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Copper-Catalyzed Aminosulfonylation of *O*-Homoallyl Benzimidates with Sodium Sulfinates to Access Sulfonylated 1,3-Oxazines

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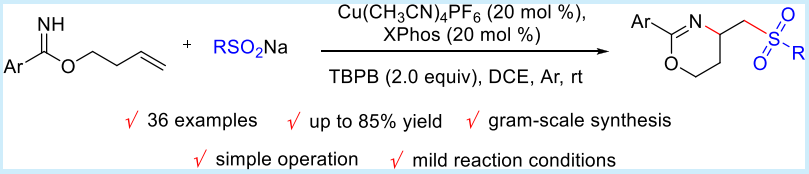

ABSTRACT: A facile copper-catalyzed aminosulfonylation of *O*-homoallyl benzimidates with sodium sulfinates in the presence of *tert*-butyl peroxybenzoate (TBPB) and XPhos ligand has been developed. By using this protocol, a variety of potentially bioactive 1,3-oxazines were directly synthesized. This method has the merits of a cheap catalyst, easily available and stable sulfone reagents, and simple operation.

Sulfonylated heterocycles are recognized as an important class of organic molecules, having extensive applications in the field of organic chemistry,[1] pharmaceuticals,[2] and materials science.[3] As such, considerable efforts have been made in the construction of the sulfonylated heterocycle framework.[4] Among them, significant progress in the cascade difunctionalization/cyclization reaction of alkenes involving sulfonyl radical has been made, and a variety of complex sulfonylated heterocyclics have been conveniently synthesized in a step- and atom-economic way. Traditionally, the strategy of this methodology is as follows: First, the sulfonyl radical was generated under oxidation or photoredox conditions, which attacked the carbon−carbon double bond of olefin substrate to produce an alkyl radical intermediate **I**. Then, the alkyl radical **I** was captured by carbon-containing unsaturated groups (including aryl groups,[5] -C≡C-,[6] and -C≡N[7]) or oxygen-based nucleophilic functional groups (such as -COOH,[8] -OH,[9] and carbonyl groups[10]) of the alkene substrate to obtain the corresponding sulfonylated cyclic products (Scheme 1a). Although elegant studies have been provided, research on this area has mainly been restricted to carbosulfonylation/cyclization and oxysulfonylation/cyclization reaction. The use of nitrogen-based nucleophilic functional groups to achieve aminosulfonylation/cyclization reaction has been less explored and remains a challenging task. Therefore, there is an urgent need to develop new strategies. Recently, the Wu group reported an *N*-radical-initiated aminosulfonylation/cyclization of alkenyl oxime acetates with silyl enolate through the insertion of sulfur dioxide in the presence of visible light, producing a range of sulfonated pyrrole derivatives.[11] Further, the Wu group,[12] our group,[13] and Rao group[14] realized the aminosulfonylation/cyclization of alkenyl acids/amides by using $Ru(bpy)_3(PF_6)_2$, $Cu(NO_3)_2{\cdot}3H_2O$, and $Cu(OAc)_2$ respectively to construct a series of sulfonated lactams (Scheme 1b). With our continuing interest in tandem sulfonylation cyclization reactions[13,15] and nitrogen-containing heterocycles synthesis,[16] herein, we intend to establish an efficient and general protocol for the rapid synthesis of sulfonylated 1,3-oxazines by direct annulation of *O*-homoallyl benzimidates and sodium sulfinates via a copper-catalyzed vicinal aminosulfonylation under mild conditions (Scheme 1c). This reaction provides a complementary method to the aminosulfonylation/cyclization of alkenes.

To achieve this idea, we selected the easily prepared *O*-homoallyl benzimidate **1a** and sodium *p*-toluenesulfinate **2a** as model substrates for optimizing the reaction conditions (Table 1). The transformation was initially conducted in DCM by using $Cu(CH_3CN)_4PF_6$ (20 mol %) as the catalyst and TBPB (2 equiv) as the oxidant at room temperature under argon atmosphere for 12 h. To our delight, the desired product **3aa** was obtained in 55% yield (Table 1, entry 1). Subsequently, several other solvents, such as CH_3OH, THF, MeCN, and DCE, were also tested and revealed that DCE was the best solvent, which improves the yield of **3aa** to 57% (Table 1, entries 2−5). We next took a brief screening of several oxidants, including $Na_2S_2O_8$, *m*-CPBA, $PhI(OAc)_2$,

