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Photoinduced copper-catalyzed asymmetric radical three-component cross-coupling of 1,3-enynes with oxime esters and carboxylic acids†

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Catalytic radical difunctionalization of 1,3-enynes has recently been established as a potentially robust platform for construction of valuable allenes and propargylic compounds. Despite the considerable advances made in the realm of radical 1,4-difunctionalizations, there has been little progress in the radical 1,2-difunctionalizations, particularly regarding enantioselective variants. Herein, we report the first regio- and enantioselective radical three-component coupling of 1,3-enynes, oxime esters, and carboxylic acids through photoinduced copper catalysis. This redox-neutral protocol proceeds under mild conditions and demonstrates good functional group tolerance and 1,2-regioselectivity, providing access to a library of valuable cyanoalkylated propargylic esters with generally excellent enantioselectivity (>60 examples; up to 99% ee).

Owing to their unique structural properties and ready availability, catalytic radical-mediated difunctionalization of 1,3-enynes has recently been established as a potentially robust platform for construction of valuable substituted allenes and propargylic compounds.[1] Typically, in these processes, allenyl and propargylic radicals that are formed by the initial radical addition to the C–C bond of 1,3-enynes are involved as the key intermediates. Compared with the conventional transition metal-catalysed 2e-ionic mechanism-based methods,[2] these 1e-based radical processes have several potential advantages: (a) a wide range of radicals that could be generated *via* single-electron transfer (SET) from the relative redox-active precursors are capable of adding to 1,3-enynes; (b) the regioselectivity among radical 1,2-, 1,4-, and 3,4-difunctionalizations might be tuned by catalyst systems; (c) wide reaction profiles might be achieved due to the versatile reactivity modes of allenyl and propargylic radicals.

With the identification of various radical precursors, this fast-growing field has witnessed the implementation of various 1,4-difunctionalizations proceeding *via* radical pathways under non-photo-mediated[3–5] or photo-mediated[6–8] conditions. These transformations enabled the simultaneous installation of various C–C and C–X (X = C, S, Se, O) bonds in the target allene products. In sharp contrast, the radical-mediated 1,2-difunctionalisation of 1,3-enynes towards the formation of propargylic scaffolds (1,2-adducts) has received surprisingly less attention (Scheme 1a),[3j,9–11] probably due to the challenges in the control of chemo- and regioselectivity, as well as the conspicuous dearth of catalytic systems.

By using dual photoredox/chromium catalysis, the Glorius group recently disclosed an elegant radical three-component coupling of 1,3-enynes with aldehydes as electrophiles and Hantzsch esters as carbon radical precursors,[12] providing 1,2-adducts, densely functionalised homopropargylic alcohols, in generally high yields. Despite all the impressive advances, notable limitations exist in the field of radical 1,2-difunctionalisation of 1,3-enynes, especially regarding the scope of radical precursors and highly selective catalytic systems. Notably, to our knowledge, no effort has been made to realize catalytic asymmetric radical 1,2-difunctionalization of 1,3-enynes. As part of our continuous effort to pursue photoinduced copper-catalysed asymmetric radical difunctionalisation of alkenes,[13,14] we hypothesized that addition of the cyanoalkyl radicals, which are generated from the oxime esters *via* photoinduced SET-reduction, across 1,3-enynes would produce the propargylic radical intermediates, followed by copper-catalysed C–O coupling with nucleophilic carboxylic acids to achieve asymmetric 1,3-enyne difunctionalisation (Scheme 1b). Apparently, it is very challenging to gain satisfactory control of the chemo-, regio- and enantioselectivities in catalytic multi-

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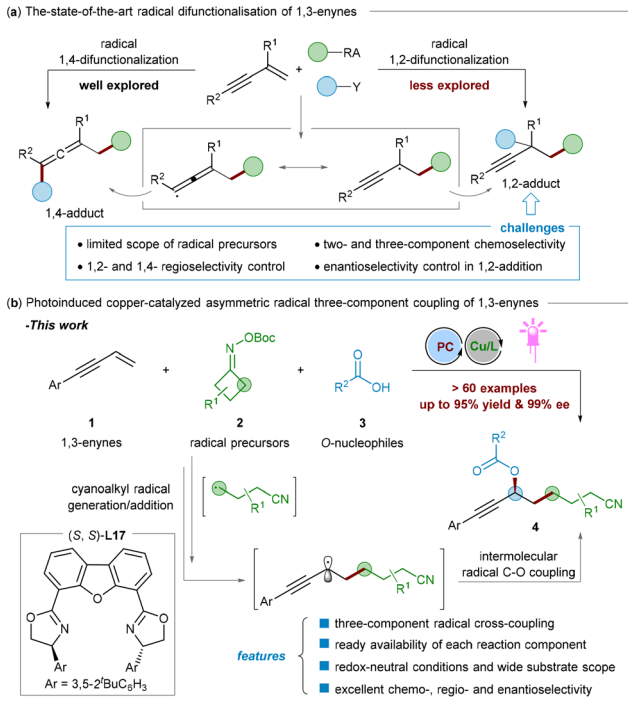


Scheme 1 (a) The-state-of-the-art catalytic radical difunctionalisation of 1,3-enynes. (b) Our reaction design.

