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Copper-Catalyzed Radical Aryl Migration Approach for the Preparation of Cyanoalkylsulfonylated Oxindoles/Cyanoalkyl Amides

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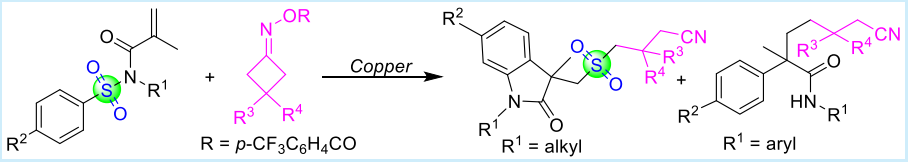
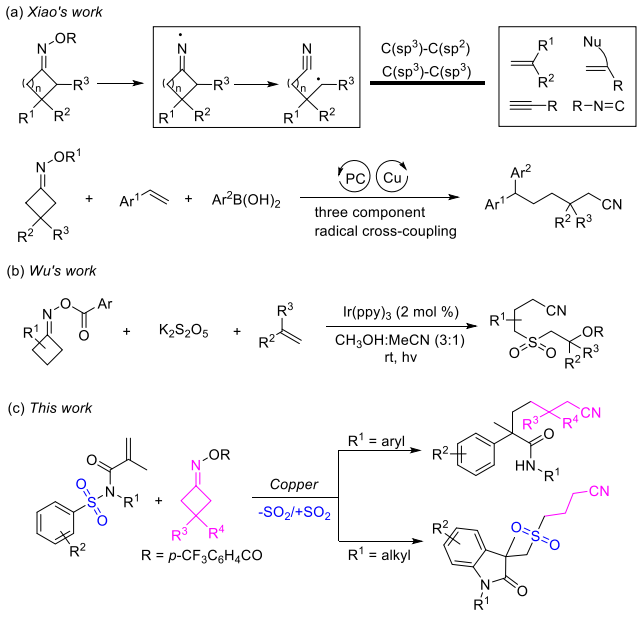


ABSTRACT: A copper-catalyzed radical cross-coupling of oxime esters and activated alkenes is accomplished for the synthesis of cyanoalkylsulfonylated oxindoles and cyanoalkyl amides via an aryl migration strategy. Specifically, the subsequent mechanism research indicates that the unique desulfonylation and sulfone addition processes were involved in the transformation. This transformation is identified as having good functional group applicability with two different quaternary stereocenter in a regioselective manner, which is controlled by the substituent group of the nitrogen.

As a versatile building blocks, cyanoalkyl is a synthetically versatile intermediate in organic synthesis and exists frequently in pharmaceutical molecules and natural products.[1] Moreover, cyanoalkyl as an active group can substantially transform into some other functional groups. Therefore, considerable attention to the incorporation of cyanoalkyl group has been noted.[2] Over the past few years, a range of elegant works have been established.[3] Among such available methodologies, C−C bond cleavage of cyclobutanone oxime esters via an iminyl radical intermediate is one of the most effective transformations.[4,5] Earlier reports for iminyl radical intermediate were disclosed by Zard and co-workers.[6] Recently, visible-light photocatalysis iminyl radical-mediated C−C bond cleavage to construct cyanoalkyl derivatives has been achieved by Xiao[7] and other groups.[8] In 2017, the group of Xiao reported a visible-light-driven iridium-catalyzed radical addition cascade of oxime esters, which involved an iminyl radical-mediated C−C bond cleavage. Soon after, a copper-catalyzed multicomponent radical cross-coupling reaction of redox-active oxime was also achieved by the Xiao group (Scheme 1a).[9]

Sulfur-containing derivatives are widely used in the fields of pharmacy and organic chemistry synthesis.[10] Particularly, sulfones are widely prevalent in agrochemicals, pharmaceuticals, and bioactive natural products.[11] Thus, development of a convenient route for the synthesis of sulfone has aroused comprehensive attention from organic chemists.[12] Although sulfur dioxide as a readily available and inexpensive reagent could be used to introduce SO_2, specialized equipment and safety concerns restricted the practicability. Considering the

