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

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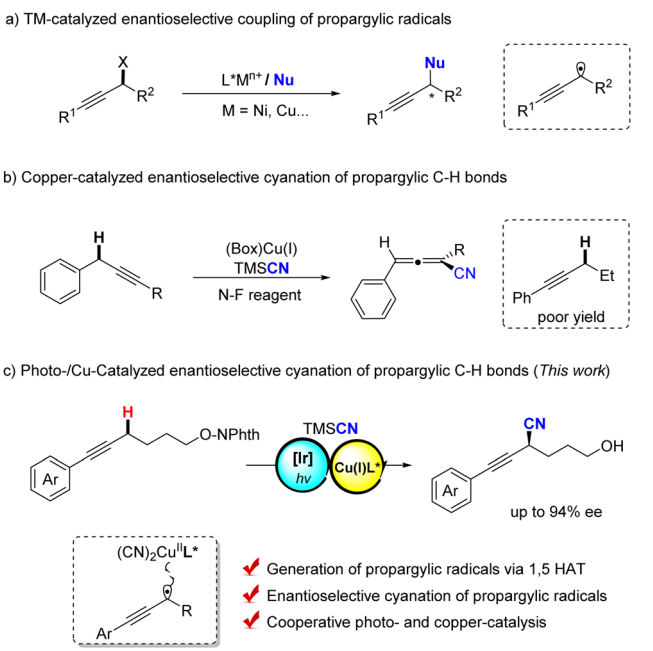
Herein, we report an enantioselective cyanation of propargylic C–H bonds by combining photoredox catalysis with a copper-catalyzed radical relay in which the propargylic radical was generated by an intramolecular 1,5-HAT process. This reaction provides easy access to optically pure propargyl nitrile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

Optically pure alkynes are important unsaturated compounds that are frequently found in natural products, bioactive compounds and polymer materials[1] 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 oxidation[9] 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 stragety.[13–15] Very recently, we have disclosed an enantioselective cyanation of propargylic



Scheme 1 Catalytic asymmetric functionalization of propargylic radicals.

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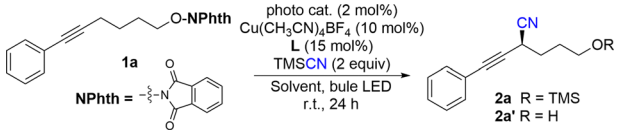
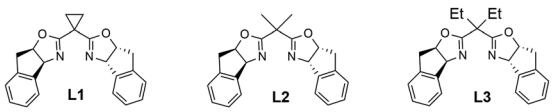
C–H bonds for the construction of structurally diverse chiral allenyl nitriles.[16] However, we found that the substrate of phenyl-substituted alkynes exhibited extremely poor reactivity toward the asymmetric C–H cyanation, where the BDE of propargylic C–H bonds is significantly higher than those of previous substrates, resulting in the insufficient HAT process under the reaction conditions. In comparison, the intermolecular 1,5-hydrogen atom transfer pathway has been widely used for the generation of sp^3 carbon radicals, thereby achieving the functionalization of remote sp^3 C–H bonds.[17] Therefore, we reasoned that, if a 1,5-HAT process can be developed to cooperate with copper catalysis, the enantioselective cyanation of propargylic C–H bonds would be realized. Herein, we communicate a novel enantioselective cyanation of propargylic C–H bonds *via* copper-catalyzed radical relay, which allows for the straightforward and efficient synthesis of optically pure propargylic cyanoalcohols from readily accessible hydroxyl-tethered alkynes (Scheme 1c).

With our previous study,[18] the reaction of **1a** was started under cooperative photoredox and copper catalysis. As shown in Table 1, the reaction of **1a** and TMSCN under irradiation of 2 × 3 W blue LEDs, with *fac*-Ir(ppy)$_3$ (2 mol %) and Cu(CH$_3$CN)$_4$BF$_4$ (10 mol %)/**L1** (15 mol %) in DCM at room temperature can afford the desired cyanation product in a 40% yield with 84% ee (entry 1). It should be noted that the generated alcohol product **2a′** will react with TMSCN to form TMS protected product **2a**, without the detection of allenyl nitrile. The radical coupling reaction with chiral Cu(II) cyanides is significantly affected by the steric hindrance of radicals. In this reaction, the result might be attributed to the less steric propargylic radical than allenyl radical. Other photocatalysts with higher oxidation potentials, such as Ir(ppy)$_2$(dtbbpy)PF$_6$ (**[Ir]-1**) and Ru(bpy)$_3$Cl$_2$ (**[Ru]**) did not affect the enantioselectivity (84% ee), but afforded the product mixture in lower yields (entries 2, 3). The organic photocatalyst Eosin Y was not suitable for this asymmetric cyanation reaction (entry 4). Further optimization of solvents indicated that the reaction in chlorobenzene afforded product **2a** and **2a′** in a comparable yield with the same ee value, and the mass balance was better than that of the reaction in DCM (entries 5–7). Replacement of the cyclopropane unit in the box ligand with an acyclic one slightly increased the yield, but without the loss of enantioselectivity and **L2** was the best (entries 8–11). Since the active hydroxyl group in **2a′** will react with TMSCN to generate **2a**, the yield can be improved to 80% with 4.0 equivalents of TMSCN, lower catalyst loading and prolonged reaction time making the reaction complete (entries 12 and 13). Finally, lowering the reaction temperature can increase the enantioselectivity of the reaction to 88% (entry 14). Control experiments indicated that both photocatalyst and visible light are essential for this reaction (entry 15).

