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Merging Photoredox and Copper Catalysis: Enantioselective Radical Cyanoalkylation of Styrenes

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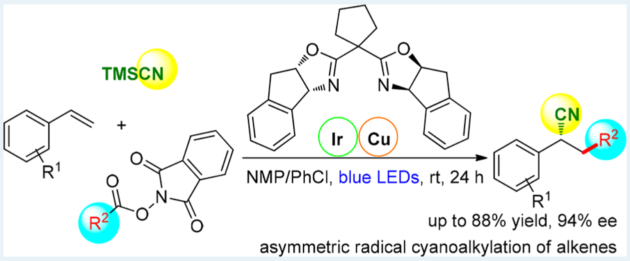
Supporting Information

ABSTRACT: A photoredox and copper catalyzed asymmetric cyanoalkylation reaction of alkenes has been developed, which uses alkyl *N*-hydroxyphthalimide esters as alkylation reagents. In this radical cyanoalkylation reaction, the photoredox induced alkyl radical adds to styrene, and the generated benzylic radical couples with a chiral Box/CuII cyanide complex to achieve the enantioselective cyanation. This reaction features mild conditions, operational simplicity, broad substrate scope, high yields, and high enantioselectivities, which represents an efficient method for the asymmetric radical difunctionalization of alkenes.



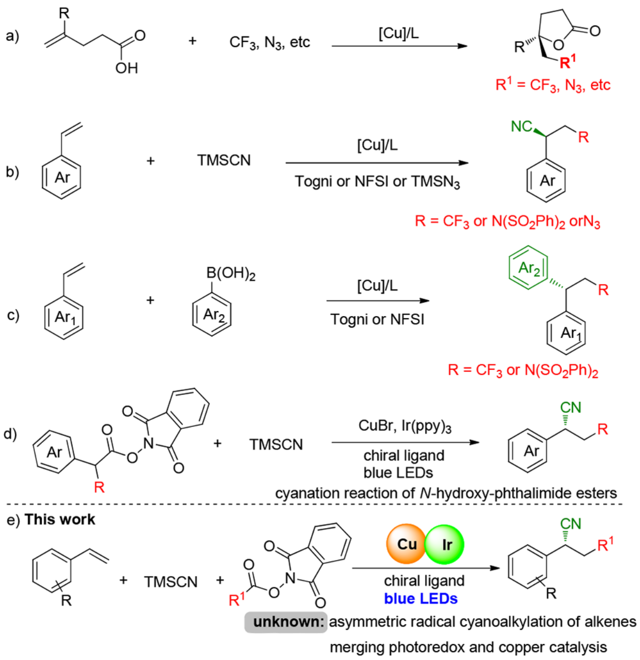
KEYWORDS: *asymmetric radical reaction, cyanoalkylation, photoredox, Cu catalysis, difunctionalization of alkene*

Carboxylic acids are the most common compounds in numerous biologically active natural products and drug molecules. Furthermore, they are inexpensive and abundant in nature, and also are among the most basic building blocks in synthetic organic chemistry.[1] In recent years, decarboxylation of carboxylic acids has exhibited obvious advantages for organic synthesis, such as inexpensive materials, CO_2 as the nontoxic byproduct, and so on. Importantly, radical decarboxylation of alkyl carboxylic acid, catalyzed by a visible light-induced photoredox catalyst, has witnessed a significant advancement.[2] Meanwhile, the alkyl *N*-hydroxyphthalimide esters (NHP esters) derived from alkyl carboxylic acids have been extensively developed as alkylating reagents in alkylation cross-coupling reactions through the elimination of CO_2.[3]

Difunctionalization of alkenes is a powerful and efficient tool for organic synthesis, which can introduce two groups into an alkene in one step via the addition of a C−C double bond, enhancing the molecular complexity. Several functional groups, such as cyano, trifluoromethyl, azido, amino, thiocyano, and so on, have been introduced into molecules via these difunctionalization reactions.[4] However, the difunctionalization of alkenes containing an alkylation process still includes great challenges,[5] as the previously reported related alkylation reactions require harsh conditions, strong nucleophiles, or explosive substrates.

