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Copper-Catalyzed Aliphatic C−H Amination with an Amidine Moiety

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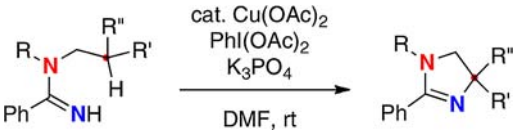
ABSTRACT



A method for amination of aliphatic C−H bonds of *N*-alkylamidines is described that utilizes $Cu(OAc)_2$ as the catalyst in the presence of $PhI(OAc)_2$ and K_3PO_4. The resulting products, dihydroimidazoles and tetrahydropyrimidines, could be converted into the corresponding diamines by hydride reduction.

Amination of omnipresent sp^3 C−H bonds can potentially result in rapid assembly of azaheterocyclic frameworks as well as various amino compounds, which are the key components of numerous biologically active natural alkaloids and potent pharmaceutical drugs.[1] Thus, the exploitation of the catalytic reaction that enables C−H amination with predictable chemo-, regio-, and stereoselective manners is one of the most challenging issues in synthetic chemistry.[2] The C−H amination reactions through nitrene insertion have been extensively explored commonly with assistance of transition metal catalysts as the-state-of-the-art aliphatic C−H amination,[3−6] while radical-mediated (non-nitrene-based) C−H amination represented by the Hofmann−Löffler−Freytag reaction[7] has also shown great potential as a radical strategy for sp^3 C−H bond functionalization.[8]

We have recently investigated the molecular transformation of readily available amidine derivatives that is initiated by Cu-catalyzed single-electron oxidation of amidine moieties.[9] For example, we disclosed Cu-catalyzed aerobic reactions of *N*-alkylamidines for C−H oxygenation, affording dihydrooxazoles (Scheme 1A).[9b] The reaction proceeds via 1,5-H-radical shift[10] of putative amidinyl

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(2) For recent reviews on C−H amination, see: (a) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Rec.* **2012**, *45*, 911. (b) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758. (c) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926. (d) Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347. (e) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (f) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379.

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(6) Very recently, Brewer reported stereospecific intramolecular C−H amination of 1-aza-2-azoniaallene salts; see: Bercovici, D. A.; Brewer, M. *J. Am. Chem. Soc.* **2012**, *134*, 9890.

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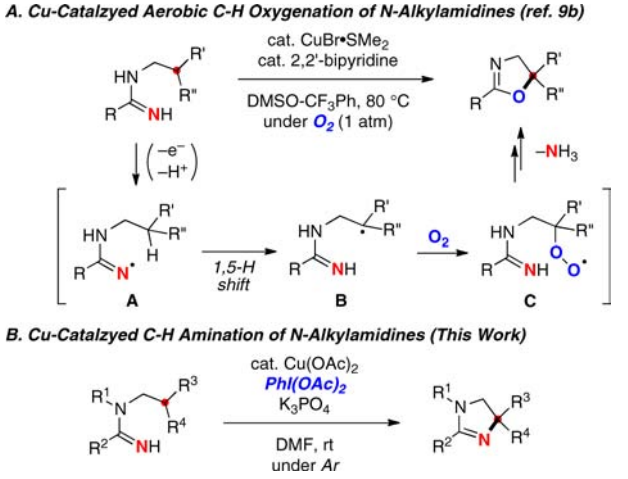
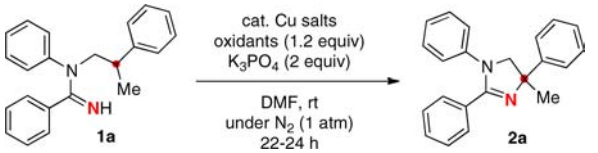
radical **A** formed by single-electron oxidation and deprotonation of the amidines, that is followed by C−O bond formation through trapping of the resulting carbon radical **B** with molecular O_2 to form superoxy radical **C**. Reductive fragmentation of **C** to the alkoxide followed by cyclization finally delivers the product. This aerobic C−H oxygenation of *N*-alkylamidines sparked us into exploitation of the C−H *amination* directed by the amidine moiety under an inert atmosphere (in the absence of molecular O_2), in which trapping of the resulting carbon radical species **B** with the amidine nitrogen was envisioned. Herein, we report a copper-catalyzed $PhI(OAc)_2$-mediated oxidative C−H amination of aliphatic C−H bonds directed by an amidine moiety(Scheme 1B).

