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Copper-catalyzed aerobic oxidative C–O bond formation for the synthesis of 3,5-disubstituted isoxazoles from enone oximes†

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A direct access to 3,5-disubstituted isoxazoles has been accomplished through an intramolecular oxidative coupling reaction of enone oximes using a catalytic quantity of Cu(OAc)₂. This method features an inexpensive metal catalyst, molecular oxygen as a green oxidant, good functional group tolerance and readily available starting materials. This attractive method for the synthesis of isoxazole derivatives is of great significance due to the product's versatile reactivity for further transformations.

Transition-metal-catalyzed direct C–H functionalization toward C–C and C–Het (Het = heteroatom) bonds formation is one of the most challenging classes of oxidation reactions, and has attracted extensive interest in the past few decades.^{1,2} However, most efforts have been focused on using noble metal catalysts, such as Rh, Ru, Pd, *etc.*^{3–8} Compared with the methods based on noble metals, copper-catalyzed methods for organic synthesis are obviously economically attractive.^{9,10} In view of the increasing demand for environmentally benign organic synthesis and green chemistry, molecular oxygen is undoubtedly the ideal terminal oxidant, because of its remarkable advantages, such as being inexpensive, high atom efficiency, and in most cases with nontoxic water as the byproduct.¹¹ To date, the copper-catalyzed aerobic cross-coupling between two C–H bonds or C–H and Het–H bonds have been a green and atom-economic approach for construction of heterocycles.^{12–20} Recently, Buchwald and Nagasawa described the copper-catalyzed aerobic oxidative cyclization of amidines and benzanilides to give benzimidazoles and benzoxazoles, respectively.^{21,22}

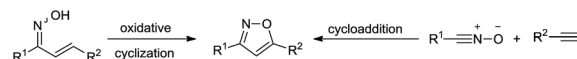
Isoxazole derivatives represent a privileged class of five-membered nitrogen heterocycles and are extensively found in numerous biologically active molecules with anticancer, antidepressant, antibiotic, and analgesic activities.^{23–26} Moreover, they are used as key building blocks in materials science and as various complex synthetic intermediate in organic synthesis.^{27,28} Owing to their good reactivity and synthetic utility, the development of more efficient synthetic methods for isoxazoles is of great importance to organic chemists.^{29–40} Among them, there

are two classical strategies for construction of 3,5-disubstituted isoxazoles: 1,3-dipolar cycloaddition and oxidative cyclization (Scheme 1). Nonetheless, the latter methods commonly require the use of stoichiometric amounts of oxidants, such as TEMPO, hypervalent iodine, DDQ, metal salt and so on, which caused heavy burden to the environment.^{41–46} It is no doubt that the catalyzed oxidation with pure oxygen or air as the oxidant is a green solution. Herein, we disclose a new copper(II)-catalyzed synthesis of 3,5-disubstituted isoxazoles from enone oximes through a C–H functionalization/C–O bond-forming process that uses oxygen as the terminal oxidant and water as the only direct waste product.

Inspired by the recent development of copper-catalyzed aerobic oxidative C–O bond formation for the construction of heterocycles⁴⁷ and our continuing interest in developing C–Het bond formation reactions,⁴⁸ we envisioned a direct synthesis of 3,5-disubstituted isoxazoles *via* copper-catalyzed dehydrogenative coupling reaction of enone oximes involving intramolecular C–O bond formation. Therefore, we first studied the reaction of chalcone oxime **1aa** in DMSO using Cu(OAc)₂ as the catalyst under 1 atm of O₂ without adding any additives. To our delight, the desired isoxazole **2aa** was obtained in 30% yield (Table 1, entry 1). This result prompted us to screen suitable reaction conditions (Table 1). Further investigation revealed that the additive played a critical role for this transformation (entries 2–8). Using Brønsted acid such as HOAc as the reaction additive provided poor result of desired product (entry 2). Detailed examination of base as the additive suggested that Cs₂CO₃, NaHCO₃, Na₂CO₃, Et₃N, and pyridine gave moderate

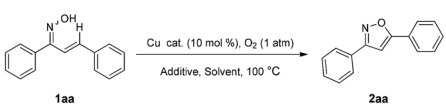
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Scheme 1 Two classical strategies for the construction of 3,5-disubstituted isoxazoles.