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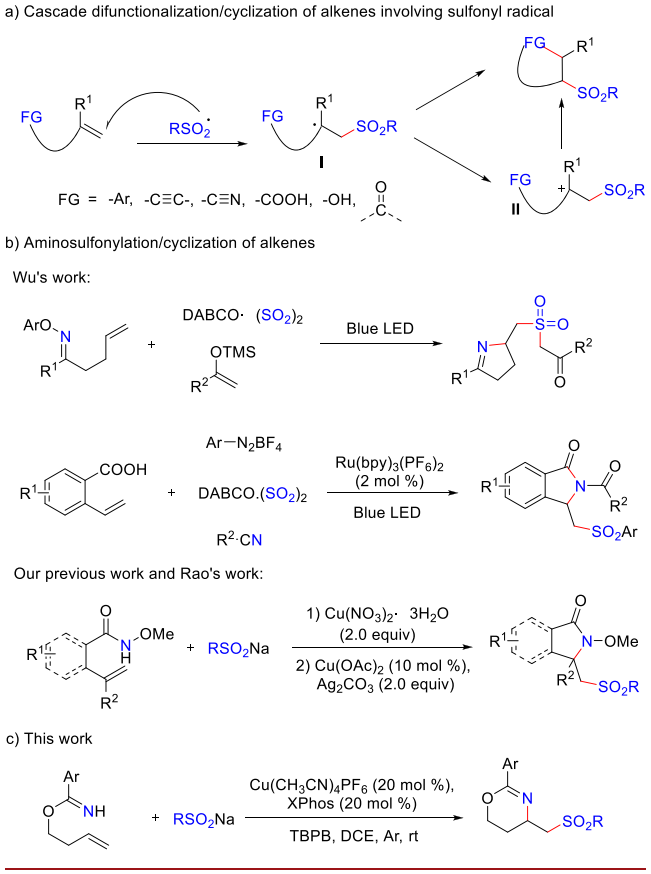
Scheme 1. Aminosulfonylation/Cyclization of Alkenes



TBHP, and DCP, which did not afford better results (entries 6−10). The reaction failed without any oxidants (Table 1, entry 11). We continued to evaluate the effect of ligands: PPh_3, 1,10-Phenanthroline, 2,2′-bipyridine, XantPhos, XPhos, and ^{t}BuXPhos (Table 1, entries 12−17), and the conversion performance was greatly improved following the use of XPhos as the ligand, giving **3aa** in 83% yield (Table 1, entry 16). Encouraged by the results, we then investigated the influence of some other Cu catalysts, such as $Cu(OTf)_2$, CuBr, $Cu(OAc)_2{\cdot}H_2O$, and $Cu(ClO_4)_2{\cdot}6H_2O$; however, regretfully, there were no better results (Table 1, entries 18−21). When the loading of $Cu(CH_3CN)_4PF_6$ was reduced to 10 mol %, the yield of **3aa** was decreased to 58% (Table 1, entry 22). The control experiment showed that the Cu catalyst plays a crucial role in the reaction (Table 1, entry 23). Changing the temperature of the reaction could not improve the yield of the desired product (Table 1, entries 24−25). Furthermore, when the reaction proceeded under an air atmosphere, the yield of **3aa** was decreased to 44% (Table 1, entry 26).