Scheme 1. Aliphatic C−H Functionalization with Amidines



We commenced our investigation with the Cu-catalyzed reactions of *N*-phenyl-*N*-(2-phenylpropyl)benzimidamide (**1a**) using $PhI(OAc)_2$ as a stoichiometric oxidant under an Ar atmosphere (Table 1). As expected, when **1a** was treated with $CuBr\cdot SMe_2$ (20 mol %) in the presence of $PhI(OAc)_2$ (1.2 equiv) and K_3PO_4 (2 equiv) in DMF, the reaction proceeded even at rt to afford a C−H amination product, dihydroimidazole **2a**, in 49% yield with recovery of a 35% yield of **1a** (entry 1). Further optimization of the reaction conditions revealed that other Cu sources regardless of their oxidation states (either I or II) showed the catalytic activity (entries 2−5), and the highest yield (80% isolated yield) with full conversion was provided by $Cu(OAc)_2$ (entry 4). It is noted that the reaction using 2 equiv of $Cu(OAc)_2$ without $PhI(OAc)_2$ did not provide **2a** at rt (entry 6). The reactions with $PhI(OCOt\text{-}Bu)_2$ proceeded to give a 61% yield of **2a** (entry 7), whereas those with iodosobenezne (PhIO) or with selectfluor resulted in almost no reaction (entries 8 and 9). Interestingly, the reaction only with $PhI(OAc)_2$ as an oxidant proceeded, which was, however, very sluggish and not completed even after stirring for 48 h (entry 10).

Table 1. Optimization of Reaction Conditions[a]



entry	Cu salts (mol %)	oxidants	yield (%)[b,c]
1	$CuBr\cdot SMe_2$ (20)	$PhI(OAc)_2$	49 (35)
2	CuTC (20)	$PhI(OAc)_2$	58 (26)
3	$CuBr_2$ (20)	$PhI(OAc)_2$	52 (36)
4	$Cu(OAc)_2$ (20)	$PhI(OAc)_2$	80[d]
5	$Cu_2(esp)_2\cdot 2H_2O$ (10)	$PhI(OAc)_2$	62 (15)
6[e,f]	$Cu(OAc)_2$ (200)	–	0
7	$Cu(OAc)_2$ (20)	$PhI(OCOt\text{-}Bu)_2$	61 (18)
8	$Cu(OAc)_2$ (20)	PhI=O	5 (86)
9[f]	$Cu(OAc)_2$ (20)	Selectfluor	trace (82)
10[g]	–	$PhI(OAc)_2$	30 (40)

[a] The reactions were carried out using 0.3 mmol of amidine **1a** with $PhI(OAc)_2$ (1.2 equiv) and K_3PO_4 (2 equiv) in DMF (0.1 M) at rt under an Ar atmosphere. [b] ^1H NMR yields. [c] Recovery yields of **1a** were shown in parentheses. [d] Isolated yields. [e] The reaction was conducted in the absence of $PhI(OAc)_2$. [f] When the reaction was heated up at 80 °C for 16 h, a 12% yield of **2a** was formed along with a 72% recovery of **1a**. [g] The reaction was run without Cu salts for 48 h. TC = thiphene-2-carboxylate; esp = α,α,α′,α′,-tetramethyl-1,3-benzenedipropionate; Selectfluor = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

Having optimized the reaction conditions, we next examined the generality of this C−H amination of *N*-alkylamidines **1** for synthesis of dihydroimidazoles **2** (Scheme 2). Amination of tertiary C−H bonds resulted in efficient formation of dihydroimidazoles **2** (for **2a**−**e**), while the yield of 4,4-dimethyl-4,5-dihydroimidazole **2f** was low. It is noteworthy that the reaction of amidine **1g** bearing secondary benzylic C−H bonds proceeded well to give dihydroimidazole **2g** in 95% yield. By varying substituents R^2 of *N*-alkylamidines with secondary benzylic C−H bonds, it was shown that various aromatic rings including 2-methylphenyl (for **2h**), 2-naphthyl (for **2i**), 4-bromophenyl (for **2k**), and thienyl groups (for **2l**) were tolerated, although amidine **1j** bearing a 1-naphthyl group as R^2 gave desired **2j** only in 30% yield along with formation of the corresponding *O*-acetylamidoxime **3j** (30% yield) generated via *N*-acetoxylation of **1j** and cyanamide **4j**[11] (26% yield) formed through rearrangement of the 1-napthyl group (see the Supporting Information (SI) for mode