Table 1 Optimization of the reaction conditions[ab]



Entry	Photo cat.	Ligand	Solvent	conversion	**2a**+**2a′** Yield[b] (ee)
1	Ir(ppy)$_3$	L1	DCM	77%	40% (84)%
2	**[Ir]-1**	L1	DCM	12%	11% (84%)
3	**[Ru]**	L1	DCM	15%	Trace (n. d.)
4	EosinY	L1	DCM	0	0%
5	Ir(ppy)$_3$	L1	DMF	13%	0%
6	Ir(ppy)$_3$	L1	PhCl	37%	37% (84%)
7	Ir(ppy)$_3$	L1	CH$_3$CN	66%	36% (71%)
8	Ir(ppy)$_3$	L2	DCM	100%	57% (84%)
9	Ir(ppy)$_3$	L3	DCM	95%	51% (84%)
10	Ir(ppy)$_3$	L2	PhCl	59%	55% (84%)
11	Ir(ppy)$_3$	L3	PhCl	71%	51% (84%)
12[c]	Ir(ppy)$_3$	L2	PhCl	100%	62% (84%)
13[cd]	Ir(ppy)$_3$	L2	PhCl	100%	80% (84%)
14[cde]	Ir(ppy)$_3$	L2	PhCl	100%	78% (88%)
15[f]	—	L2	DCM	0	0

