Letter

Copper-Catalyzed Oxidative Oxyamination/Diamination of Internal Alkenes of Unsaturated Oximes with Simple Amines

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Copper-Catalyzed Oxidative Oxyamination/Diamination of Internal Alkenes of Unsaturated Oximes with Simple Amines

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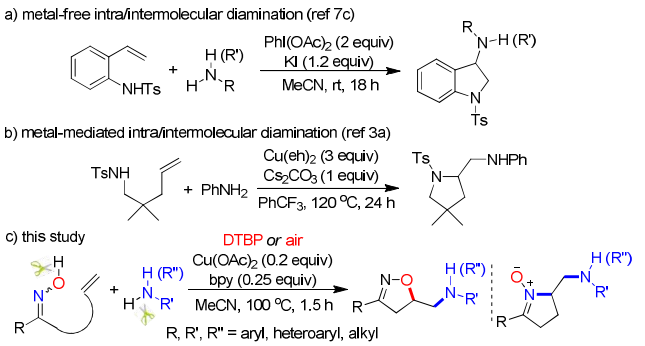
ABSTRACT: A convenient and versatile oxidative intra/inter-molecular oxyamination and diamination of unactivated alkenes has been developed through copper-catalyzed radical reactions of *β,γ*- and *γ,δ*-unsaturated ketoximes with electron-rich aryl and aliphatic amines. These reactions were carried out by employing di-*tert*-butyl peroxide (DTBP) or air as the terminal oxidant, and a series of useful nitrogen-containing 4,5-dihydroisoxazoles and cyclic nitrones were formed.

alkene, Cu, diamination, iminoxyl radicals, oxyamination

The vicinal oxyamination and diamination of unactivated alkenes have received wide attention in recent years because they provide rapid and efficient approaches towards structurally important vicinal amino alcohol and diamine moieties.[1] A number of nitrogen sources such as ureas,[2] amides,[3] diaziridines,[4] amidines,[5] and azides[6] have been explored for framing these skeletons. However, the alkyl and arylamines, which are abundant, cheap but important chemicals, are difficult to participate in these processes.[7] To achieve this goal, several methods have been developed, but they all require the use of stoichiometric amount of environmentally unfriendly oxidants such as hypervalent iodines[7a-d] (Scheme 1, a) and copper salts (Scheme 1, b)[3a] or highly toxic heavy metal salts.[7e-f] Very recently, an elegant copper-catalyzed alkene diamination and oxyamination was reported by Wang et al., but their nitrogen sources are only limited to secondary benzoyloxyamines.[7i-j] Thus, more efficient and general catalytic methodologies for the simple primary and secondary amine-involved oxyamination and diamination of unactivated alkenes are still in demand.

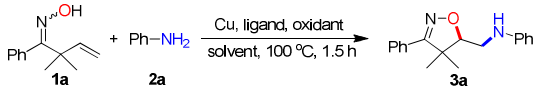
Iminoxyl radicals belong to a group of typical σ-radicals with the single electron spin delocalized on both the O and N atoms.[8] Iminoxyl radicals can be conveniently generated from oximes via oxidation. Our recent studies demonstrate that the readily prepared *β,γ*- and *γ,δ*-unsaturated ketoximes can be initiated to the corresponding iminoxyl radicals, which would undergo radical cyclization to produce carbon-centered radicals. Depending on the position of the tethered olefins, the cyclization occur either in a O-5-*exo*-trig or N-5-*exo*-trig pattern.[9] The thus-formed C-centered radicals can be captured by trapping agents such as 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) and diethyl azodicarboxylate (DEAD). In this way, dioxygenation, oxyamination, and diamination of unactivated alkenes can be realized. Although these reactions are synthetically useful, they have some limitations in scope due to the use of expensive and structurally special radical traps. To overcome this obstacle, herein we wish to report a simple and efficient amine-involved catalytic radical method for the intra/intermolecular oxidative oxyamination and diamination of *β,γ*- and *γ,δ*-unsaturated ketoximes[10] The reactions were realized by using di-*tert*-butyl peroxide (DTBP) or air as the oxidant and $Cu(OAc)_2$ as the catalyst, and through which a variety of useful nitrogen-containing isoxazolines and cyclic nitrones were obtained (Scheme 1, c). These heterocyclic compounds possess broad biochemical and pharmaceutical properties.[11] To the best of our knowledge, the current reactions constitute the first metal-catalyzed oxidative oxyamination and diamination of unactivated alkenes with aryl and aliphatic amines as the nitrogen source. This new protocol is highly environmentally friendly as air can be used as the stoichiometric oxidant.

