ChemPubSoc Europe

DOI: 10.1002/cctc.201901695

CHEMCATCHEM Communications

Copper-Catalyzed Radical Cross-Coupling of Oxime Esters and Sulfinates for Synthesis of Cyanoalkylated Sulfones

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Sulfones and alkylnitriles play a significant role in both organic and medicinal chemistry, as versatile synthetic building blocks and privileged pharmacophores in many natural products and bioactive compounds. Herein, a room-temperature, copper-catalyzed radical cross-coupling of redox-active cycloketone oxime esters and sulfinate salts is described for the first time. Key to the success of this process involves catalytic generation of a cyclic iminyl radical and ensuing ring-opening C–C bond cleavage. The resultant cyanoalkyl radical is then engaged in cross-coupling with nucleophilic sulfinate to form cyanoalkylated sulfones.

Sulfones are a valuable class of pharmaceutically relevant motifs due to their wide profile of biological activities,[1] such as bicalutamide (**A**, treatment of prostate cancer)[2] and mesotrione (**B**, herbicide)[3] (Figure 1). Moreover, the sulfonyl groups have also been considered as chemical chameleons with versatile synthetic applications in organic chemistry.[4] Not surprisingly, a large number of preparative methods have been developed for the construction of structurally diverse sulfones.[5] The vast majority of the classical methods falls into four categories, including oxidation of sulfides/sulfoxides, aromatic sulfonylation, alkylation/arylation of sulfinates, and radical addition to alkenes/alkynes. Recently, sulfur dioxide-based multicomponent reaction[6] as well as metal-catalyzed coupling of sulfinates and sulfonyl halides have also emerged as intriguing alternatives to the traditional processes. Despite some impressive advances achieved in transition-metal-catalyzed cross-coupling of sulfinates as nucleophiles,[7] however, the substrate scope of electrophilic coupling partners is still quite limited and harsh conditions (e.g., elevated temperature) are typically required. Due to the readily availability of diverse radical precursors, transition-metal-catalyzed radical cross-coupling (RCC) has recently been established as a promising and enabling tool for assembly of a wide variety of C–C and C-heteroatom bonds under mild conditions.[8]

Owing to their distinct electronic properties and structural features, alkylnitriles also play an important role in many fields of applications. A large number of biologically active natural products (e.g., **C** and **D**) and pharmaceuticals contain such structural motifs (e.g., **F**, piritramide, treatment of postoperative pain) (Figure 1).[9] The nitrile group also serves as versatile synthetic building block in organic chemistry, because it can be easily transformed into many other important functional groups through routine manipulation.[10] Numerous approaches toward their synthesis have been developed. In particular, the exploration of efficient methods for synthesis of nitriles without use of metal- or metalloid-bound cyanide sources have been a subject of increasing interest.[11] Considering the importance of both sulfone and alkylnitrile groups, it would be highly desirable to develop new synthetic methods to construct novel molecules that contain such both structural motifs. We surmised that incorporation the features of both cyanoalkyl and sulfonyl motifs into a single scaffold would probably lead to a new class of compounds, and such molecular hybridization[12] would also be highly desirable for exploring new biologically relevant chemical space.[13]

Drawing the inspiration from the pioneering works of Forrester[14] and Zard[15] on the chemistry of iminyl radicals, we

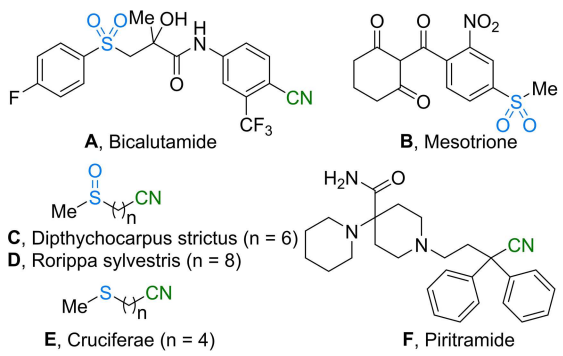

Figure 1. Examples of compounds containing sulfone and alkylnitrile moieties.