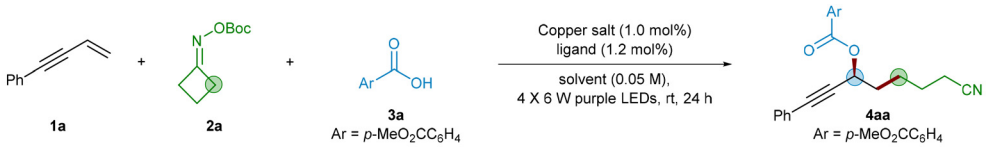
component radical processes,[15] considering the involvement of both interconvertible propargylic radicals and allenyl radicals. Herein, we disclose the implementation of this reaction design plan.

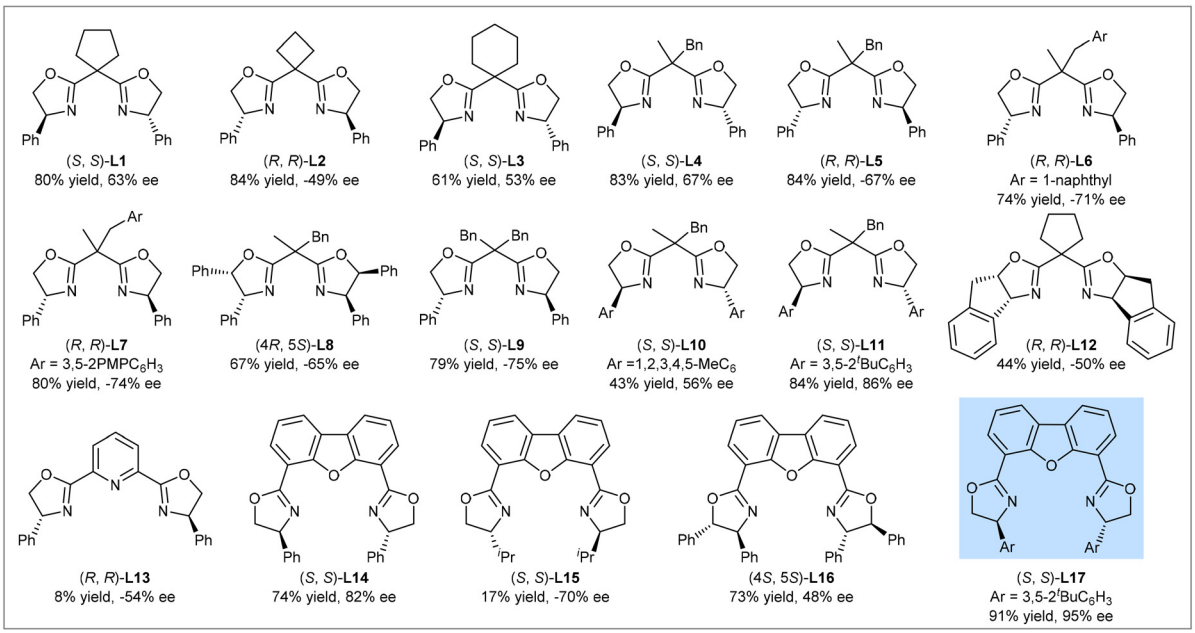
In analogy with our previous reports on photoinduced copper-catalysed asymmetric radical C–O coupling,[13] we began our study by investigating the model three-component reaction of 1,3-enyne **1a**, redox-active oxime ester **2a**,[16] and *para*-ester-substituted benzoic acid **3a** in a 3 : 2 : 1 molar ratio under photoinduced copper catalysis (Table 1).[17] According to our design plan, several radical intermediates such as oxime ester **2a**-derived cyanoalkyl radicals, allenyl or propargylic radicals should be involved; thus, some competing side reactions might be encountered. Pleasingly, it was found that the desired reaction proceeded smoothly to give product **4aa** in 63% NMR yield with 60% ee (Table 1, entry 1), when using a combination of $Cu(CH_3CN)_4PF_6$ (1.0 mol%) and chiral bisoxazoline (Box) ligand **L1** (1.2 mol%) under irradiation of purple LEDs at room temperature for 24 h in 1,2-dichloroethane (DCE). Distinct from our previous report,[13c] no side products such as these resulting from two-component coupling of **2a** and **3a** were detected in this process. Encouraged by this initial outcome, we further simply screened a range of other commonly used solvents and copper salts and discovered that the reaction was very sensitive to these reaction parameters. For example, the use of THF, toluene, or EtOAc led to no formation of desired product (entry 2), while the use of DCM as a solvent produced **4aa** in moderate yield with 34% ee (entry 3). Switching to other copper(I) salts such as CuOAc, CuCN, and CuOTf resulted in no formation of **4aa** or very low yield (entry 4), while $Cu(OTf)_2$ could give comparable results (entry 5, 54% yield, 58% ee). Notably, at 2.0 mol% copper loading, complete conversion into the product was achieved, increasing the yield of **4aa** to 80% with the enantioselectivity maintained (entry 6). A further increase of the catalyst loading did not cause any improvement (entry 7).