Scheme 1. Diamination and Oxyamination of Unactivated Alkenes Employing Electron-rich Amines



We commenced our study by the subjecting a mixture of *β,γ*-unsaturated ketoxime **1a** and aniline **2a** to the conditions of DTBP and Cu_2O in acetonitrile at 100 °C under an argon atmosphere for 1.5 h. To our delight, the desired oxyamination product **3a** was obtained in a yield of 44% (Table1, entry 1). Several copper salts were then tested for their catalytic capacity, and it was found that using $Cu(OAc)_2$ as catalyst delivered the best yield of **3a** (72%) (Table 1, entries 2−5). The yield can be further improved by the addition of 2,2′-bipyridine, but adding 1,10-phenanthroline, 1,4-diazabicyclo-octane triethylenediamine (DABCO), or pyridine had no beneficial effect on the reaction (Table 1, entries 6−9). Besides DTBP, *tert*-butyl hydroperoxide (TBHP), dicumyl peroxide (DCP) and *tert*-butyl peroxybenzoate (TBPB) can also act as the terminal oxidant, but with them the yield was lower (Table 1, entries 10−12). No better yield was obtained when other solvents such as toluene, benzotrifluoride and DMF were used (Table 1, entries 13−15). Although using DTBP as oxidant gave a satisfactory result (Table 1, entry 6, conditions **A**), we went on with our exploration by using air as oxidant. From economicand environmental points of view, air is an ideal

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

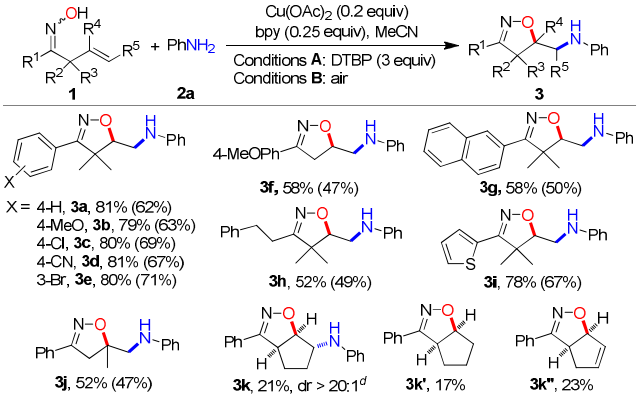
entry	Cu	ligand	solvent	oxidant	yield (%)[b]
1	Cu_2O		CH_3CN	DTBP	44
2	CuCl		CH_3CN	DTBP	17
3	$Cu(OAc)_2$		CH_3CN	DTBP	72
4	$CuBr_2$		CH_3CN	DTBP	31
5	$CuCl_2$		CH_3CN	DTBP	21
6	**$Cu(OAc)_2$**	**bpy**	**CH_3CN**	**DTBP**	**81**
7	$Cu(OAc)_2$	Phen	CH_3CN	DTBP	63
8	$Cu(OAc)_2$	DABCO	CH_3CN	DTBP	69
9	$Cu(OAc)_2$	pyridine	CH_3CN	DTBP	62
10	$Cu(OAc)_2$	bpy	CH_3CN	TBHP	40
11	$Cu(OAc)_2$	bpy	CH_3CN	DCP	52
12	$Cu(OAc)_2$	bpy	CH_3CN	TBPB	80
13	$Cu(OAc)_2$	bpy	DMF	DTBP	61
14	$Cu(OAc)_2$	bpy	$PhCH_3$	DTBP	53
15	$Cu(OAc)_2$	bpy	$PhCF_3$	DTBP	54
16	**$Cu(OAc)_2$**	**bpy**	**CH_3CN**	**air**	**62**
17		bpy	CH_3CN	DTBP	0
18[c]	$Cu(OAc)_2$	bpy	CH_3CN		65

[a]Reaction conditions: **1a** (1 equiv, 0.3 mmol), **2a** (3 equiv, 0.9 mmol), copper salt (0.2 equiv, 0.06 mmol), oxidant (3 equiv, 0.9 mmol), ligand (0.25 equiv, 0.075 mmol), solvent (1 mL), 100 °C, 1.5 h. [b]Isolated yield. DTBP = di-*tert*-butylperoxide, TBHP = *tert*-butyl hydroperoxide, DCP = dicumyl peroxide, TBPB = *tert*-butyl peroxy benzoate, bpy = 2,2′-dipyridyl, Phen = 1,10-phenanthroline, DABCO = triethylenediamine. [c]$Cu(OAc)_2$ (3 equiv, 0.9 mmol) was used as the oxidant.