In recent decades, asymmetric radical reactions have tremendously enriched the research content of asymmetric chemistry by trapping alky radicals with reactive chiral transitional metal species.[6] Compared to these previously developed direct coupling reactions, the Buchwald group realized an asymmetric cascade reaction by using unsaturated carboxylic acids with Togni's reagent and other reagents (Scheme 1a).[7] In 2016, the Liu group reported work realizing enantioselective cyanation of benzylic C−H bonds via a

Scheme 1. Asymmetric Radical Difunctionalization of Alkenes



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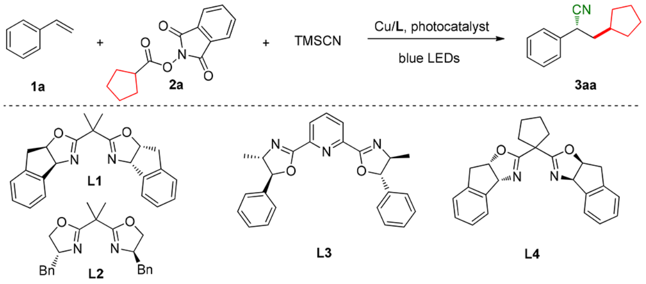
copper-catalyzed radical relay.[8] Based on this report, they proposed and developed a series of asymmetric radical difunctionalizations of alkenes (Scheme 1b).[9] Besides TMSCN, boronic acid was also developed as a nucleophilic reagent adding to alkenes in asymmetric radical reactions (Scheme 1c).[10]

Based on the photocatalyst's activity, merging photoredox and metal catalysis could realize some difficult transformations under mild reaction conditions.[11] In 2017, the Liu group developed an enantioselective decarboxylative cyanation reaction of *N*-hydroxy-phthalimide esters by merging photoredox catalysis with copper catalysis, which provides a new access to chiral alkyl nitriles (Scheme 1).[11c] Recently, the Macmillan, and Wang groups have independently developed the decarboxylative cross-coupling of carboxylic acids with electrophiles or nucleophiles.[12] Notably, a radical generated via photoredox catalysis and an aryl-metal(II) species are the two key intermediates in these reactions. According to this strategy, Fu and Macmillan realized an asymmetric decarboxylative arylation reaction by using a photocatalyst, nickel catalyst, and chiral ligand.[12c] Inspired by these elegant reports and our previous work on asymmetric radical reactions,[13] we proposed a photoredox and copper-catalyzed asymmetric cyanoalkylation reaction of alkenes by using alkyl *N*-hydroxyphthalimide esters as alkylation reagents (Scheme 1e). To the best of our knowledge, an asymmetric cyanoalkylation reaction of alkenes has never been developed. Furthermore, this work represents the first example of photoredox and copper-catalyzed radical difunctionalization of alkenes.

At the outset, we selected styrene **1a**, cyclopentyl NHP ester **2a**, and TMSCN as model substrates for the optimization of racemic reaction conditions (for details, see Supporting Information (SI)). We found that the reaction of **1a**, **2a**, and TMSCN catalyzed by the combination of Ir(ppy)$_3$/CuBr/2,6-bis(4,5-dihydrooxazol-2-yl)pyridine (**L7**) with NMP as solvent, under blue LEDs at room temperature, afforded (±)-**3aa** in 58% yield. Then, we carried out the study of condition optimization for the asymmetric radical reaction. First, we selected Cu(CH$_3$CN)$_4$PF$_6$ as a metal catalyst, **L1** as a chiral ligand, and Ir(ppy)$_3$ as a photocatalyst for this asymmetric difunctionalization reaction. To our delight, the corresponding product **3aa** can be obtained with a 30% yield and −59% ee at room temperature, under 5 W blue LEDs after 24 h (entry 1, Table 1). Next, other chiral ligands were tried in this reaction to improve the reaction efficiency. We found that the chiral ligand **L4** could catalyze the reaction smoothly, affording the desired product (*R*)-**3aa**[14] with obviously increased enantioselectivity (70% ee, entry 4). With **L4** as ligand and DCM as the solvent, different metal catalysts were then screened for this system, and the results of entries 5−8 indicated that CuBr exhibited good performance (39% yield and 79% ee, entry 5). To improve the yield and enantioselectivity, several regular solvents were then tried for this reaction (entries 13−18). The reactions with PhCl or THF as the solvent resulted in product **3aa** with excellent enantioselectivity, but with poor yields (entries 10 and 14). Prolonging the reaction time to 36 h has no effect on this yield (entry 15). To our delight, increasing the loading amount of **1a** to 4.0 equiv resulted in the corresponding product **3aa** with a 78% yield and 77% enantioselectivity (entry 16). To our surprise, mixed solvent had a favorable effect on this reaction, and the ee was further increased to 84% (entry 17). Finally, control experiments demonstrated that a photocatalyst, visible light, and a metal catalyst were all essential for this reaction (entries 18−20).

Table 1. Optimization of Reaction Conditions[a]

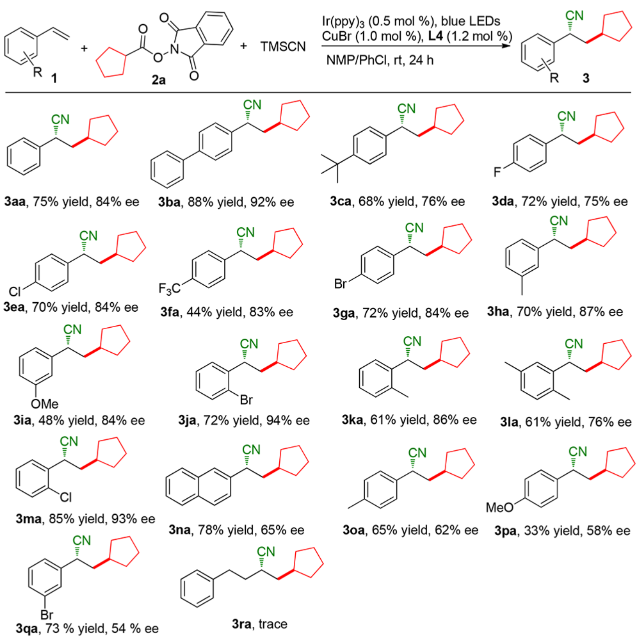


entry	1a (mmol)	catalyst	L	solvent	yield (%)[b]	ee (%)[c]
1	0.2	Cu(CH$_3$CN)$_4$PF$_6$	**L1**	DMF	30	−59
2	0.2	Cu(CH$_3$CN)$_4$PF$_6$	**L2**	DMF	37	57
3	0.2	Cu(CH$_3$CN)$_4$PF$_6$	**L3**	DMF	45	16
4	0.2	Cu(CH$_3$CN)$_4$PF$_6$	**L4**	DMF	44	70
5	0.2	CuBr	**L4**	DCM	34	79
6	0.2	CuCl	**L4**	DCM	31	75
7	0.2	CuCN	**L4**	DCM	27	76
8	0.2	CuOAc	**L4**	DCM	25	79
9	0.2	CuBr	**L4**	*m*-xylene	trace	–
10	0.2	CuBr	**L4**	PhCl	26	87
11	0.2	CuBr	**L4**	NMP	58	76
12	0.2	CuBr	**L4**	MeOH	trace	
13	0.2	CuBr	**L4**	DMSO	trace	
14	0.2	CuBr	**L4**	THF	41	84
15	0.2	CuBr	**L4**	THF	41	85[d]
16	0.8	CuBr	**L4**	NMP	78	77
17	0.8	CuBr	**L4**	NMP/PhCl	75	84[e]
18	0.8	–	–	NMP/PhCl	–	–[e]
19	0.8	CuBr	**L4**	NMP/PhCl	–	–[e,f]
20	0.8	CuBr	**L4**	NMP/PhCl	–	–[e,g]

[a] Reaction conditions: **1a**, **2a** (0.2 mmol), TMSCN (1.1 equiv), Ir(ppy)$_3$ (0.5 mol %), metal catalyst (1.0 mol %), ligand (1.2 mol %), solvent (1 mL), at room temperature, 5 W blue LEDs, 24 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 36 h. [e] NMP (0.4 mL) and PhCl (0.6 mL). [f] No photocatalyst. [g] In the dark.

With the optimized conditions in hand, we then explored the reactivity of various alkenes by reacting with cyclopentyl NHP ester **2a**, and the results were summarized in Scheme 2. First, we examined the styrene derivatives with substitution at the *para*-position on the aromatic ring. As depicted in Scheme 2, both electron-donating and -withdrawing groups were well tolerated in this system and afforded the desired product with good reaction outcomes (**3aa**−**3ga**). In particular, the substrate bearing *para*-phenyl gave an excellent yield and high enantioselectivity (**3ba**, 88% yield and 92% ee). Then, the styrene derivatives with the *meta*-substituted group on the phenyl moieties were applied to this reaction. To our delight, the reactions also proceeded very well to give the corresponding product (**3ha** and **3ia**) with moderate yields but good enantioselectivities (87% ee and 84% ee, respectively). Several styrenes with *ortho*-subsituted phenyl were tried in this reaction to investigate the effect of steric hindrance. As expected, these substrates **1j**−**1m** worked better in this system and resulted in good yields and excellent

Scheme 2. Substrate Scope of Different Alkenes[a,b,c]

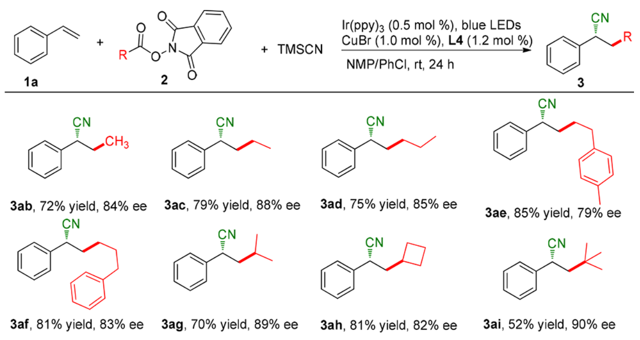


[a] Reaction conditions: **2a** (0.2 mmol), alkenes **1** (4.0 equiv), TMSCN (1.1 equiv), Ir(ppy)$_3$ (0.5 mol %), CuBr (1.0 mol %), **L4** (1.2 mol %), NMP (0.4 mL), and PhCl (0.6 mL), at room temperature, 5 W blue LEDs, for 24 h. [b] Isolated yields. [c] Enantioselectivity was determined by chiral HPLC.

enantioselectivities. Especially, in the case of *ortho*-bromostyrene **1j**, the highest enantioselectivity was obtained (**3ja**, 94% ee). Finally, one inactive alkene, but-3-en-1-ylbenzene **1r**, was tried in this reaction. Unfortunately, almost no desired product **3ra** was obtained.

Encouraged by the results from different alkenes with **2a**, we undertook another part of the substrate scope study of alkyl NHP esters by using styrene **1a** as the coupling partner, and the results are shown in Scheme 3. Primary alkyl NHP esters such as methyl, ethyl, and propyl worked very well in the reaction and resulted in the corresponding product **3ab**−**3ad** with good yields and high enantioselectivity (84−88% ee). Next, aryl ethyl and aryl propyl NHP ester were applied to this reaction, which also proceeded smoothly to afford **3ae** and **3af** with good yields and enantioselectivity. It should be mentioned that the reaction showed excellent regioselectivity compared to the previous methods.[8,15] We also explored whether secondary alkyl NHP esters could adapt to this reaction. It was noted that both isopropyl NHP ester **2g** and cyclobutyl NHP ester **2h** could be well tolerated, and the products **3ag** and **3ah** were obtained with excellent yields and enantioselectivities. Finally, the tertiary alkyl NHP ester was also found to be a suitable substrate for this asymmetric radical reaction, and the corresponding product **3ai** could be obtained with a 52% yield and 90% enantioselectivity.