It has been well documented that the structural modification of Box-type ligands played a significant role in the copper-catalysed radical cross-coupling reactions.[14,18] So, we proceeded to extensively examine the effect of ligands on the reaction efficiency and enantioselectivity at 2.0 mol% loading, most of which are commercially available or easily prepared. A range of Box-type ligands with cyclic (**L2**, **L3**) and acyclic (**L4–L7**) *gem*-disubstituents were first examined, but did not give significantly improved results in terms of yield or enantioselectivity. Moreover, when using ligand **L8** with double phenyl groups on the oxazoline moiety and the sterically more encumbered ligands **L9–12**, significant improvement of enantioselectivity was observed in the case of ligand **L11**, with **4aa** being formed with 86% ee. In contrast, phenyl-substituted PyBOX ligand **L13** led to very low reaction efficiency. To our delight, further screening of the linker of Box-type ligands disclosed that the 4,6-dibenzofuran dicarboxylic acid-derived bisoxazoline family (*e.g.*, **L14–17**) was viable for the reaction, with the sterically bulkier ligand **L17** bearing 3,5-bis(*tert*-butyl) phenyl groups at the oxazoline scaffold being identified to be the best one of choice, affording the best results (entry 8, 91% yield, 95% ee). A range of control experiments carried out in the absence of visible light irradiation, copper salt or a ligand suggested that each parameter is essential for the current transformation (entries 9–11). Notably, in this process, the chiral copper catalyst works not only as a photoredox catalyst, but also as a coupling catalyst.

With the optimal conditions established, we first explored the substrate scope of 1,3-enynes by reacting with oxime ester **2a** and *para*-ester-substituted benzoic acid **3a** (Table 2). Aside from the neutral 1,3-enyne **1a**, a range of 3-aryl-substituted 1,3-enyne derivatives **1b–k** having an electron-donating (*e.g.*, Me, OMe, ^{n}Pr, ^{t}Bu, Ph) or electron-withdrawing group (*e.g.*, F, CF_3, OCF_3, CO_2Me) at the *para*-position of the aromatic ring were all well tolerated, giving the desired products **4ba–ka** in generally high yields (78–94%) with excellent enantioselectivities (85–96% ee) and exclusive 1,2-regioselectivity. Moreover, 1,3-enynes **1l–r** with functional groups having various electronic properties at the *meta*- or *ortho*-position also reacted well to afford the corresponding cross-coupled products **4la–ra** in 83–94% yields with 93–98% ee. These results demonstrated that variation of the substitution patterns or steric hindrance of the phenyl ring has no deleterious influence on both the reaction efficiency and the regio- and enantioselectivity. Notably, the halogen atoms may be subjected to further synthetic manipulations *via* transition-metal-catalysed coupling at the halogenated positions (products **4ha**, **4oa** and **4ra**). Again, 1,3-enynes **1s** and **1t** with a naphthyl substituent were also proved to be suitable for the reaction, forming products **4sa**

Table 1 Optimisation of the reaction conditions[a]





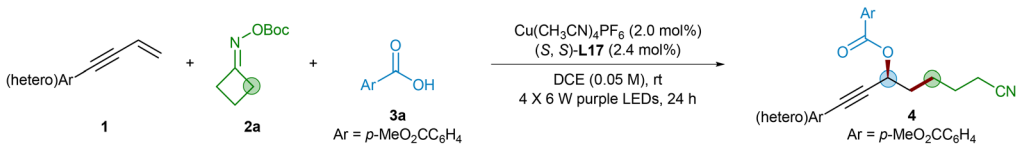
Entry	Copper salt	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	$Cu(CH_3CN)_4PF_6$	(*S*,*S*)-**L1**	DCE	63	60
2	$Cu(CH_3CN)_4PF_6$	(*S*,*S*)-**L1**	THF/toluene/EtOAc	Trace	—
3	$Cu(CH_3CN)_4PF_6$	(*S*,*S*)-**L1**	DCM	33	34
4	CuOAc/CuCN/CuOTf	(*S*,*S*)-**L1**	DCE	<10	<29
5	$Cu(OTf)_2$	(*S*,*S*)-**L1**	DCE	54	58
6[d]	$Cu(CH_3CN)_4PF_6$	(*S*,*S*)-**L1**	DCE	80	63
7[e]	$Cu(CH_3CN)_4PF_6$	(*S*,*S*)-**L1**	DCE	81	60
8[d]	$Cu(CH_3CN)_4PF_6$	(*S*,*S*)-**L17**	DCE	91	95
	Variation from the standard conditions (entry 8)				
9	No light			17	95
10	No $Cu(CH_3CN)_4PF_6$			—	
11	No ligand (*S*,*S*)-**L17**			11	—

[a] Reaction conditions: **1a** (0.3 mmol, 3.0 equiv.), **2a** (0.2 mmol, 2.0 equiv.), **3a** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (0.001 mmol, 1.0 mol%) and chiral ligand (0.0012 mmol, 1.2 mol%) in 2.0 mL of 1,2-dichloroethane (DCE) at rt (25 °C) under an argon atmosphere and irradiation with 4 × 6 W purple LEDs (λ_{max} = 390 nm) for 24 h. [b] NMR yield determined by using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral HPLC. [d] $Cu(CH_3CN)_4PF_6$ (0.002 mmol, 2.0 mol%) and chiral ligand (0.0024 mmol, 2.4 mol%). [e] With $Cu(CH_3CN)_4PF_6$ (0.005 mmol, 5.0 mol%) and chiral ligand **L17** (0.006 mmol, 6.0 mol%).

