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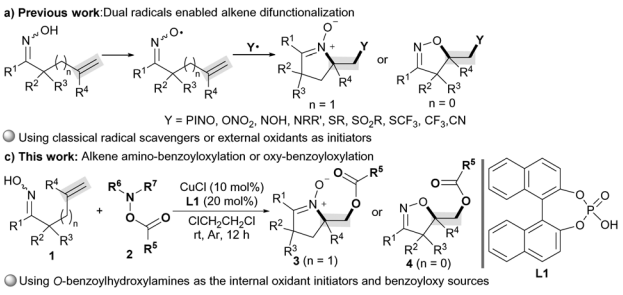
External-oxidant-free amino-benzoyloxylation of unactivated alkenes of unsaturated ketoximes with *O*-benzoylhydroxylamines†

Jiangfei Chen,[a] Yan-Ping Zhu,[b] Jin-Heng Li[abcd] and Qiu-An Wang*[a]

A new copper-catalyzed two-component amino-benzoyloxylation of unactivated alkenes of unsaturated ketoximes with *O*-benzoylhydroxylamines as the benzoyloxy sources is developed. Chemoselectivity of this method toward amino-benzoyloxylation or oxy-benzoyloxylation of alkenyl ketoximes relies on the position of the tethered olefins, and provides an external-oxidant-free alkene difunctionalization route that directly utilizes *O*-benzoylhydroxylamines as the benzoyloxy radical precursors and internal oxidants for the divergent synthesis of cyclic nitrones and isoxazolines.

The alkene difunctionalization reaction has been considered as one of the most powerful methodologies for increasing molecular complexity in synthesis because it can introduce two functional groups across the C=C double bond in a single reaction step.[1,2] In particular, difunctionalization of alkenes of unsaturated ketoximes is appealing and has attracted considerable attention over the past few decades because it can assemble highly valuable functionalized O- and N-heterocycles through intramolecular cyclization and external functional group incorporation cascades.[2–5] Classical methods for the difunctionalization of alkenes of unsaturated ketoximes focus on electrophile addition across the C=C bonds followed by intramolecular cyclization[3] or transition-metal-catalyzed intramolecular cyclization followed by nucleophile addition.[4] Despite significant advances in the field, these approaches suffer from the limited external functional reagents and/or requirement of noble transition-metal catalysts (such as palladium, and nickel).[3,4] Alternatively, radical-mediated two-component difunctionalization of alkenyl ketoximes has been developed recently and is particularly attractive because this method proceeds *via* the intramolecular addition of oxime radicals across the C=C double bonds to generate the carbon-centered radicals and then cross coupling with a wide range of external functional radical trapping functional reagents wherein oxime radicals can selectively serve as the iminoxyl oxygen-centered radicals or iminoxyl nitrogen-centered radicals to divergently access isoxazolines and cyclic nitrones relying on the position of the tethered olefins (Scheme 1a).[5] In 2012, Han and coworkers first reported dioxygenation, oxyamination, and diamination of β,γ- and γ,δ-unsaturated ketoximes with external radical trapping functional reagents, such as 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) and diethyl azodicarboxylate (DEAD).[5a] This dual radicals-enabled alkene difunctionalization strategy has been proven to be synthetically useful and has been widely applicable to dioxygenation, oxyamination, diamination, carbooxygenation, carboamination, oxyhalogenation, oxysulfonylation and oxythioetherization of alkenyl ketoximes with various radical trapping functional reagents.[5] However, these approaches are limited to the requirement of stoichiometric classical radical scavengers (such as TENPO, DEAD and ^{t}BuONO) or external



Scheme 1 Radical-mediated difunctionalization of alkenyl oximes.