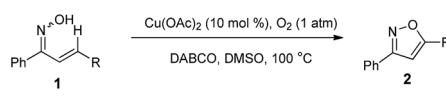
Table 1 Optimization of reactions^a


| Entry | Catalyst | Additive | Solvent | Yield ^b (%) |
|-----------------|----------------------|---------------------------------|------------------|------------------------|
| 1 | Cu(OAc) ₂ | — | DMSO | 30 |
| 2 | Cu(OAc) ₂ | HOAc | DMSO | 15 |
| 3 | Cu(OAc) ₂ | CS ₂ CO ₃ | DMSO | 53 |
| 4 | Cu(OAc) ₂ | NaHCO ₃ | DMSO | 45 |
| 5 | Cu(OAc) ₂ | Na ₂ CO ₃ | DMSO | 58 |
| 6 | Cu(OAc) ₂ | Et ₃ N | DMSO | 40 |
| 7 | Cu(OAc) ₂ | Pyridine | DMSO | 34 |
| 8 | Cu(OAc) ₂ | DABCO | DMSO | 85 |
| 9 | CuBr | DABCO | DMSO | 46 |
| 10 | CuCl | DABCO | DMSO | 59 |
| 11 | Cu(OAc) ₂ | DABCO | DMF | 66 |
| 12 | Cu(OAc) ₂ | DABCO | <i>o</i> -Xylene | 62 |
| 13 ^c | Cu(OAc) ₂ | DABCO | DMSO | 73 |
| 14 ^d | Cu(OAc) ₂ | DABCO | DMSO | 70 |
| 15 | — | DABCO | DMSO | 0 |

^a Reaction conditions: **1aa** (0.20 mmol), catalyst (0.02 mmol), additive (0.06 mmol) in solvent (2 mL), 100 °C, 12 h. ^b Isolated yield. ^c Reaction was performed at 80 °C. ^d Reaction was performed under air.

yields and DABCO was the best choice (entries 3–8). We speculated that DABCO possibly act as both ligand and base to promote the product formations. The effects of different copper salts were also studied, such as CuBr and CuCl were employed as the catalyst and exhibited lower efficiencies than Cu(OAc)₂ (entries 9 and 10). Solvent evaluation revealed that DMSO was the best solvent, while other solvents just led to moderate yields (entries 11 and 12). Lowering the temperature was not suitable for this transformation (entry 13). The reaction was less effective when proceeding under air atmosphere (entry 14). In the absence of the copper source, no desired product was obtained (entry 15). Thus, the optimal reaction conditions consist of Cu(OAc)₂ (10 mol%) and DABCO (30 mol%) in DMSO at 100 °C under an oxygen atmosphere.

Under the optimized conditions, we sought to explore the scope and generality of the process. As the representative results shown in Table 2 attest, this methodology is compatible with a variety of electron-donating and electron-withdrawing groups. Substituted enone oximes derived from mono-substituted arylaldehydes possessing electron-donating groups such as –CH₃ and –OCH₃, all gave 3,5-disubstituted isoxazoles **2ab–2ad** in good yields (Table 2). Similarly substrates possessing electron-withdrawing groups such as –Cl, –Br, –NO₂ underwent C–H functionalization to give 3,5-disubstituted isoxazoles **2ae–2aj** in excellent yields. As can be seen from Table 2, compared to substrates bearing electron-donating groups, electron-withdrawing substrates gave better yields. Nevertheless, same substituents at the *para*, *meta*, and *ortho* positions were also effective substituents in this transformation furnishing the corresponding products (**2ae**, **2af**, and **2ag**) in good yields.

Table 2 Synthesis of isoxazoles with varying substitutions at C5^{a,b}


| | | |
|------------------|------------------|------------------|
| 2aa , 85% | 2ab , 79% | 2ac , 80% |
| 2ad , 77% | 2ae , 88% | 2af , 86% |
| 2ag , 87% | 2ah , 86% | 2ai , 85% |
| 2aj , 93% | 2ak , 76% | 2al , 89% |
| 2am , 88% | 2an , 85% | 2ao , 83% |

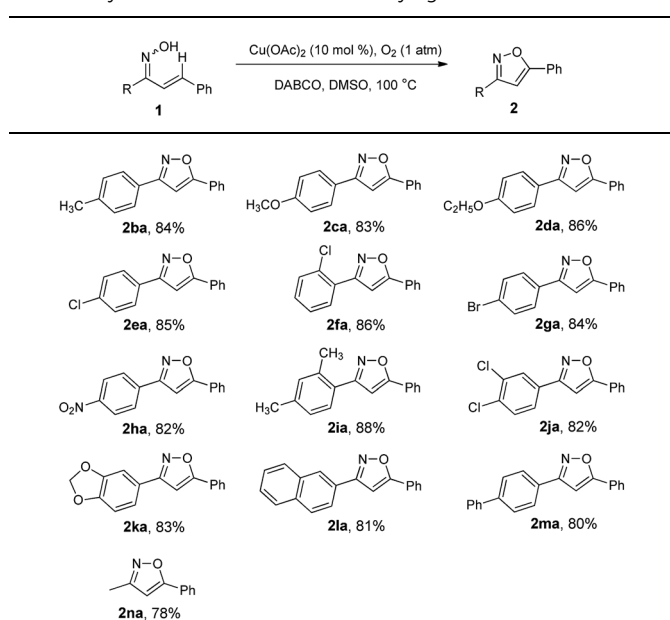
^a Reaction conditions: **1** (0.20 mmol), Cu(OAc)₂ (10 mol%), DABCO (30 mol%) in 2.0 mL of DMSO at 100 °C for 12 h. ^b Isolated yield.

