Communication

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Asymmetric Propargylic Radical Cyanation Enabled by Dual Organophotoredox and Copper Catalysis

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Supporting Information Placeholder

ABSTRACT: The first asymmetric propargylic radical cyanation was realized through a dual photoredox and copper catalysis. An organic photocatalyst serves to both generate propargyl radicals and oxidize Cu(I) species to Cu(II) species. A chiral Cu complex functions as an efficient organometallic catalyst to resemble the propargyl radical and cyanide in an enantio-controlled manner. Thus, a diverse range of optically active propargyl cyanides were produced with high reaction efficiency and enantioselectivities (28 examples, 66-97% yields and 83-98% ee). Moreover, mechanistic investigations including experiments and density functional theory (DFT) calculations were performed to illustrate on the reaction pathway and stereochemical results.

Alkynes are fundamentally important unsaturated compounds that are ubiquitous in many natural isolates and artificial functional materials (i.e., pharmaceuticals, agrochemicals and polymer materials). In addition, the alkyne group is also one the most versatile synthetic handles for obtaining many other functional groups. Because of the unique physical, chemical and biological properties of alkynes, a number of protocols have been developed for their synthesis.[1] Among the methods to prepare alkynes, the elaboration of propargyl alcohols and their derivatives, pioneered by Nicholas in the 1970s[2] and later named as the Nicholas reaction, has been demonstrated to be one of the most powerful and widely used tools in laboratory synthesis and in the pharmaceutical industry (Figure 1a).[3] However, Nicholas himself recognized that "Ultimately, systems for catalytic propargylation eventually may be developed through careful selection of reaction conditions, metal, and auxiliary ligand."[3a] In 1994[4] and 2000,[5] Cu- and Ru-catalyzed propargylic substitutions of propargyl esters, chlorides and alcohols by heteroatom nucleophiles were reported, respectively (Figure 1b). Benefiting from these pioneering discoveries, various propargylic transformations, especially catalytic asymmetric processes promoted by chiral ligands, have flourished over the past two decades.[6] Notably, the key to this success is the catalytic formation of a γ-electrophilic metal-allenylidene intermediates that can be captured by a series of nucleophiles via two-electron pathways. However, one drawback to this approach is that the mechanism renders the inner alkyne analogues not applicable to this protocol, thus requiring new strategies for developing the general catalytic asymmetric propargylation process.

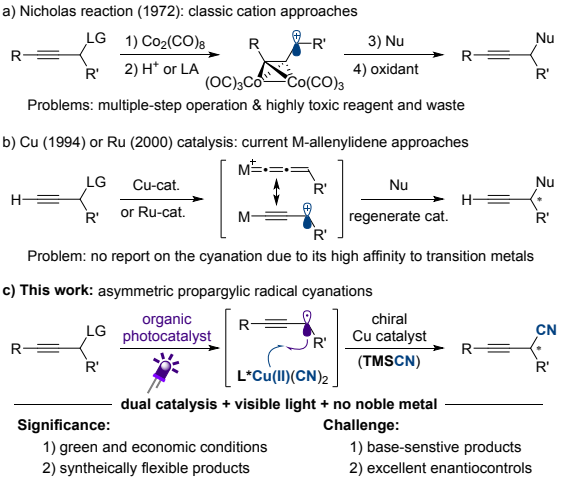


Figure 1. Strategies for propargylic substitution. LG, leaving group; Nu, nucleophile; M, Cu or Ru; CN: cyanide.

Propargylic cyanides are belong to a class of versatile building blocks in synthetic chemistry.[7] To this end, in 1989, Stuart and Nicholas disclosed the first cobalt-mediated propargylic cyanation of propargyl ester and acetylenic acetals.[8a] In 1994, Marson and Grabowska reported a propargylic cyanation of propargyl bromide involving stoichiometric copper cyanide and lithium bromide.[8b] In the following decades, to our knowledge, no catalytic propargylic cyanation reactions have been reported, possibly due to the high affinity of cyanide to many transition metals, which inhibits the activity of catalysts by generating inactive complexes.[9] Much recently, the Liu group developed a series of elegant benzyl radical cyanation reactions with high levels of enantiocontrol through asymmetric copper catalysis.[10] Inspired by the Liu

cyanation and as a continuation of our long-time interest in visible-light-driven organic photochemical synthesis,[11] we intend to develop an asymmetric propargylic radical cyanation (APRC) reaction through a photoredox/copper dual catalysis strategy. Here, we disclose the first catalytic asymmetric propargylic radical cyanation of propargyl esters by merging organophotoredox catalysis with asymmetric copper catalysis (Figure 1c). This dual catalysis strategy avoids a multiple-step operation and stoichiometric metal activating reagents, thus providing a straightforward route to chiral propargyl cyanides with excellent enantiocontrols under mild reaction conditions. In addition, this study also constitutes a rare case of asymmetric cross-coupling reactions synergistically catalyzed by photoredox catalysts and chiral organometallic catalysts.[12]