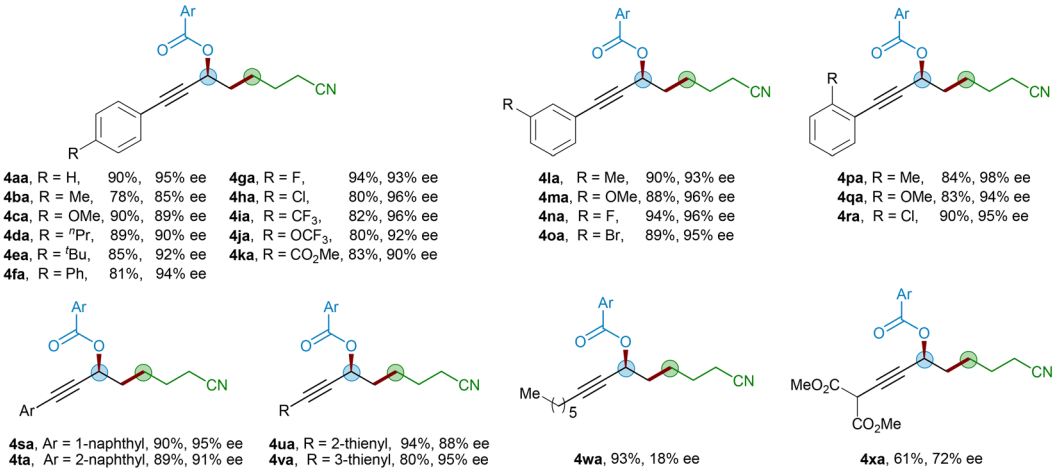
and **4ta** with satisfactory results. Note that 1,3-enynes bearing 2-thiophenyl or 3-thiophenyl were found to be competent substrates, producing **4ua** and **4va** in high yields, with 88% and 95% ee, respectively. We also examined alkyl-substituted 1,3-enynes **1w** and **1x** that contain linear alkyl or ester groups under the standard conditions. Both substrates reacted with **2a** and **3a** smoothly, affording the desired products **4wa** and **4xa** in high yields, but with moderate to good enantioselectivities.

Next, we proceeded to briefly investigate the substrate scope of oxime esters easily prepared from cyclobutanone derivatives by reacting with **1a** and carboxylic acids **3a** or **3c** under the standard conditions (Table 3). The variation of the ring moiety of the oxime ester has no deleterious effect on this three-component coupling. For example, the reactions of sterically congested 3,3-disubstituted oxime esters **2b** and **2c** proceeded smoothly to deliver products **5ba** and **5ca** with good outcomes. Geometrically strained oxime ester **2d**, derived from (1*R*,5*S*)-bicyclo[3.2.0]hept-2-en-6-one, could also react well to give the desired cross-coupled product **5da** with good yield and enantioselectivity but with 1 : 1.2 dr, because of the loss of stereochemical information of one stereogenic center during the iminyl radical-mediated ring-opening process of **2d**.

Table 2 Scope of the 1,3-enynes for photoinduced copper-catalysed asymmetric radical three-component cross-coupling[a]



1 2a 3a Ar = *p*-$MeO_2CC_6H_4$ 4 Ar = *p*-$MeO_2CC_6H_4$



4aa, R = H, 90%, 95% ee
4ba, R = Me, 78%, 85% ee
4ca, R = OMe, 90%, 89% ee
4da, R = ^{n}Pr, 89%, 90% ee
4ea, R = ^{t}Bu, 85%, 92% ee
4fa, R = Ph, 81%, 94% ee
4ga, R = F, 94%, 93% ee
4ha, R = Cl, 80%, 96% ee
4ia, R = CF_3, 82%, 96% ee
4ja, R = OCF_3, 80%, 92% ee
4ka, R = CO_2Me, 83%, 90% ee

4la, R = Me, 90%, 93% ee
4ma, R = OMe, 88%, 96% ee
4na, R = F, 94%, 96% ee
4oa, R = Br, 89%, 95% ee

4pa, R = Me, 84%, 98% ee
4qa, R = OMe, 83%, 94% ee
4ra, R = Cl, 90%, 95% ee

4sa, Ar = 1-naphthyl, 90%, 95% ee
4ta, Ar = 2-naphthyl, 89%, 91% ee

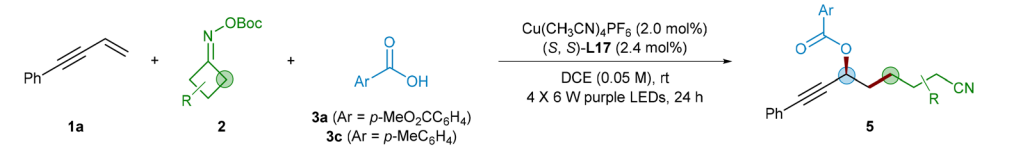
4ua, R = 2-thienyl, 94%, 88% ee
4va, R = 3-thienyl, 80%, 95% ee