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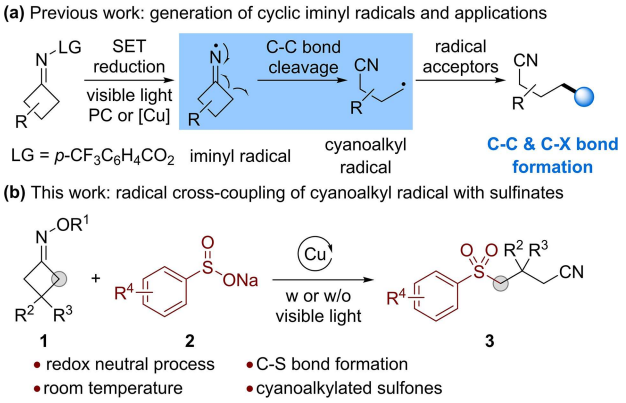
Supporting information for this article is available on the WWW under https://doi.org/10.1002/cctc.201901695

This manuscript is part of the Special Issue on New Concepts in Homogeneous Catalysis.

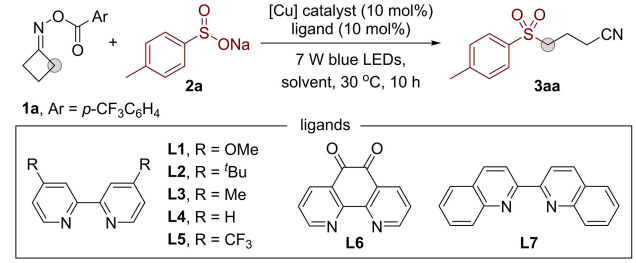


Scheme 1. Generation of iminyl radicals from cycloketone oxime esters by SET-reduction strategy and application to C–C bond cleavage/functionalization.

have recently developed a visible light-driven SET-reduction strategy, which enables facile conversion of cycloketone oxime esters to iminyl radicals, and subsequent ring-opening C–C bond cleavage to give cyanoalkyl radicals.[16] With the suitable radical acceptors, a range of C–C bond-forming radical reactions were developed, providing access to diversely functionalized nitriles (Scheme 1a). Many other research groups have also been involved in this active area, and significantly expanded the coupling partners, allowing installation of diverse functionalities at the sp^3-hybridized carbon.[17–21] Despite these impressive advances, however, the radical cross-coupling of readily available nucleophilic sulfinates with cycloketone oxime esters is still unexplored.[16f,21] Thus, the implementation of this protocol would provide access potentially useful compounds that contain both sulfone and alkylnitrile moieties (Scheme 1b).

Building on our recent work on visible light-driven, copper-catalyzed cross-coupling of oxime esters,[16d] we initially examined the feasibility of the model reaction of cyclobutanone oxime ester **1a** and sodium sulfinate **2a** under copper catalysis and visible light irradiation (Table 1).[22] To our delight, using Cu $(OAc)_2$ as catalyst and 4,–4′-dimethoxy-2,2′-bipyridine (**L1**) as ligand in DMF under visible light irradiation, the reaction indeed worked smoothly, giving the cross-coupled product **3aa** in 65% yield (entry 1). A brief examination of commonly used copper catalysts revealed that $Cu(CH_3CN)_4PF_6$ proved to be superior to others, leading to a 73% yield of **3aa** (entry 2). When using DMSO as the solvent, the yield could be further improved to 79% (entry 5). The redox properties of the copper complexes can be easily tuned by the structural variation of ligands.[23] Thus, with $Cu(CH_3CN)_4PF_6$ as catalyst and DMSO as reaction media, we further screened several other *N*,*N*-bidentate ligands (**L2**-**L7**) as ligands; the outcomes of entries 6–11 disclosed obvious ligand effects; and ligand **L1** was still the best candidate. When changing the ratio of two components **1a** and **2a** to 1.5:1, **3aa** was obtained in 84% yield (entry 12). Interestingly, the control experiments without copper catalyst, ligand **L1** or visible light irradiation confirmed that the current reaction should proceed through a copper catalytic process

Table 1. Exploring reaction conditions.[a]



Entry	[Cu] catalyst	Ligand	Solvent	Yield [%][b]
1	$Cu(OAc)_2$	**L1**	DMF	65
2	$Cu(CH_3CN)_4PF_6$	**L1**	DMF	73
3	CuI	**L1**	DMF	60
4	CuCN	**L1**	DMF	40
5	$Cu(CH_3CN)_4PF_6$	**L1**	DMSO	79
6	$Cu(CH_3CN)_4PF_6$	**L2**	DMSO	64
7	$Cu(CH_3CN)_4PF_6$	**L3**	DMSO	66
8	$Cu(CH_3CN)_4PF_6$	**L4**	DMSO	57
9	$Cu(CH_3CN)_4PF_6$	**L5**	DMSO	49
10	$Cu(CH_3CN)_4PF_6$	**L6**	DMSO	55
11	$Cu(CH_3CN)_4PF_6$	**L7**	DMSO	49
12[c]	$Cu(CH_3CN)_4PF_6$	**L1**	DMSO	84
13[c]	–	**L1**	DMSO	0
14[c]	$Cu(CH_3CN)_4PF_6$	–	DMSO	67
15[c,d]	$Cu(CH_3CN)_4PF_6$	**L1**	DMSO	83

