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Facile synthesis of 2,5-disubstituted oxazoles via a copper-catalyzed cascade reaction of alkenes with azides

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A novel and efficient approach to 2,5-disubstituted oxazoles is developed *via* a 1,3-dipolar cycloaddition/ring cleavage/1,2-H migration/denitrogenation/copper-catalyzed aerobic oxidative dehydrogenative cyclization cascade. The desired products can be obtained from readily available aromatic terminal alkenes and azides employing air as the oxidant under mild conditions, and it offers an attractive alternative method for the synthesis of oxazole derivatives.

Oxazoles are privileged scaffolds found in many pharmacologically active synthetic molecules and natural products, which exhibit attractive biological activities, including antibacterial, antifungal, antiviral, and antitumor properties.[1] Consequently, a variety of protocols have been developed for the synthesis of oxazoles, such as the classical intramolecular cyclization of acyclic precursors,[2] oxidation of oxazolines,[3] the coupling of prefunctionalized oxazoles with organometallic reagents,[4] and other elegant methods recently reported.[5] However, some of these methods face the limitation of low atom efficiency, inaccessible starting materials or the utilization of stoichiometric amounts of sometimes toxic transition-metal catalysts or oxidants. In the interests of atom economy and green chemistry, new approaches to oxazoles from readily available starting materials, in addition to generating minimal and nontoxic waste, are highly desirable.

Transition-metal-catalyzed C–H functionalization has proven to be a versatile and highly functional-group-compatible approach for the synthesis of diverse heterocycles.[6] Among them, the copper-catalyzed C–H functionalization, especially the copper/O_2 catalyzed system,[7] has triggered widespread interest in recent years due to the fact that: copper is an inexpensive and low toxicity transition metal, air (O_2) is abundant, low cost, and sustainable, and in most cases water is the byproduct. Herein, we present a method for the synthesis of 2,5-disubstituted oxazoles *via* sequential azide-alkene 1,3-dipolar cycloaddition/ring cleavage/1,2-H migration/denitrogenation, followed by copper-catalyzed aerobic oxidative dehydrogenative cyclization of the resulting imines. This cascade reaction employs naturally abundant air as the sole oxidant as well as the oxygen source and generates nitrogen and water as by-products. To the best of our knowledge, such a construction of oxazoles from simple, easily available terminal alkenes and azides has not been reported, and it offers an attractive alternative method for the synthesis of many oxazole derivatives.

We initiated our research on the model reaction of styrene (**1a**) with benzyl azide (**2a**) under different reaction conditions (Table 1). Under an atmosphere of air, the 2,5-disubstituted oxazole (**3a**) was obtained in 82% isolated yield upon treatment of a 1: 1.2 mixture of **1a** and **2a** with 10 mol % CuCl in toluene at 80 °C for 8 h (Table 1, entry 1). Without any catalysts, TLC analysis indicated no desired product formation (Table 1, entry 2). Other Cu salts, regardless of their oxidation state (either I or II), also showed catalytic activity, but they were found to be less effective (Table 1, entries 3–9). On the other hand, metal catalysts, such as Ce(OTf)₃, Pd(OAc)₂, In(OTf)₃, [Rh(COD)Cl]₂ or Ag(OAc), were not productive for this conversion (Table 1, entries 10-14). Next, the effect of different solvents was surveyed. The reaction was obviously restrained when it was performed in 1,4-dioxane, DMF, DMSO or DCE (Table 1, entries 15-18). It is worth noting that 10 mol % of the CuCl was sufficient to promote the reaction effectively, and the yield of **3a** was only slightly increased when 1 equiv of CuCl was used, which clearly indicated that the reaction proceeded in a catalytic manner (Table 1, entry 19 *vs*. entry 1). When the reaction was conducted under

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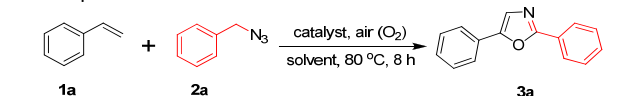
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argon, no desired product was obtained, confirming that air (O_2) plays a key role in the formation of oxazole **3a** (Table 1, entry 20).
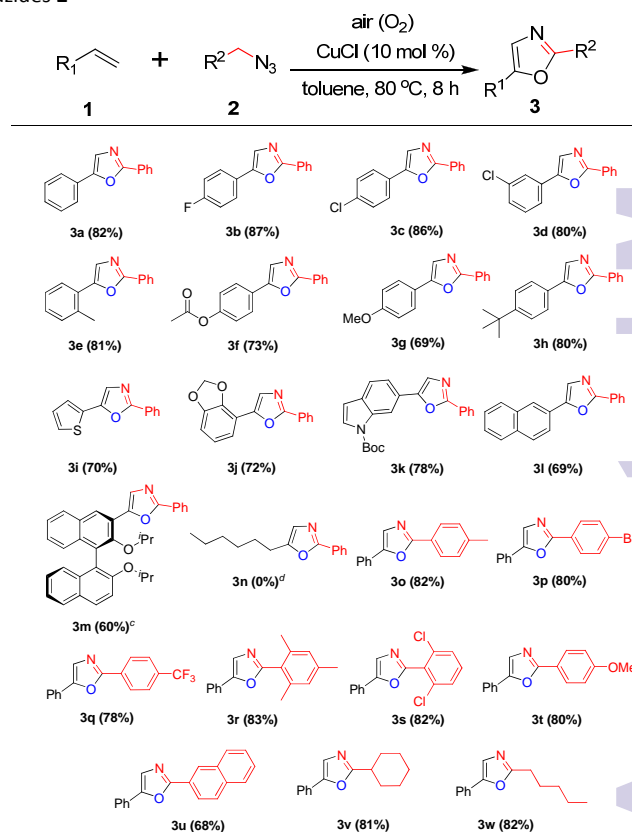
Table 1 Optimization of reaction conditions[a]