Scheme 1. Previous Studies of Oxime Esters and Alkene



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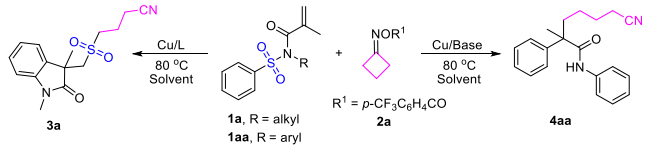
disadvantages of sulfur dioxide, some of the sulfur dioxide surrogates such as DABCO·$(SO_2)_2$[13] or inorganic sulfites[14] were exploited. Specifically, the combination of aryldiazonium tetrafluoroborates with DABCO·$(SO_2)_2$ has provided an efficient protocol to insert SO_2 in synthetic chemistry, and significant works have been achieved.[15] In this field, a range of crucial reports for sulfonylation of the C(sp^2)−H functionalization were disclosed by Wu[16] and other groups;[17] however, the insertion of sulfur dioxide into the C(sp^3)−H bond is still rare.[18] In 2019, Wu and co-workers reported photoredox-catalyzed sulfonylation reaction for building the alkylsulfony compound by using potassium metabisulfite as the source of sulfur dioxide (Scheme 1b).[19] Still, consideration of the inconvenience of the preparation of DABCO $(SO_2)_2$ and the redox property of salt metabisulfite, developing an easy and redox-neutral reaction system is a challenge.

Over the past decade, Nevado[20] and other groups developed radical addition to the double bond of the tosyl acrylamides system which was successfully implemented for oxindoles and amides constructions. In this transformation, a quaternary stereocenter was constructed via an intramolecular 1,4-aryl migration/5-*ipso* cyclization and desulfonylation. Encouraged by these elegant works, herein, we reported an efficient copper-catalyzed radical ring-opening process of cycloketone oximes with activated alkenes to prepare various oxindoles or amides under thermal reaction conditions.

Building on the reports of iminyl radical generation from cycloketone oximes, activated alkenes **1a** with cycloketone oxime ethers **2a** were utilized as the model substrates to verify our prediction. The expected product **3a** was isolated in 40% yield in the presence of Cu(OTf)$_2$ and 2,2′-bipyridine under an argon atmosphere at 80 °C for 24 h in toluene (Table 1, entry 1). A brief screening of other commonly used solvents indicated that toluene still was the best choice (entries 2 and 3). Then, a series of ligands were investigated, in which 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline L_1 presented effectively (entries 4−6). To further improve the yield, other copper salts such as Cu(OAc)$_2$, CuSCN, and CuI were examined with inapparent improvement observed (entries 7−9). The control reaction indicated that the ligand could be beneficial to this reaction (entry 10). Thereafter, the optimized reaction conditions for the preparation of **4aa** were attempted by using activated alkenes **1aa** with cycloketone oxime ethers **2a** in MeCN under an argon atmosphere at 80 °C for 24 h. With the addition of CuI/phen, only a trace amount of desired product **4aa** was observed (entry 11). Pleasingly, with the addition of K_2CO_3, the desired amide could be increased to 43% (entry 12). A subsequent short survey on the base indicated that $NaHCO_3$ gave the highest yield (entries 13 and 14). Then, copper salts were further examined, which identified that $CuCl_2$ was the best one and afforded 68% yield (entries 15 and 16). Replacing $CuCl_2$/phen with Cu(phen)Cl_2 resulted in the final product **4aa** in 75% yield (entry 17). The control experiment indicated that copper is indispensable in this transformation (entry 19).

With the optimal reaction conditions established, the scope of activated alkenes **1** with cycloketone oxime ethers **2a** were first investigated on a 0.2 mmol scale. As shown in Scheme 2, this transformation proved to be well tolerated for various activated alkenes under reaction conditions A. For instance, a range of activated alkenes bearing different substituents on the aryl ring preformed smoothly with cycloketone oxime ethers **2a** to deliver the relevant products **3a**−**3o** in moderate to good