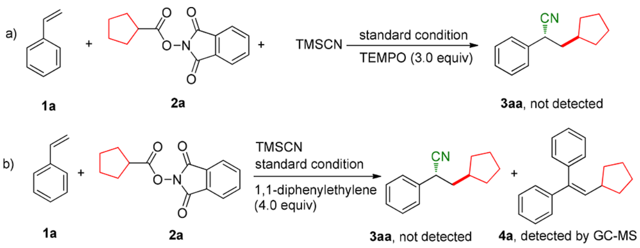
Scheme 3. Scope of Alkyl NHP Esters[a,b,c]



[a] Reaction conditions: NHP esters **2** (0.2 mmol), **1a** (4.0 equiv), TMSCN (1.1 equiv), Ir(ppy)$_3$ (0.5 mol %), CuBr (1.0 mol %), **L4** (1.2 mol %), NMP (0.4 mL), and PhCl (0.6 mL), at room temperature, 5 W blue LEDs, for 24 h. [b] Isolated yields. [c] Enantioselectivity was determined by chiral HPLC.

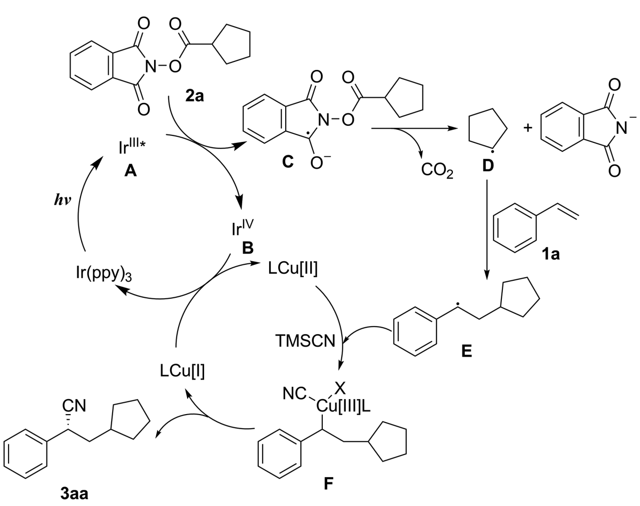
To gain the insight into this reaction mechanism, a radical scavenger, TEMPO (2,2,6,6,-tetramethyl-1-piperidinyloxy), was applied in the reaction. The reaction was totally suppressed and the desired product **3aa** was not detected, which indicates that a radical process may be involved (Scheme 4a). To confirm the formation of an alkyl radical, another radical scavenger 1,1-diphenylalkene was added to the reaction under standard reaction conditions. The desired product **3aa** was again not detected. However, the adduct **4a** of the cyclopentyl radical with ethene-1,1-diyldibenzene was detected by GC-MS (Scheme 4b).

Scheme 4. Mechanistic Investigation



According to the above experimental results and previous studies, a possible mechanism was shown in Scheme 5.[8−10,11c,12c,13,16] Initially, the photoredox catalyst Ir(ppy)$_3$ is irradiated to the activated state **A**, from which **2a** abstracts an electron to form a radical anion **C** and the photocatalyst intermediate **B**. The radical anion **C** generates the alkyl radical **D**, the phthalimide anion, via release of CO$_2$. Subsequently, the alkyl radical **D** adds to styrene **1a** to generate the key benzylic radical **E**. Meanwhile, the intermediate **B** oxidizes a copper(I)

Scheme 5. Proposed Mechanism



catalyst to release photocatalyst Ir(ppy)$_3$ and form the chiral Box/Cu(II) state. Then, the chiral Box/Cu(II) is oxidized by benzylic radical **E** and reacts with TMSCN to give the chiral intermediate Box/Cu(III)[17] **F**. Finally, the intermediate **F** proceeds through reductive elimination to give the final product **3aa** and regenerates the Cu(I) catalyst for the next catalytic cycle.

In summary, we have developed a novel photoredox and copper catalyzed asymmetric cyanoalkylation of alkenes. In this reaction, a photocatalyt and metal catalyst play a vital role. This reaction can be compatible with various alkenes and multiple alkyl NHP esters including primary, secondary, and tertiary alkyl substituted esters. Furthermore, this reaction features mild conditions, simple operation, moderate to excellent yields, and high enantioselectivities, which enriches the research content of the asymmetric radical reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b01863.

Experimental details, characterization data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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