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A copper-catalyzed three-component reaction of alkenes, cycloketone oximes and DABCO·$(SO_2)_2$: Direct C(sp^2)-H cyanoalkylsulfonylation

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ABSTRACT

A copper-catalyzed three-component reaction of alkenes, cycloketone oximes and DABCO·$(SO_2)_2$ is developed, which provides a convenient route for the synthesis of diverse (*E*)-cyanoalkylsulfonyl alkenes in moderate to good yields with excellent regio- and stereoselectivity. A broad substrate scope with excellent functional group tolerance is observed. A plausible radical pathway is proposed, which involves copper-catalyzed ring-opening C–C bond cleavage of *O*-acyl oxime and insertion of sulfur dioxide. During the reaction process, cyanoalkyl radical and cyanoalkylsulfonyl radical are the key intermediates.

Alkyl nitriles are particularly attractive and versatile building blocks in organic synthetic chemistry [1–4], due to the presence of useful cyano group, which can be readily transformed into other valuable functional groups. Additionally, aliphatic nitriles are important structural motifs of biologically active pharmaceuticals and natural products [5–10]. Therefore, methods for the synthesis of alkyl nitriles are highly desired and remarkable progress has been made in recent years. Especially, radical-mediated β-C-C bond cleavage of cyclokteone oximes has been successfully applied to generate cyanoalkyl radicals, affording an attractive approach for the preparation of various aliphatic nitriles [11–30].

On the other hand, owing to the extensive application of sulfones in synthetic chemistry and medicinal chemistry [31–35], our group has continuously involved in the methods development for the synthesis of sulfonyl compounds *via* the fixation of sulfur dioxide by using DABCO·$(SO_2)_2$ or potassium/sodium metabisulfite as the sulfur dioxide surrogates [36–60]. Particularly, vinyl sulfones attracted our attention [61–69], since they were used as the neuroprotective agents for Parkinson's disease therapy [70]. In 2019, our group realized the cyanoalkylsulfonylation *via* the cascade reaction of β-C-C bond cleavage of cyclokteone oximes with the insertion of sulfur dioxide, giving rise to a range of cyano-containing sulfones [71]. Prompted by this strategy and recent advance in the radical-based C–C bond cleavage of cycloketone oximes [72–82], we envisioned that vinyl sulfones could be generated through a direct C(sp^2)-H cyanoalkylsulfonation of olefins *via* a radical-type insertion of sulfur dioxide. Herein, we report a copper-catalyzed three-component reaction of olefins, cycloketone oximes and DABCO·$(SO_2)_2$, providing a stereoselective pathway for the preparation of (*E*)-cyanoalkylsulfonated alkenes.

To verify the hypothesis above, initial studies were carried out for the direct C(sp^2)-H cyanoalkylsulfonation of styrene **1a**, cyclobutanone *O*-benzoyl oxime **2a** and DABCO·$(SO_2)_2$ in 1,2-dichloroethane (DCE) at 80 °C. Fortunately, this reaction occurred in the presence of copper(I) iodide (10 mol%) as the catalyst and 1,10-phenanthroline (**L1**, 12 mol%) as the ligand, giving rise to the desired product **3aa** in 63% yield (Table 1, entry 1). Further exploration showed that other copper catalysts were not as efficient as copper(I) iodide (Table 1, entry 2, for details see Supporting information). Subsequently, we shifted our focus to other ligands, and a range of *N,N*-bidentate ligands were screened. Gratifyingly, the corresponding product **3aa** was obtained in 72% yield by employing 4,7-dphenyl-1,10-phenanthroline (**L2**) as the ligand (Table 1, entry 3). However, the results were inferior when other ligands were used instead of **L2** (Table 1, entry 4, for details see Supporting information). The solvent effect was then evaluated, and MeCN was demonstrated as the best choice (74% yield, Table 1, entries 5 and 6). Interestingly, comparable yields were afforded when the