(8) For recent examples for radical-mediated (non-nitrene-based) aliphatic C−H amination reactions, see: (a) Amaoka, Y.; Kamijo, S.; Hoshikawa, T.; Inoue, M. *J. Org. Chem.* **2012**, *77*, 9959. (b) Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 2547. (c) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 1244. (d) Gephart, R. T., III; Huang, D. L.; Aguila, M. J. B.; Schmidt, G.; Shahu, A.; Warren, T. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6488. (e) Sakagushi, S.; Hirabayashi, T.; Ishii, Y. *Chem. Commun.* **2002**, 516. (f) Togo, H.; Harada, Y.; Yokoyama, M. *J. Org. Chem.* **2000**, *65*, 926.

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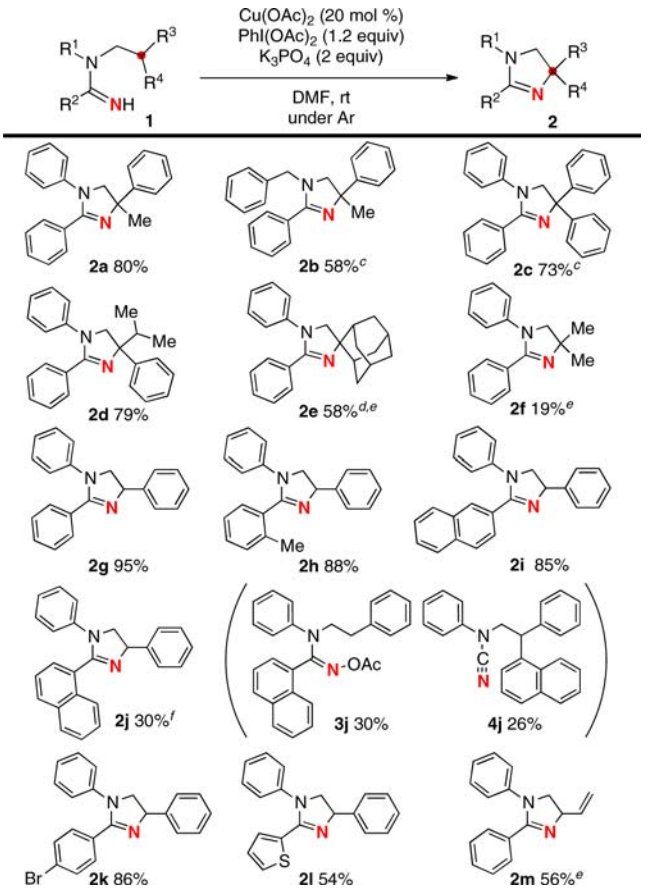
(10) For reviews, see: (a) Cekovic, Z. *Tetrahdron* **2003**, *59*, 8073. (b) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095.

(11) The structures of **2n** and **4j** were determined by X-ray crystallographic analysis; see the SI for more details.

details). Allylic C−H amination of **1m** also proceeded to give **2m** in 56% yield.

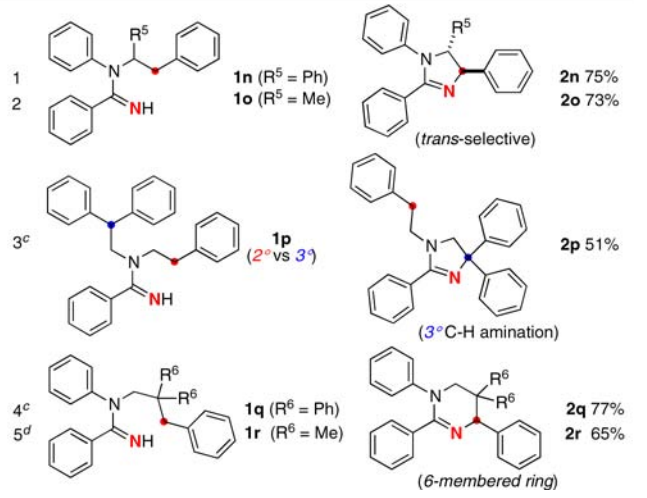
Scheme 2. Substrate Scope on C−H Amination of **1**[a]



