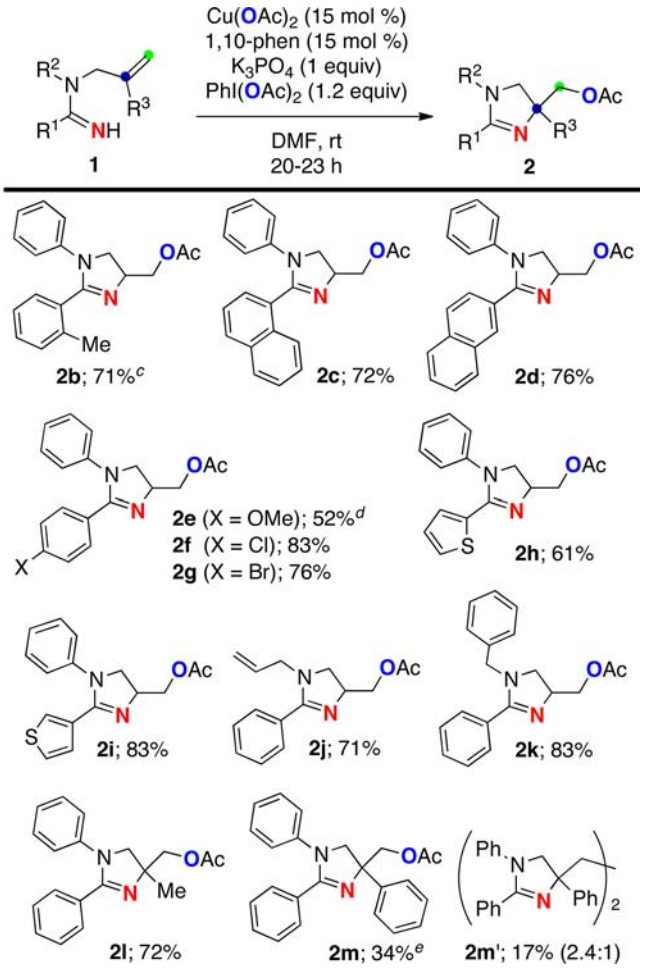


entry	$Cu(OAc)_2$ (mol %)	ligand (mol %)	base (1 equiv)	yield (%)[b]
1	20	–	–	59
2	20	2,2′-bipyridine (20)	–	62
3	20	pyridine (20)	–	60
4	20	1,10-phenanthroline (20)	–	71
5	20	1,10-phenanthroline (20)	K_2CO_3	71
6	15	1,10-phenanthroline (15)	K_3PO_4	86[c]
7	10	1,10-phenanthroline (10)	K_3PO_4	70
8	15	chiral bis-oxazoline (15)[d]	K_3PO_4	40 (48)[e]
9[f]	200	–	K_3PO_4	0
10	0	–	K_3PO_4	0

[a] Unless otherwise noted, the reactions were carried out using 0.5 mmol of amidines **1a**. [b] Isolated yields were recorded. [c] The reaction was carried out using 4.1 mmol (0.97 g) of **1a**, giving 3.5 mmol (1.04 g) of **2a**. [d] 2,2′-Methylene bis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] was used (see Supporting Information for more details). [e] The enantiomeric excess examined by the chiral HPLC (see Supporting Information for more details). [f] The reaction was conducted in the absence of $PhI(OAc)_2$.

by examining inorganic bases revealed that the presence of K_3PO_4 (1 equiv) rendered the formation of **2a** more efficient (86% yield in gram scale preparation) even under a 15 mol % catalytic loading (entry 6), while usage of 10 mol % catalysts dropped the yield of **2a** to 70% (entry 7). The reaction with a chiral bis-oxazoline ligand, 2,2′-methylene bis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline], provided 48% ee of **2a**, which suggests that copper species could most likely be involved in the present N−C bond forming process (entry 8). It was confirmed that the reaction of **1a** only with

Scheme 3. Substrate Scope for Synthesis of 4-Acetoxymethyl-4,5-dihydroimizazoles[a,b]