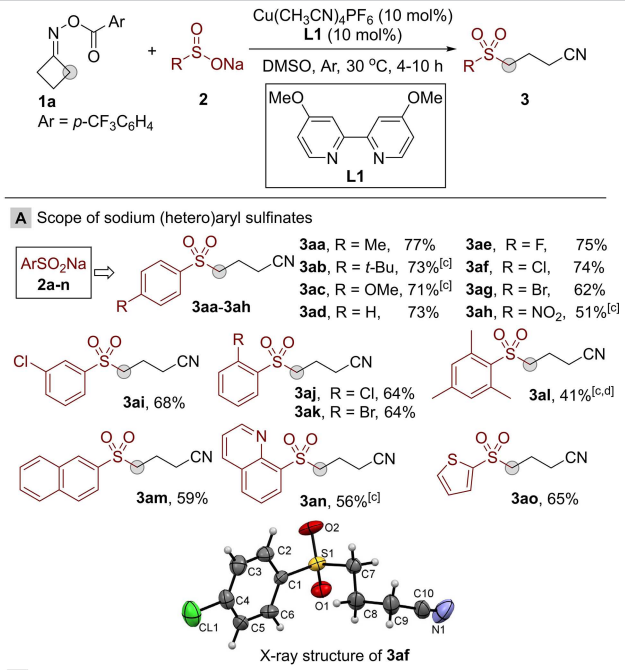
[a] Reaction Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), [Cu] catalyst (0.02 mmol, 10 mol%), solvent (2.0 mL), 7 W blue LEDs, Ar, 30 °C, 10 h, [b] Yields were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard, [c] Using **1a** (0.3 mmol) and **2a** (0.2 mmol), [d] Without visible light irradiation. DMF = *N*,*N*-dimethylformamide.

(entry 13), and visible light irradiation is not necessary (entry 15).[24] Accordingly, a catalytic system consisting of Cu $(CH_3CN)_4PF_6$, **L1**, and DMSO is the optimum system for this cross-coupling reaction, giving **3aa** in 83% yield (entry 15).

With the above standard conditions established, we first investigated the substrate scope by reacting **1a** with a representative set of sodium (hetero)aryl sulfinates **2** on a 0.4 mmol scale. As highlighted in Table 2A, the catalytic system proved to be tolerant of a wide range of differently substituted sodium sulfinates. For example, in the cases of sodium aryl sulfinates **2a–h** with either electron-donating (e.g., Me, ^{t}Bu, OMe) or electron-withdrawing (e.g., F, Cl, Br, NO_2) substituents at the *para*-position of the phenyl ring, all of the reactions proceeded smoothly to furnish the corresponding products **3aa–ah** with 51–77% yields. As shown in the reactions of **2i**–**2k**, variation of the substitution pattern and steric hindrance on the phenyl ring has no obvious influence on the reaction efficiency; while very sterically demanding **2l** led to moderate yield of **3al**. Furthermore, the reactions of the fused aromatic and heteroaromatic group substituted sulfinates **2m** and **2n** as well as simple heteroarene substituted substrate **2o** also participated in the cross-coupling reaction very well, affording **3am-ao** in good yields. The structure of product **3af** was also ambiguously determined by X-ray crystallographic analysis, confirming the C–S bond formation in the reaction.[25]