Entry	Catalyst	Solvent	Yield (%)[b] of **3a**
1	**CuCl (10 mol %)**	**toluene**	**82**
2	none	toluene	0
3	CuBr (10 mol %)	toluene	79
4	CuI (10 mol %)	toluene	72
5	$CuCl_2$ (10 mol %)	toluene	58
6	$CuBr_2$ (10 mol %)	toluene	55
7	CuI_2 (10 mol %)	toluene	45
8	$Cu(OTf)_2$ (10 mol %)	toluene	35
9	$Cu(OAc)_2$ (10 mol %)	toluene	34
10	$Ce(OTf)_3$ (10 mol %)	toluene	0
11	$Pd(OAc)_2$ (10 mol %)	toluene	0
12	$In(OTf)_3$ (10 mol %)	toluene	<5
13	Ag(OAc) (10 mol %)	toluene	<5
14	$[Rh(COD)Cl]_2$ (10 mol %)	toluene	0
15	CuCl (10 mol %)	1,4-dioxane	69
16	CuCl (10 mol %)	DMF	63
17	CuCl (10 mol %)	DMSO	56
18	CuCl (10 mol %)	DCE	30
19[c]	CuCl (1 equiv.)	toluene	84
20[d]	CuCl (10 mol %)	toluene	0

[a] Reaction conditions: styrene **1a** (0.5 mmol, 1 equiv.), benzyl azide **2a** (0.6 mmol, 1.2 equiv.), catalyst (0.05 mmol, 10 mol %), solvent (3.0 mL), 80 °C, 8 h under air (except for entry 2 and entry 20). [b] Isolated yield of pure product based on **1a**. [c] CuCl (0.5 mmol, 1 equiv.) was used. [d] The reaction was carried out under argon atmosphere (1 atm). Entry in bold highlights optimized reaction conditions.

Under the optimized reaction conditions, the scope of terminal alkenes **1** was firstly investigated. As summarized in Table 2, aromatic terminal alkenes bearing electron-withdrawing substituents on the aryl ring participated in the cascade reaction in excellent yield (**3b**-**3d**), and electron-rich aromatic alkenes also reacted smoothly in good yields (**3e**-**3h**). Moreover, substitution at the *meta* (**3d**) and *ortho* (**3e**) positions were not detrimental to the reaction yield. Heteroaryl-substituted alkenes were also tolerated in this transformation, generating the corresponding 2,5-disubstituted oxazoles **3i**, **3j** and **3k** in 70%, 72% and 78% isolated yields, respectively. Naphthyl-substituted alkene afforded **3l** in 69% yield. When optically active alkene (*R*)-2,2'-diisopropoxy-3-vinyl-1,1'-binaphthalene was examined as a substrate, to our delight, (*R*)-5-(2,2'-diisopropoxy-[1,1'-binaphthalen]-3-yl)-2-phenyloxazole **3m** was formed in 60% yield. Unfortunately, aliphatic terminal alkenes or internal alkenes did not work under these reaction conditions (**3n**). In addition, the azide substrates were further examined. It was found that the substituents at the phenyl ring of the benzyl azides little influenced the reactivity of the substrate, and the desired oxazole products were produced in high yields (**3o**-**3t**). Especially,

steric hindrance did not seem to adversely affect the efficiency and **3s**). Furthermore, 2-(azidomethyl)naphthalene could smoothly transformed into the corresponding product in 68% yield (**3u**). It is noteworthy that alkyl azides such as (azidomethyl)cyclohexane and 1-azidohexane were well tolerated in the reaction and led to excellent yields (**3v** and **3w**).

Table 2 Substrate scope for the reaction of terminal Alkenes **1** and azides **2**[a,b]

3a (82%) 3b (87%) 3c (86%) 3d (80%)
3e (81%) 3f (73%) 3g (69%) 3h (80%)
3i (70%) 3j (72%) 3k (78%) 3l (69%)
3m (60%)[c] 3n (0%)[d] 3o (82%) 3p (80%)
3q (78%) 3r (83%) 3s (82%) 3t (80%)
3u (68%) 3v (81%) 3w (82%)

[a] Reactions conditions: 0.5 mmol of **1** and 0.6 mmol of **2** in the presence of CuCl (10 mol %) in 3.0 mL of toluene at 80 °C for 8 h under air. [b] Isolated yield of pure product based on **1**. [c] (*R*)-2,2'-Diisopropoxy-3-vinyl-1,1'-binaphthalene was used as the substrate. [d] Oct-1-ene was used as the substrate.

Some control experiments were carried out in order to explore the possible reaction pathway. The reaction of **1a** and **2a** in the presence of $^{18}O_2$ (1 atm) generated ^{18}O-labeled product [^{18}O]-**3a** in 81% isolated yield under the standard conditions [Eq. (1), the ^{18}O was determined by HRMS, see the Supporting Information], indicating that the oxygen atom of the oxazole product originated from molecular oxygen. The reaction of acetophenone (**4**) and **2a** under the standard conditions could not generate **3a** [Eq. (2)], which might exclude **4** as the intermediate of this oxidative transformation. In addition, when 1 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was added, the yield of **3a** fell to 8% [Eq. (3)]. The experiment result suggested a possible radial mechanism.
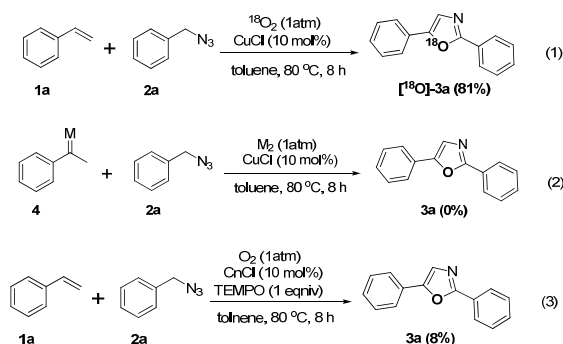
A plausible mechanism for this cascade reaction is shown in Scheme 1. The first step is the regioselective 1,3-dipolar cycloaddition of benzyl azide **2a** with styrene **1a** to form the triazoline intermediate **A**. Subsequently, **A** decomposes to the zwitterionic species **B**, which undergoes 1,2 H-shift with the loss of nitrogen to give the imine **C**.[8] Then, one-electron oxidation of **C** by the higher-oxidation-state Cu[II] species generated from Cu[I]Cl with molecular oxygen[2f, 9] yields a radical intermediate **D**, and **D** could then be envisaged reacting with molecular oxygen to give peroxy radical **E**. The latter could then undergo a 1,5-hydrogen atom abstraction[2f, 5d, 10] to afford intermediate **F** with regeneration of the Cu[II] species. Finally, intramolecular radical coupling would afford the 4,5-dihydrooxazole intermediate **G**, which could be easily oxidized by air to the final oxazole product **3a**.[3d, 5d]

ESI/MS experiments were performed to gain evidence for the possible intermediates in the proposed mechanism. Under an argon atmosphere, a mixture of **1a** (0.5 mmol), **2a** (0.6 mmol) and CuCl (0.05 mmol) in toluene (3.0 mL) was reacted at 80 ^{o}C for 8 h and 50 µL of the mixture was used for the ESI analysis in CH$_3$OH. The ESI/MS analyses showed a peak at *m/z* 210.1270, which was identified as an imine species (see the Supporting Information). Although the unstable imine **C** underwent decomposition during the column chromatography, this result supported the generation of the imine intermediate **C**.
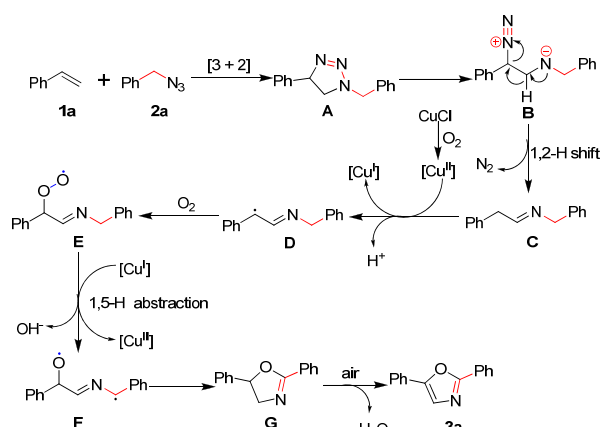
Scheme 1 A plausible mechanism for the cascade reaction of terminal alkenes and azides.

In summary, we have demonstrated a novel approach for the synthesis of 2,5-disubstituted oxazoles that operates *via* sequential azide-alkene 1,3-dipolar cycloaddition/ring cleavage/1,2 imine migration/denitrogenation, followed by copper-catalyzed aerobic oxidative dehydrogenative cyclization of the resulting imines. The use of naturally abundant air as an oxidant as well as an oxygen source, easily available starting materials including the copper catalyst, and an experimentally convenient catalytic process are the added advantages of the present protocol. Further investigations on the synthetic applications of this reaction are ongoing in our laboratory.

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