Table 1. Optimization of the Reactions Conditions[a]



entry	copper/L	base	solvent	yield[b] (%)
1	Cu(OTf)$_2$/bpy		toluene	**3a**/40
2	Cu(OTf)$_2$/bpy		MeCN	**3a**/30
3	Cu(OTf)$_2$/bpy		dioxane	**3a**/20
4	Cu(OTf)$_2$/dtbpy		toluene	**3a**/50
5	Cu(OTf)$_2$/phen		toluene	**3a**/60
6	Cu(OTf)$_2$/L_1		toluene	**3a**/68
7	Cu(OAc)$_2$/L_1		toluene	**3a**/45
8	CuSCN/L_1		toluene	**3a**/52
9	CuI/L_1		toluene	**3a**/44
10	Cu(OTf)$_2$		toluene	**3a**/50
11	CuI/phen		MeCN	**4aa**/trace
12	CuI/phen	K_2CO_3	MeCN	**4aa**/43
13	CuI/phen	Na_2CO_3	MeCN	**4aa**/44
14	CuI/Phen	$NaHCO_3$	MeCN	**4aa**/50
15	$CuBr_2$/Phen	$NaHCO_3$	MeCN	**4aa**/56
16	$CuCl_2$/phen	$NaHCO_3$	MeCN	**4aa**/68
17	Cu(phen)Cl_2	$NaHCO_3$	MeCN	**4aa**/75
18	$CuCl_2$	$NaHCO_3$	MeCN	**4aa**/60
19		$NaHCO_3$	MeCN	**4aa**/n. r.

[a]Reaction conditions A: **1a** (0.2 mmol), **2a** (0.4 mmol), copper catalyst (10 mol %), ligand (10 mol %), solvent (2 mL), Ar, 80 °C, 24 h. Reaction conditions B: **1aa** (0.2 mmol), **2a** (0.3 mmol), copper catalyst (10 mol %), ligand (10 mol %), base (2.5 equiv), MeCN (3 mL), Ar, 80 °C, 24 h. L_1 = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline. [b]Isolated yields.

yields though the *meta*-position substituted benzosulfonamide substrates resulted in a regioisomers reaction mixture (**3f**, **3l**, **3m**, **3o**). The introduction of a larger steric hindrance group on the *para* position was well tolerated and gave the desired product **3d** in 72% yield. Similarly, 2-naphthalene benzosulfonamide substrate **1q** was also efficiently transformed in this reaction. In addition, the substrates with strong electron-withdrawing groups (CF_3 or CN) also proceeded smoothly and delivered the corresponding products (**3j**, **3k**) in 53% and 41% yields, respectively. Multisubstituted allylamine **1n** was also applied with 50% yield obtained in this conversion. It was noteworthy that alkene with aromatic heterocyclic worked well and isolated oxindole **3p** in a satisfactory yield. The influence for the substituent of the N atom also was studied, resulting an excellent yield (**3r**). The structure of products **3i** and **3j** were also confirmed by X-ray crystal structure analysis (see the Supporting Information).

Then, the reaction pattern for the construction of amides was also investigated, and the results are summarized in Scheme 3. Both electron-rich and -deficient groups on the arylsulfonyl moiety were well tolerated under optimal reaction conditions B. Substitutions on the *ortho* position, such as Me, Cl, on the benzenesulfonyl group had no significant effect on the yields, giving the target products **4af**, **4am** in good yields. Sterically demanding *butyl* and 1-naphthalene groups were also accommodated, affording the cyanoalkyl derivative **4ad**, **4an** in moderate yields. Substrates bearing CF_3, OCF_3, CN, or NO_2 furnished the corresponding transformation into the desired amides **4ah**−**4aj**, **4al** in satisfactory yields. Notably, this