4wa, 93%, 18% ee

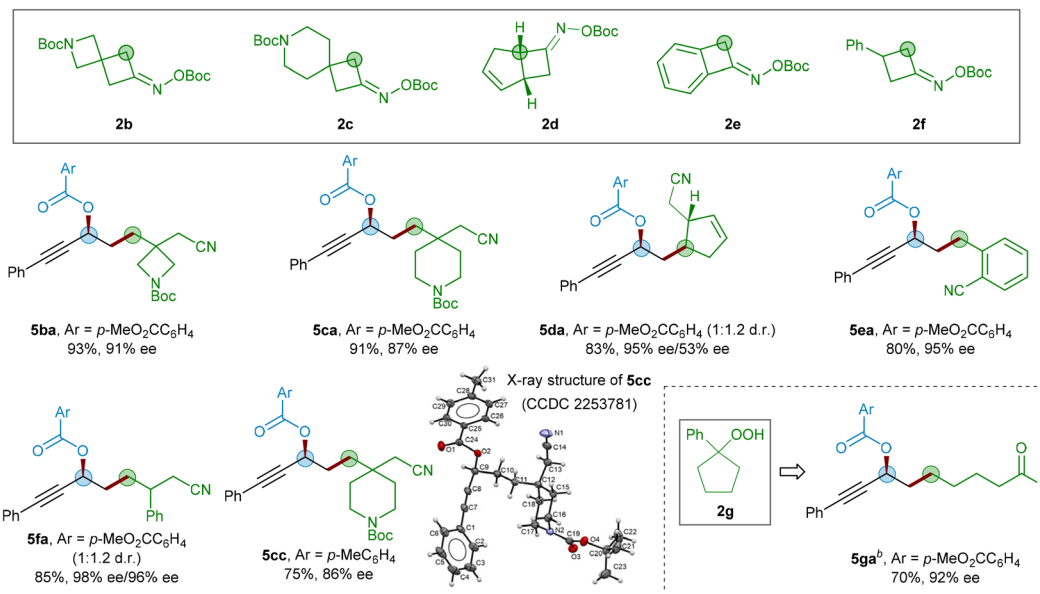
4xa, 61%, 72% ee

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), **3a** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (2.0 mol%), chiral ligand **L17** (2.4 mol%), 1,2-dichloroethane (DCE) (2.0 mL), 4 × 6 W purple LEDs (λ_{max} = 390 nm), rt (25 °C), 24 h; isolated yield.

Table 3 Scope of the oxime esters for photoinduced copper-catalysed asymmetric radical three-component cross-coupling[a]



1a 2 3a (Ar = *p*-$MeO_2CC_6H_4$) 3c (Ar = *p*-MeC_6H_4) 5



2b **2c** **2d** **2e** **2f**

5ba, Ar = *p*-$MeO_2CC_6H_4$, 93%, 91% ee

5ca, Ar = *p*-$MeO_2CC_6H_4$, 91%, 87% ee

5da, Ar = *p*-$MeO_2CC_6H_4$ (1:1.2 d.r.), 83%, 95% ee/53% ee

5ea, Ar = *p*-$MeO_2CC_6H_4$, 80%, 95% ee

5fa, Ar = *p*-$MeO_2CC_6H_4$, (1:1.2 d.r.), 85%, 98% ee/96% ee

5cc, Ar = *p*-MeC_6H_4, 75%, 86% ee

X-ray structure of **5cc** (CCDC 2253781)