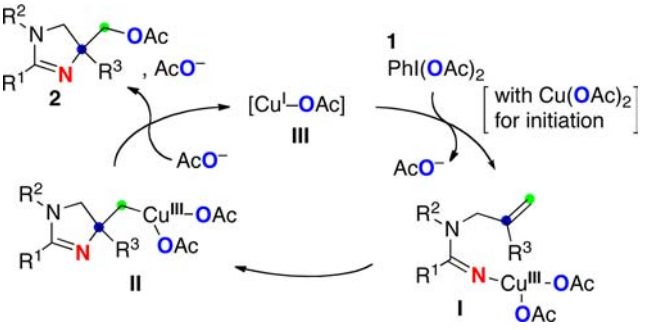


[a] Unless otherwise noted, the reactions were carried out using 2.5−6.6 mmol of amidines **1** with $Cu(OAc)_2$ (15 mol %) and 1,10-phenanthroline (15 mol %) in the presence of K_3PO_4 (1 equiv) and $PhI(OAc)_2$ (1.2 equiv) at rt under a N_2 atmosphere (see Supporting Information for more details). [b] Isolated yields are recorded above. [c] 0.5 mmol of **1b** was used. [d] As a side reaction, *N*-acetoxylation proceeded to give *O*-acetyloxime in 7% yield. [e] 1.2 mmol of **1m** was used, and dimer **2m′** was formed in 17% yield as a mixture of meso and diastereomer forms.

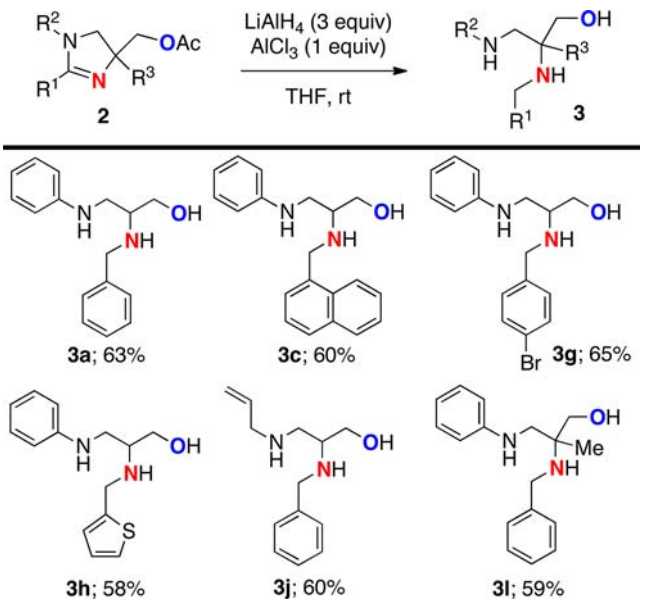
2 equiv of $Cu(OAc)_2$ and that with 1.2 equiv of $PhI(OAc)_2$ do not form **2a** at all (entries 9 and 10).

With the optimized conditions in hand, we next examined the substrate scope for the synthesis of 4-acetoxymethyl-4,5-dihydroimidazoles **2** (Scheme 3). By varying substituents R^1 of amidines **1**, it was shown that various kinds of aromatic rings could be installed. The reactions proceeded smoothly with sterically hindered aromatic rings as R^1 (**2b**−**2d**). While the reaction with an electron-rich 4-methoxybenzene ring afforded the corresponding imidazole **2e**, the yield was moderate (52%) and the corresponding *O*-acetyloxime was formed in 7% yield as a side product. Halogen substituents were tolerated, as the C−X (X = Cl or Br) bond remained intact (for **2f**, **2g**). The present process allowed for installation of 2- and 3-thienyl groups on R^1 (for **2h**, **2i**). As the substituents R^2, benzyl,

Scheme 4. A Proposed Catalytic Cycle



Scheme 5. Conversion of 4-Acetoxymethyl-4,5-dihydroimidazoles into 2,3-Diamino-1-propanols[a,b]



[a] The reactions were carried out by treatment of $AlCl_3$ (1 equiv) in THF with $LiAlH_4$ (3 equiv) at 0 °C followed by addition of dihydroimidazoles **2** (1.1−3.7 mmol) and stirring at room temperature (see Supporting Information for more details). [b] Isolated yields were recorded.

and allyl groups could be installed to provide the corresponding dihydroimidazoles in good yields (for **2j**, **2k**). By introducing a substituent on R^3, the construction of the quaternary carbon center at the C(4) of dihydroimidazoles was achieved, while the yield of **2m** bearing a phenyl group was moderate and dimer **2m′** was isolated as a side product in 17% yield.[11]

Based on these results, a proposed catalytic cycle of this aminoacetoxylation is outlined in Scheme 4.[12] Since it was confirmed that no reaction is observed by treatment of amidine **1a** only with 2 equiv of $Cu(OAc)_2$ or with 1.2 equiv of $PhI(OAc)_2$ in DMF at room temperature,[13] the present

(11) The amidine **1n** and **1o** bearing 3,3-dimethylallyl and 3-phenallyl groups, respectively, gave complex mixtures of unidentified compounds; see Supporting Information for more details.

process might be initiated by the formation of higher valent N−Cu(III) species **I** generated from amidine **1**, $Cu(OAc)_2$, and $PhI(OAc)_2$. The resulting *N*-Cu(III) species **I** undergoes 5-*exo* aminocupration onto the alkenyl moiety to give organocopper(III) species **II**.[14] The subsequent reaction of **II** with an acetate ion, probably via an S_N2 type substitution reaction,[15] forms the C−O bond to afford 4-acetoxymethyl-4,5-dihydroimidazole **2** along with CuOAc **III** that could maintain further catalytic turnover with $PhI(OAc)_2$.

Having developed a preparation method of 4-acetoxymethyl-4,5-dihydroimidazoles **2** through the present oxidative intramolecular aminooxygenation, we finally explored their concise transformation to 2,3-diamino-1-propanols (Scheme 5). It was found that reduction of **2** by aluminum hydride (AlH_3, prepared *in situ* from $LiAlH_4$ and $AlCl_3$)[16] proceeded smoothly to give 2,3-diamino-1-propanols **3** in good to moderate yields.

In summary, we have developed Cu-catalyzed aminooxygenation of alkenes with amidine moieties for synthesis of 4-acetoxymethyl-4,5-dihydroimidazoles, which could be further converted into 2,3-diamino-1-propanols with concise AlH_3 reduction. Further investigation related to the scope, detailed mechanisms, development of an asymmetric version of the process, and synthetic applications of the present strategy to other azaheterocycles is currently underway.

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Supporting Information Available. Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) Blakey reported aminoacetoxylation of *N*-(4-pentenyl)nosylamides catalyzed by $Cu(CH_3CN)_4PF_6$ with $PhI(OAc)_2$ (see ref 5a), while the reactions from the substrates bearing a terminal alkene provided piperidine derivatives as a major product via 6-*endo* cyclization. The result could be rationalized by the proposed reaction mechanism including electrophilic activation of the alkene by the putative Cu(III) species followed by nucleophilic attack of the acetate ion. In contrast, the present reaction delivered 5-exo cyclization product **2** exclusively even from **1l** and **1m**. Based on these observations, the pathway involving electrophilic activation of the alkene is most likely ruled out from the mechanistic possibilities of the present process.

(13) Chang recently reported intramolecular diamination and aminooxygenation of alkene using $PhI(OAc)_2$ under transition metal-free conditions; see: Kim, H. J.; Cho, S. H.; Chang, S. *Org. Lett.* **2012**, *14*, 1424.

(14) Organocopper species **II** might be under equilibrium with carbon radical species and $Cu(OAc)_2$. In the reaction of **1m**, dimerization of the radical species might deliver the dimer **2m′**.

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