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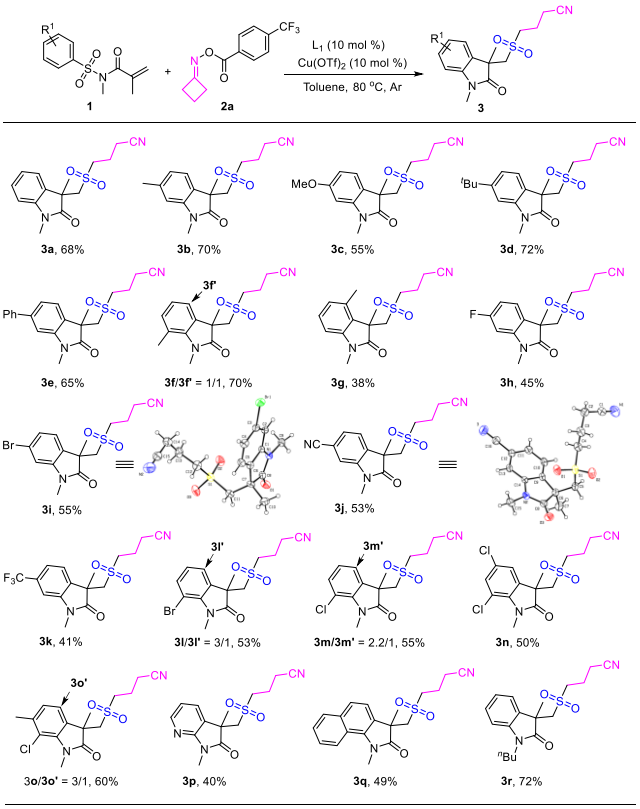
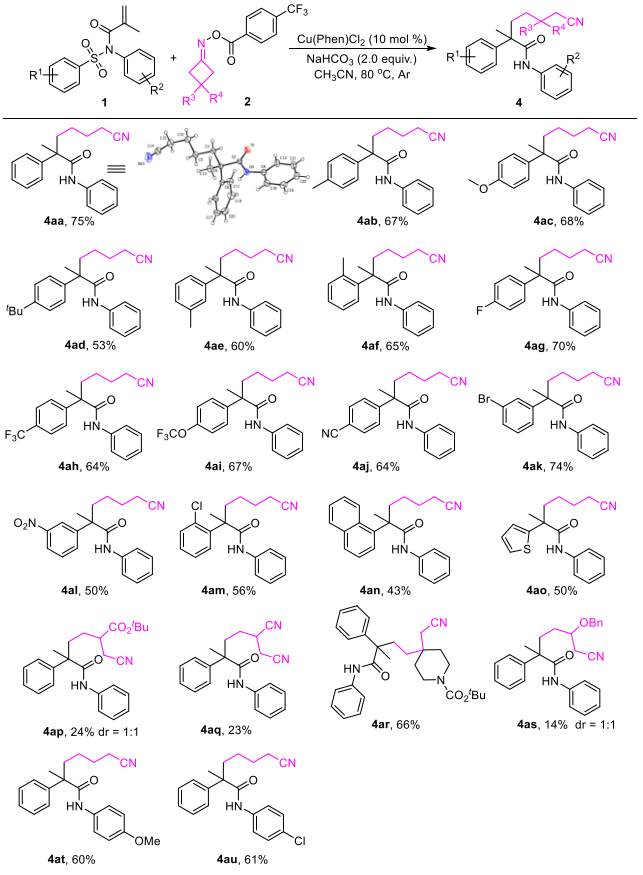
Scheme 2. Cu-Catalyzed Alkylnitriles/Sulfone Addition/Desulfonylation/Cyclization[a]



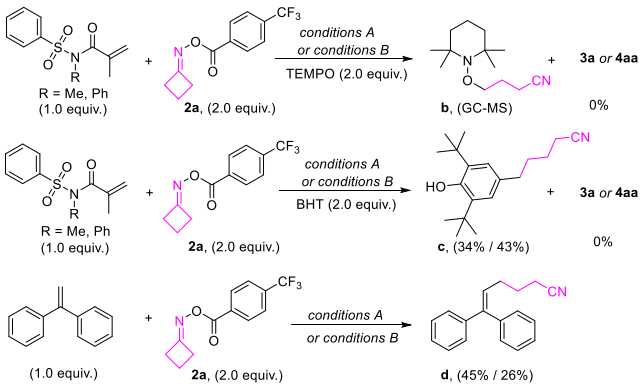
[a]Reaction conditions A: **1a** (0.2 mmol, 1 equiv), **2a** (0.4 mmol), $Cu(OTf)_2$ (10 mol %), L_1 (10 mol %), toluene (2 mL), Ar, 80 °C, 24 h. L_1 = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline. [b]Isolated yields.

Scheme 3. Scope of the Alkylnitriles Reaction[a]



[a]Reaction conditions B: **1** (0.2 mmol, 1 equiv), **2** (0.3 mmol), Cu(phen)Cl_2 (10 mol %), $NaHCO_3$ (2.5 equiv), MeCN (3 mL), Ar, 80 °C, 24 h. [b]Isolated yields.