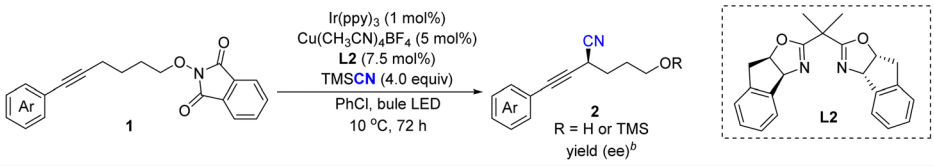


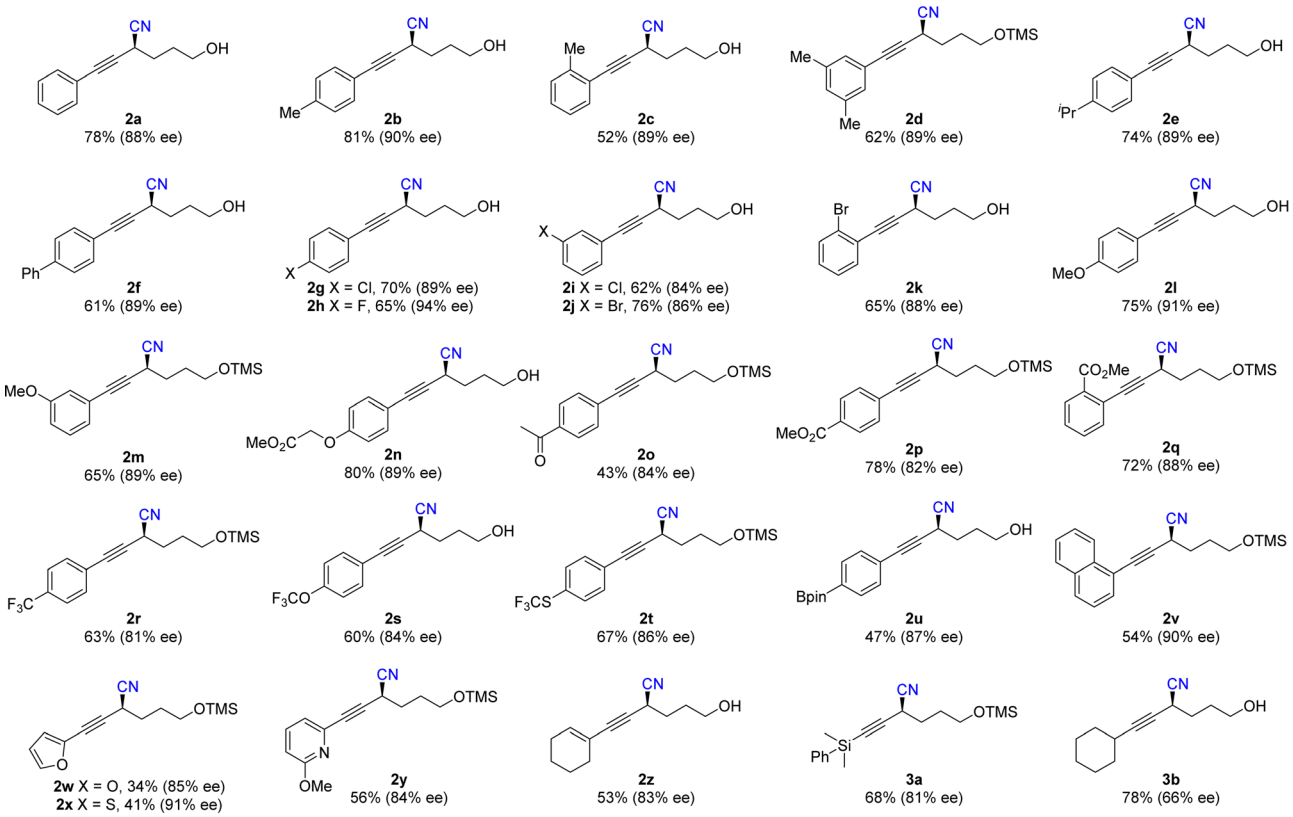
[a] The reactions were conducted on a 0.1 mmol scale with photocatalyst (2 mol%) and Cu(CH$_3$CN)$_4$BF$_4$ (10 mol%) in solvent (1 mL) at room temperature, irradiated with 2 × 3 W blue LEDs. [b] Crude ^{1}H NMR yield with CH_2Br_2 as an internal standard; an enantiomeric excess (ee) value of **2a′** was determined by HPLC on a chiral stationary phase. [c] With photocatalyst (1 mol%), Cu(CH$_3$CN)$_4$BF$_4$ (5 mol%). [d] With 4.0 equiv. TMSCN and 60 h. [e] At 10 °C for 72 h. [f] Without Ir(ppy)$_3$ or in the dark. **[Ir]-1** = Ir(ppy)$_2$(dtbbpy)PF$_6$. **[Ru]** = Ru(bpy)$_3$Cl$_2$.

With the optimized reaction conditions in hand, the substrate scope and functional group tolerance were further examined. As shown in Table 2, various phenylethynyl-tethered NHP esters derived from simple alcohols were compatible with the reaction conditions to provide the corresponding products **2a**–**2q** in good yields (43–81%) and excellent enantioselectivities (84–94% ee). A series of functional groups, such as halides, ethers, ketones and esters, were very well tolerated. Fluorine-containing groups such as trifluoromethyl, trifluoromethoxyl and thiotrifluoromethyl groups were tolerated in this reaction (**2r**–**2t**). Moreover, aryl boronic ester (Bpin) was also tolerated in the reaction to provide product **2u** with excellent enantioselectivity (87% ee), which allows for further transformation. Substrates with *meta*- and *ortho*-substituent aryl groups did not affect the reaction. The reaction of 1-alkynyl naphthalene proceeded well to give **2v** in 54% yield with 90% ee. Notably, heterocycles including furyl and thianaphthenyl were also suitable for the enantioselective propargylic C–H cyanation to give products **2w** and **2x** in slightly decreased yields and good enantioselectivities. The reason might be due to the conversion of the corresponding free alcohol products to racemic allenyl nitriles in the presence of fluorides. A 2-methoxyl pyridyl group was also tolerated to deliver **2y** in a 56% yield with an 84% ee. More importantly, in addition to aryl-substituted alkynes, enyne **1z** was also compatible, giving the target product **2z** in 53% yield and 83% ee and the silyl-substituted allkynyl substituents were suitable to give **3a** in 68% yield with slightly decreased enantioselectivity. However, the reaction of the alkyl substituted alkyne afforded **3b** only in moderate enatioselectivity.