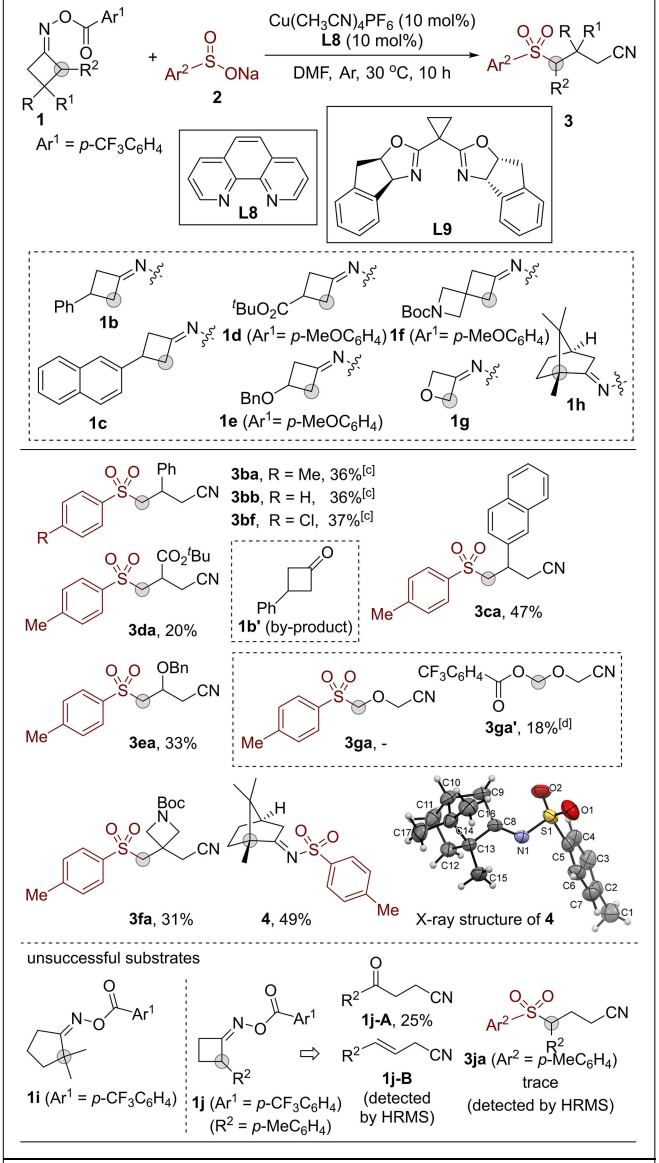
Notably, the current catalytic system could also be successfully extended to sodium alkyl sulfinates (Table 2B). For

Table 2. Scope with respect to sodium sulfinates.[a,b]



[a] **1a** (0.6 mmol), **2** (0.4 mmol), $Cu(CH_3CN)_4PF_6$ (0.04 mmol, 10 mol%), **L1** (0.04 mmol, 10 mol%), DMSO (4.0 mL), Ar, 30 °C, 4–10 h, [b] Yield of isolated product after flash chromatograph, [c] **1a**/**2** = 1:2. [d] 0.2 mmol scale, [e] With **L8** shown in Table 3 as ligand in DMF.

Table 3. Scope with respect to cycloketone oxime esters.[a,b]



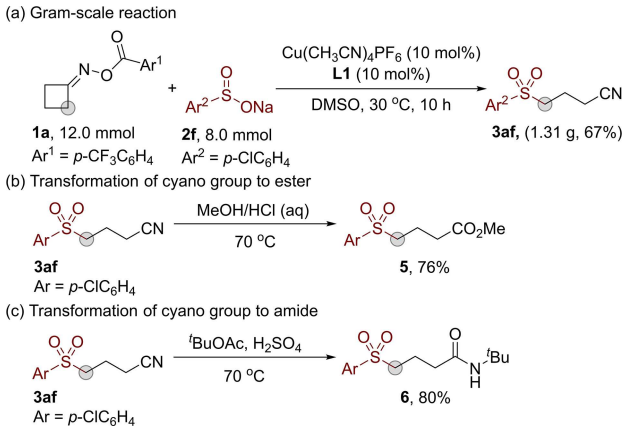
[a] **1** (0.4 mmol), **2** (0.8 mmol), $Cu(CH_3CN)_4PF_6$ (0.04 mmol, 10 mol%), **L8** (0.04 mmol, 10 mol%), DMF (4.0 mL), Ar, 30 °C, 10 h, [b] Yield of isolated product after flash chromatograph, [c] 0.2 mmol scale, [d] Purified by preparative HPLC.

instance, sodium benzyl sulfinate **2p** reacted well with O-acyl oxime **1a**, giving product **3ap** in 60% yield. Sodium methanesulfinate **2q** and sodium ethanesulfinate **2r** were also coupled well with O-acyl oxime **1b** to give **3bq** and **3br** in fair yields, when using **L8** as ligand in DMF. However, under the current conditions, sodium trifluoromethyl sulfinate proved to be not suitable for the reaction.

