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Enantioselective Remote C(sp^3)−H Cyanation via Dual Photoredox and Copper Catalysis

Hui Chen, Weiwei Jin, and Shouyun Yu*

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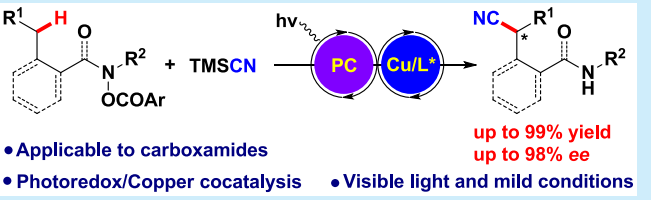
ABSTRACT: The remote C(sp^3)−H cyanation of carboxamides has been described by merging photoredox and copper catalysis in a site-selective and enantiocontrolled manner. The protocol is the integration of photoinduced and nitrogen-centered radical-mediated intermolecular hydrogen atom transfer with chiral copper-complex-catalyzed radical cyanation. This strategy gives enantio-enriched cyanated amides in high yields.



Visible-light photoredox catalysis can generate radicals or radical ions, which are otherwise difficult to access, under mild and synthetically useful conditions.[1] Its application has therefore been rapidly booming in organic synthesis during the past several decades,[2] and the enantioselective version of this catalytic mode has gained more and more attention.[3] Visible-light photoredox catalysis combined with enantioselective transition-metal catalysis leads to the development of novel enantioselective transformations.[4] Dual photoredox and copper catalysis has emerged as a powerful synergistic catalytic system for incorporating functional groups into molecules.[5] Because of the persistent radical effect,[6] copper can efficiently trap and thus stabilize reactive radical species generated under photoredox catalytic conditions.[5a] In this dual-catalytic system, the single electron transfer is mediated by the photocatalyst, and the enantioselectivity is introduced by the copper with a chiral ligand.[5a,b] Although considerable advances in this dual catalysis have been made in the past few years, generalizing and expanding the scope of enantioselective reactions still need to be further investigated.

The Hofmann−Löffler−Freytag (HLF) reaction has constituted a significant breakthrough in the remote functionalization of inherently inert C(sp^3)−H bonds since it emerged in the late 19th century.[7] This reaction converts acyclic amines into cyclic amines through an intermolecular hydrogen atom transfer (HAT) process under ultraviolet photolysis or thermal conditions in a strong acidic medium. The requirement of harsh conditions has limited its applications in organic synthesis. The synergism of visible-light photoredox catalysis with intramolecular HAT lead to the renaissance of the HAT-mediated remote functionalization of C(sp^3)−H bonds.[8] These nitrogen-centered-radical (NCR)-triggered radical translocation processes provide an appealing strategy for the selective and controllable remote functionalization of C-(sp^3)−H bonds.[9] The direct formation of new carbon−carbon (C−C) bonds[10] and carbon−heteroatom (C−O,[11] C−N,[12] and C−X[13]) bonds from remote C(sp^3)−H bonds can be achieved using this strategy. It has emerged as a distinct approach to unlock unique synthetic planning in modern organic synthesis. Despite these advances, enantioselective HLF-type remote C(sp^3)−H functionalization is still synthetically challenging and remains mainly unexplored. Recently, Liu et al. reported an oxygen-centered radical-mediated enantioselective remote C(sp^3)−H cyanation by dual photoredox and copper catalysis.[14] More recently, Nagib[15] and Wang[16] independently realized a copper-catalyzed enantioselective remote C(sp^3)−H cyanation of *N*-fluorosulfonamides, which represents a highly enantioselective HLF-type reaction (Figure 1a). Inspired by the pioneering works of Liu on copper-catalyzed enantioselective radical cyanation[17] and other

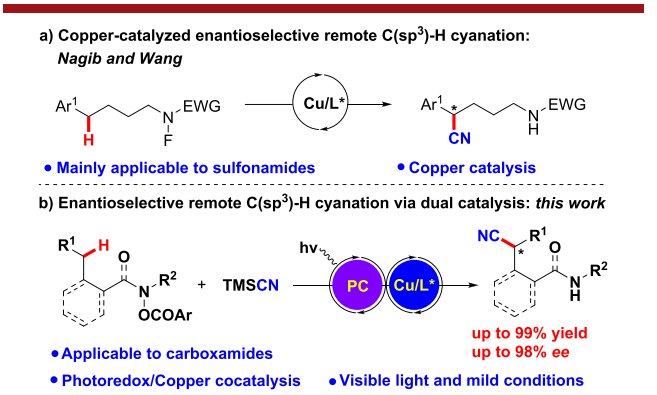


Figure 1. Enantioselective remote C(sp^3)−H cyanation of (sulfon)-amides.

