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Enantioselective cyanation of propargylic C–H bonds *via* cooperative photoredox and copper catalysis†

Yunshun Deng,^{‡a} Ronghua Lu,^{‡b} Pinhong Chen^{ID *b} and Guosheng Liu^{ID *ab}

Herein, we report an enantioselective cyanation of propargylic C–H bonds by combining photoredox catalysis with a copper-catalyzed radical relay in which the propargylic radical was generated by an intramolecular 1,5-HAT process. This reaction provides easy access to optically pure propargyl nitrile compounds under mild conditions.

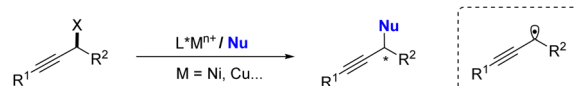
Optically pure alkynes are important unsaturated compounds that are frequently found in natural products, bioactive compounds and polymer materials¹ as well as important and useful synthons in organic synthesis.² Therefore, the synthesis of these chiral alkynes has received much attention and exploring efficient methods is of great significance. The transition metal-catalyzed propargylic functionalization reaction serves as a powerful and attractive tool.³ For instance, transition metal-catalyzed enantioselective propargylic substitutions of propargyl esters, chlorides and alcohols by different nucleophiles have been extensively reported.⁴ In contrast, owing to the easy availability of simple alkynes, functionalization of propargylic C–H bonds presents the most efficient streamline for their synthesis;⁵ however, asymmetric reactions still remain a formidably challenging task.⁶

Recently, transition metal-catalyzed asymmetric radical transformations (ARTs) have been rapidly developed as a powerful tool to construct enantiomeric organic compounds.⁷ For instance, Fu and coworkers reported an elegant work on the nickel-catalyzed enantioselective arylation of propargylic radicals, which derived from propargylic bromides (Scheme 1a).^{7d} In addition, Xiao and Lu disclosed a dual photo- and copper-catalyzed asymmetric cyanation of propargylic acetates, where the propargylic radical

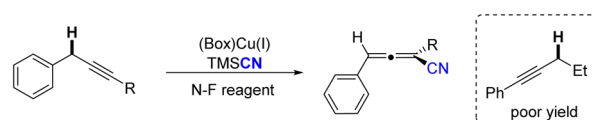
intermediate was generated and trapped by chiral Cu(II) cyanide species in an enantioselective manner.⁸ However, for the Kharasch-type propargylic C–H oxidation⁹ that also involves the propargylic radical intermediates, the enantioselective control is extremely difficult and the asymmetric version is far from success.^{9c}

Since 2016, our group has demonstrated copper-catalyzed radical relays as a powerful strategy for asymmetric radical reactions,¹⁰ such as cyanation of benzylic and allylic C–H bonds,¹¹ in which a carbon-centred radical could be enantioselectively trapped by a chiral (Box)Cu^{II}(CN)₂ species.¹² Moreover, the asymmetric arylation and alkynylation of benzylic C–H bonds were also achieved *via* this strategy.^{13–15} Very recently, we have disclosed an enantioselective cyanation of propargylic

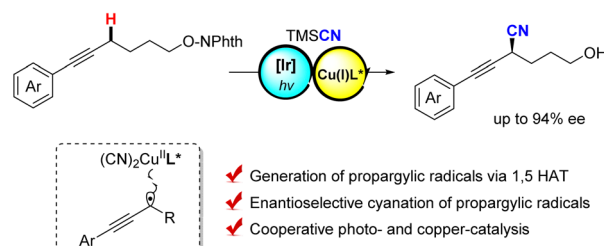
a) TM-catalyzed enantioselective coupling of propargylic radicals



b) Copper-catalyzed enantioselective cyanation of propargylic C–H bonds



c) Photo-/Cu-Catalyzed enantioselective cyanation of propargylic C–H bonds (This work)



Scheme 1 Catalytic asymmetric functionalization of propargylic radicals.