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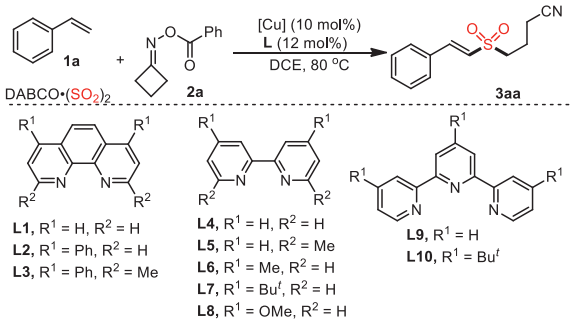
Table 1
Initial studies for the direct C(sp^2)-H cyanoalkylsulfonation of styrene **1a**, cyclobutanone *O*-benzoyl oxime **2a** and DABCO•(SO_2)$_2$.[a]

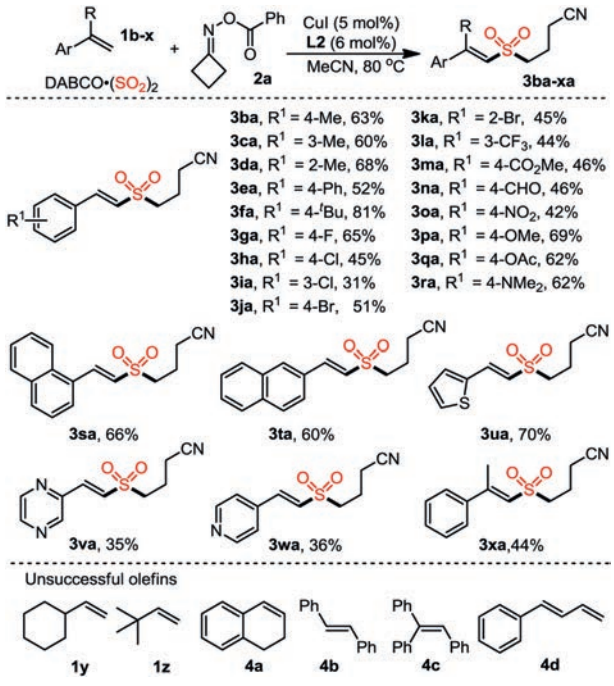


Entry	Variation of conditions	Yield (%)[b]
1	None	63
2	Other copper catalysts instead of CuI	14–57
3	**L2** instead of **L1**	72
4	Other ligands instead of **L1**	47–65
5[c]	MeCN instead of DCE	74
6[c]	Other solvents instead of DCE	54–72
7[d]	5 mol% CuI and 6 mol% **L2**	75 (71)
8[d]	5 mol% CuI and 7.5 mol% **L2**	76
9[e]	50 °C	50
10[d]	In the absence of CuI and **L2**	n.d.
11[d]	In the absence of **L2**	23

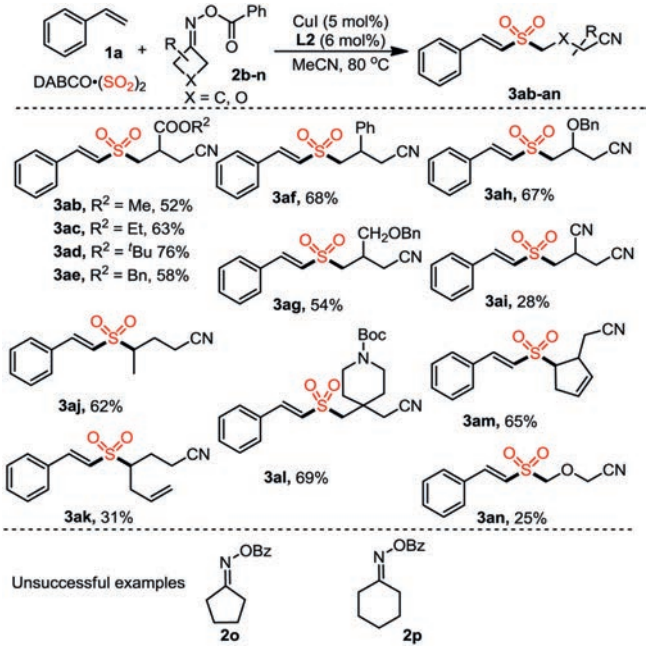
[a] Reaction conditions: styrene **1a** (0.3 mmol), cyclobutanone *O*-benzoyl oxime **2a** (0.45 mmol, 1.5 equiv.), DABCO•(SO_2)$_2$ (0.45 mmol, 1.5 equiv.), CuI (10 mol%), **L1** (12 mol%), DCE (1.5 mL), N_2, 80 °C, 12 h.
[b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard (isolated yield in parentheses).
[c] **L2** was used.
[d] MeCN was used as the solvent.
[e] In the presence of CuI (5 mol%), **L2** (6 mol%) in MeCN.