oxidant. Using air as the terminal oxidant would render this protocol more attractive in practical synthesis and sustainable chemistry. To our great delight, when the reaction was carried out under the air atmosphere, **3a** was obtained in 62% yield (Table 1, entry 16, conditions **B**), along with a small amount the oxygen captured isoxazoline (See Supporting Information.). Our control experiment shows that copper was essential for the reaction to take place. Without copper, no compound **3a** was detected under the otherwise same conditions (Table 1, entry 17). When a stoichiometric amount of $Cu(OAc)_2$ was used alone as oxidant, on the other hand, **3a** was obtained in a yield of 65% (Table 1, entry 18).

With the optimal conditions in hand, the scope of the reaction was then examined. Firstly various *β,γ*-unsaturated ketoximes **1** was allowed to react with aniline **2a**, and the results are summarized in Scheme 2. The reaction proceeded well for both aryl and alkyl substituted *β,γ*-unsaturated ketoximes, delivering the desired oxyamination products isoxazalines **3a**–**h** in good to excellent yields. Thiophene-substituted *β,γ*-unsaturated ketoxime was also suitable for the process, with the corresponding product **3i** being generated in good yield. In addition, this oxyamination method is applicable to 1,1-disubstituted alkenes such as **3j**. When the alkene moiety was merged into a ring, as in the case of **1k**, the reaction gave the oxyamination product **3k** in 21% yield, along with the isoxazoline-fused cyclopentanone **3k′** and cyclopentenone **3k″** in 17% and 23% yields, respectively.[12]

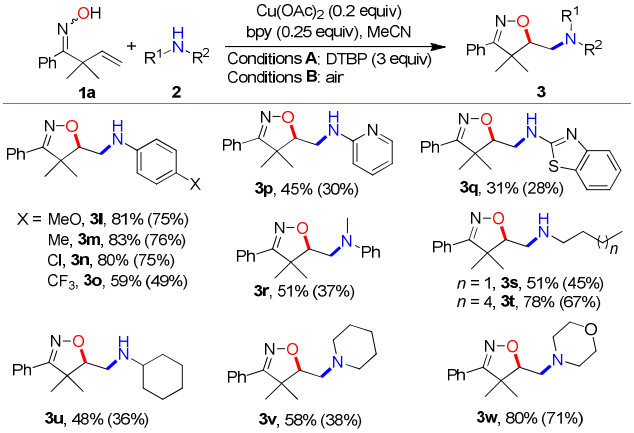
Scheme 2. Scope of *β,γ*-Unsaturated Oximes[a,b,c]



[a]All reactions run in 0.3 M MeCN using oxime **1** (0.3 mmol), ammine **2a** (3 equiv), bpy (0.25 equiv), and $Cu(OAc)_2$ (0.2 equiv) at 100 °C for 1.5 h. Conditions **A**: DTBP (3 equiv) used as the oxidant; Conditions **B**: Air used as the oxidant. [b]Isolated yields. [c]Yields in parentheses were obtained under conditions **B**. [d]The configuration of diastereomer was determined by coupling constants of ^1H NMR and NOE.

Next, we explored the applicability of the protocol by employing a vast variety of aromatic and aliphatic amines. Our results show that both aromatic and aliphatic amines are good aminating reagents under the standard reaction conditions (Scheme 3). 4-Substituted anilines with a broad range of

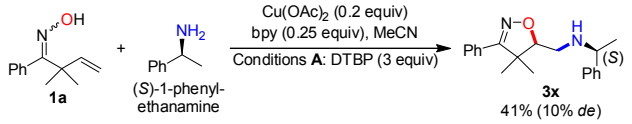
Scheme 3. Scope of Amines[a,b,c]



[a]All reactions run in 0.3 M MeCN using oxime **1a** (0.3 mmol), ammine **2** (3 equiv), bpy (0.25 equiv), and $Cu(OAc)_2$ (0.2 equiv) at 100 °C for 1.5 h. Conditions **A**: DTBP (3 equiv) used as the oxidant Conditions **B**: Air used as the oxidant. [b]Isolated yields. [c]Yields in parentheses were obtained under conditions **B**.