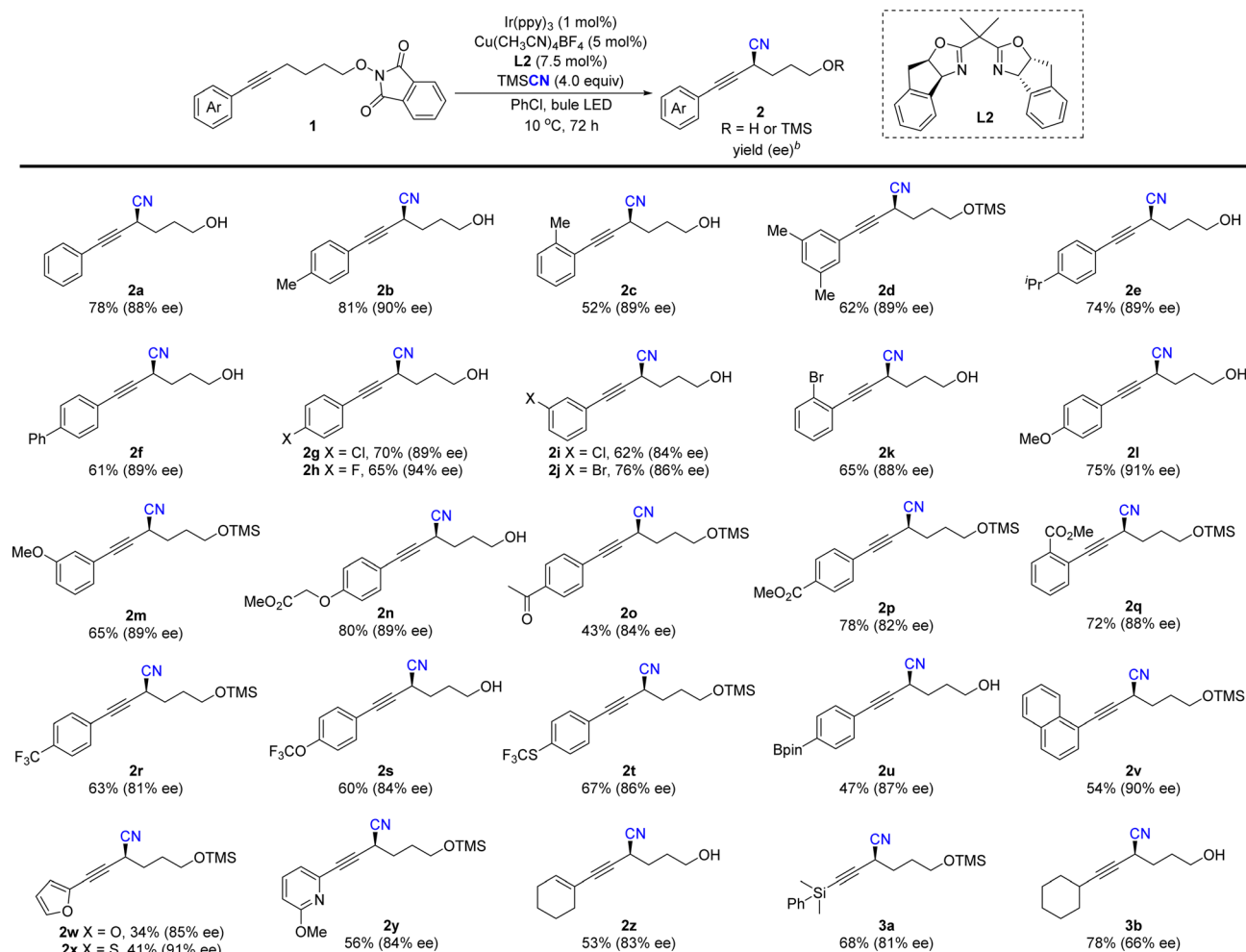
^a Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China. E-mail: gliu@mail.sioc.ac.cn

^b State Key Laboratory of Organometallic Chemistry, and Shanghai Hongkong Joint Laboratory in Chemical Synthesis, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China. E-mail: pinhongchen@mail.sioc.ac.cn

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‡ These authors contributed equally.

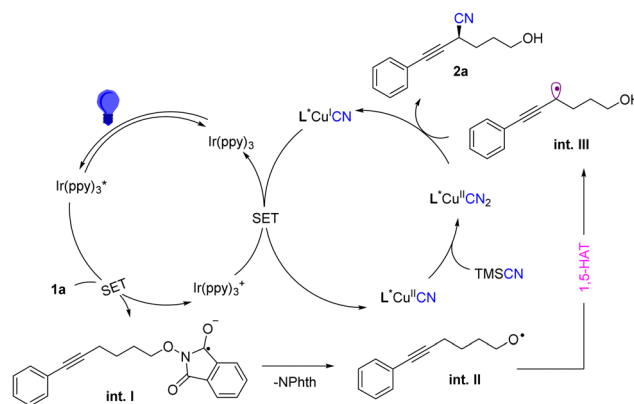


Table 2 Substrate scope^{a,b}

^a All the reactions were conducted on a 0.2 mmol scale. ^b Isolated yields after treatment with 1 M HCl for alcohols and direct separation for TMS-protected alcohols; enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase.

SCE in MeCN (see ESI[†]). The reduction potential of the excited-state photosensitizer Ir(ppy)_3^* is ($E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = -1.73 \text{ V}$ (vs. SCE)),¹⁹ which indicates that the excited-state photosensitizer can be quenched by substrate **1a**. At the same time, Stern-Volmer fluorescence quenching experiments demonstrated the emission intensity of Ir^{III}^* in the presence of substrate **1a** (see ESI[†]). Finally, the light turn on-off experiments suggested a possible nonchain radical process in this reaction (See ESI[†]).

Based on our mechanistic experiments and previous studies,^{16,18} we proposed a mechanism as depicted in Scheme 2. Firstly, the photocatalyst Ir(ppy)_3 was excited to generate Ir(ppy)_3^* under the irradiation of a blue LED. The photoexcited Ir(ppy)_3^* could undergo single electron transfer (SET) reduction with substrate **1** to form radical anion **int.I**. Subsequently, the radical anion could quickly generate oxygen radical **int.II** through a cleavage of the N–O bond. Then, the oxygen radical **int.II** was converted into propargylic radical **int.III** via a 1,5-HAT process. At the same time, the oxidized Ir(ppy)_3^+ was then reduced by $\text{L}^*\text{Cu}^{\text{I}}\text{CN}$ to regenerate the ground-state Ir(ppy)_3 and formed $\text{L}^*\text{Cu}^{\text{II}}\text{CN}$ rapidly, which



Scheme 2 Plausible mechanism.

could further react with TMSCN to form $\text{L}^*\text{Cu}^{\text{II}}(\text{CN})_2$. Finally the combination of $\text{L}^*\text{Cu}^{\text{II}}(\text{CN})_2$ with the propargylic radical gives the target product with a reported stereinduction model.⁸



In conclusion, we have developed an asymmetric cyanation of intramolecular propargylic C–H bonds *via* copper-catalyzed radical relay, in which a propargylic radical was formed *via* a photoredox-catalyzed intramolecular 1,5-HAT process. This reaction provides easy access to optically pure propargyl nitrile compounds under very mild conditions. Fluorescence quenching experiments indicated that the reaction was initiated by the oxidative quenching of excited-state photosensitizers.

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Conflicts of interest

There are no conflicts to declare.

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