loading amount of copper(I) iodide and ligand **L2** were reduced (Table 1, entries 7 and 8). The yield of product **3aa** was decreased when the reaction temperature was reduced to 50 °C (Table 1, entry 9). A control experiment showed that no product **3aa** was detected in the absence of copper catalyst and ligand (Table 1, entry 10). Another control experiment confirmed the necessity of ligand, giving rise to **3aa** in 23% yield in the absence of ligand (Table 1, entry 11).

Under the above optimized conditions, the substrate scope of alkenes was then explored. The results are summarized in Scheme 1. It was found that *para*-, *meta*- and *ortho*-methyl phenylethylene derivatives could react with cyclobutanone *O*-benzoyl oxime **2a** and DABCO·(SO_2)$_2$ well, affording the corresponding products **3ba**-**3da** in 60%–68% yields. Generally, alkenes bearing substituents of electron-donating (^{t}Bu, Ph, OMe, OAc, NMe_2) and electron-withdrawing (CF_3, COOMe, CHO, NO_2, F, Cl, Br) groups on the aryl moieties were converted smoothly to the desired cyanoalkylsulfonated products **3fa**-**3ra** in moderate to good yields. Notably, reaction of 1-methyl-2-vinylbenzene **1d** or 1–bromo-2-vinylbenzene **1k** could give rise to product **3da** or **3ra** in 68% and 45% yield, indicating the reaction was insensitive to the steric property of vinylbenzene. Additionally, reactions of alkenes incorporated with α- or β-naphthyl group proceeded smoothly as well, leading to the desired products **3sa** and **3ta** in 66% and 60% yield. Alkenes bearing heterocyclic units were also compatible in this transformation, providing products **3ua**, **3va** and **3wa** in 70%, 35% and 36% yield, respectively. Furthermore, trisubstituted cyanoalkylsulfonated alkene **3xa** could be afforded by using prop–1-en-2-ylbenzene **1x** as the substrate. Unfortunately, alkyl substituted terminal olefins vinylcyclohexane **1y** and 3,3-dimethylbut-1-ene **1z** were not compatible for the standard



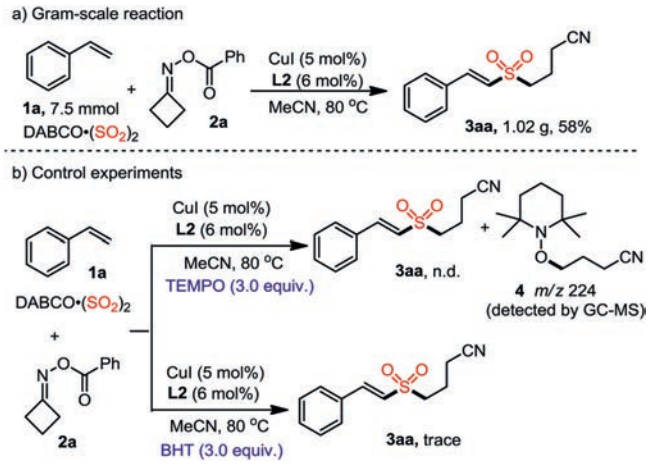
Scheme 1. Substrate scope of alkenes **1b-x**. Isolated yield.