[a] State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China. E-mail: jhli@hnu.edu.cn, wangqa@hnu.edu.cn
[b] School of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation, Ministry of Education, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Yantai University, Shandong, Yantai, 264005, China. E-mail: chemzyp@foxmail.com
[c] Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China
[d] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

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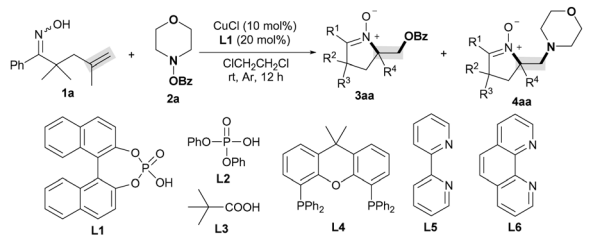
oxidants to trigger these processes. Moreover, to our knowledge, radical-mediated two-component amino-benzoyloxylation or oxy-benzoyloxylation of alkenyl ketoximes with the external benzoyloxy radical precursors remains an unexplored area. Thus, the development of new radical-mediated strategies, especially involving an external-oxidant-free strategy using internal oxidants as the radical trapping functional reagents, to allow new alkenyl ketoxime difunctionalization modes is desirable.

Herein, we report a new radical-mediated two-component amino-benzoyloxylation of unactivated alkenes of unsaturated ketoximes with *O*-benzoylhydroxylamines[6] using copper catalysis for accessing benzoyloxy-possessing cyclic nitrones (Scheme 1c). This reaction employs *O*-benzoylhydroxylamines as both the benzoyloxy sources and internal oxidants to enable selective amino-benzoyloxylation or oxy-benzoyloxylation of alkenyl ketoximes for producing carbon-quaternary-center-containing cyclic nitrones and isoxazolines[7] which depends on the position of the tethered olefins.

We investigated the amino-benzoyloxylation reaction between 2,2,4-trimethyl-1-phenylpent-4-*en*-1-one oxime (**1a**) and morpholino benzoate (**2a**) for optimization of the reaction conditions (Table 1). Upon surveying various reaction parameters, we found that treatment of oxime **1a** with benzoate **2a**, 10 mol% CuCl, and 20 mol% 1,1-binaphthyl-2,2-diyl hydrogenphosphate (BNPA) ligand **L1** in $ClCH_2CH_2Cl$ at room temperature efficiently afforded the desired cyclic nitrone product **3aa** in 76% yield along with a trace of **4aa** (entry 1). It is noted that no desired reaction occurs in the absence of a Cu catalyst (entry 2), and a higher loading of CuCl (20 mol%) slightly decreased the yield (entry 3). A series of Cu catalysts, such as CuBr, $Cu(MeCN)_4PF_4$, CuOAc and $Cu(OAc)_2$, were examined: the CuBr catalyst showed identical catalytic activity to CuCl (entry 4), but the other Cu catalysts (*e.g.*, $Cu(MeCN)_4PF_4$, CuOAc, $Cu(OAc)_2$) were less efficient than CuCl along with no side-reactions (entries 5–7). The reason might be that such three Cu catalysts (entries 5–7) are more basic than CuCl (entry 1) or CuBr (entry 4), thus resulting in a decrease of the Lewis acid properties to coordinate and activate the *in situ* generated radical intermediates. The results showed that ligands could affect the reaction but were not the key to the success of the reaction, as the omission of **L1** resulted in the formation **3aa** in 49% yield and **4aa** in 6% yield (entry 8). While both acidic ligands **L2–L3** and a basic bipyridine **L5** could improve the reaction (entries 9–10 and 12), phosphine **L3** completely suppressed the reaction (entry 11) and 1,10-phenanthroline **L6** had no effect (entry 13). Other solvents, including CH_2Cl_2, toluene and MeCN, were inferior to $ClCH_2CH_2Cl$ (entries 14–16). A higher temperature (50 °C) gave identical results to those at room temperature (entry 17). Notably, the reaction with a scale up to 1 mmol of **2a** was performed smoothly in good yield (entry 18).

Table 1 Optimization of reaction conditions[a]

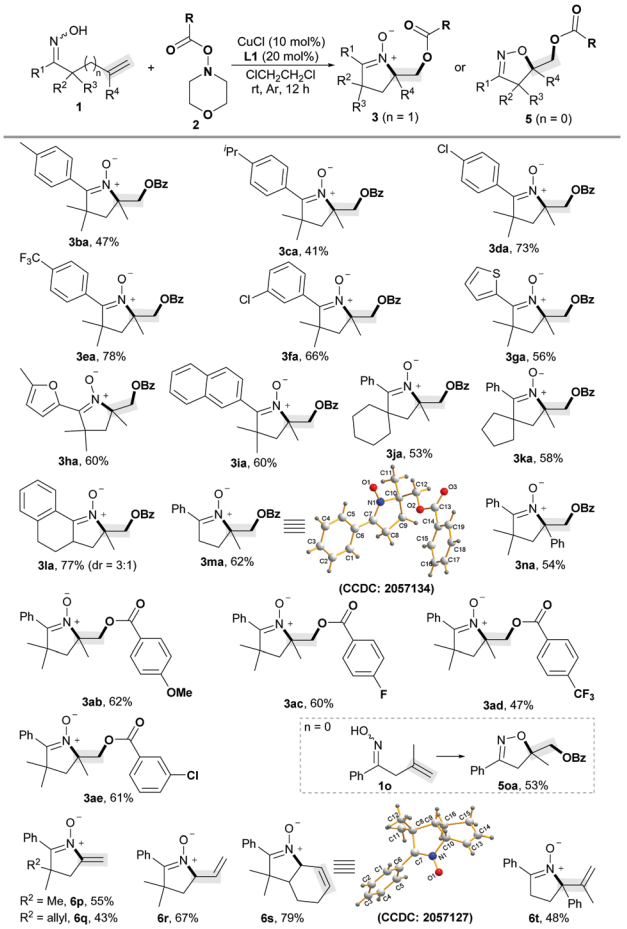


Entry	Variation from the standard conditions	Isolated yield (%) 3aa	4aa
1	None	76	Trace
2	Without CuCl	0	0
3	CuCl (20 mol%)	70	Trace
4	CuBr instead of CuCl	69	Trace
5	$Cu(MeCN)_4PF_4$ instead of CuCl	55	Trace
6	CuOAc instead of CuCl	44	Trace
7	$Cu(OAc)_2$ instead of CuCl	66	Trace
8	Without **L1**	49	6
9	**L2** instead of **L1**	65	Trace
10	**L3** instead of **L1**	63	Trace
11	**L4** instead of **L1**	Trace	Trace
12	**L5** instead of **L1**	61	Trace
13	**L6** instead of **L1**	45	Trace
14	CH_2Cl_2 instead of $ClCH_2CH_2Cl$	58	Trace
15	Toluene instead of $ClCH_2CH_2Cl$	48	Trace
16	MeCN instead of $ClCH_2CH_2Cl$	53	Trace
17	At 50 °C	73	Trace
18[b]	None	70	Trace

[a] Standard reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), CuCl (10 mol%), **L1** (20 mol%), $ClCH_2CH_2Cl$ (2 mL), argon, room temperature and 12 h. [b] **2a** (1 mmol) and 24 h.

After establishing the optimized reaction conditions, the substrate scope of this alkene amino-benzoyloxylation protocol with respect to oximes **1** and morpholino benzoates **2** was explored (Table 2). The substitution effect on the aryl ring of 1-arylpent-4-*en*-1-one oximes was initially examined in the presence of morpholino benzoate (**2a**), CuCl, and BNPA **L1** (**3ba–fa**). We found that substituents, including Me, i-Pr, Cl and CF_3, were well tolerated, and both the electronic effect and steric hindrance had a fundamental influence on the reaction. While oximes **1b–c** bearing an electron-donating Me or i-Pr group furnished **3ba–ca**, respectively, in moderate yields, oximes **1d–f** bearing an electron-withdrawing Cl or CF_3 group afforded **3da–fa** in good yields. However, oxime **1f** having an *m*-Cl group was less reactive than oxime **1d** having a *p*-Cl group **1d** bearing a *p*-Cl group in terms of yields (**3da, 3fa**). Strikingly, heteroaryl and naphthalen-2-yl-substituted pent-4-*en*-1-one oximes **1g–i** accommodated to the optimized conditions, giving **3ga–ia** in moderate yields. This alkene amino-benzoyloxylation protocol could be applicable to the construction of spiro-cyclic rings and polycyclic compounds (**3ja–la**). For example, using (1-(2-methylallyl)cyclohexyl)(phenyl)methanone oxime **1j** smoothly afforded 2-azaspiro[4.5]dec-1-*ene* 2-oxide **3ja** in 53% yield. For 2-(2-methylallyl)-3,4-dihydronaphthalen-1(2*H*)-one oxime **1l** the reaction efficiently executed to construct functionalized 3,3*a*,4,5-tetrahydro-2*H*-benzo[*g*]indole 1-oxide **3la**. The reaction was compatible with 4-methyl-1-phenylpent-4-*en*-1-one oxime **1m**, furnishing **3ma** in 62% yield.[8] Replacement of the Me group at the 4 position of the alkene moiety by a Ph group accommodated to the reaction (**3na**). Delightfully, the use of 2,2-dimethyl-1,3-diphenylbut-3-*en*-1-one oxime **1o** resulted in

Table 2 Variations of the unsaturated oximes (**1**) and morpholino benzoates (**2**)[a]

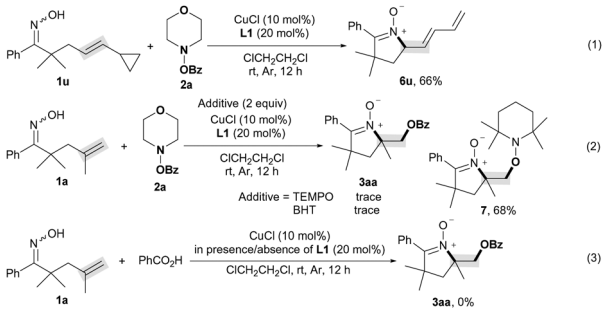


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), CuCl (10 mol%), **L1** (20 mol%), $ClCH_2CH_2Cl$ (2 mL), argon, room temperature and 12 h.

the formation of 4,5-dihydroisoxazole **5oa**, a five-membered O-heterocyclic ring, through intramolecular oxygen atom addition across the C=C bond.

Next, we set out to investigate the scope of morpholino benzoates **2** under the optimized conditions. Morpholino benzoates **2b–e** bearing an electron-donating (*e.g.*, MeO) or an electron-withdrawing group (*e.g.*, F, CF_3, Cl) on the aryl ring of the benzoate moiety were successfully converted to **3ab–ae** in moderate to good yields, leaving these groups intact for further derivatization. Notably, the electron-donating group (**3ab**) displayed higher reactivity than the electron-withdrawing groups (**3ac–ae**). To our surprise, both monosubstituted terminal alkenes **1p–q** and internal alkenes **1r–t** underwent intramolecular nitrogen addition across the C=C bond and isomerization to afford alkenyl 3,4-dihydro-2*H*-pyrrole 1-oxides **6p–t**.[8]

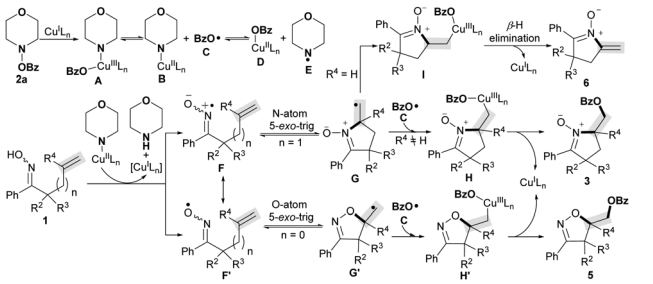
As shown in Scheme 2, internal alkene **1u** containing a cyclopropyl ring was converted to highly valuable (*E*)-2-(buta-1, 3-dien-1-yl)-3,4-dihydro-2*H*-pyrrole 1-oxide **6u** *via* intramolecular nitrogen addition across the C=C bond, ring-opening and



Scheme 2 Control Experiments.

isomerization cascades (equation 1), suggesting that the reaction involves a radical process. The control experiments also support a radical process and confirm the generation of the oxygen-centered radical (the iminoxyl radical)/the resonance nitrogen-centered radical cation as the reaction was completely inhibited in the presence of a radical scavenger (such as TEMPO and BHT) and afforded the phthalimido-*N*-oxyl-containing 3,4-dihydro-2*H*-pyrrole 1-oxide **7** in 68% yield (equation 2). The results of entry 10 in Table 1 showed that the presence of PivOH could improve the reaction. However, no reaction of oxime **1a** with benzoic acid was observed in the presence/absence of **L1** (equation 3). These results imply that the formation of the BzO• radical intermediate is crucial to the accomplishment of the desired reaction.

Consequently, the possible mechanisms for this alkene amino-benzoyloxylation reaction were proposed on the basis of the present results and precedent literature (Scheme 3).[5,6] The highly reactive O–$Cu^{III}L_n$–N intermediate **A** is formed from the reaction between the active $Cu^{I}L_n$ species and morpholino benzoate **2a** through the insertion of the C–O bond, which also gives resonance structures **B/C** and/or **D/E**.[6] Under the external-oxidant-free conditions, the intermediates **B/C** are more reactive than the intermediates **D/E**. Subsequently, oxidative single electron transfer between oxime **1a** and the N–$Cu^{II}L_n$ intermediate **B** occurs to afford the nitrogen-centered radical cation **F** (n = 1) or the resonance oxygen-centered radical (the iminoxyl radical) **F′** (n = 0). Intramolecular 5-exo-trig N-cyclization of the intermediate **F** occurs to form the N-heterocyclic radical intermediates **G**, followed by coupling with the intermediate **C** and reductive elimination to forge the desired N-heterocycle product **3** and regenerate the active $Cu^{I}L_n$ species.[5] When R^4 = H in unsaturated oxime **1**, the β-H elimination of the intermediate **I** takes place to afford the desired product **6**.



Scheme 3 Proposed reaction mechanisms.

On the other hand, intramolecular 5-exo-trig O-cyclization of the intermediate **F′** affords the O-heterocyclic radical intermediates **G′**, which sequentially undergoes coupling with the intermediate **C** to deliver the C–Cu^{III}–OBz intermediate **H′** and then reductive elimination to access the desired O-heterocycle product **5** and regenerate the active $Cu^{I}L_n$ species.[5]

In summary, we have developed a new copper-catalyzed two-component amino-benzoyloxylation of unactivated alkenes of unsaturated ketoximes with *O*-benzoylhydroxylamines for selectively producing cyclic nitrones and isoxazolines under external-oxidant-free conditions. This method enables the preferential formation of the benzoyloxyl radical intermediates to form two new carbon–heteroatom bonds in a single reaction step, and represents the first external-oxidant-free copper-catalyzed alkene amino-benzoyloxylation route through intermolecular cross coupling with the benzoyloxyl radicals using *O*-benzoylhydroxylamines as the benzoyloxyl sources and internal oxidants.

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Conflicts of interest

There are no conflicts to declare.

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8 CCDC 2057134 (**3ma**) and 2057127 (**6s**) contains the supplementary crystallographic data for this paper†.