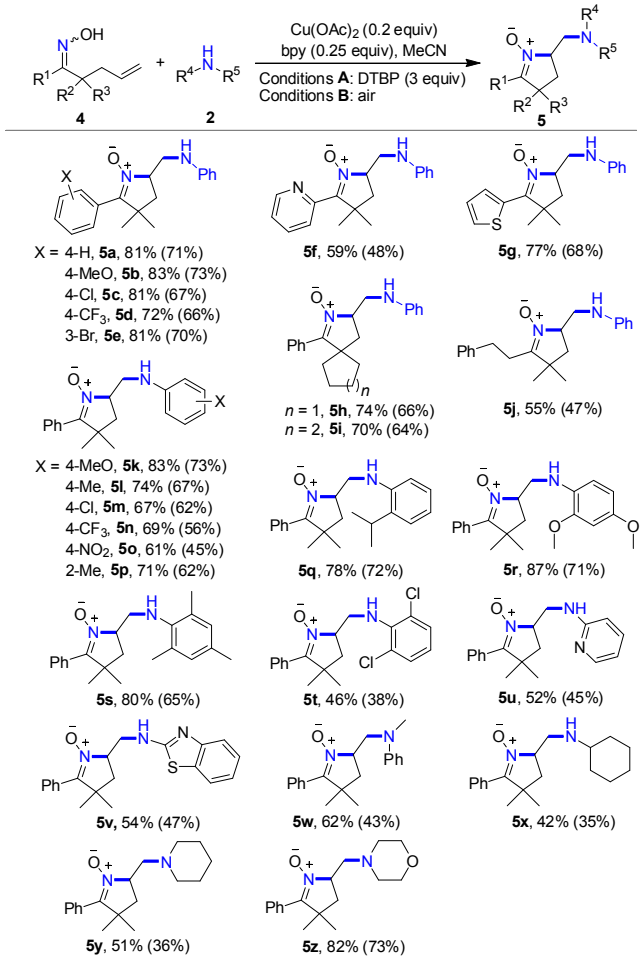
electronic properties participated smoothly in the reaction, affording the corresponding oxyamination products **3l**–**o** in good to excellent yields. Heterocyclic primary amines and secondary anilines are also suitable for this transformation (**3p**–**r**). Moreover, it is noteworthy that both primary and secondary aliphatic amines, such as 1-butylamine, 1-heptylamine, cyclohexylamine, piperidine, and morpholine, which have seldom been employed in direct amination, are good aminating reagents as well; with them the oxyamination products **3s**–**w** in moderated to good yields under both conditions. Significantly, chiral amine such as (*S*)-1-phenylethanamine was also suitable for the protocol, and gave the chirality retained product **3x** in 41% yield and 10% *de* (Scheme 4).

Scheme 4. Chiral Amine-Involved Reaction



Encouraged by the success of oxyamination of *β,γ*-unsaturated ketoximes, we wondered whether their *γ,δ*-unsaturated counterparts could undergo diamination through an analogous N-atom 5-*exo*-trig cyclization as demonstrated in our previous work.[9] Gratifyingly, the desired intra/intermolecular diamination of unactivated alkenes could be easily implemented by subjecting *γ,δ*-unsaturated ketoximes and amines to both conditions **A** and **B**. In this way, a variety of useful nitrogen-containing cyclic nitrones **5a**–**z** were obtained as shown in the Scheme 5. Noticeably, the sterically hindered

Scheme 5. Scope of *γ,δ*-Unsaturated Oximes and Amines[a,b,c]

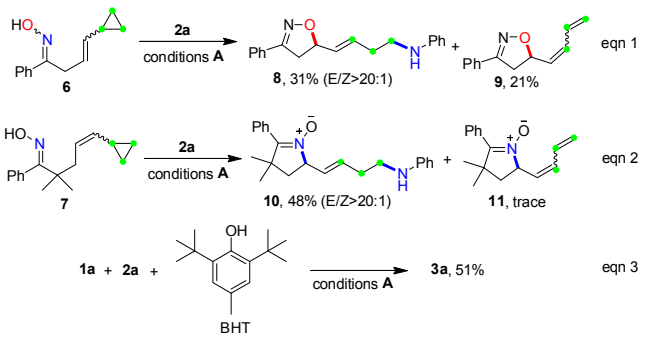


[a]All reactions run in 0.3 M MeCN using oxime **4** (0.3 mmol), ammine **2** (3 equiv), bpy (0.25 equiv.), and $Cu(OAc)_2$ (0.2 equiv) at 100 °C for 1.5 h. Conditions **A**: DTBP (3 equiv.) used as the oxidant Conditions **B**: Air used as the oxidant. [b]Isolated yields. [c]Yields in parentheses were obtained under conditions **B**.