2g

5ga[b], Ar = *p*-$MeO_2CC_6H_4$, 70%, 92% ee

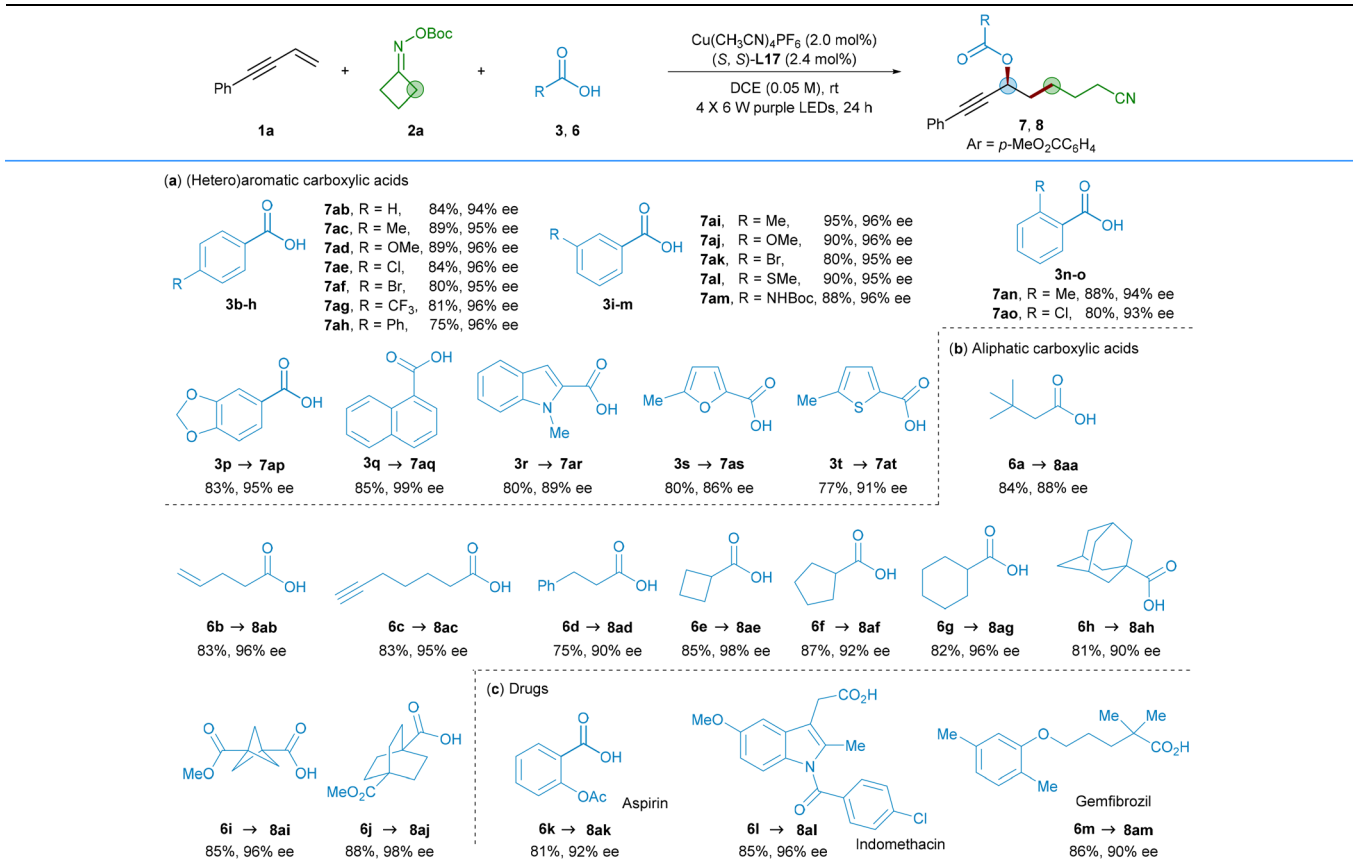
[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), **3a** or **3c** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (2.0 mol%), chiral ligand **L17** (2.4 mol%), 1,2-dichloroethane (DCE) (2.0 mL), 4 × 6 W purple LEDs (λ_{max} = 390 nm), rt (25 °C), 24 h; isolated yield. [b] Without light.

Moreover, benzocyclobutenone-derived oxime ester **2e** participated in the reaction very well to afford product **5ea** in 80% yield with 95% ee. Notably, 3-phenyl-substituted oxime ester **2f** was also found to be a viable substrate, producing **5fa** with excellent yield and enantioselectivity, but with moderate diastereoselectivity. The reaction of oxime ester **2b** with 1,3-enyne **1a** and carboxylic acid **3c** led to the formation of the desired **5cc** with good yield and enantioselectivity. And the newly formed propargylic stereocenter of **5cc** was unambiguously determined to be (*S*)-configuration by X-ray crystallography. Therefore, other three-component cross-coupling products can be tentatively assigned by analogy. Remarkably, peroxide **2g** that is bench-stable and easy-to-handle could also work as an alkyl radical precursor to react with **1a** and **3a** under our catalytic system without light irradiation, furnishing the corresponding 1,2-adduct **5ga** in good yield with 92% ee, highlighting the potential application of our catalytic strategy.

Finally, we turned our attention to investigating the substrate scope of carboxylic acids, all of which are commercially available. First, we found the scope of aromatic and heteroaromatic carboxylic acids to be remarkably wide (Table 4a). For example, a wide variety of aromatic carboxylic acids **3b–h** with electron-neutral (H), electron-donating (*e.g.*, Me, OMe), electron-withdrawing (*e.g.*, Cl, Br, CF_3), as well as phenyl substituents at the *para*-position of the phenyl ring were all accommodated, giving the corresponding products **7ab–am** in good yields with excellent enantioselectivity (94–96% ee). Furthermore, variation of the substitution patterns and steric hindrance of the aromatic ring was also tolerated. As shown in the case of carboxylic acids **1i–o**, various common substituents at the *meta*- or *ortho*-position were all compatible with this transformation, with the expected products **7ai–ao** being isolated with consistently high yields (80–95%) and excellent enantioselectivities (93–96% ee). Again, both disubstituted carboxylic acid **3p** and fused aromatic carboxylic acid **3q** were viable substrates, affording products **7ap** and **7aq** with 95% ee and 99% ee, respectively. Note that the reaction could also be successfully extended to five-membered heteroaryl-substituted carboxylic acids such as **3r–t**, with the corresponding products **7ar–at** being obtained with satisfactory results.