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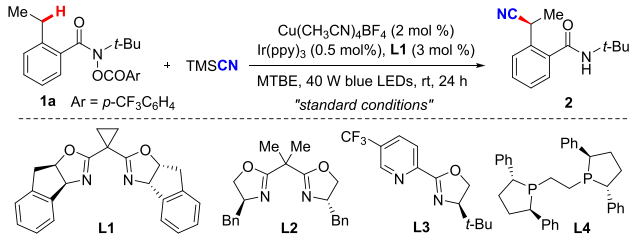
asymmetric remote C(sp^3)−H functionalizations[18] as well as our recent investigation on this topic,[19] we would like to provide our solution to the enantioselective remote C(sp^3)−H cyanation of carboxamides using dual photoredox and copper catalysis (Figure 1b).

We commenced our investigation by selecting *O*-acyl hydroxamide (**1a**) as a model substrate with TMSCN (Table 1). Reaction conditions screening disclosed that the reaction

Table 1. Reaction Conditions Optimization[a]



entry	variation of reaction conditions	yield (%)[b]	*ee* (%)[c]
1	none	>99 (97)[d]	96
2	**L2** instead of **L1**	78	83
3	**L3** instead of **L1**	52	9
4	**L4** instead of **L1**	42	0
5	$Ru(bpy)_3(PF_6)_2$ instead of $Ir(ppy)_3$	0	
6	Eosin Y instead of $Ir(ppy)_3$	0	
7	CH_2Cl_2 instead of MTBE	86	94
8	CH_3CN instead of MTBE	>99	93
9	MeOH instead of MTBE	>99	86
10	without light or $Ir(ppy)_3$	0	
11	air instead of N_2	0	
12	without $Cu(CH_3CN)_4BF_4$	6	
13	without ligand	27	0

[a]Reaction parameters: **1a** (0.1 mmol), TMSCN (2.0 equiv), photocatalyst (0.5 mol %), $Cu(CH_3CN)_4BF_4$ (2.0 mol %), **L** (3.0 mol %), solvent (1.0 mL), rt, 40 W blue LEDs. [b]GC yields with an internal standard (tetradecane). [c]Enantiomeric excess (*ee*) values were based on HPLC analysis on a chiral stationary phase. [d]Isolated yield on a 0.2 mmol scale.

was best conducted with $Cu(CH_3CN)_4BF_4$ (2.0 mol %)/chiral box-type ligand **L1** (3.0 mol %) and photocatalyst $Ir(ppy)_3$ (0.5 mol %) in MTBE irradiated by 40 W blue light-emitting diodes (LEDs) at room temperature for 24 h. (For details, see the Supporting Information.) The remote C(sp^3)−H cyanated amide **2** was obtained in >99% GC yield (97% isolated yield) with 96% *ee* (entry 1). The reactivity and enantioselectivity were significantly affected by chiral ligands. When box ligand **L2** was employed, lower reactivity and enantioselectivity were obtained (78% GC yield, 83% *ee*, entry 2). Replacing chiral box-type ligand **L1** with other ligands, such as chiral pyrox-type ligand **L3** and (*R*,*R*)-Ph-BPE (**L4**), resulted in significantly lower or no enantioselectivity (9% *ee* for **L3** and 0% *ee* for **L4**, respectively, entries 3 and 4). Several other photocatalysts ($Ru(bpy)_3(PF_6)_2$ and Eosin Y) were also examined, but no desired product was observed, and most of starting material **1a** (>90%) was recovered (entries 5 and 6). Replacing MTBE with other solvents (such as DCM, CH_3CN, and MeOH) showed inferior results (entries 7−9). Control experiments showed that visible light, the photocatalyst, the copper catalyst, the ligand, and the nitrogen atmosphere are all critical to the success of the reaction (entries 10−13).

After establishing the optimized reaction conditions, we then focused on investigating the generality and limitations of this enantioselective remote C(sp^3)−H cyanation. As shown in Figure 2, *O*-acyl hydroxamides **1a−e** with different alkyl groups

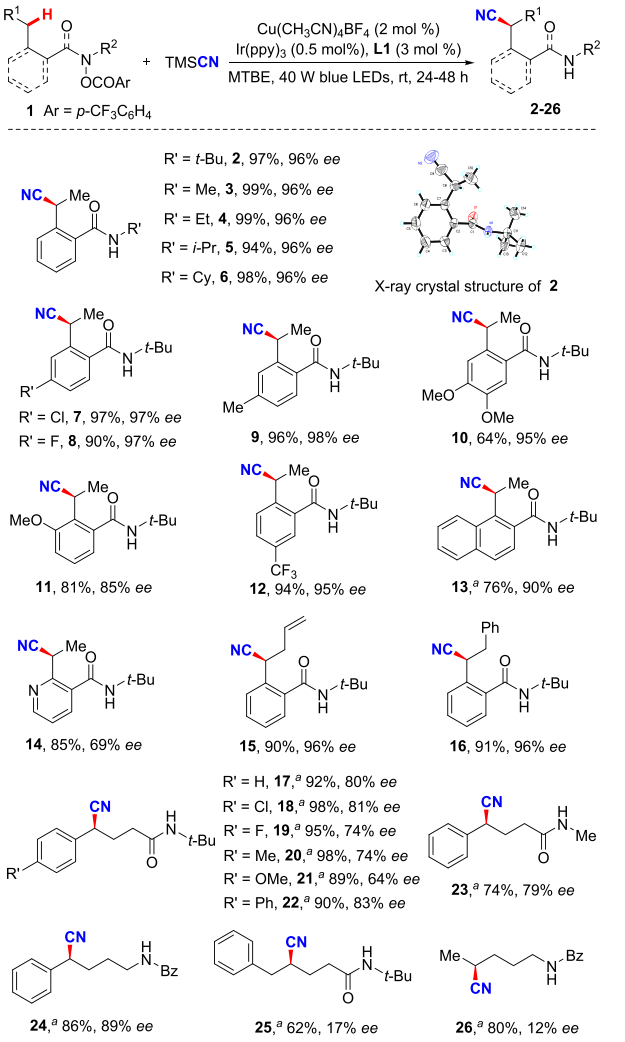


Figure 2. Substrate scope. Reaction parameters: **1** (0.2 mmol), TMSCN (2.0 equiv), $Ir(ppy)_3$ (0.5 mol %), $Cu(CH_3CN)_4BF_4$ (2.0 mol %), **L1** (3.0 mol %), MTBE (2.0 mL), rt, 40 W blue LEDs. Yields are based on the isolated products. [a]CH_2Cl_2 was used as the solvent instead of MTBE.

on the nitrogen atom could participate in this enantioselective reaction very well and afford cyanated amides **2−6** in excellent yields (94−99%) with excellent enantioselectivities (96% *ee*). The substitutions of the nitrogen atom have almost no impact on the reactivity and selectivity in these *O*-acyl hydroxamides. The (S)-configuration of **2** was established by analyzing its X-ray diffraction. *O*-acyl hydroxamides **1f−k** with electron-rich groups (OMe and Me) or electron-poor groups (Cl, F, and CF_3) on the benzene ring all proved to be suitable starting materials, and the desired products **7−12** were provided in good yields (64−97%) with excellent enantioselectivities (85−98% *ee*). *O*-acyl hydroxamide with a naphthalene ring could go through this transformation smoothly (76% yield and 90% *ee* for **13**). *O*-acyl hydroxamide bearing a pyridine ring could tolerate this dual-catalytic system, but with significantly lower enantioselectivity (85% yield and 69% *ee* for **14**). Gratifyingly,

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O-acyl hydroxamides possessing two active sites for HAT were examined, and only 1,5-HAT products **15** (90% yield and 96% *ee*) and **16** (91% yield and 96% *ee*) were produced in excellent yields with excellent enantioselectivities. γ-Aryl linear aliphatic carboxamides were proven successful for this transformation, and the corresponding products **17**−**23** were provided in 74−98% yields with 64−83% *ee*. Enantio-enriched *N*-(4-cyano-4-phenylbutyl)benzamide **24** could be provided in 86% yield with 89% *ee*. Limited success was achieved on nonbenzylic remote C(sp^3)−H cyanation. Low enantioselectivities were observed (17% *ee* for **25** and 12% *ee* for **26**), albeit with good yields (62% yield for **25** and 80% yield for **26**).

To show the synthetic utility of our method, a scale-up experiment and transformation of the resultant chiral nitrile were conducted (Figure 3). A gram-scale reaction of **1a** (1.97 g, 5.0 mmol) with TMSCN was conducted under the standard conditions (Figure 3a). Satisfactorily, chiral nitrile **2** was afforded in 98% yield (1.13 g) with 96% *ee*. Furthermore, the enantio-enriched chiral nitrile **2** could be converted to Boc-protected amine **27** by reduction and amide **28** by hydrolysis, respectively, without a loss of optical purity (Figure 3b).

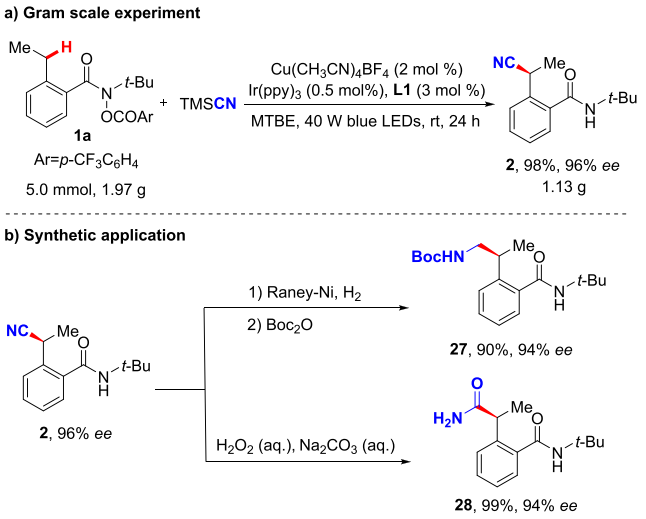

Figure 3. Gram-scale experiment and synthetic application.

To gain some insights into the mechanism of this dual-catalytic system, several control experiments were performed. Upon the addition of radical inhibitors TEMPO and BHT into the model reaction, the formation of **2** was inhibited (Figure 4a). Moreover, the radical-clock experiment with *O*-acyl hydroxamide (±)-**1z** led to the ring-opening/cyanation product (**29**) in 81% yield with 80% *ee* (Figure 4b). These phenomena suggest the radical nature of this reaction. Furthermore, the cyclic voltammogram studies revealed that the reduction potential of **1a** is −1.22 V vs Ag/Ag^+ in MeCN (Figure S2), thus indicating that **1a** can be easily reduced by the excited-state photocatalyst Ir(III)* ($E_{1/2}^{IV/*III}$ = −1.73 V vs SCE).[20] A luminescence quenching experiment also showed that the excited photocatalyst Ir(III)* is efficiently quenched by the *O*-acyl hydroxamide **1a** (Figure S3).

On the basis of these results and literature precedents,[14,17b,18a] the proposed mechanism of this cooperative photoredox and copper catalysis is depicted in Figure 5. Initially, *O*-acyl hydroxamide **1a** reductively quenches the excited photocatalyst Ir(III)* to form an amidyl radical **A**, together with a carboxylate anion ($ArCO_2^-$) and Ir(IV).[19c,d,21]

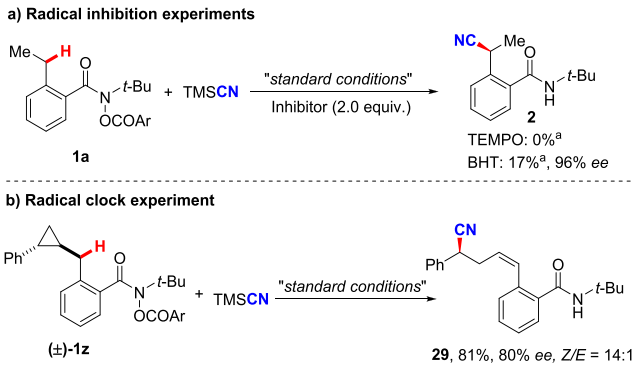

Figure 4. Mechanistic investigation. [a]GC yields with an internal standard (tetradecane). Ar = *p*-$CF_3C_6H_4$.

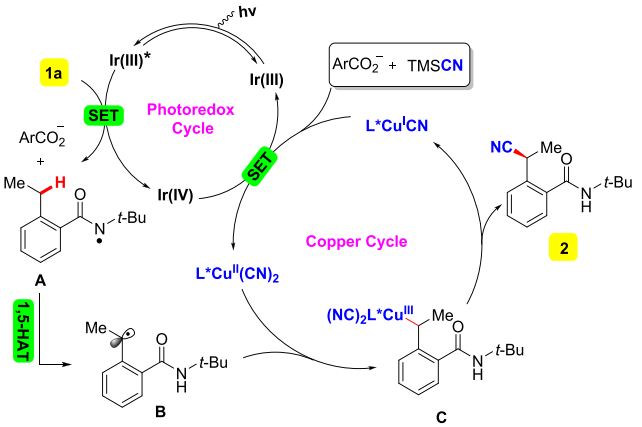

Figure 5. Proposed mechanism.

The Ir(IV) species oxidizes **L***Cu^ICN to **L***$Cu^{II}(CN)_2$ and regenerate Ir(III) in the presence of TMSCN and a carboxylate anion.[18a,22] The side product $ArCO_2TMS$ can be detected by GC-MS (Figure S4). The benzylic radical **B**, which is generated from amidyl radical **A** by the 1,5-HAT,[8] is trapped by **L***$Cu^{II}(CN)_2$ to afford Cu^{III} species **C**. Finally, reductive elimination gives enantio-enriched product **2** and regenerates the **L***Cu^ICN species.[17,22b,23]

In summary, we have developed an asymmetric remote C(sp^3)−H cyanation of carboxamides by the synergism of photoredox and copper catalysis. *O*-acyl hydroxamides are employed as benign internal oxidants and precursors of NCRs in this dual-catalytic process. The protocol is enabled by the integration of a photoinduced and amidyl-radical-mediated intramolecular 1,5-HAT process with the chiral copper-complex-catalyzed radical cyanation in a site-selective and enantiocontrolled manner. This strategy gives structurally diverse cyanated amides in decent yields with decent enantioselectivities and good functional group tolerance. Further discoveries of enantioselective remote C(sp^3)−H transformations enabled by this dual-catalytic strategy are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02008.

General methods, conditions optimization, procedures for starting material preparation, analytic data and copies

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of NMR spectra for starting materials and products, HPLC chromatograms for products, and X-ray crystal structure of **2** (PDF)

Accession Codes

CCDC 2009244 contains 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.

AUTHOR INFORMATION

Corresponding Author

Shouyun Yu − *State Key Laboratory of Analytical Chemistry for Life Science, Jiangsu Key Laboratory of Advanced Organic Materials, Chemistry and Biomedicine Innovation Center (ChemBIC), School of Chemistry and Chemical Engineering, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China;* orcid.org/0000-0003-4292-4714; Email: yushouyun@nju.edu.cn

Authors

Hui Chen − *State Key Laboratory of Analytical Chemistry for Life Science, Jiangsu Key Laboratory of Advanced Organic Materials, Chemistry and Biomedicine Innovation Center (ChemBIC), School of Chemistry and Chemical Engineering, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China*

Weiwei Jin − *State Key Laboratory of Analytical Chemistry for Life Science, Jiangsu Key Laboratory of Advanced Organic Materials, Chemistry and Biomedicine Innovation Center (ChemBIC), School of Chemistry and Chemical Engineering, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02008

Notes

The authors declare no competing financial interest.

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