To get more insights into the reaction mechanism, we first measured the reduction potential of **1a** to be $E_p^{0/-1} = -1.51$ V *vs.*

Table 2 Substrate scope[a,b]

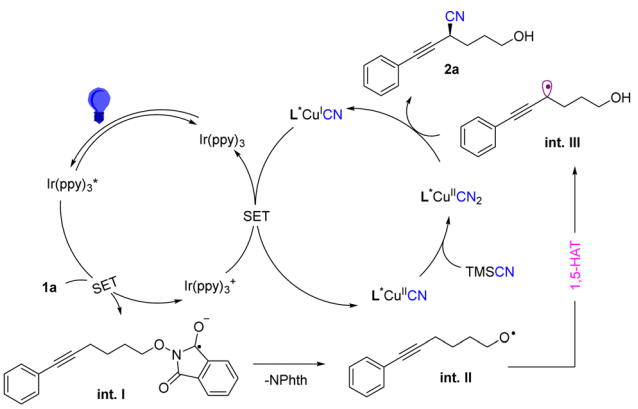




[a] All the reactions were conducted on a 0.2 mmol scale. [b] Isolated yields after treatment with 1 M HCl for alcohols and direct separation for TMS-protected alcohols; enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase.

SCE in MeCN (see ESI†). The reduction potential of the excited-state photosensitizer $Ir(ppy)_3$* is ($E_{1/2}$ ($Ir^{IV}/^{III}$ = −1.73 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 L*Cu^{I}CN to regenerate the ground-state $Ir(ppy)_3$ and formed L*Cu^{II}CN rapidly, which could further react with TMSCN to form L*$Cu^{II}(CN)_2$. Finally the combination of L*$Cu^{II}(CN)_2$ with the propargylic radical gives the target product with a reported stereoinduction model.[8]



Scheme 2 Plausible mechanism.

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.

Notes and references

1 (*a*) A. Boulton, B. Davis, D. Durden, L. Dyck, A. Juorio, X. Li, I. Paterson and P. Yu, *Drug Dev. Res.*, 1997, **42**, 150; (*b*) B. M. Trost, and C.-J. Li, *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*, Wiley-VCH, New York, 2014; (*c*) D. Huang, Y. Liu, A.-J. Qin and B.-Z. Tang, *Polym. Chem.*, 2018, **9**, 2853.

2 (*a*) K. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207; (*b*) C. Li, *Acc. Chem. Res.*, 2010, **43**, 581; (*c*) R. Gleiter and D. B. Werz, *Chem. Rev.*, 2010, **110**, 4447; (*d*) V. K. Tiwari, B. B. Mishra, K. B. Mishra, N. Mishra, A. S. Singh and X. Chen, *Chem. Rev.*, 2016, **116**, 3086.

3 (*a*) Y. Miyake, S. Uemura and Y. Nishibayashi, *ChemCatChem*, 2009, **1**, 342; (*b*) C.-H. Ding and X.-L. Hou, *Chem. Rev.*, 2011, **111**, 1914; (*c*) D.-Y. Zhang and X.-P. Hu, *Tetrahedron Lett.*, 2015, **56**, 283.

4 (*a*) K. Nakajima, M. Shibata and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2015, **137**, 2472; (*b*) R.-Z. Li, H. Tang, K. Yang, L.-Q. Wan, X. Zhang, J. Liu, Z. Fu and D. Niu, *Angew. Chem., Int. Ed.*, 2017, **56**, 7213; (*c*) W. Shao, Y. Wang, Z.-P. Yang, X. Zhang and S.-L. You, *Chem. – Asian J.*, 2018, **13**, 1103; (*d*) X. Gao, R. Cheng, Y.-L. Xiao, X.-L. Wan and X. Zhang, *Chemistry*, 2019, **5**, 2987.

5 (*a*) D. Cheng and W. Bao, *J. Org. Chem.*, 2008, **73**, 6881; (*b*) R. D. Grigg, J. W. Rigoli, S. D. Pearce and J. M. Schomaker, *Org. Lett.*, 2012, **14**(280), 6; (*c*) T. Wang, W. Zhou, H. Yin, J.-A. Ma and N. Jiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 10823; (*d*) H. Lu, C. Li, H. Jiang, C. L. Lizardi and X. P. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7028; (*e*) Y. Wang, J. Zhu, A. C. Durham, H. Lindberg and Y.-M. Wang, *J. Am. Chem. Soc.*, 2019, **141**, 19594.

6 (*a*) M. Ju, E. E. Zerull, J. M. Roberts, M. Huang and J. M. Schomaker, *J. Am. Chem. Soc.*, 2020, **142**, 12930; (*b*) T. Li, X. Cheng, P. Qian and L. Zhang, *Nat. Catal.*, 2021, **4**, 164.