Next, we turned our attention to evaluation of the generality of the cross-coupling reaction by using a range of cycloketone oxime esters **1b–g** (Table 3). Under the standard conditions, a significant amount of side-product, the original cycloketone precursors, such as **1b′** were typically formed together with the desired products. Upon minor modification of the conditions, we found that a combination of $Cu(CH_3CN)_4PF_6$ and 1,10-phenanthroline, and a 1:2 ratio of substrates **1** to **2** could lead to much cleaner reaction. Substrate **1b** reacted well with sodium sulfinates **2a**, **2b** and **2f**, giving the corresponding products with moderate yields. A range of monosubstituted substrates with 2-naphthyl, ester, and benzyloxy groups at the 3-position also proceed to be suitable for the reaction, giving the cross-coupled products **3ca**, **3da** and **3ea** in 20–47% yields. Substrate **1f** with a nitrogen heterocycle was well tolerated to form the desired product **3fa**. Surprisingly, in the case of oxetan-3-one derived oxime ester **1g**, we did not detect any expected product **3ga**; instead, the side-product **3ga′** was isolated in 18% yield, which should result from the cross-coupling between cyanoalkyl radical and carboxylate anion. In case of camphor-derived oxime ester **1h**, we did not detect any amount of the expected ring-opening/cross-coupling product; instead, the product (–)-camphorsulfonylimine **4** resulting from the N–S bond forming reaction was isolated as the sole product.[25,26] As for the reaction of the five-membered cyclic ketone-derived oxime ester **1i** and **2a**, despite complete consumption of **1i**, the reaction only gave rise to complex mixture and no desired product was detected under standard conditions. It was found that the reaction of **1j** of **2a** resulted in only trace amount of desired product **3ja**. Our preliminary

efforts to achieve asymmetric version of the reaction of **1j** by using chiral bisoxazoline **L9** met failure either, resulting a trace amount of **3ja** together with side products **1j-A** and **1j-B**.[22]

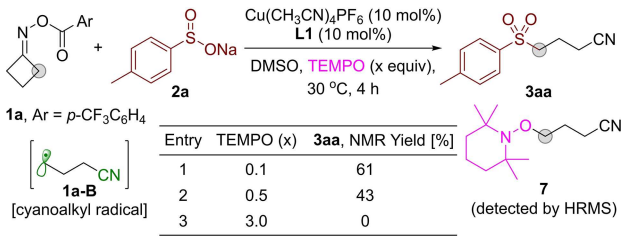
To further demonstrate the practicality of the protocol, a gram-scale reaction of **1a** and **2f** was also evaluated under the standard conditions (Scheme 2a). The reaction proceeded well



Scheme 2. Synthetic applications.

to give the desired product **3af** in 67% yield. With the nitrile group as a synthetically versatile handle, several diversifications of the thus-obtained cyanoalkylated sulfone **3af** were performed. For instance, **3af** could undergo methanolysis to give methyl ester **5** in 76% yield (Scheme 2b).[27] Moreover, product **3af** could be easily transformed into *N*-tert-butylated acetamide **6** in 80% yield through a modified Ritter reaction (Scheme 2c).[16d]

In order to gain some insight into the mechanism, we first carried out several control experiments with model substrates **1a** and **2a** by addition of variable amounts of radical scavenger, TEMPO (Scheme 3). It was found that the addition of TEMPO



Entry	TEMPO (x)	**3aa**, NMR Yield [%]
1	0.1	61
2	0.5	43
3	3.0	0

Scheme 3. Radical trapping experiments with TEMPO.

has substantial effect on the reaction; the formation of desired product **3aa** was entirely inhibited in the presence of 3.0 equivalents of TEMPO. The ESI-HRMS analysis of these reaction mixtures suggested formation of cyanoalkyl radical trapping adduct **7**. These outcomes suggested the radical nature of this process and involvement of cyanoalkyl radical **1a-B**.