arylamines, such as *ortho*-toluidine, *ortho*-cumidine, 2,4-dimethoxylphenyl-amine, 2,4,6-trimethylphenylamine, and 2,5-dichlorophenylamine are amenable to this reaction, giving the diamination products **5p**–**t** in moderate to good yield.

To confirm the iminoxyl radicals were involved in these oxyamination and diamination reactions, compounds **6** and **7** were prepared as the radical probe[13] and then subjected to conditions **A** as illustrated in Scheme 6. When **6** was allowed to react with **2a** under conditions **A**, the anticipated ring-opening amination product **8** was obtained in 31% yield along with the ring-opening elimination product 1,3-diene **9** in 21% yield (Scheme 6, eqn 1). The formation of the latter is consistent with the fact that homoallylic carbon radicals derived from ring-opening tend to undergo elimination to form 1,3-diene in the presence of copper salts.[12c] A similar result was also obtained in the case of **7**, where the ring-opening amination product **10** was obtained in 48% yield accompanied by the 1,3-diene **11** in trace amount (Scheme 6, eqn 2). In both cases, no corresponding anilinomethylcyclopropane was detected by ^{1}H NMR analysis. Further evidence for the involvement of iminoxyl radicals came from the trapping experiment with butylated hydroxytoluene (BHT). When 1.5 equiv of BHT was added into the reaction system under standard conditions **A**, the BHT−oxime adduct was detected in the crude product by the ESI-HRMS measurement (Figure 1),[14] while the yield of desired product was lowered to 51% (Scheme 6, eqn 3).

Scheme 6. The Radical Probe and BHT Scavenging Experiments



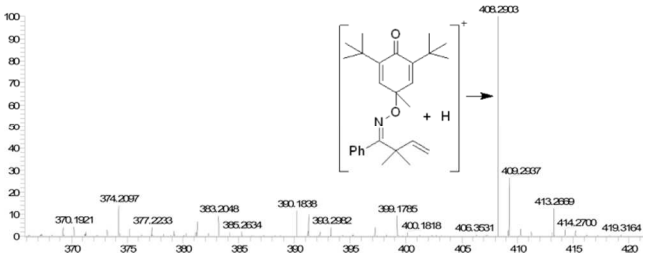
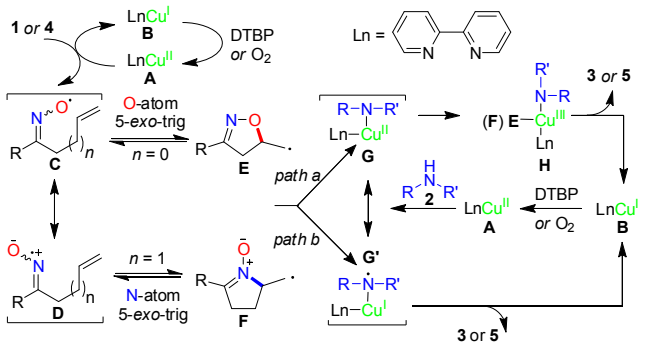


Figure 1. Analytical data of ESI-HRMS.

Based on the above-mentioned study, an iminoxyl radical mechanism is proposed to rationalize the present oxyamination and diamination reactions as shown in Scheme 7. A single-electron transfer process occurs firstly between Cu(II) species **A** and oxime **1** or **4** to produce Cu(I) species **B** and the iminoxyl radical. This minoxyl radical possesses an electronic structure with single-electron spin density delocalized on both the O-atom and N-atom (resonance structures **C** and **D**),[9] and it then undergoes dichotomous O- and N-atom 5-*exo*-trig radical cyclization depending on the position of the tethered alkene, yielding the formed C-centered radicals **E** and **F**, respectively. Meanwhile, the Cu(I) species **B** is oxidized by DTBP or O_2 to Cu (II) species **A** which then bind with the amine to produce the intermediate [LnCu(II)–NRR′]. Ultimately, the intermolecular radical coupling takes place

