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Copper-catalyzed redox-neutral C–H amination with amidoximes[†]

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Cul-catalyzed reactions of *N*-alkylamidoximes afforded dihydroimidazoles *via* sp³ C–H amination. On the other hand, the reactions of *N*-benzoylamidoximes resulted in sp² C–H amination to form quinazolinones. The reaction mechanisms could be characterized as a redox-neutral radical pathway including a Cu(η)–Cu(η)

Abundance of nitrogen-containing heterocycles (azaheterocycles) in biologically active alkaloids and pharmaceutical drugs has stimulated synthetic chemists to develop a variety of reactions enabling efficient construction of them.^{1,2} Among these methodologies, intramolecular C–H amination offers atom- and step-economical routes to access the azaheterocyclic frameworks, and various sets of the strategies have recently been exploited, especially with transition-metal catalysts.³

Our group has worked on the development of C-H oxidation based on radical-mediated (non-nitrene-based) tactics,⁴ where we have recently made use of amidine derivatives for Cu-catalyzed aliphatic C-H oxidation reactions towards the synthesis of azaheterocycles.5,6 For example, we disclosed Cu-catalyzed PhI(OAc)2-mediated C-H amination of N-alkyl amidines for the synthesis of dihydroimidazoles (Scheme 1).^{5a} This strategy is initiated by the 1,5-H-radical shift of amidinyl radical A oxidatively generated from the amidine, which results in the formation of C-radical B. Further oxidation of C-radical B leads to carbocation C that is subsequently aminated to give the dihydroimidazole. However, the drawback of this reaction is that it requires a stoichiometric use of PhI- $(OAc)_2$ to maintain the catalytic turnover, obviously because of the redox nature of this strategy, needing two-electron oxidation (for the generation of amidinyl radical A from the amidine and the oxidation of transient C-radical B to carbocation C) to realize the aliphatic C-H amination.



Scheme 1 Cu-catalyzed Phl(OAc)₂-mediated C–H amination with amidines (our previous work).



Scheme 2 Redox-neutral C-H amination with amidoximes (this work).

To develop an entirely catalytic system for the C–H amination, employment of amidoximes as a precursor of the amidinyl radical **A** was envisioned.⁷ As shown in Scheme 2, the reaction is initiated by reduction of the oxime N–O bond with Cu(I) species, generating amidinyl radicals **A** along with Cu(II) species.⁸ After the 1,5-H shift, the resulting C-radicals **B** are oxidized to the carbocation **C** by the Cu(II)⁹ to result in the formation of dihydroimidazole products and re-generation of Cu(I) species. This reductive initiation–oxidative termination sequence with amidoximes potentially enables redox-neutral C–H amination.^{10–13}

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Table 1 Optimization of the reaction conditions^a



^a The reactions were carried out using 0.3 mmol of 1a in solvents (0.1 M). Unless otherwise noted, the major isomer of amidoxime **1a** was utilized for this optimization. ^b Isolated yields. ^c The yield of **2a** in the reaction of the minor isomer of **1a**. ^{*d*} The yield of **2a** in the reaction of the 1.3:1 mixture of major/minor isomers of oxime 1a. TC = 2-thiophene carboxylate. Bn = benzyl.

With the hypothesis outlined in Scheme 2, our investigation commenced with the reaction of amidoxime 1a for the construction of dihydroimidazole 2a (Table 1). Amidoxime 1a was synthesized by treatment of benzaldoxime with NCS followed by the secondary amine (see the ESI[†] for more details) and was obtained as a 1.7:1 mixture of E/Z isomers (the stereochemistry was not determined). First of all, the major isomer of oxime 1a was utilized for the optimization of the reaction conditions. Treatment of amidoxime 1a with a series of Cu(I) salts as a catalyst (20 mol%) in the presence of K₃PO₄ in DMF resulted in the formation of 2a in moderate to good yields (entries 1-6) and the best yield of 2a was provided by CuI (72% yield, entry 3). Screening of the solvents (entries 7-9) revealed that toluene is optimal for this transformation (entry 9). The catalyst loading of CuI could be reduced to 10 mol% in toluene, giving 2a in 76% yield (entry 10). These optimized reaction conditions (10 mol% of CuI in toluene at 100 °C) were applicable to the minor isomer of amidoxime 1a as well as the 1.3:1 mixture of major/minor isomers of 1a, affording comparable yields of dihydroimidazole 2a (77% and 74% yields, respectively).