Then, we continued to explore the scope of aliphatic acids, and the results are summarized in Table 4b. Pleasingly, a representative set of linear aliphatic acids **6a–d** with various lengths of alkyl chains were all well accommodated, to provide the corresponding products **8aa–ad** in good to high yields with high enantioselectivity (88–95% ee). Notably, as shown in the

Table 4 Scope of the carboxylic acids for photoinduced copper-catalysed asymmetric radical three-component cross-coupling[a]

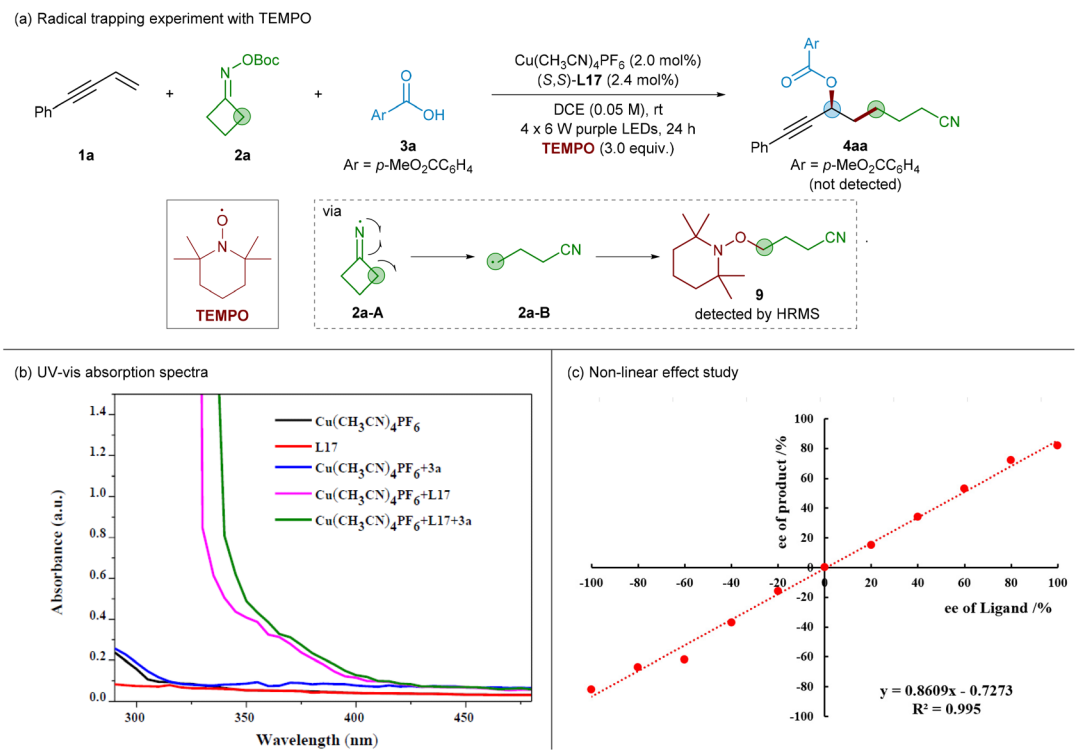


[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), **3** or **6** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (2.0 mol%), chiral ligand **L17** (2.4 mol%), 1,2-dichloroethane (DCE) (2.0 mL), 4 × 6 W purple LEDs (λ_{max} = 390 nm), rt (25 °C), 24 h; isolated yield.

cases of **8ab** and **8ac**, the radical-sensitive terminal alkene and alkyne groups remain intact, allowing their further synthetic elaboration. Moreover, sterically more hindered α-branched cyclic secondary alkyl carboxylic acids **6e–g** all were compatible to give products **8ae–ag** with satisfactory results (82–87% yields, 92–98% ee). Impressively, the reactions of biologically interesting and sterically very demanding α-tertiary carboxylic acids, such as adamantly acid **6h**, bicyclo[1.1.1]pentane (BCP)-containing carboxylic acid **6i**, and bicyclo[2.2.2]octane-1,4-dicarboxylic acid hemimethyl ester **6j** all proved to be suitable for the reaction, giving the cross-coupled products **8ah–aj** with high yields and enantioselectivity. Given the prevalence of the carboxylic acid group in numerous pharmaceuticals and good functional group tolerance of this protocol, we also evaluated several carboxylic acid group-containing marked drugs to further highlight the robustness of the developed cross-coupling reaction (Table 4c). Under the standard conditions, simple Aspirin **6k** participated in the reaction smoothly to give cross-coupled product **8ak** in 81% yield with 92% ee. Meanwhile, aliphatic primary carboxylic acid-based and structural complex indomethacin **6l** and encumbered Gemfibrozil **6m** were both well tolerated to afford the desired products **8al** and **8am** in high yields with 96% and 90% ee, respectively.