Scheme 4. Control Experiments



reaction proceeded efficiently for the substrate including a heterocyclic group (2-thienyl) with good compatibility, which isolated the desired products in 50% yield. Next, the scope of the cyclobutanone derived O-acyl oximes **2** was also evaluated. The sterically more demanding substrate **1ar** was also applicable to this reaction. In contrast, the presence of electron withdrawing group at the 3-position of O-acyl oximes obviously decreased the yields (**4ap**, **4aq**). Finally, the analogous *N*-aryl-substituted substrates **1at** and **1au** furnished the expected amides in 60% and 61% yields, respectively. In addition, the structure of **4aa** was determined by X-ray crystal structure analysis. Also, the gram-scale experiment was conducted to explore the practical applicability of this method. As such, when this transformation was expanded to the 5 mmol scale, **4aa** could be acquired in 68% yield.

To gain some insights into the mechanism of these transformations, a series of control experiments were performed under the optimal reaction conditions (Scheme 4). Upon the addition of 2.0 equiv of radical quenchers TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), reactions of compound **1** were strongly inhibited, and the trapping product **b** could be detected by GC-MS. Moreover, in the presence of BHT (2,6-di-*tert*-butyl-4-methylphenol), the corresponding capture product **c** was isolated under reaction conditions A/B with 34%/ 43% yield. Finally, when stoichiometric amounts of 1,1-diphenylene were added, the relevant radical trapping product **d** was also isolated.

On basis of the control experiments and previous research,[20a,c,21] we proposed a plausible catalytic cycle for this transformation in Scheme 5. Initially, iminyl radical species **A** is generated via a single electron transfer (SET) and N−O bond cleavage of substrate **2a** under the copper catalyst. Then, cyclic iminyl radical **A** undergoes a *β*−C−C bond scission to afford cyanoalkyl radical **B**, which adds to a sulfonic, forming radical **C** (R^2 = alkyl group). Next, radical **B**/**C** interacts with the activated alkene **1** to give a new radical intermediate **D**. Further, an *ipso*-cyclization on the sulfonyl aromatic ring took place and delivered intermediate **E**, which underwent rapid

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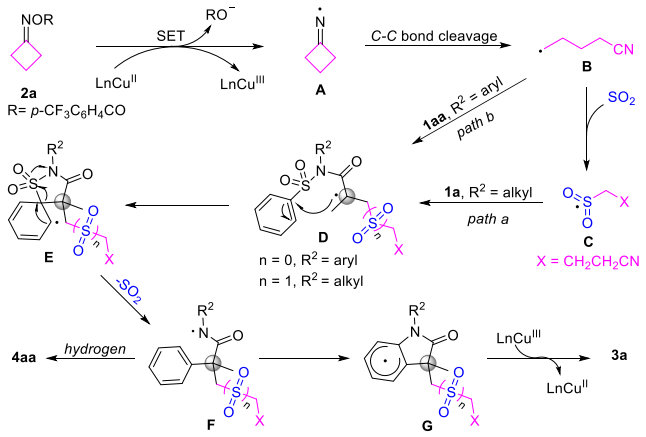
Scheme 5. Plausible Catalytic Cycles



desulfonylation, delivering a new C(sp^2)−C(sp^3) bond to produce a key amidyl radical **F**. Finally, amidyl radical **F** captures a hydrogen to offer product **4aa** (R^2 = aryl group). Differently, when the substituent R^2 on the N atom is an alkyl group, amidyl radical **F** could undergo subsequent cyclization to give the aryl radical **G**, which could go through an SET process and β-H elimination to acquire the target product **3a**. It is worth noting that generation of a small number of product **3a′**, which has no SO_2 added in the product **3a**, provides the initial sulfur dioxide in this transformation.

In conclusion, we have established a multicomponent reaction of cycloketone oximes, sulfur dioxide, and activated alkenes in the presence of copper catalyst. The transformation affords cyanoalkylsulfonylated oxindoles and cyanoalkyl amides, constructing a quaternary stereocenter with the manner of regioselectivity. In this reaction, in situ desulfonylation inserts sulfur dioxide, avoiding the addition of extra sulfur dioxide. Further, this method exhibits good compatibility with a broad range of activated alkenes, affording the desired products in moderate to good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03973.

Experimental procedures, compound characterization, and NMR spectra (PDF)

Accession Codes

CCDC 2047428−2047430 contain 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 data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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