This CuI-catalyzed redox-neutral aliphatic C-H amination was extended to various amidoximes 1 as compiled in Table 2. The scope was first explored by varying the substituents R^1 , in which sterically hindered aromatic rings (2b, 2c) and both electron-rich (2d) and -deficient (2e, 2f) ones as well as 3-pyridyl motif (for 2g) could be installed. A cyclohexyl group could be used as the R¹, while the yield of dihydroimidazole 2h was moderate (40% yield). The method allowed installing not only a benzyl (Bn) but also *n*-butyl and phenyl groups (2i and 2j) as the substituent R². The tertiary carbon aminated (marked in blue) could possess a bulky isopropyl group (2i), a diphenyl





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^a The reactions were carried out using 0.3 mmol of 1 with CuI (10 mol%) and K₃PO₄ (1 equiv.) in toluene (0.1 M) at 100 °C under an Àr atmosphere. ^b Isolated yields were recorded above. ^c The reaction was conducted with the corresponding O-pivaloyl oxime 1p.

moiety (2k), and an indolyl part (2l) to afford the corresponding dihydroimidazoles 2 in good yields, while the yield of C-H amination on non-benzylic dimethyl methine carbon was moderate (2m in 50% yield). Spirocyclic structures could be nicely constructed by the present method (2n-p), while amination of a non-benzylic adamantyl C-H bond (2p) resulted in moderate yield.

The reaction of oximes 1q and 1r with a secondary methylene C-H bond delivered aromatic imidazoles 3q (30% yield) and 3r (36% yield) as well as uncyclized amidine 4q (41% yields) and 4r (42% yield), respectively (Scheme 3-a). To prevent the formation of imidazoles 3 presumably via oxidative aromatization of putative dihydroimidazole intermediates, the reaction of N-acetylamidoxime 1s was examined (Scheme 3-b). While dihydroimidazole 2s was isolated as expected, the yield of 2s was low (24% yield) and amide 5 was obtained in 57% yield via C-N bond fission. In sharp contrast, the reaction of N-benzovl amidoxime 6a produced guinazolinone 7a in 60% yield via addition of the amidinyl radical A to the benzoyl part (marked in green) (Scheme 3-c). This redox neutral sp^2 C–H amination inspired us further to examine its scope and limitation for the synthesis of substituted quinazolinones.

Optimization of the reaction conditions¹⁴ revealed that the reactions of O-pivaloyl oximes 6b-h with 10 mol% of CuI in *m*-xylene at 130 °C were optimal for this quinazolinone formation (Table 3). By varying substituents R^1 , benzene rings bearing electron-donating and -withdrawing groups as well as



Ar atmosphere. ^b Isolated yields were recorded above.

a cyclohexyl motif could be installed (**7b–7e**). As R², not only benzyl and *p*-methoxybenzyl (for **7f**) but also *n*-butyl and cyclopropyl units (**7g**, **7h**) were introduced.

Previous precedents of the quinazolinone formation by cyclization of the amidinyl radical to the benzoyl benzene ring^{15,16} demonstrated that the addition of amidinyl radical **A**

Organic & Biomolecular Chemistry happens to not only the *ortho*-carbon to the carbonyl (marked

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happens to not only the *ortho*-carbon to the carbonyl (marked in green, *path a*) but also the *ipso*-carbon (marked in purple, *path b via* carbamoyl radical **D**), which resulted in the formation of regioisomeric mixtures of quinazolinones 7 and 7' (Scheme 4-a). We also observed the same cases when



Scheme 4 Formation of regioisomeric quinazolinones 7 and 7'.

additional substituents \mathbb{R}^3 were put on the benzoyl benzene rings. By installing *para*-substituents \mathbb{R}^3 , the reactions provided *ortho*-addition products $7\mathbf{i}$ - $7\mathbf{k}$ as major products along with minor *ipso*-addition products $7\mathbf{i}'$ - $7\mathbf{k}'$ regardless of the electronic nature of the substituents \mathbb{R}^3 (Scheme 4-b).¹⁷ On the other hand, putting a methyl group at the *ortho* position (for the reaction of **61**) rendered the *ipso* addition product $7\mathbf{l}'$ major presumably because the helical sense of the C–C bond due to the *ortho* methyl group made interaction between the amidinyl radical and the *ipso* carbon smoother (*path b*) (Scheme 4-c). In the case of *N*-2-naphthoylamidoxime **6m**, the amination reaction exclusively occurred with the *ortho* α -carbon (marked in green) to give **7m** in 79% yield (Scheme 4-d).

Conclusions

In summary, we have developed CuI-catalyzed redox neutral sp^3 and sp^2 C–H amination reactions of readily available *N*-alkyl- and *N*-benzoylamidoximes, affording dihydro-imidazoles and quinazolinones, respectively. Application of these catalytic redox-neutral radical strategies to intermole-cular C–H amination is now under investigation in our laboratory.

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