With the optimized reaction conditions established (Table 1, entry 16), we examined the scope and limitations of this reaction concerning various substituted *O*-homoallyl imidates **1**, and the results are described in Scheme 2. First, the effect of the substituents on the phenyl ring of *O*-homoallyl benzimidates was evaluated. As expected, substrates **1b−1f** with electron-donating groups (Me and OMe) and electron-withdrawing substituents (F, Cl, and I) at the para-position proceeded well under the standard reaction conditions and afforded the corresponding sulfonylated 1,3-oxazines (**3ba−3fa**) in good yields. Note that the structure of **3ea** was unambiguously confirmed by X-ray analysis.[17] Besides, it was found that the benzimidates bearing meta- or disubstituted groups on the aromatic ring were also compatible (**3ga−3ka**). It is worth mentioning that introducing naphthyl substituent into imidate could give the desired 1,3-oxazine product (**3la**) in moderate yield. The thiophene-containing imidate (**1m**) also proved to be an applicable substrate and gave the product in a yield of 81% yield. In addition, the *O*-homoallyl trichloroacetimidate (**1n**) and 1-phenylhex-5-en-1-imine (**1o**) were not compatible with this aminosulfonylation/cyclization reaction. Then, the reaction of 1-(4-methoxyphenyl)-substituted *O*-homoallyl benzimidate substrate (**1p**) was investigated under standard conditions, and interestingly, the sulfonylated 7-membered tetrahydro-1,3-oxazepine (**4pa**) was obtained in a yield of 29%. However, when the 2-phenyl-substituted alkene substrate (**1q**) was tested, it failed to produce the desired product and the substrate was decomposed. We also investigated pent-4-en-1-yl benzimidate (**1r**), but it was not suitable for this transformation, giving the unexpected vinyl sulfone product (**5ra**) in 34% yield. Moreover, to expand the scope of this reaction, substrate **1s** was tested and afforded the desired product **3sa** in 51% yield with 7:1 dr.

Having successfully achieved the aminosulfonylation/cyclization with *O*-homoallyl imidates, we shifted our attention to explore the scope of sodium sulfinates **2**. The reactions of a collection of sodium sulfinates with **1a** were examined, and the results are shown in Scheme 3. Sodium sulfinates bearing substituents, such as H, OMe, ^{t}Bu, F, Cl, and Br, at the para-position of the aromatic ring readily worked well in the reaction, giving the sulfonylated 1,3-oxazines (**3ab−3ag**) in medium to good yields. While sodium *p*-phenylbenzenesulfinate **2h** was only transformed to the corresponding product in 27% yield. Additionally, some representative substituted aryl sodium sulfinates with Me, F, Br, and Cl at the meta- or ortho-position of the benzene ring could also react with **1a** to give the corresponding products (**3ai−3al**) in 43−81% yields. Moreover, sodium naphthalene-2-sulfinate was transformed into the target product **3am** in 54% yield. Remarkably, sodium alkanesulfinates were also suitable substrates for the reaction under the standard conditions, giving the aminosulfonylation compounds **3an−3aq** in moderate to good yields with them. Furthermore, we investigated sodium trifluoromesylate **2r** and found that it was not suitable for this cascade aminosulfonylation.

To further explore the synthetic practicability and potentiality of this transformation, gram-scale synthesis of sulfonylated 1,3-oxazine **3** and their follow-up derivatizations were tested. As shown in Scheme 4, the reaction of *O*-homoallyl benzimidate **1a** and sodium *p*-toluenesulfinate **2a** on a gram scale afforded **3aa** in a yield of 82% (1.074 g). Then, considering that $Cu(OAc)_2{\cdot}H_2O$ is a cheaper catalyst (Table 1, entry 20), we also conducted a gram-scale reaction by using $Cu(OAc)_2{\cdot}H_2O$ (20 mol %), giving **3aa** in a yield of 74% (0.979 g). Next, **3aa** could be hydrolyzed to sulfonylated *γ*-amido alcohol **6** (95%) by treatment with 2 M HCl in THF at room temperature for 3 h. In addition, the iodinated product **3af** could be employed in palladium-catalyzed Sonagashira coupling reaction to quickly achieve additional molecular complexity, affording the corresponding 2-(4-(phenylethynyl)phenyl)-4-(tosylmethyl)-5,6-dihydro-4*H*-1,3-oxazine **7** in 97% yield.

To gain insights into the reaction mechanism, two control experiments were conducted (Scheme 5). First, when the