To gain some insight into the mechanism, we carried out some mechanistic studies (Scheme 2). When the stoichiometric radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the model reaction of **1a**, **2a** and **3a**, the formation of the desired product **4aa** was completely suppressed (Scheme 2a). Instead, the corresponding TEMPO-trapping adduct **9** could be detected by high-resolution mass spectrometry (HRMS), implying the radical property of the process and possible involvement of cyanoalkyl radical **2a-B** that should be formed from iminyl radical **2a-A** *via* β-C–C bond cleavage.[16]

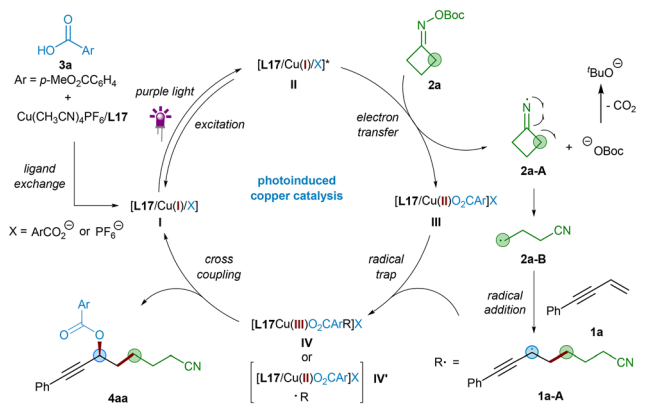
To further probe the photo-reactivity of the copper species that might be engaged in the process, we achieved the UV-vis absorption spectra of each reaction component and related mixtures (Scheme 2b). We found that a DCE solution of Cu$(CH_3CN)_4PF_6$, chiral ligand **L17** or a mixture of Cu$(CH_3CN)_4PF_6$ and carboxylic acid **3a** did not display any obvious absorption band in the visible-light region, with absorptions all having wavelengths of around <320 nm. In sharp contrast, the solution of a mixture of Cu$(CH_3CN)_4PF_6$ and chiral ligand **L17** demonstrated absorption within the visible-light region, and further addition of acid **3a** resulted in a slight bathochromic shift and an obvious absorption enhancement in the range of 370–420 nm. These observations suggest that photoactive species Cu/**L17** or a more photoactive species Cu/**L17**/**3a** complex formed *in situ* by the ligand exchange process should be operative in both iminyl radical generation and the subsequent radical C–O cross-coupling event. Furthermore, a complete linear relationship between the enantiopurities of the product **4aa** and ligand **L14** (Scheme 2c) was observed. These results suggest that the active catalyst species for the enantio-induction in the C–O bond-forming step was consistent with a 1 : 1 ratio of Cu$(CH_3CN)_4PF_6$ and the chiral ligand.



Scheme 2 Mechanistic studies. (a) Reactions in the presence of radical trappers. (b) UV-vis absorption spectroscopy studies (c = 2.5 mM in DCE). (c) Nonlinear effect study with ligand **L14**.

Based on these mechanistic studies and previous literature reports,[18,19] we proposed a plausible mechanism for this three-component radical cross-coupling reaction with model substrates (Scheme 3). Initially, irradiation of a light-absorbing species **I** that should be **L17**/Cu(I) or **L17**/Cu(I)/**3a** with purple light could lead to its excited state **II**. Then, the highly reducing species **II** could engage in a single electron transfer (SET) process with the redox-active oxime ester **2a** to generate iminyl radical **2a-A** and Cu(II) species **III**, with the release of a carboxylic anion ($BocO^-$). Meanwhile, iminyl radical **2a-A** undergoes a facile ring-opening β-C–C cleavage to give cyanoalkyl radical **2a-B**, which further adds to the terminal carbon of the alkene moiety of the 1,3-enyne **1a** to form stabilized propargyl radical **1a-A**.[20] Considering the great capability of Cu(II) complexes to intercept carbon radicals, the Cu(II) complex **II** might bind with **1a-A** to form Cu(III) complex **IV**, which undergoes enantioselective reductive elimination to afford the final C–O cross-coupled product **4aa**. It is noteworthy that Cu(III) complex **IV** might also exist in equilibrium with hybrid propargyl radical-type Cu(II) complex **IV′**, which would then engage in an out-sphere enantioselective radical transfer or SET-oxidation event.[18b] At this stage, these alternative pathways cannot be ruled out though we prefer the Cu(I)/(II)/(III)-based catalytic pathway depicted in Scheme 3. Notably, in this process, the *in situ*-formed chiral copper catalyst functionalises not only as a photoredox catalyst, but also as the origin of enantioselective induction in propargyl C–O cross-coupling. Moreover, the overall process is also redox neutral and avoids the addition of any external oxidant or reductant.

In conclusion, we have developed for the first time a visible-light-induced copper-catalysed asymmetric radical three-component coupling of 1,3-enynes, oxime esters, and carboxylic acids. This protocol is distinguished by its exquisite 1,2-regioselectivity, excellent enantioselectivity, and wide substrate scope, thus providing a practical approach for the construction of valuable chiral cyanoalkylated propargylic esters. Work on the further expansion of the scope of radical precursors and nucleophilic coupling partners is ongoing in our laboratory.



Scheme 3 Proposed catalytic cycle.

Conflicts of interest

There are no conflicts to declare.

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