The design is depicted in Figure 2. It comprises an intertwined photocatalysis cycle and a Cu catalysis cycle. We envisioned that the redox-active propargyl esters (**1a**, LG = 3,5-2$(CF_3)_2$BzO: $E^{1/2}$[**1a**/**1a**$^{\bullet-}$] = -1.66 V vs. saturated calomel electrode (SCE) in CH_3CN)[13] can accept a single electron from the excited state of organo-photocatalyst **Ph-PTZ*** ($E_{1/2}$[**Ph-PTZ**$^{\bullet+}$/**Ph-PTZ***] = -1.97 V vs. SCE),[14a,b] which reaches the excited state from the base state of photocatalyst **Ph-PTZ** (absorption wavelength: 300-400 nm) upon irradiation with visible light. The homolysis of the reduced species of propargyl ester **1** simultaneously generates a propargyl radical **I** and a carboxylic anion LG$^-$. Radical **I**, which has a prochiral stereocenter, can be captured in a stereoselective manner by **L*Cu(II)(CN)$_2$** to form chiral Cu(III) species **III** (**II** → **III**). Reductive elimination of intermediate **II** would deliver the final chiral propargyl cyanide **3** and regenerate the chiral Cu(I) catalyst. Cyanide anion (CN^-) can be slowly released after the reaction between the cyanide source, TMSCN, with the carboxylic anion LG$^-$ and then, coordinate with the chiral Cu(I) catalyst to form **L*Cu(I)(CN)$_2$** species.[10a] The SET process between the oxidized state of **Ph-PTZ**$^+$ ($E_{1/2}$[**Ph-PTZ**$^{\bullet+}$/**Ph-PTZ**] = 0.815 V vs. SCE) and **L*Cu(I)(CN)$_2$** ($E_{1/2}$[Cu(II)/Cu(I)] = 0.36 V vs. SCE)[10d] encloses both photocatalysis and Cu catalysis cycles. According to this design, the mild and base-free reaction conditions avoid the isomerization of propargylic cyanides to allenyl nitriles.[15]

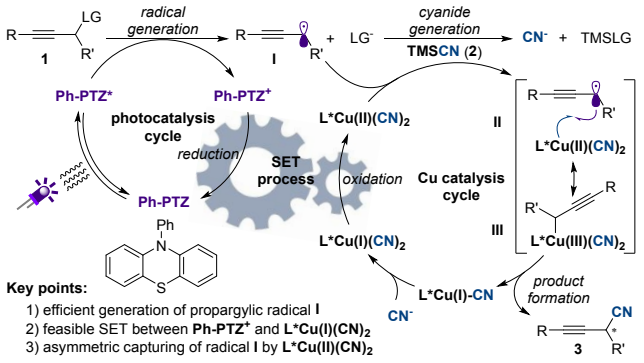
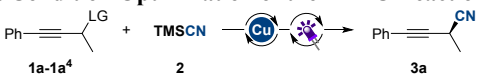


Figure 2. Reaction design: a photoredox/copper dual catalysis cycle for the APRC reaction. Ph-PTZ: 10-phenyl-10H-phenothiazine; TMSCN: trimethylcyanosilane.

To substantiate the aforementioned reaction design, we investigated the APRC reaction by evaluating various chiral copper catalysts. After irradiating propargyl ester **1a** and TMSCN with visible light (2 × 3 W, purple LEDs, 390nm; Figure S1 and S2) for 24 h in the presence of organic photocatalyst **Ph-PTZ**, $Cu(MeCN)_4BF_4$ and chiral bisoxazoline (box) ligand **L1**, we were delighted to detect the propargyl cyanide product **3a** in 90% yield and 91% ee. Notably, this product was the major regioisomer observed through ^{1}H NMR analysis of the reaction mixture; the allenyl nitrile was not detected. Employing other combinations of Cu sources and chiral ligands (Table 1, entries 2-9) resulted in substantially decreased reactivity and enantioselectivity, excepting the combination of $CuCl_2$ and **L1** which provided a similar result (Table 1, entry 4). Impressively, reducing the loading of chiral Cu catalyst from 10 mol% to 2.5 mol% still afforded the desired product with the same level of reaction efficiency and enantiocontrol (Table 1, entry 10). Replacement of the cyclopropane unit in the box ligand with an acyclic one did not affect the enantioselectivity (Table 1, entries 10 and 11: **L1** *vs.* **L2**). Control experiments indicated that the $Cu(MeCN)_4BF_4$/**L1** system, photocatalyst and visible light are indispensable for this APRC reaction (Table 1, entries 12-14). Other propargyl esters **1a^1**-**1a^4**, which lack sufficiently oxidative potentials (Figure S4-8), cannot be used as efficient substrates (Table 1, entry 15).