[a] Unless otherwise noted, the reactions were carried out using 0.3 mmol of amidines **1** using 20 mol % of $Cu(OAc)_2$ with 1.2 equiv of $PhI(OAc)_2$ and 2 equiv of K_3PO_4 in DMF at rt under an Ar atmosphere. [b] Isolated yields were recorded above. [c] The reaction was run at 60 °C. [d] The reaction was run using 1.8 equiv of $PhI(OAc)_2$ at 60 °C. [e] 20 mol % of 1,10-phenanthroline was additionally used for the reaction. [f] Along with **2j**, *O*-acetyloxime **3j** and *N*-phenylcyanamide **4j** were formed in 30% and 26% yields, respectively. For more details, see the SI.

We further explored the potential of the present C−H amination reactions from the standpoint of several selectivity issues (Table 2). The diastereoselectivity of the C−H amination was first examined by installing the substituent R^5 onto the *N*-alkylamidines **1**. The reactions of **1n** and **1o** proceeded smoothly to give the corresponding dihydroimidazoles **2n**[11] and **2o**, respectively, in good yields with perfect *trans*-selectivity (entries 1 and 2). We next investigated the chemoselectivity of this C−H amination using amidine **1p** bearing secondary and tertiary benzylic C−H bonds, which resulted exclusively in tertiary C−H amination product **2p** (entry 3). While these C−H amination processes are likely initiated by a 1,5-H-radical shift (see Scheme 3), blocking the 5-position as the quaternary carbon enabled six-membered-ring formation via a 1,6-H-radical shift, affording tetrahydropyrimidines **2q** and **2r** in good yields (entries 4 and 5).

Table 2. Investigation of the Selectivity on the C−H Amination[a]



[a] Unless otherwise noted, the reactions were carried out using 0.3 mmol of amidines **1** using 20 mol % of $Cu(OAc)_2$ with 1.2 equiv of $PhI(OAc)_2$ and 2 equiv of K_3PO_4 in DMF at rt under an Ar atmosphere. [b] Isolated yields were recorded above. [c] The reaction was run at 40 °C. [d] The reaction was run using 1.6 equiv of $PhI(OAc)_2$ at 60 °C.

Based on these results, a proposed mechanistic possibility is outlined in Scheme 3 (the scenario of the reaction of **1a**). Since no reaction was observed only with 2 equiv of $Cu(OAc)_2$ in the absence of $PhI(OAc)_2$ (Table 1, entry 6), the present process might be initiated by the formation of higher valent N−Cu(III) species **I** generated from amidine **1a**, $Cu(OAc)_2$, and $PhI(OAc)_2$. Subsequent homolytic cleavage of the N−Cu(III) bond of **I** provides N-radical **II**, which may undergo a 1,5-H radical shift to afford C-radical **III**. Further Cu-mediated one-electron oxidation of C-radical **III** generates carbocation **IV**,[12] the intramolecular cyclization of which with the amidine moiety leads to the formation of dihydroimidazole **2a**. The presence of C-radical and carbocation species **III** and **IV** could be