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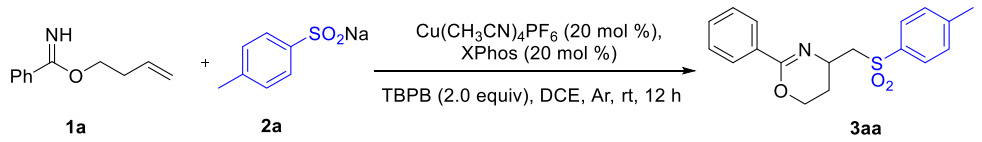
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	solvent[b]	[Cu]	oxidant[c]	ligand[d]	t (°C)	yield[e](%)
1	DCM	$Cu(CH_3CN)_4PF_6$	TBPB	-	rt	55
2	CH_3OH	$Cu(CH_3CN)_4PF_6$	TBPB	-	rt	36
3	THF	$Cu(CH_3CN)_4PF_6$	TBPB	-	rt	10
4	CH_3CN	$Cu(CH_3CN)_4PF_6$	TBPB	-	rt	36
5	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	-	rt	57
6	DCE	$Cu(CH_3CN)_4PF_6$	$Na_2S_2O_8$	-	rt	4
7	DCE	$Cu(CH_3CN)_4PF_6$	*m*-CPBA	-	rt	4
8	DCE	$Cu(CH_3CN)_4PF_6$	$PhI(OAc)_2$	-	rt	trace
9	DCE	$Cu(CH_3CN)_4PF_6$	TBHP	-	rt	trace
10	DCE	$Cu(CH_3CN)_4PF_6$	DCP	-	rt	trace
11	DCE	$Cu(CH_3CN)_4PF_6$	-	-	rt	0
12	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	PPh_3	rt	51
13	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	1,10-Phenanthroline	rt	15
14	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	2,2′-bipyridine	rt	11
15	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	XantPhos	rt	51
16	**DCE**	**$Cu(CH_3CN)_4PF_6$**	**TBPB**	**XPhos**	**rt**	**83**
17	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	^{t}BuXPhos	rt	58
18	DCE	$Cu(OTf)_2$	TBPB	XPhos	rt	62
19	DCE	CuBr	TBPB	XPhos	rt	65
20	DCE	$Cu(OAc)_2{\cdot}H_2O$	TBPB	XPhos	rt	81
21	DCE	$Cu(ClO_4)_2{\cdot}6H_2O$	TBPB	XPhos	rt	80
22[f]	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	XPhos	rt	58
23	DCE	-	TBPB	XPhos	rt	0
24	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	XPhos	40	75
25	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	XPhos	60	53
26[g]	DCE	$Cu(CH_3CN)_4PF_6$	TBPB	XPhos	rt	44

[a]All reactions were performed by using **1a** (0.2 mmol), **2a** (2.0 equiv), copper salts (20 mol %), oxidant (2.0 equiv), ligand (20 mol %), and solvent (2 mL) under argon and stirred at room temperature for 12 h, unless noted otherwise. [b]DCM, dichloromethane; CH_3OH, methanol; THF, tetrahydrofuran; CH_3CN, acetonitrile; DCE, dichloroethane. [c]TBPB, *tert*-butyl peroxybenzoate; *m*-CPBA, 3-chloroperbenzoic acid; TBHP, *tert*-butyl hydroperoxide (6 M in decane); DCP, dicumyl peroxide. [d]XantPhos, 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; XPhos, dicyclohexyl(2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)phosphine; ^{t}BuXphos, di-*tert*-butyl(2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)phosphine. [e]Isolated yield. [f]10 mol % of $Cu(CH_3CN)_4PF_6$ was used. [g]Under air.

radical scavenger 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO, 2.0 equiv) was added to the reaction system, the aminosulfonylation was inhibited and **1a** was recovered in 56% yield. Next, this transformation was also terminated in the presence of BHT (butylated hydroxytoluene, 2.0 equiv); substrate **1a** was recovered in 71% yield, and in the presence of BHT product **8** was obtained in 25% yield. Together, these results indicated that a radical pathway with sulfonyl radical intermediate is likely involved in this aminosulfonylation reaction.