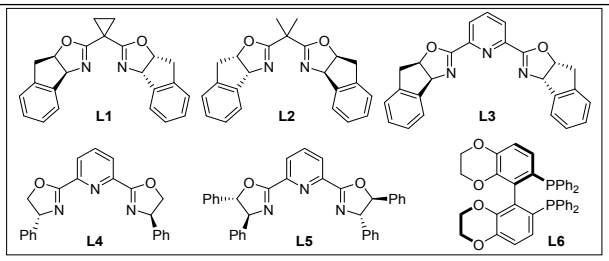
Table 1. Condition Optimization of the APRC Reaction[a]



for entries 1-14: LG = 3,5($CF_3)_2$-BzO (**1a**); for entry 15: LG = AcO (**1a^1**), BocO (**1a^2**), BzO (**1a^3**), *p*-MeO-BzO (**1a^4**)

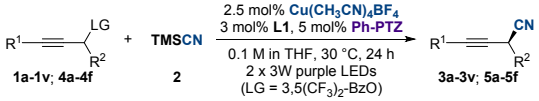
entry	Cu source	chiral ligand	yield (%)[b]	ee[c]
1	$Cu(MeCN)_4BF_4$	**L1**	90	91
2	CuI	**L1**	NR	ND
3	$Cu(OTf)_2$	**L1**	67	82
4	$CuCl_2$	**L1**	88	89
5	$Cu(acac)_2$	**L1**	34	90
6	$Cu(MeCN)_4BF_4$	**L3**	NR	ND
7	$Cu(MeCN)_4BF_4$	**L4**	NR	ND
8	$Cu(MeCN)_4BF_4$	**L5**	31	47
9	$Cu(MeCN)_4BF_4$	**L6**	17	18
10[d]	$Cu(MeCN)_4BF_4$	**L1**	94 (91)[e]	92
11[d]	$Cu(MeCN)_4BF_4$	**L2**	88	-92
12[d,f]	$Cu(MeCN)_4BF_4$	**L1**	NR	ND
13[d,g]	$Cu(MeCN)_4BF_4$	**L1**	NR	ND
14[d,h]	$Cu(MeCN)_4BF_4$	**L1**	NR	ND
15[d,i]	$Cu(MeCN)_4BF_4$	**L1**	NR	ND

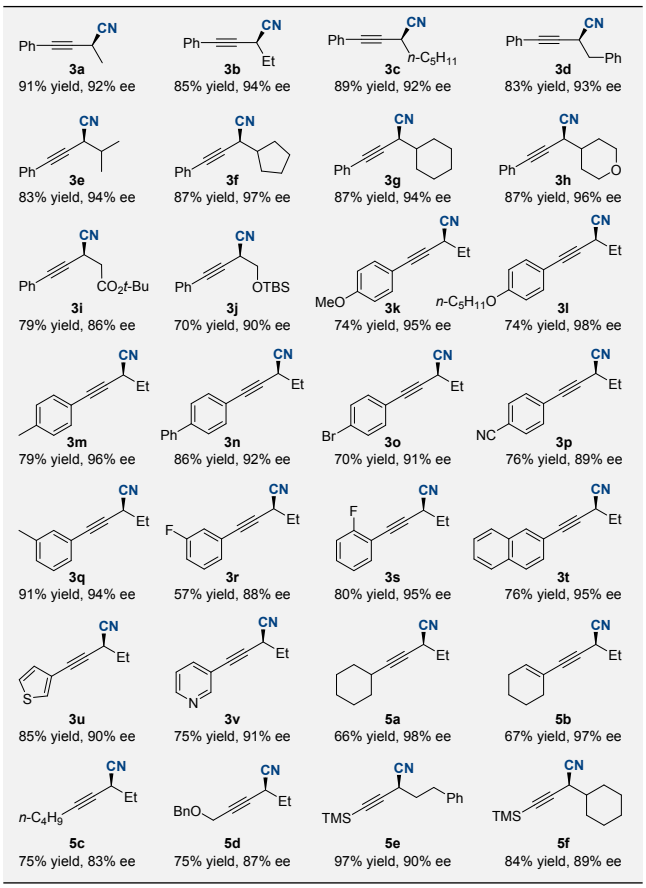
[a]Conditions: propargyl ester **1a** (0.2 mmol), **2** (0.6 mmol), Cu source (10 mol%), chiral ligand (12 mol%), **Ph-PTZ** (5 mol%) in anhydrous THF (2 mL) at 30 °C for 24 h under the irradiation of 2 x 3 W purple LEDs (light intensity = 37.4 mw/cm^2). [b]NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by chiral HPLC analysis. [d]Using Cu source (2.5 mol%) and chiral ligand (3 mol%). [e]Isolated yield in parentheses. [f]In dark. [g]In the absence of photocatalyst. [h]In the absence of chiral Cu catalysts. [i]Propargyl ester **1a^1**, **1a^2**, **1a^3** or **1a^4** (0.2 mmol) was used in place of **1a**. Ac, acetyl; Boc, *tert*-butyloxycarboryl; Bz, benzoyl.