To confirm the redox states of the copper catalyst that might be engaged in the reaction, we then used the EPR technique to explore the possible redox process between Cu $(CH_3CN)_4PF_6$ and substrates **1a** and **2a** in the presence or without ligand **L1** (Figure 2). As shown in Figure 2a and 2b, the

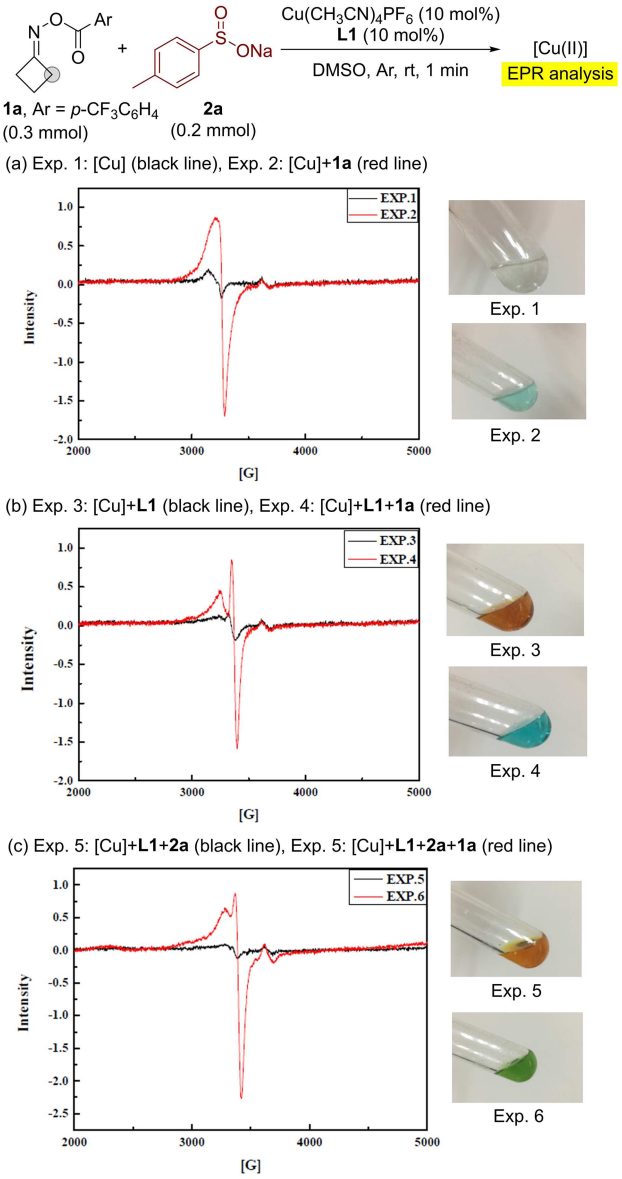
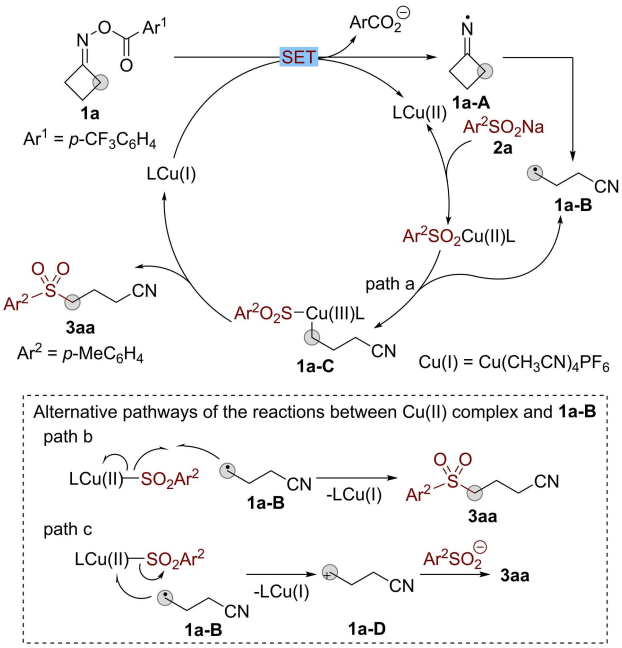


Figure 2. EPR spectra (X brand, 9.8 GHz, rt). [Cu] = $Cu(CH_3CN)_4PF_6$. Exp. 1: Cu $(CH_3CN)_4PF_6$ (0.02 mmol), DMSO (2.0 mL); Exp. 2: $Cu(CH_3CN)_4PF_6$ (0.02 mmol), **1a** (0.3 mmol), DMSO (2.0 mL); Exp. 3: $Cu(CH_3CN)_4PF_6$ (0.02 mmol), **L1** (0.02 mmol), DMSO (2.0 mL); Exp. 4: $Cu(CH_3CN)_4PF_6$ (0.02 mmol), **L1** (0.02 mmol),**1a** (0.3 mmol), DMSO (2.0 mL).

addition of substrate **1a** to the solutions of $Cu(CH_3CN)_4PF_6$ and $Cu(CH_3CN)_4PF_6$/**L1** in DMSO instantly resulted in obvious Cu^{II} signals, which are in agreement with the literature.[28] In sharp contrast, no characteristic signal was observed in the solution of $Cu(CH_3CN)_4PF_6$/**L1**/**2a**; and further addition of **1a** to such solution led to appearance of Cu^{II} signals (Figure 2c). Taken together, these results suggested that an SET process should



Scheme 4. Proposed mechanism.

occur between **1a** and Cu^{I} complex, thus enabling generation of the corresponding iminyl radical by N–O bond fragmentation.

On the basis of the above experimental results, a plausible reaction mechanism involving a $Cu^{I}/Cu^{II}/Cu^{III}$-based catalytic cycle was then proposed (Scheme 4). First, a SET reduction of oxime ester **1a** by LCu^{I} complex occurred, followed by fragmentation to afford cyclic iminyl radical **1a-A** and oxidized [$Cu^{(II)}$] complex. Next, cyclic iminyl radical **1a-A** undergoes regioselective ring-opening C–C bond cleavage to form cyanoalkyl radical **1a-B**. Meanwhile, a transmetalation event between the originally formed $LCu^{(I)}$ complex and nucleophilic sodium sulfinate **2a** occurred to give $LCu^{(II)}SO_2Ar^2$ species. At this point, cyanoalkyl radical **1a-B** was intercepted by $LCu^{II}SO_2Ar^2$ species to furnish the high-valent $Cu^{(III)}$ complex **1a-C**. Ultimately, a reductive elimination of **1a-C** complex resulted in the cross-coupled product **3aa** with regeneration of [$Cu^{(I)}$] catalyst. At the current stage, we could not rule out the following two alternative pathways. It should be noted that the trap of the cyanoalkyl radical **1a-B** could also proceed through two other pathways: (1) the out-sphere direct ligand-transfer (path b) and (2) SET-oxidation of the cyanoalkyl radical **1a-B** by the Cu(II) complex to a carbon cation that can be trapped by the nucleophilic sulfinate anion (path c).[29] Remarkably, the reaction is a redox-neutral process and does not require any external oxidant.

In conclusion, we have developed a room-temperature, copper-catalyzed radical cross-coupling of redox-active cyclo-ketone oxime esters and sulfinate salts for the first time. This protocol features broad substrate scope, good functional group tolerance, and mild reaction conditions, providing practical access to structurally diverse and potentially useful cyanoalkylated sulfones.[30] Current interest in our laboratory is toward extension of this protocol to other nucleophiles.

Acknowledgements

We are grateful to the NNSFC (91856119,21971081, 21622201, 21820102003, and 21772053), the Science and Technology Department of Hubei Province (2016CFA050 and 2017AHB047), and the Program of Introducing Talents of Discipline to Universities of China (111 Program, B17019) for the support of this research.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: copper · cross-coupling · nitrogen radicals · oxime esters · sulfones

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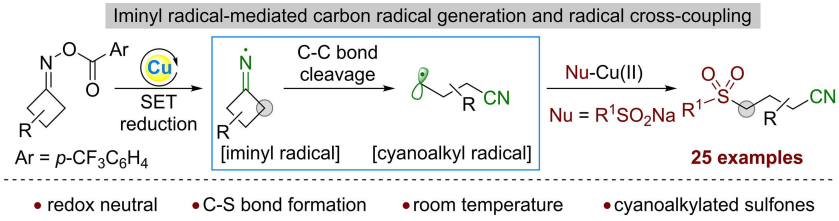
Manuscript received: September 8, 2019
Revised manuscript received: September 30, 2019
Accepted manuscript online: September 30, 2019
Version of record online: ■■, ■■■

COMMUNICATIONS



Cu-catalyzed radical reactions: Herein, a room temperature, copper-catalyzed radical cross-coupling of redox-active cycloketone oxime esters and sulfinate salts is described for the first time. Key to the success of this process involves catalytic generation of a cyclic iminyl radical and ensuing ring-opening C–C bond cleavage. The resultant cyanoalkyl radical is then engaged in cross-coupling with nucleophilic sulfinate to form cyanoalkylated sulfones.

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