Scheme 7. Proposed Mechanism



between **E** or **F** and intermediate [LnCu(II)–NRR′] to produce the desired products **3** or **5** with Cu(I) species **B** being released.[15,16]

Prior mechanistic study reveals that there exist two pathways for the reaction of C-centered radicals with [LnCu(II)–NRR′] species. One is that a C-radical first couples with Cu(II)-atom to form a Cu(III) species; the Cu(III) species then undergoes reductive elimination (Scheme 7, *path a*).[15] The other is the direct coupling of C-radical with N-atom of the [LnCu(II)–NRR′] intermediate (Scheme 7, *path b*). This latter process is recently proposed by Warren *et. al.*[16] The mechanistic and DFT studies by Warren *et. al.* reveal that a [(Cl_2NN)Cu(II)–HNArCl_3] (Cl_2NN = (2,6-dichlorophen-yl) ((2Z,4E)-4-((2,6-dichlorophenyl) imino) pent-2-en-2-yl) amide, ArCl_3 = 2,4,6-trichlorophenyl) species possesses an electronic structure with the single-electron spin delocalized on both the N-atom from the aniline and the Cu-atom; the trapping of a carbon-centered radical by such a species at the N-center is thermodynamically more favorable (ΔG = -4.0 kcal/mol) than the capture at the Cu-center (ΔG = +20.8 kcal/mol). In Scheme 7, the [LnCu(II)–NRR′] species can be drawn as the resonance structures **G** and **G′,** and thus trapping of **E** or **F** by the nitrogen would also deliver **3** or **5**. Warren's study shows that in case that the single-electron spin appears on the nitrogen atom in the [LnCu(II)–NHAr] intermediate, bimolecular N–N radical coupling might occur to give the hydrazine ArNH–NHAr, which is apt to be further oxidized to diazene ArN=NAr.[17b-d] In our trapping experiment with BHT (Scheme 6, eqn 3), we detected both hydrazine PhNH–NHPh and diazene PhN=NPh in the ESI-HRMS spectra (Figure 2),

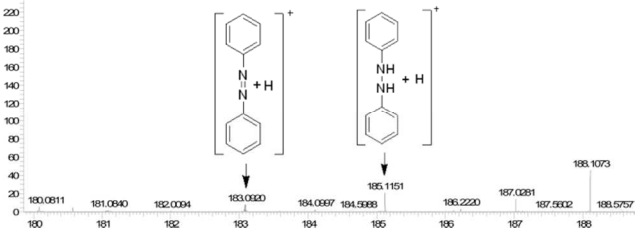


Figure 2. Analytical data of ESI-HRMS.

thus it is possible that in the [LnCu(II)–NHAr] intermediate shown in Scheme 7, the single-electron spin would also be delocalized on both the N-atom and the Cu-atom. Although this result did not constitutes an concrete evidence for the existence of *path b*, it at least points to the possibility that the direct C–N coupling provides an alternative pathway to the commonly accepted C–Cu coupling/reductive elimination (*path a*) in the present reactions.[16,17]

In summary, a novel, efficient and environmentally friendly copper-catalyzed direct oxidative strategy has been successively developed for the oxyamination and diamination of unactivated alkenes by using unsautrated ketoximes and simple amines as the readily accessible substrates and DTBP or air as the oxidant. These reactions not only provide the first example of metal-catalyzed oxyamination and diamination of unactive alkenes with the electron-rich amines as the nitrogen source, but also make possible the facile synthesis of structurally important useful nitrogen-containing isoxazolines and cyclic nitrones. Further studies on the mechanisms details of this reaction and more iminoxyl radicals-involved reactions are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and spectral data for all products are provided. This material is available free of charge via the Inter-net at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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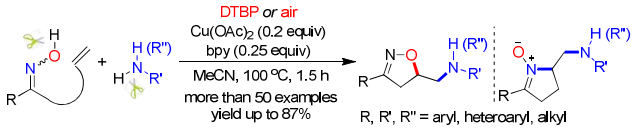

ABSTRACT: A convenient and versatile oxidative intra/inter-molecular oxyamination and diamination of unactivated alkenes has been developed through copper-catalyzed radical reactions of *β,γ*- and *γ,δ*-unsaturated ketoximes with electron-rich aryl and aliphatic amines. These reactions were carried out by employing di-*tert*-butyl peroxide (DTBP) or air as the terminal oxidant, and a series of useful nitrogen-containing 4,5-dihydroisoxazoles and cyclic nitrones were formed.