On the basis of our preliminary mechanistic observations and the aforementioned control experiment, a proposed mechanism for this copper-catalyzed cascade sequence was illustrated in Scheme 6. Cu^I first reduces TBPB to generate Cu^{II}, *tert*-butoxyl radical and benzoic acid anion. Then, substrate **1a** was captured by Cu^{II} under benzoic acid anion/*tert*-butoxide condition to afford intermediate **A** and benzoic acid/ *tert*-butanol. The former likely undergoes an intramolecular aminocupration to furnish intermediate **B** via *exo*-cyclization manner. Meanwhile, sodium sulfinate **2a** was oxidized by *tert*-butoxyl radical to give a sulfonyl radical **D** and a *tert*-butoxide. Subsequently, intermediate **B** coupled with sulfonyl radical **D** to give intermediate **C**, which was followed by a reductive elimination process to get the corresponding product **3aa** and regenerate Cu^I. In addition, another possible pathway cannot be ruled out (Scheme 1a): First, Cu^I assists the cleavage of TBPB to generate Cu^{II} and *tert*-butoxyl radical, which then reacted with sodium sulfinate **2a** affording sulfonyl radical. Then the sulfonyl radical would attack the alkene substrate **1a** giving rise to alkyl radical intermediate **I**, which reacted with Cu^{II} to produce the carbocation intermediate **II** and regenerate Cu^I. The former subsequently underwent intramolecular nucleophilic attack by the NH of the imidate, leading to the desired sulfonylated 1,3-oxazine **3aa**.

In summary, we have demonstrated a facile copper-catalyzed aminosulfonylation method of *O*-homoallyl-benzimidates with sodium sulfinates under mild conditions for the synthesis of sulfonylated 1,3-oxazines, which are important frameworks in medicinal and biological chemistry. Preliminary mechanistic investigations reveal that sulfonyl radical intermediate might be involved in this reaction. Moreover, this strategy represents an appealing and complementary methodology to construct sulfonylated nitrogen heterocycles. Further studies of this aminosulfonylation/cyclization strategy of alkenes are currently underway in our laboratory.

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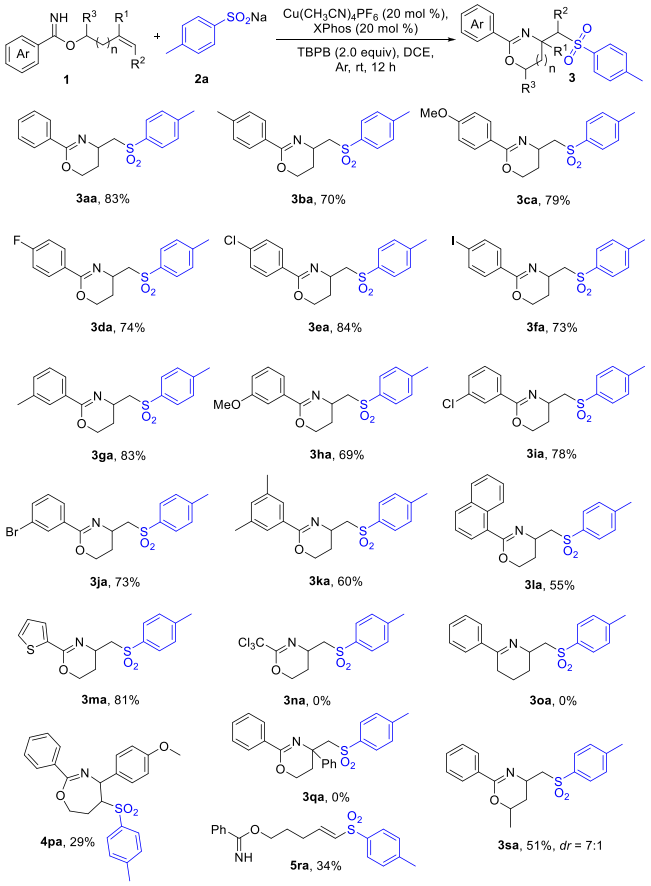
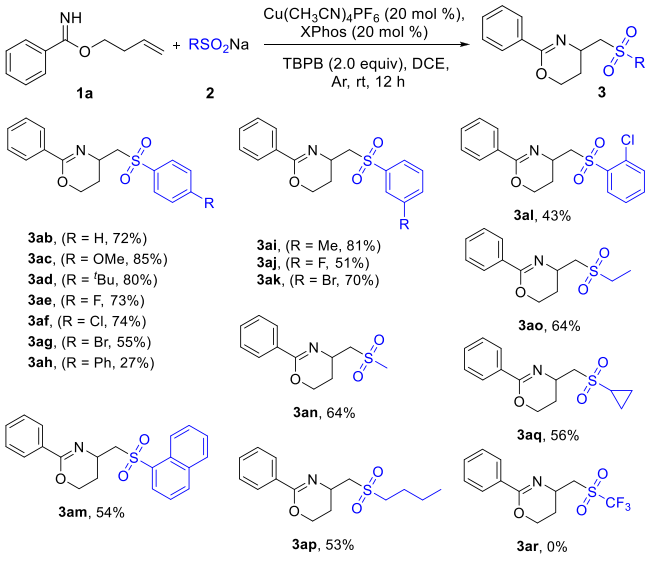
Scheme 2. Scope of *O*-Homoallyl Imidates[a,b]