Scheme 3. A Proposed Catalytic Cycle

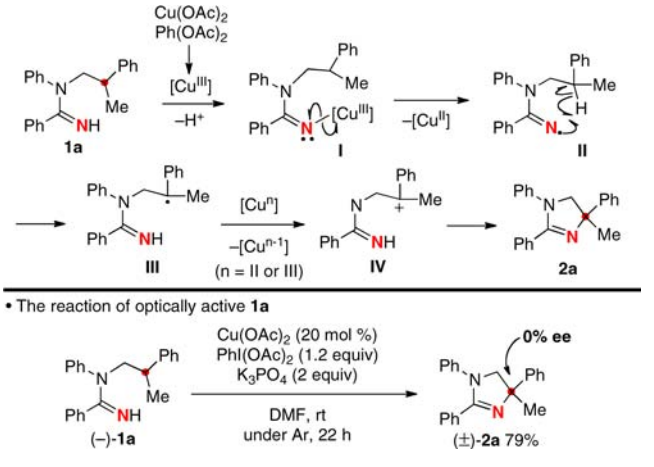
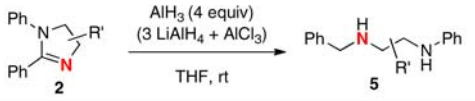
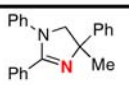
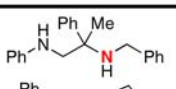
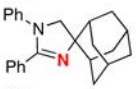
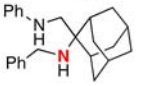
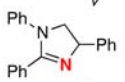
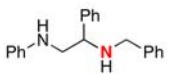
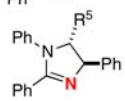
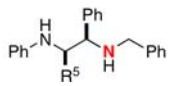


Table 3. Reductive Transformation of Dihydroimidazoles **2** into Vicinal Diamines **5**[a]



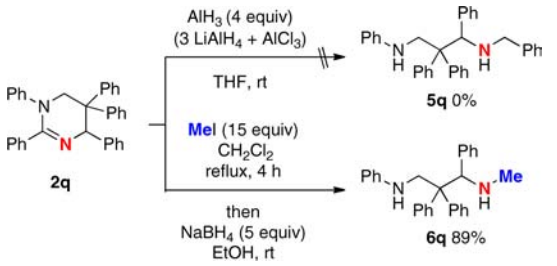
entry	substrates **1**		diamines **5**	yields[b]
1		**2a**		**5a** 89%
2[c]		**2e**		**5e** 75%
3		**2g**		**5g** 82%
4[d] 5		**2n** (R^5 = Ph) **2o** (R^5 = Me)		**5n** 88% **5o** 97%

[a] Unless otherwise noted, 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 **2** (0.2−0.3 mmol) and stirring at rt. [b] Isolated yields were recorded above. [c] The reaction was performed with $AlCl_3$ (3 equiv) and $LiAlH_4$ (9 equiv) under reflux conditions. [d] The reaction was performed under reflux conditions.

proven by the reaction of optically active **1a**,[13] which resulted in the formation of racemic **2a** under the standard reaction conditions.

Vicinal 1,2-diamine functionalities are privileged as the structural elements in biologically active molecules as well as ligands for transition metal catalysts.[14] Having developed a preparation method of dihydroimidazoles **2** through the present C−H amination, concise reductive transformation of them to the corresponding vicinal diamines **5** was examined (Table 3). By using aluminum hydride (AlH_3, prepared *in situ* from $LiAlH_4$ and $AlCl_3$),[15] reduction of dihydroimidazoles **2** proceeded smoothly to give the corresponding vicinal 1,2-diamines **5** bearing a benzyl protecting group on one of the nitrogen atoms (marked in red).

Scheme 4. Reductive Ring Opening of Tetrahydropyrimidine **2q**



However, tetrahydropyrimidine **2q** totally resisted the AlH_3 reduction (Scheme 4). In this case, reductive ring opening of tetrahydropyrimidine **2q** could be achieved by treatment of **2q** with MeI followed by reduction of the resulting *N*-methyl iodonium salt with $NaBH_4$[16] and subsequent hydrolysis, forming *N*-methylated 1,3-diamines **6q** in 89% yield.

In summary, copper-catalyzed amidine-directed C−H amination of aliphatic C−H bonds has been exploited for the synthesis of dihydroimidazoles or tetrahydropyrimidines, which could be further converted into the corresponding diamines by hydride reduction. Combined with facile preparation of *N*-alkylamidines through the Lewis acid mediated reaction of the corresponding alkylamines and carbonitriles,[17] the overall process of the present strategy could be summarized as a β- or γ-C−H amination of alkylamines. Further investigations aim to develop other types of oxidative C−H functionalization methodologies using the amidine moiety as a potential directing group.

Acknowledgment. This work was supported by funding from Nanyang Technological University and Singapore Ministry of Education (Academic Research Fund Tier 2: MOE2012-T2-1-014).

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

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(13) Optically active amidine **1a** was prepared from commercially available optically active (*R*)-(+)-β-methylphenethylamine; see SI.
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