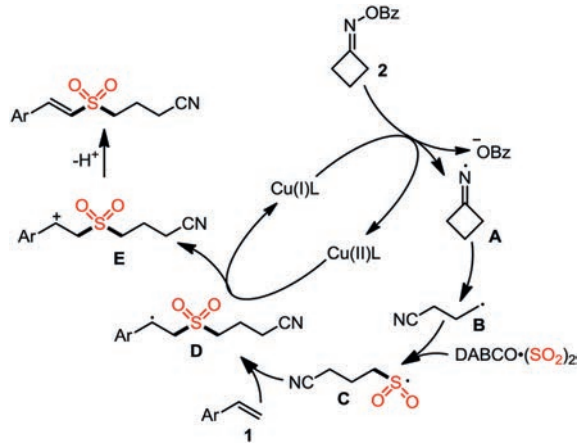
Scheme 2. Substrate scope of alkenes **1b-x**. Isolated yield.

conditions and the desired products were not detected. In addition, (*Z*)–1,2-di-substituted alkene **4a**, (*E*)–1,2-di-substituted alkene **4b**, trisubstituted alkene **4c** and 1,3-dienes **4d** were employed instead of styrenes, leading to the corresponding products in only trace yields.

We further evaluated the substrate scope by employing diverse *O*-benzoyl oximes with styrene **1a** and DABCO·(SO_2)$_2$ under the standard conditions. As shown in Scheme 2, a range of *O*-benzoyl oximes **2b**-**2n** with different substituents were well compatible, giving rise to the desired products in 25%–76% yields. It is noteworthy that β-substituted *O*-benzoyl oximes could undergo selective C–C bond cleavage to form more stable secondary alkyl rad-



Scheme 3. Gram-scale reaction and control experiments.



Scheme 4. Proposed mechanism.

ical, thus leading to products **3ak** and **3al**. Interestingly, reaction of oxygen-containing substrate **2n** was also workable, generating the target product **3an**. Moreover, we also tested cyclopentanone oxime derivative **2o** and cyclohexanone oxime derivative **2p** under the standard conditions, but there were no desired products were detected. Besides, a gram-scale cyanoalkylsulfonylation of styrene was carried out, and product **3aa** was obtained in 58% yield (1.02 g, Scheme 3a).

Since we initially hypothesized that this transformation might undergo a radical process, therefore, several control experiments were performed (Scheme 3b). The model reaction of styrene **1a**, cyclobutanone *O*-benzoyl oxime **2a** and DABCO·$(SO_2)_2$ was completely suppressed in the presence of 2,2,6,6-tetramethylpiperidin-1-oxy (TEMPO) under the standard conditions. The radical trapping product **4**, which was formed by cyanoalkyl radical and TEMPO, was detected by GC–MS. Additionally, only a trace amount of product **3aa** was detected when butylated hydroxytoluene (BHT) was added as the radical scavenger in the reaction system.

On the basis of the above observation and related reports [11-30,83], a plausible mechanism is proposed as shown in Scheme 4. We reasoned that initially, a single-electron transfer process between *O*-benzoyl cycloketone oxime **2** and Cu(I) species would lead to the formation of iminyl radical intermediate **A** and Cu(II) complex. Subsequently, β-C-C bond cleavage of iminyl radical intermediate **A** would occur, giving rise to cyanoalkyl radical **B**. This cyanoalkyl radical **B** would then react with sulfur dioxide, providing cyanoalkylsulfonyl radical **C**. Followed by the addition of cyanoalkylsulfonyl radical **C** to alkene **2**, a more stable benzyl radical **D** would be formed. Then, an oxidative single electron transfer between benzyl radical **D** and Cu(II) complex would provide cation intermediate **E** with the release of Cu(I) species to complete the catalytic cycle. Further deprotonation of cation intermediate **E** would result in the formation of cyanoalkylsulfonyl alkene **3**.

In summary, we have developed a copper-catalyzed three-component reaction of alkenes, cycloketone oximes and DABCO·$(SO_2)_2$, which provides a convenient route for the synthesis of diverse (*E*)-cyanoalkylsulfonyl alkenes in moderate to good yields with excellent regio- and stereoselectivity. A broad substrate scope with excellent functional group tolerance is observed. A plausible radical pathway is proposed, which involves copper-catalyzed ring-opening C–C bond cleavage of *O*-acyl oxime and insertion of sulfur dioxide. During the reaction process, cyanoalkyl radical and cyanoalkylsulfonyl radical are the key intermediates.

Declaration of competing interest

The authors declare that they have no financial and personal relationships with other people or organizations that can inappropriately influence the work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.11.009.

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