7 (*a*) G. C. Fu, *ACS Cent. Sci.*, 2017, **3**, 692; (*b*) J. Choi and G. C. Fu, *Science*, 2017, **356**, eaaf7230; (*c*) Q. Lu and F. Glorius, *Angew. Chem., Int. Ed.*, 2017, **56**, 49; (*d*) S. W. Smith and G. C. Fu, *J. Am. Chem. Soc.*, 2008, **130**, 12645; (*e*) A. J. Oelke, J. Sun and G. C. Fu, *J. Am. Chem. Soc.*, 2012, **134**, 2966; (*f*) N. D. Schley and G. C. Fu, *J. Am. Chem. Soc.*, 2014, **136**, 16588; (*g*) F.-D. Lu, X. Jiang, L.-Q. Lu and W.-J. Xiao, *Acta Chim. Sin.*, 2019, **77**, 803; (*h*) L. An, F.-F. Tong, S. Zhang and X. Zhang, *J. Am. Chem. Soc.*, 2020, **142**, 11884.

8 F.-D. Lu, D. Liu, L. Zhu, L.-Q. Lu, Q. Yang, Q.-Q. Zhou, Y. Wei, Y. Lan and W.-J. Xiao, *J. Am. Chem. Soc.*, 2019, **141**, 6167.

9 (*a*) H. Kropf, R. Schröer and R. Fösing, *Synthesis*, 1977, 894; (*b*) L. X. Alvarez, M. L. Christ and A. B. Sorokin, *Appl. Catal., A*, 2007, **325**, 303; (*c*) J. S. Clark, K. F. Tolhurst, M. Taylor and S. Swallow, *Tetrahedron Lett.*, 1998, **39**, 4913.

10 For reviews, see: (*a*) F. Wang, P. Chen and G. Liu, *Acc. Chem. Res.*, 2018, **51**, 2036; (*b*) Z. Zhang, P. Chen and G. Liu, *Chem. Soc. Rev.*, 2022, **51**, 1640; (*c*) F. Wang, P. Chen and G. Liu, *Nat. Synth.*, 2022, **1**, 107.

11 For some examples, see: (*a*) W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl and G. Liu, *Science*, 2016, **353**, 1014; (*b*) J. Li, Z. Zhang, L. Wu, W. Zhang, P. Chen, Z. Lin and G. Liu, *Nature*, 2019, **574**, 516.

12 For selected asymmetric radical cyanations, see: (*a*) F. Wang, D. Wang, X. Wan, L. Wu, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2016, **138**, 15547; (*b*) D. Wang, F. Wang, P. Chen, Z. Lin and G. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 2054; (*c*) D. Wang, N. Zhu, P. Chen, Z. Lin and G. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 15632; (*d*) G. Zhang, L. Fu, P. Chen, J. Zou and G. Liu, *Org. Lett.*, 2019, **21**, 5015; (*e*) W. Zhuang, P. Chen and G. Liu, *Chin. J. Chem.*, 2021, **39**, 50; (*f*) S. Zhou, G. Zhang, L. Fu, P. Chen, Y. Li and G. Liu, *Org. Lett.*, 2020, **22**, 6299; (*g*) L. Wu, L. Wang, P. Chen, Y.-L. Guo and G. Liu, *Adv. Synth. Catal.*, 2020, **362**, 2189.

13 (*a*) W. Zhang, L. Wu, P. Chen and G. Liu, *Angew. Chem., Int. Ed.*, 2019, **58**, 6425; (*b*) L. Fu, Z. Zhang, P. Chen, Z. Lin and G. Liu, *J. Am. Chem. Soc.*, 2020, **142**, 12493.

14 For selected asymmetric arylations, see: (*a*) L. Wu, F. Wang, X. Wan, D. Wang, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 2904; (*b*) D. Wang, L. Wu, F. Wang, X. Wan, P. Chen, Z. Lin and G. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 6811; (*c*) L. Wu, F. Wang, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2019, **141**, 1887.

15 For selected asymmetric alkynylation, see: (*a*) L. Fu, S. Zhou, X. Wan, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2018, **140**, 10965; (*b*) Z. Hu, L. Fu, P. Chen and G. Liu, *Org. Lett.*, 2020, **23**, 129.

16 R. Lu, T. Yang, X. Chen, W. Fan, P. Chen, Z. Lin and G. Liu, *J. Am. Chem. Soc.*, 2021, **143**, 14451.

17 (*a*) M. E. Wolff, *Chem. Rev.*, 1963, **63**, 55; (*b*) L. M. Stateman, K. M. Nakafuku and D. A. Nagib, *Synthesis*, 2018, 1569.

18 Z. Cheng, P. Chen and G. Liu, *Acta. Chim. Sin.*, 2019, **77**, 856.

19 K. C. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322.