Substituted enone oximes derived from multi-substituted arylaldehydes reacted well in this transformation (**2ak**, **2al**, and **2am**). In a similar manner, 5-(naphthalen-2-yl)-3-phenylisoxazole **2an** was obtained in 85% yield. Very interestingly, enone oxime **1ao** with two potential reaction centers selectively underwent the desired transformation to deliver the corresponding product **2ao** in 83% yield.

To expand the scope of this methodology, a series of enone oximes derived from arylacetones were also used under the optimized conditions (Table 3). A variety of enone oximes, bearing electron-donating groups (–Me, –OMe, and –OEt) or electron-withdrawing groups (–Cl, –Br, and –NO₂) on the benzene ring, reacted smoothly to afford the corresponding 3,5-substituted isoxazoles **2ba–2ha** in good yields. Nevertheless, enone oximes bearing multi-substituents (2,4-dimethyl, 3,4-dichloro, and 3,4-methylenedioxy) at the benzene ring were also effective substituents in this transformation furnishing the corresponding products (**2ia**, **2ja**, and **2ka**) in good yields. To our delight, enone oximes originating from other aromatic ketones such as naphthalene and biphenyl were also investigated and found to form the desired products **2la** and **2ma** in 81% and 80% yields, respectively. Moreover, enone oxime derived from other aliphatic ketones such as acetone can also be successfully transformed into the desired isoxazole product **2na** in good yield.

To further demonstrate the synthetic application of our developed protocol, we performed experiments using **2aa** as the starting materials for diversification of isoxazole derivatives (Scheme 2). We first examined the electrophilic aromatic bromination of **2aa** at the 4-position, and **2aa** react smoothly with NBS to give corresponding bromination product **3**.⁴⁹ Additionally, we were able to affect Sonogashira and Suzuki–Miyaura cross-couplings on 4-bromo-3,5-diphenylisoxazole **3**. By allowing

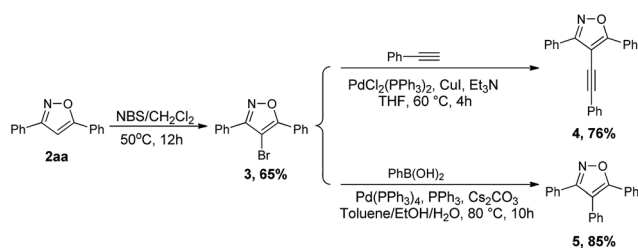


Table 3 Synthesis of isoxazoles with varying substitutions at C3^{a,b}

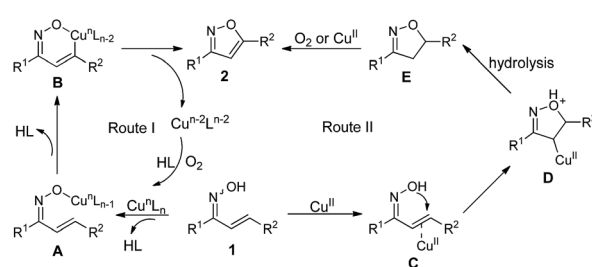
^a Reaction conditions: **1** (0.20 mmol), Cu(OAc)₂ (10 mol%), DABCO (30 mol%) in 2.0 mL of DMSO at 100 °C for 12 h. ^b Isolated yield.

compound **3** to react with phenyl acetylene under standard Sonogashira conditions, 3,5-diphenyl-4-(phenylethynyl)isoxazole **4** was obtained in 76% yield. Also, allowing compound **3** to react with phenylboronic acid under Suzuki–Miyaura reaction conditions provided the desired arylation product **5** in excellent yield.

Based on our experimental data and previous report,^{50–52} a plausible reaction mechanism for formation of 3,5-disubstituted isoxazoles **2** is proposed (Scheme 3). In route I, the reaction of enone oxime **1** with copper catalyst presumably led to the formation of Cu–O species **A**. Then, Cu–O species **A** underwent concurrent deprotonation/metalation at the sp² C–H bond to give a metallacycle **B**, followed by reductive elimination and C–O bond formation leading desired isoxazoles **2** with the generation of reduced copper species,^{53–55} which could be oxidized by oxygen to achieve catalytic cycle. In route II, enone oxime **1** coordinated with Cu^{II} presumably led to intermediate **C**, which should induce the intramolecular nucleophilic addition to generate intermediate **D**. The subsequent deprotonation and hydrolysis of intermediate **D** gave intermediate **E**. Finally,



Scheme 2 Synthetic application of the isoxazole products.



Scheme 3 Possible reaction mechanism.

intermediate **E** was oxidized by oxygen or Cu^{II} to the final product **2**.

In summary, we have developed a novel copper-catalyzed intramolecular oxidative C–O bond coupling reaction for the synthesis of 3,5-disubstituted isoxazoles that complements the commonly used strategies for the synthesis of isoxazoles. Advantages of our procedure include simplicity of operation, diverse substrates, the inexpensive catalytic system, oxygen as the environmentally oxidant and water as nontoxic byproduct. Further investigation of reaction mechanism and synthetic application are ongoing in our group.

Conflicts of interest

There are no conflicts to declare.

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