After establishing the optimal reaction conditions, we sought to define the generality of the methodology by exploring the variety of propargyl esters. As summarized in Table 2, a wide range of optically enriched propargyl cyanides were produced through the visible-light-induced APRC reactions. For example, various esters with alkyl substituents linked to the ester unit, including linear, branched and cyclic substituents, can participate in this asymmetric transformation very well. Functional groups such as oxa-heterocycles, esters and OTBS were also compatible with this dual catalysis system. In all of these cases, good reaction efficiencies (**3a-3j**: 70-91% yields) were observed together with high levels of enantiocontrols ranging from 86% ee to 97% ee. We thereafter probed the variety of alkyne partner on the propargyl ester under the standard conditions. As highlighted in Table 2, a range of substrates with aryl alkynes are applicable to this photochemical APRC process. Irrespective of the electronic proprieties and positions of the substituents on the benzene ring, the corresponding chiral propargyl cyanides were efficiently afforded in generally good yields and with excellent enantioselectivity (**3k-3t**: 57-91% yields and 88-98% ee). Moreover, propargyl esters bearing heteroaryl substituents that might affect the Cu catalyst were tolerated by this catalyst system (**3u**: 85% yield and 90% ee; **3v**: 75% yield and 91% ee). In addition to the aryl- and heteroaryl-

Table 2. Generality of APRC Reactions[a]





[a]All the reaction were performed in 0.2 mmol scale; isolated yields; ee values were determined by chiral HPLC or GC analysis. TBS: *tert*-butyl dimethyl silicyl.

containing substrates, many other substrates with alkyl substituents and functional groups such as alkenyl, ether and TMS were proven successful for the present transformation.[16] Generally, good yields and excellent enantioselectivity were observed (**5a-5e**: 66-97% yields and 83-98% ee). More importantly, this APRC reaction can be carried out at the gram scale, without obviously effects on the reaction efficiency and enantiocontrol (Figure 3 and S3). Notably, the redox-active elements, including the organic photocatalyst **Ph-PTZ** and 3,5-(ditrifluoromethyl) benzoic acid, were recovered in good yields.

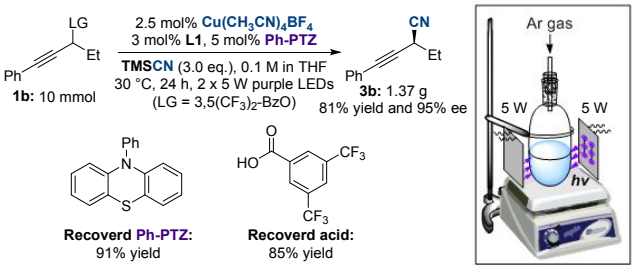


Figure 3. A gram-scale APRC reaction performed in a 250 mL flask.

Next, we performed a set of experiments to determine the reaction mechanism and stereochemical results. First, luminescence quenching experiments indicated that the excited state of photocatalyst **Ph-PTZ** was efficiently quenched by the redox-active propargyl esters (Figure S9). Second, the light/dark experiments (Figure S10) and the quantum yield (0.652)

