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Copper-Catalyzed Oxidative Coupling of AIBN and Ketone-Derived Enoxysilanes to γ-Ketonitriles

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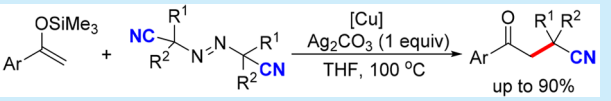
Supporting Information

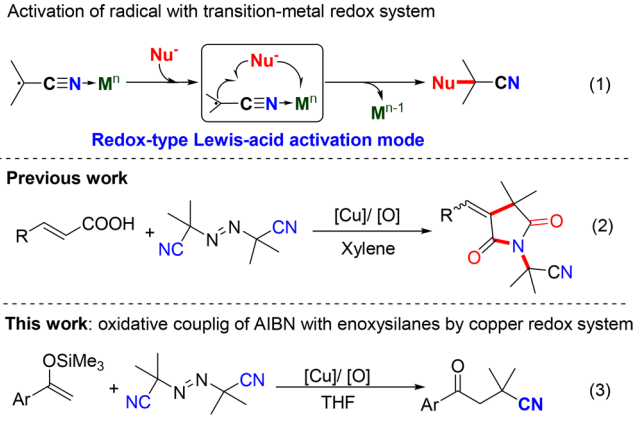
ABSTRACT: A new and efficient oxidative coupling reaction between enoxysilane and alkylnitrile radicals derived from readily available AIBN and its analogues has been developed by using redox-active metal as a catalyst in which the redox-active copper is used for enhancing the electrophilicity of a free radical via coordination and bringing the radical and nucleophilic enol ether closer to facilitate the single-electron transfer. The present catalytic protocol afforded a variety of γ-ketonitriles in good to excellent yields with good functional group tolerance.



Nitriles are prevalent functional groups in biologically active molecules and important synthetic intermediates for fine chemicals and materials.[1] In particular, ketonitriles are important building blocks for the synthesis of various pharmaceuticals and bioactive compounds, such as pyridinones,[2] α-hydroxy ketones,[3] and thiophenes.[4] The direct installation of a CN functional group into an enone via nucleophilic addition is one attractive route to γ-ketonitriles. However, a long-standing challenge that plagues these reactions is to find an active and less toxic CN source. In this context, a series of less toxic CN sources such as TMSCN and cyanohydrin have been explored and employed in these reactions.[5] However, a tedious procedure was generally required for preparation of these CN sources, which reduced the appeal of these processes and hindered large-scale applications. On the other hand, alkyl nitriles could also be utilized as nitrile sources through the direct C−H functionalization, which represents one of the most efficient and low-toxic strategies for the synthesis of substituted nitriles.[6] In this context, a radical involved process toward γ-ketonitriles from alkyl nitriles and simple alkenes has been developed by Wang and co-workers, in which the C−H bond of the alkyl nitriles was cleaved via a radical process in the presence of a superstoichiometric amount of strong oxidants.[7] However, this system suffered from lower yields, limited substrate scope. Therefore, it is desirable and challenging to explore simple and nontoxic nitrile sources as well as an efficient method to prepare γ-ketonitriles.

Azobis(isobutyronitrile) (AIBN) is a commercially available radical precursor and is one of the most widely used radical initiators in polymer chemistry and radical-mediated synthetic organic chemistry. In general, AIBN usually does not get involved as a reactant in radical reactions or polar reactions, although it might be used as a good "CN" source from the viewpoint of utility in organic synthesis.[8] This is largely due to the inherently lower nucleophilicity and electrophilicity of the isobutyronitrile radical derived from AIBN.[9] Recently, we developed an efficient strategy for directing and accelerating the single electron transfer between a free radical and a nucleophile via bridging them with a metal complex (Scheme 1, eq 1).[11] This strategy has been successfully applied to harness the reactivity of the isobutyronitrile radical derived from AIBN and has enabled a novel cascade reaction with AIBN and cinnamic acids (Scheme 1, eq 2). Mechanistic studies have been conducted and have disclosed that the energy of the SOMO of the isobutyronitrile radical was reduced via coordination of its nitrile group with the copper, enabling the radical species to be more electrophilic to be attacked by the MBH-enolate, furnishing an oxidative coupling reaction in the presence of oxidant. Naturally, we have been interested in determining whether this strategy is general and

Scheme 1. Background of the Method Development



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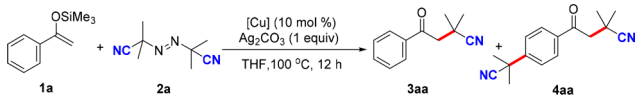
can be employed for reaction partners other than MBH-enolates. For example, we were intrigued by the possibility of synthesizing γ-ketonitriles via the treatment of AIBN with ketone-derived enoxysilanes through the above strategy. Herein, we report a novel copper-catalyzed oxidative coupling reaction between AIBN and enoxysilanes. The present reaction provides a new route to γ-ketonitriles with good to excellent yields from simple starting materials (Scheme 1, eq 3).

We initiated our studies by implementation of the reaction of trimethyl((1-phenylvinyl)oxy)silane (**1a**) with AIBN (**2a**) in the presence of a catalytic amount of CuCl and a stoichiometric amount of Ag_2CO_3. To our delight, the desired product **3aa** was obtained in 45% yield together with **4aa** was obtained as byproduct when the reaction was conducted at 100 °C in anisole (Table 1, entry 1). Solvent screening revealed

Table 1. Optimization of Reaction Conditions[a]



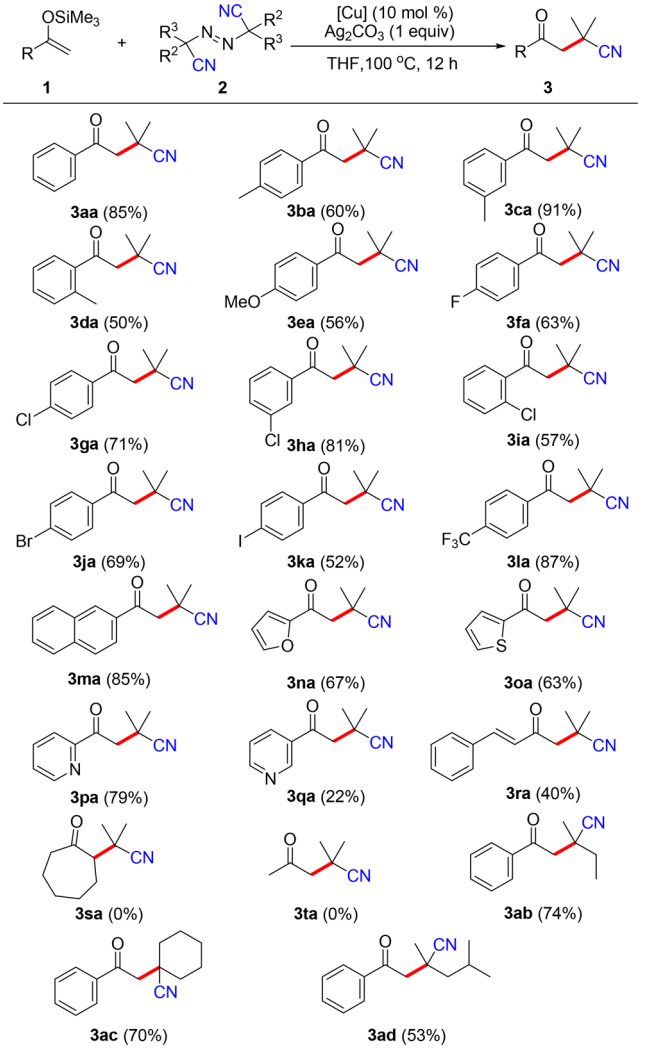
entry	[Cu]	solvent	temp (°C)	yield (%) 3aa	4aa
1	CuCl	anisole	100	45	28
2	CuCl	DCE	100	41	47
3	CuCl	xylene	100	35	32
4	CuCl	THF	100	60	20
5	CuBr	THF	100	66	24
6	CuCN	THF	100	61	25
7	$Cu(CH_3CN)_4PF_6$	THF	100	50	8
8	$Cu_3(PO_4)_2$	THF	100	52	30
9	$Cu(CF_3COCH_2COCF_3)_2$	THF	100	72	<5
10	**$Cu(CH_3COCHCO_2C_2H_5)_2$**	**THF**	**100**	**85**	<5
11[b]	$Cu(CH_3COCHCO_2C_2H_5)_2$	THF	100	77	<5
12[c]	$Cu(CH_3COCHCO_2C_2H_5)_2$	THF	100	69	<5
13[d]	$Cu(CH_3COCHCO_2C_2H_5)_2$	THF	100	44	<5
14[e]	$Cu(CH_3COCHCO_2C_2H_5)_2$	THF	100	84	<5
15	$Cu(CH_3COCHCO_2C_2H_5)_2$	THF	80	78	13
16	$Cu(CH_3COCHCO_2C_2H_5)_2$	THF	120	75	<5
17		THF	100	66	<5
18[f]	$Cu(CH_3COCHCO_2C_2H_5)_2$	THF	100	38	15
19[g]	$Cu(CH_3COCHCO_2C_2H_5)_2$	THF	100	74	<5

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), [Cu] (0.05 mmol, 10 mol %), Ag_2CO_3 (0.5 mmol), solvent (2.0 mL), 100 °C, 12 h, isolated yield. [b]**2a** (1.5 mmol). [c]**2a** (2.0 mmol). [d]100 °C, 6 h. [e]100 °C, 24 h. [f]Ag_2CO_3 (0 mmol), $Cu(CH_3COCHCO_2C_2H_5)_2$ (0.5 mmol). [g]Ag_2CO_3 (1.0 mmol).

that THF was the best choice for giving the desired product in 60% yield (Table 1, entries 1−4). Afterward, we began to optimize the reaction conditions by screening different copper catalysts. As shown in Table 1, both Cu(I) and Cu(II) can catalyze the present reaction, and $Cu(CH_3COCHCO_2C_2H_5)_2$ was found to be the most efficient catalyst, affording the desired product in 85% yield with excellent chemoselectivity (Table 1, entries 4−10). With $Cu(CH_3COCHCO_2C_2H_5)_2$ as the catalyst, other reaction parameters were screened to maximize the efficiency of this coupling reaction. This study led to the finding that increasing the amount of AIBN decreased the yield of the desired product (Table 1, entries 11 and 12). Further shortening or prolonging of the reaction time showed a negative effect on the yield (Table 1, entries 13 and 14). The yield diminished slightly when the temperature was changed from 100 to 80 °C or 120 °C (Table 1, entries 15 and 16). The desired product could be obtained in relatively lower yield when the reaction was carried out in the absence of copper catalyst under otherwise identical reaction conditions (Table 1, entry 17). Only 38% yield of the target product **3aa** was obtained when a stoichiometric amount of $Cu(CH_3COCHCO_2C_2H_5)_2$ was utilized in the absence of Ag_2CO_3 (Table 1, entry 18). Increasing the loading of Ag_2CO_3 to 2.0 equiv did not improve the yield of the desired product (Table 1, entry 19). Notably, no desired product **3aa** was observed in the absence of copper and silver salts. All together, these results strongly indicate that the combination of a suitable oxidant and copper source is critical for the present transformation.

To explore the synthetic utility of this process, we have investigated the generality of the present process. A series of enoxysilanes derived from different ketones were subjected to this process under the catalysis of $Cu(CH_3COCHCO_2C_2H_5)_2$. As shown in Scheme 2, substituted acetophenone-derived

Scheme 2. Substrate Scope of Enoxysilanes[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), $Cu(CH_3COCHCO_2C_2H_5)_2$ (10 mol %), Ag_2CO_3 (0.5 mmol), THF (2.0 mL), 100 °C, 12 h, isolated yield.

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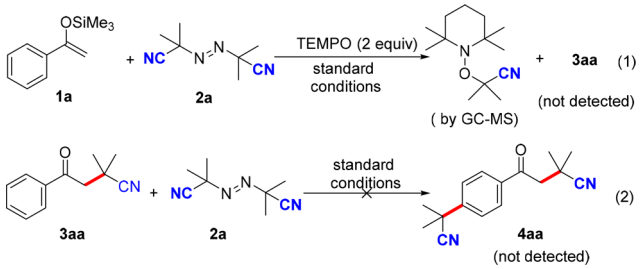
enoxysilanes, which bear substituted groups such as methyl, methoxyl, chloro, bromo, fluoro, iodine, and trifluoromethyl at the *para* or *meta* positions, all reacted smoothly to afford the desired corresponding products in good to excellent yields, except in the case of reaction with sterically hindered *ortho*-substituted substrates. These results indicate that there is no major electronic effect on the substitution pattern of the substrates. In addition, the reaction performed well with naphthyl-substituted enoxysilane to afford the desired product in 85% yield (**3ma**). Meanwhile, heteroaromatic ketone-derived enoxysilanes were also suitable for this coupling reaction. When 2-acetalfuran-, 2-acetylthiophene-, and 2-acetylpyridine-derived enoxysilanes were used as substrates, the corresponding γ-ketonitriles were obtained in good yields (**3na**−**pa**). However, only 22% yield was obtained when the 1-(pyridin-4-yl)ethan-1-one derived enoxysilane was subjected to the reaction conditions. In addition to the coupling reactions with aromatic ketone-derived enoxysilanes, we also examined the coupling reaction with enone-derived enoxysilane. Utilizing the optimized reaction conditions, benzalacetone-derived enoxysilane can be converted to the corresponding product in 40% yield (**3ra**). Unfortunately, cyclic ketone and simple aliphatic ketone derived enoxysilanes could not afford the desired products under the current reaction conditions. The lower activity observed here might be rationalized in terms of the stronger Si−O bond of the enoxysilanes derived from aliphatic ketones.[11] Further experiments demonstrated that other nitrile-containing radicals, derived from 2,2′-azobis(2-methylbutyronitrile) (**2b**), 1,1′-azobis(cyclohexane-1-carbonitrile) (**2c**), and 2,2′-azobis(2,4-dimethylvaleronitrile) (**2d**), were successfully incorporated into enoxysilane **1a** to afford the corresponding products (**3ab**−**ad**) in 53−74% yields.

To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 3). Radical trapping by

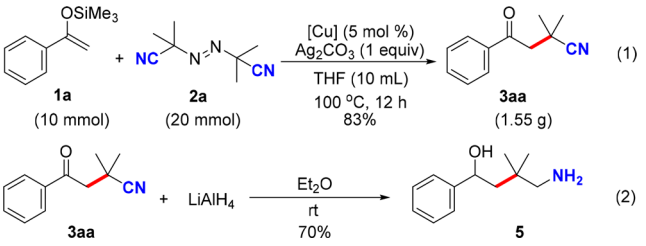
Scheme 3. Control Experiments



introducing TEMPO into the standard reaction was carried out, and the result shows that the reaction was completely inhibited. The radical-trapping product 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanenitrile was observed (Scheme 3, eq 1), which indicated that a free-radical process was indeed involved. Upon treatment of **3aa** with AIBN under the standard reaction conditions, no **4aa** was detected, and the **3aa** was fully recovered (Scheme 3, eq 2). This result suggests that the byproduct **4aa** is most likely produced from the noncatalytic background reaction of free-radical addition process between **1a** and **2a**.

To further demonstrate the synthetic utility, we tested the synthesis of γ-ketonitriles on gram scale. When 10 mmol of enoxysilane **1a** was reacted with 20 mmol of AIBN **2a** in the presence of 5 mol % of copper catalyst, the corresponding product **3aa** was obtained in 83% isolated (1.55 g, Scheme 4,

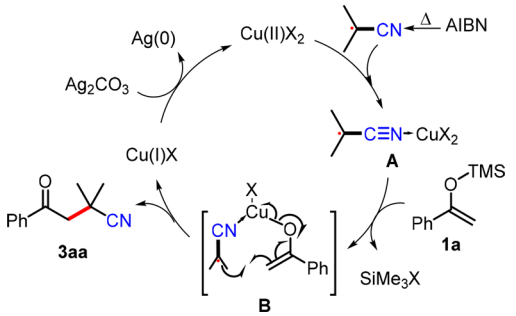
Scheme 4. Reaction Scale-up and Functional Group Transformation



eq 1). In addition, the product **3aa** could be easily transformed into amino alcohol (Scheme 4, eq 2) via treatment of the product **3aa** with $LiAlH_4$, which could find some applications in synthetic organic chemistry.

Based on the present experimental data and our precedent results,[10] a plausible reaction pathway for the present Cu-catalyzed oxidative cross-coupling reaction is proposed in Scheme 5. In this scenario, the active copper catalyst initially

Scheme 5. Plausible Reaction Mechanism



coordinates with the free isobutyronitrile radical, which was generated from AIBN on heating, to form intermediate **A**. The coordination of the nitrile group to Cu(II) makes the radical species more electrophilic to be attacked by the nucleophilic enoxysilane through the intermediate **B**, which is formed via transmetalation. The resulting Cu-bridge brings the radical and the enolate closer, which is beneficial to direct and accelerate the single-electron transfer between the radical and the enolate confined in the assembly to construct a new C−C bond, giving the desired product together with Cu(I). Finally, the Cu(I) species was oxidized to Cu(II) by Ag_2CO_3 to complete the catalytic cycle.

In summary, we have developed a novel and simple copper-catalyzed oxidative coupling reaction between AIBN and enoxysilanes. This method delivers a set of γ-ketonitriles with good functional-group compatibility. A free-radical process was involved in this method, in which the redox-active copper is used for enhancing the electrophilicity of free radical via coordination and bringing the radical and nucleophilic enol ether closer to facilitate the single electron transfer. This method provides a novel approach to C−C bond formation, which can potentially employ to a range of transition-metal-catalyzed radical involved oxidative coupling reactions. Further studies on expanding the scope of this copper-catalyzed radical activation strategy are in progress.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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