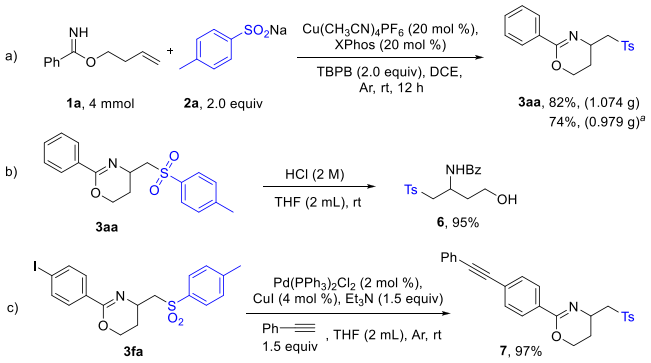
[a]All reactions were performed by using **1** (0.2 mmol), **2a** (2.0 equiv), $Cu(CH_3CN)_4PF_6$ (20 mol %), XPhos (20 mol %), TBPB (2.0 equiv), and DCE (2 mL) under argon and stirred at room temperature for 12 h. [b]Isolated yield.

Scheme 3. Scope of Sulfinate Sodiums[a,b]



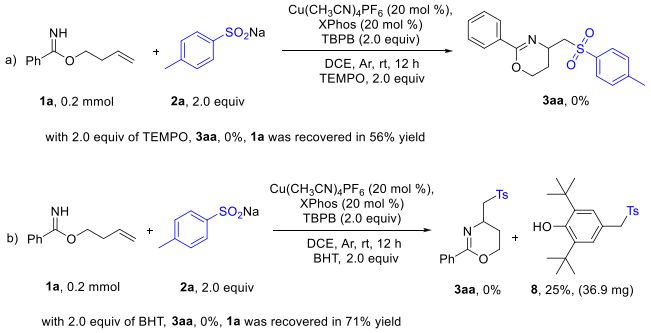
[a]All reactions were performed by using **1a** (0.2 mmol), **2** (2.0 equiv), $Cu(CH_3CN)_4PF_6$ (20 mol %), XPhos (20 mol %), TBPB (2.0 equiv), and DCE (2 mL) under argon and stirred at room temperature for 12 h. [b]Isolated yield.

Scheme 4. Application Investigation

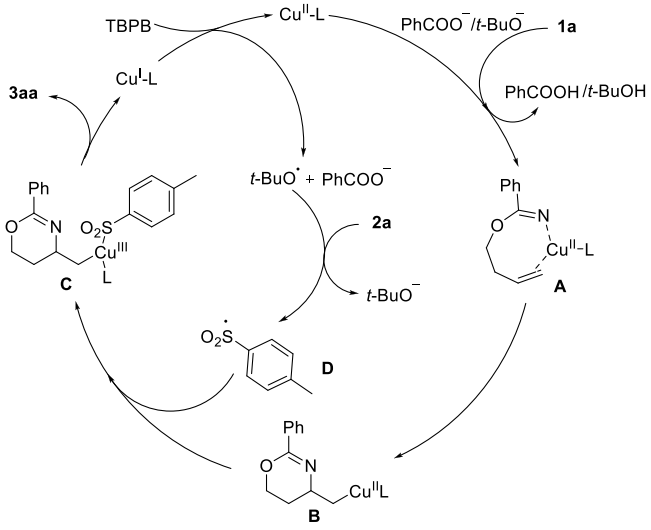


[a]The reaction was performed by using $Cu(OAc)_2{\cdot}H_2O$ (20 mol %).

Scheme 5. Mechanistic Studies



Scheme 6. Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01962.

Detailed experimental procedures and spectral data for all products; crystallographic data for compound **3ea** (PDF)

Accession Codes

CCDC 2088645 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing

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Notes

The authors declare no competing financial interest.

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