suggested a possible nonchain radical process for this APRC reaction. Third, control experiments using chiral propargyl ester (***S***)-**1a** and two chiral box ligands were carried out under the standard conditions. Given a well-established protocol for the Cu-catalyzed stereospecific propargylic substitution of aryl Grignard reagents by using chiral propargylic ammonium salts, there might be a direct stereoselective interaction between Cu catalysts and propargylic substrates.[17] However, in our case, nearly the same reaction profile and inverse enantio-induction were observed, which excluded this possibility (Figure 4a). Fourth, a linear relationship between the ee values of propargyl cyanide products and box ligands was observed, which suggests a catalysis mechanism involving a single Cu/L complex (Figure S12).[18] Fifth, a DFT calculation (DFT: density functional theory) of the stepwise oxidation/reductive elimination process was carried out to rationalize the experimentally observed stereochemical result.[19] As shown in Figure 4b, the calculations suggest that the relative free energy of the transition state corresponding to the addition of the propargylic radical to Cu(II) species **A** (**TS1**) is lower than that of reductive elimination to release product ***rac*-3a** and Cu(I) species C (**TS1**), indicating the formation of the propargyl-Cu(III) complex is reversible and that enantioselectivity is determined by the reductive elimination step. Based on this information, we then investigated the origin of enantioselectivity with the APRC reaction of propargyl ester **1b** as the model reaction. As shown in Figure 4c, the relative free energy of transition state ***S*-TS2** (leading to product ***S*-3b**) is 3.5 kcal/mol lower than that of ***R*-TS2** (leading to product ***R*-3b**), consistent with experimental observation. Further structural analysis showed that the structure of ***R*-TS2** would experience greater steric hindrance than that of ***S*-*TS2***. We therefore concluded that greater steric repulsion in ***R*-TS2** leads to the higher energy barrier observed in reductive elimination for the *R*-product compared with that for the *S*-product.

We have successfully developed the first catalytic asymmetric propargylic radical cyanation via a synergetic photoredox/copper catalysis strategy. This strategy provides unprecedented access to optically enriched propargyl cyanides with generally high reaction efficiency and enantioselectivity under mild conditions. In addition, a mechanistic investigation that included experimental evidence and DFT calculations rationally illustrated the possible reaction pathway and stereoinduction process. We believe that this work not only opens a new window for catalytic asymmetric propargylic functionalizations, but also provides a novel dual catalysis system for visible-light-induced asymmetric chemical bond formation.

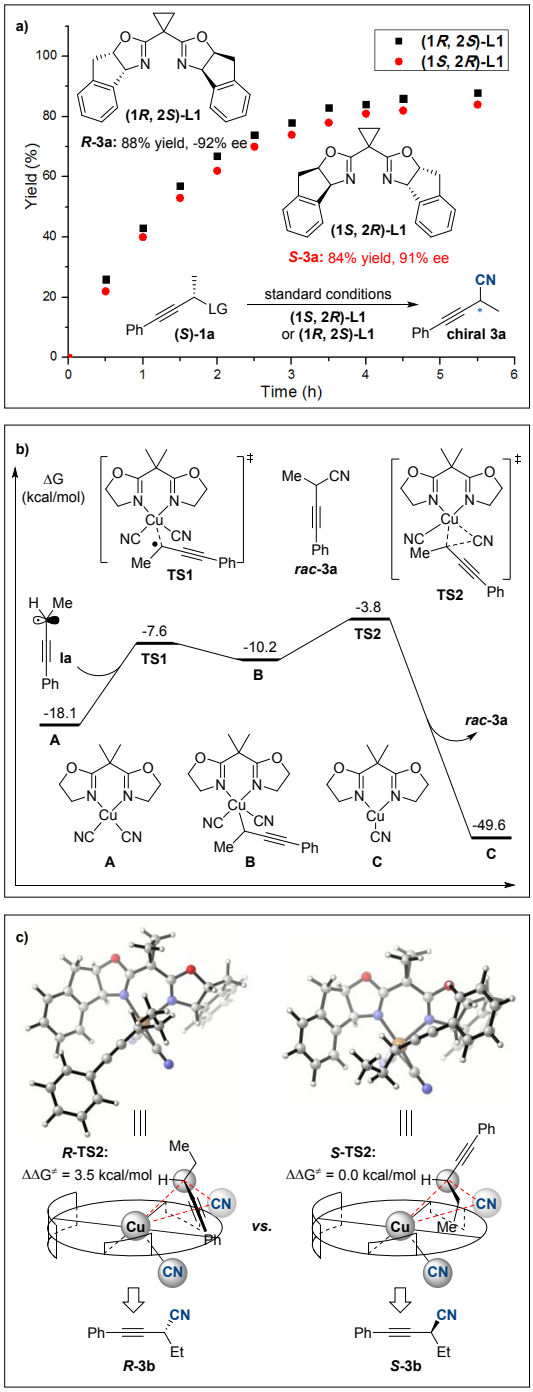


Figure 4. Mechanistic investigations: a, reaction profiles of chiral propargyl esters; b, DFT computational studies; c, proposed stereo-induction models.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, and characterization data for all the products. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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Graphic Abstract: