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Oxidative Cross-Coupling

Copper-Catalyzed Intermolecular Enantioselective Radical Oxidative C(sp^3)–H/C(sp)–H Cross-Coupling with Rationally Designed Oxazoline-Derived N,N,P(O)-Ligands

Lin Liu, Kai-Xin Guo, Yu Tian, Chang-Jiang Yang, Qiang-Shuai Gu, Zhong-Liang Li, Liu Ye, and Xin-Yuan Liu**

Dedicated to the 100th anniversary of Chemistry at Nankai University

Abstract: *The intermolecular asymmetric radical oxidative C(sp^3)–C(sp) cross-coupling of C(sp^3)–H bonds with readily available terminal alkynes is a promising method to forge chiral C(sp^3)–C(sp) bonds because of the high atom and step economy, but remains underexplored. Here, we report a copper-catalyzed asymmetric C(sp^3)–C(sp) cross-coupling of (hetero)benzylic and (cyclic)allylic C–H bonds with terminal alkynes that occurs with high to excellent enantioselectivity. Critical to the success is the rational design of chiral oxazoline-derived N,N,P(O)-ligands that not only tolerate the strong oxidative conditions which are requisite for intermolecular hydrogen atom abstraction (HAA) processes but also induce the challenging enantiocontrol. Direct access to a range of synthetically useful chiral benzylic alkynes and 1,4-enynes, high site-selectivity among similar C(sp^3)–H bonds, and facile synthesis of enantioenriched medicinally relevant compounds make this approach very attractive.*

Introduction

Asymmetric C(sp^3)–C(sp) cross-coupling has become a powerful tool to forge chiral C–C bonds.[1] Among such approaches, the direct alkynylation of C(sp^3)–H bonds represents an ideal route because of the high atom and step economy. In this regard, transition-metal-catalyzed regioselective C(sp^3)–H activation through the use of a directing group[2] and cross-dehydrogenative coupling of C(sp^3)–H bonds adjacent to heteroatoms[3] have evolved into efficient approaches for the construction of chiral C(sp^3)–C(sp) bonds. Recently, HAA-mediated C(sp^3)–H functionalization has attracted much attention, because of its good site-selectivity in the absence of directing groups and its broad application to diverse C(sp^3)–H bonds.[4–7] Thus, the HAA-initiated asymmetric alkynylation of C(sp^3)–H bonds with nucleophilic alkynylating reagents would provide a new promising approach toward chiral alkynes.[1] Our group has recently developed a catalytic system composed of copper and a chiral N,N,P-ligand based on the cinchona alkaloid[8] for the asymmetric oxidative cross-coupling of C(sp^3)–H bonds using terminal alkynes as the nucleophiles.[5e] However, the incorporation of mildly oxidative *N*-fluoroalkylamides, which tolerate both terminal alkynes and a chiral N,N,P-ligand, in the substrates to initiate an efficient intramolecular 1,5(6)-HAA process is crucial for high reaction efficiency. Recently, Liu and co-workers have reported the intermolecular asymmetric alkynylation of benzylic C–H bonds with $(MeO)_3Si$-prefunctionalized alkynes by using a copper/chiral bisoxazoline catalyst (Scheme 1a).[6d] Notably, the combination of silylated alkynes as nucleophiles and the N-F reagent as oxidant plays a key role in achieving high reaction efficiency, but terminal alkynes are not suitable for this catalytic system (see Scheme S1 in the Supporting Information). The drawback of the two strategies mentioned above is the requirement of prefunctionalized substrates or alkynyl reagents. Therefore, the development of a suitable chiral copper catalyst for the asymmetric oxidative C(sp^3)–C(sp) cross-coupling of simple starting materials with terminal alkynes is highly desirable.[9] However, some challenges need to be addressed: a) the requirement of an electrophilic hydrogen atom abstractor derived from a strong oxidant to realize the high efficiency of the intermolecular HAA process, b) the incompatibility of terminal alkynes and chiral ligands with strongly oxidative conditions in the copper catalytic system because of the readily occurring Glaser homocoupling of alkynes.[9] We envisioned that the development of a suitable copper catalytic system with both sufficient hydrogen atom abstracting ability and good compatibility with terminal alkynes and chiral ligands is critical for the success (Scheme 1b).

Inspired by our recent studies regarding the use of a Cu/N,N,P-ligand catalyst for asymmetric alkynylation with terminal alkynes,[5e,10] we initially tested the copper catalyst with the N,N,P-ligands in this cross-coupling. Unfortunately, preliminary results with **L1** showed that the use of a strong oxidant (NFSI) resulted in fast decomposition of this chiral ligand, while a mild oxidant (**N-F-1**) led to low reaction

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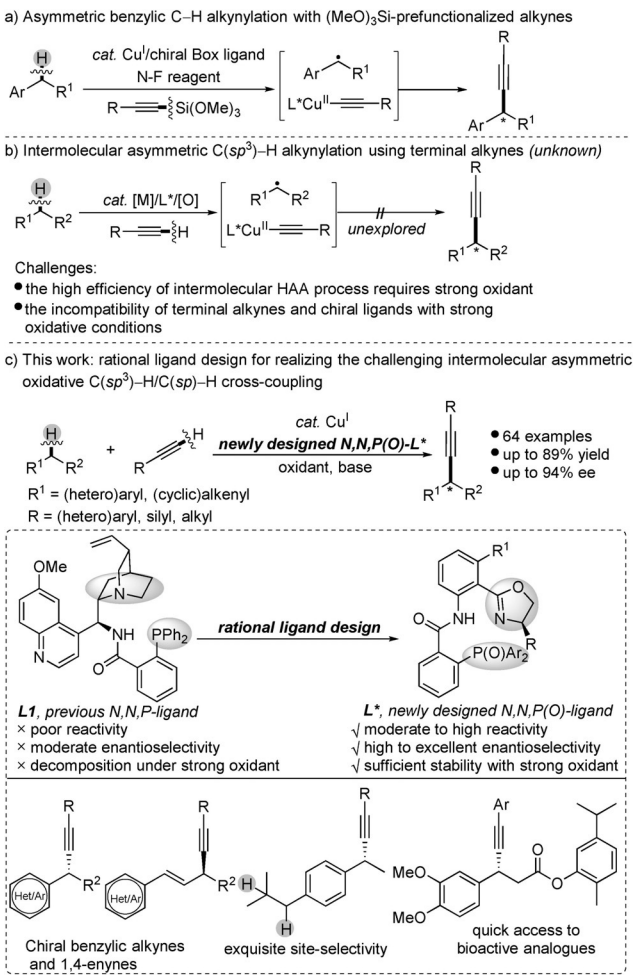


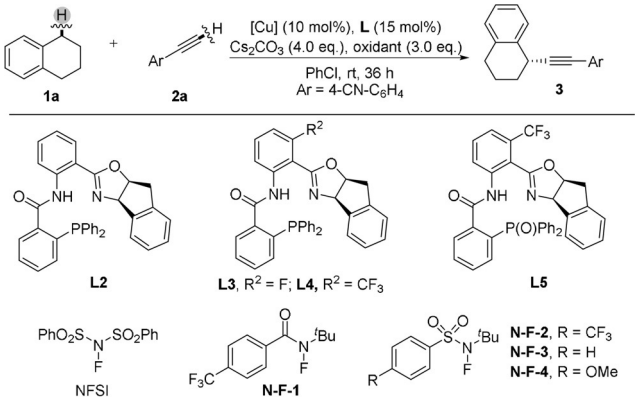
Scheme 1. Copper-catalyzed enantioselective radical oxidative C(sp^3)–C(sp) cross-coupling.

efficiency (see Scheme S2). As such, we envisaged that a rationally designed new chiral ligand scaffold, which would be not only compatible with such strong oxidative conditions but also capable of inducing excellent enantiocontrol, is critical for the achievement of such a transformation. As a consequence, we rationally designed multidentate anionic N,N,P(O)-ligands bearing chiral oxazoline and pentavalent phosphine oxide building blocks in place of the easily oxidized tertiary alkyl amine and trivalent aryl phosphine, respectively, to satisfy the above-mentioned requirements (Scheme 1c). To this end, we describe our efforts in developing a set of novel chiral oxazoline-derived anionic N,N,P(O)-ligands for the copper-catalyzed intermolecular asymmetric radical oxidative C(sp^3)–C(sp) cross-coupling of benzylic/allylic C–H bonds and terminal alkynes (Scheme 1c). This procedure allows the straightforward construction of enantioenriched benzylic alkynes and 1,4-enynes from readily accessible alkyl (hetero)arenes and (cyclic) alkenes. Notably, the reaction not only exhibits exquisite site selectivity among C(sp^3)–H bonds with similar properties, but also has found broad application in the facile synthesis of enantioenriched medicinally relevant compounds.

Results and Discussion

We initially tested the reaction of tetrahydronaphthalene (**1a**) with 4-ethynylbenzonitrile (**2a**) using *N*-fluoroalkylsulfonamide as the oxidant, which has been widely studied by Alexanian and co-workers in intermolecular HAA-type radical reactions.[11] Our endeavor toward ligand design initially focused on the modification of the tertiary alkyl amine and trivalent aryl phosphine of **L1**. We firstly replaced the tertiary alkyl amine moiety with the chiral oxazoline, which generally exhibits sufficient stability under oxidative conditions.[12] The thus-modified chiral ligand **L2** significantly improved the yield of **3** to 50% with remarkably enhanced enantioselectivity (76% *ee*) and inhibited the Glaser coupling side reaction of **2a** (Table 1, entries 1 and 2). Introducing an electron-withdrawing group on the aryl ring has a beneficial effect on the enantioselectivity, and **L4** with a CF_3 group afforded the coupling product **3** with 89% *ee* (Table 1,

Table 1: Screening of reaction conditions.[a]



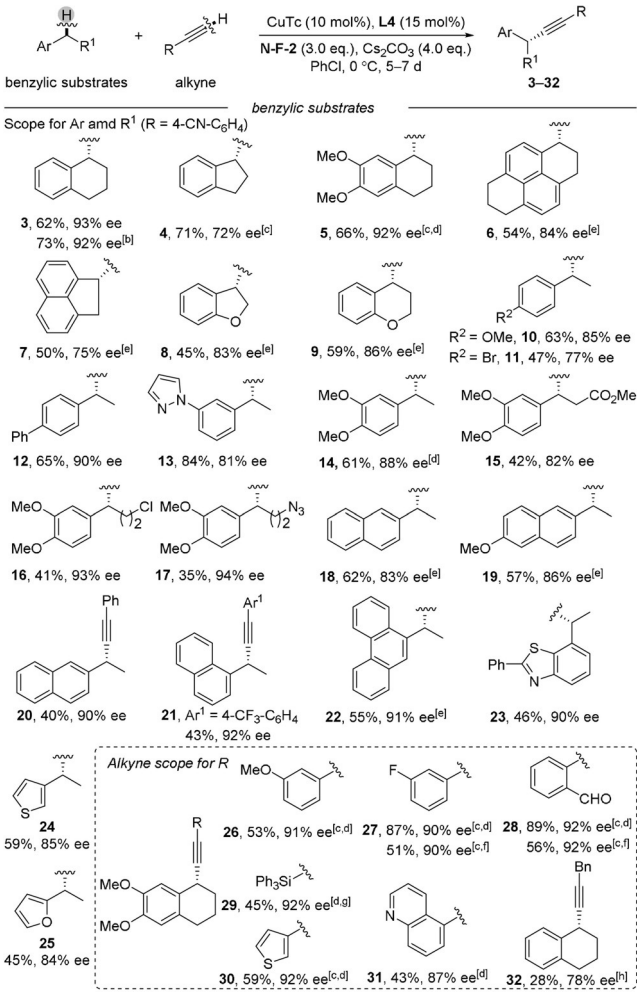
Entry	[Cu]	L	Oxidant	Yield [%][b]	*ee* [%][c]
1	$Cu(MeCN)_4BF_4$	**L1**	**N-F-2**	28	50
2	$Cu(MeCN)_4BF_4$	**L2**	**N-F-2**	50	76
3	$Cu(MeCN)_4BF_4$	**L3**	**N-F-2**	49	84
4	$Cu(MeCN)_4BF_4$	**L4**	**N-F-2**	46	89
5	$Cu(MeCN)_4BF_4$	**L5**	**N-F-2**	46	86
6	$Cu(MeCN)_4BF_4$	**L4**	oxidants	trace	ND
7	$Cu(MeCN)_4BF_4$	**L4**	**N-F-1**	22	87
8[d]	$Cu(MeCN)_4BF_4$	**L4**	NSFI	trace	ND
9	$Cu(MeCN)_4BF_4$	**L4**	**N-F-3**	39	88
10	$Cu(MeCN)_4BF_4$	**L4**	**N-F-4**	42	88
11[e]	$Cu(MeCN)_4BF_4$	**L4**	**N-F-2**	51	91
12[f]	$Cu(MeCN)_4BF_4$	**L4**	**N-F-2**	52	93
13[f]	CuTc	**L4**	**N-F-2**	62[g]	93
14[h]	CuTc	**L5**	**N-F-2**	61[g]	93
15[f,i]	CuTc	**L4**	**N-F-2**	22	95
16[f,j]	CuTc	**L4**	**N-F-2**	23	94

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.05 mmol), [Cu] (10 mol%), **L** (15 mol%), Cs_2CO_3 (0.20 mmol), and oxidant (0.15 mmol) in dry PhCl (0.4 mL) at rt for 36 h. [b] Yield based on ^{1}H NMR analysis of the crude product using $Cl_2CHCHCl_2$ as an internal standard. [c] *ee* values based on HPLC analysis. [d] Conversion of **2a** was 35%. [e] Reaction was run at 10°C for 72 h. [f] Reaction was run at 0°C for 5 days. [g] Yield of isolated **3** on a 0.10 mmol scale. [h] Reaction was run at 0°C for 7 days. [i] **1a** (1.0 equiv), **2a** (1.0 equiv) on a 0.10 mmol scale. [j] **1a** (1.0 equiv), **2a** (4.0 equiv) on a 0.10 mmol scale. ND = not determined.

entries 3 and 4). We then tested the effect of replacing the trivalent aryl phosphine moiety. Interestingly, **L5**, which possesses a pentavalent phosphine oxide moiety, is also applicable for this transformation (Table 1, entry 5). We then evaluated the effect of different types of oxidants, including $(^tBuO)_2$, $^tBuO_2H$, $PhI(OAc)_2$, and $PhCO_3{}^tBu$, and all of the reactions failed to give the desired product **3** (Table 1, entries 6–10; see also Table S1 for details). N-F reagents are the only oxidants that gave the target product. The mild oxidant *N*-fluoroalkylamide (**N-F-1**) resulted in a dramatically decreased yield of **3**. The much stronger oxidant NFSI[6,7b–d] gave only a trace amount of the desired product, likely as a result of the polymerization of **2a** induced by the attack of the less bulky imidyl radical on the terminal alkyne (Figures S1–S3). Collectively, these observations suggest that a suitable oxidant capable of abstracting a $C(sp^3)$–H bond efficiently as well as tolerating a terminal alkyne is of great importance for this reaction. Varying the substituents on the aryl ring of *N*-fluoroalkylsulfonamide had a negligible effect on the enantioselectivity, which implies that the enantioselectivity was independent of the HAA step (Table 1, entries 9 and 10). Further screening of copper salts and solvents led to no better reaction outcome (Table S1). Lowering the reaction temperature led to a higher yield and enantioselectivity (91 % *ee*; Table 1, entries 11 and 12). The use of CuTc further improved the yield of isolated **3** to 62 % (Table 1, entry 13). Screening the amount of base revealed that 4.0 equiv of base is necessary for complete consumption of **2a** (Table S2). A comparable reaction outcome was obtained with **L5** as the ligand and a prolonged reaction time (Table 1, entry 14). These results suggest that pentavalent phosphine oxide might be the active catalyst for this reaction (Table 1, entries 5 and 14; see also the mechanistic studies section). However, when C–H substrate **1a** was employed as the limiting reagent, a dramatically decreased yield of **3** was observed, no matter whether 1.0 equiv or 4.0 equiv of **2a** were added, which is indicative of the detrimental effect an excess amount of terminal alkyne can have on this transformation (Table 1, entries 15 and 16). Control experiments revealed that a copper salt, base, and ligand are indispensable for the reaction (Table S1).

With the optimized conditions in hand, the scope of the benzylic C–H substrates was first investigated (Table 2). A diverse range of cyclic benzylic C–H bonds underwent the alkynylation reaction successfully to afford the corresponding products **3**–**9** in yields of 50–71 % and 72–93 % *ee*. Notably, the reaction could be run on a gram scale to give **3** in 73 % yield without any apparent loss of enantioselectivity. The absolute configuration of **3** was determined to be *S* by comparing the HPLC spectrum of its derivative with that of the commercially available chiral material (see the Supporting Information for details). In cases where the *ee* value was not high, the reaction temperature was further decreased, but the reaction efficiency was also affected. Under such circumstances, irradiation of the reaction mixture with a blue LED is necessary, since the reducing capability of the photo-excited copper acetylide complex is strong and would promote the coupling reaction through the acceleration of single-electron transfer processes with the oxidant.[10e,13] Moreover, a variety

Table 2: Substrate scope of benzylic $C(sp^3)$–H alkynylation.[a]



[a] Reaction conditions: benzylic substrates (1.0 mmol), alkyne (0.10 mmol), CuTc (10 mol %), **L4** (15 mol %), Cs_2CO_3 (0.40 mmol), and **N-F-2** (0.30 mmol) in dry PhCl (0.8 mL) at 0 °C for 5–7 days. Yield of isolated product based on the alkyne is given. *ee* values are based on HPLC analysis. [b] **2a** was used on an 8 mmol scale and the reaction time was 12 days. [c] Reaction was run at −15 °C under irradiation with a blue LED (24 W) for 10 days. [d] Benzylic substrates (5.0 equiv). [e] $Cu(MeCN)_4BF_4$ (10 mol %). [f] Benzylic substrates (3.0 equiv). [g] At 0 °C for 4 days and then at rt for 4 days. [h] At rt for 5 days.

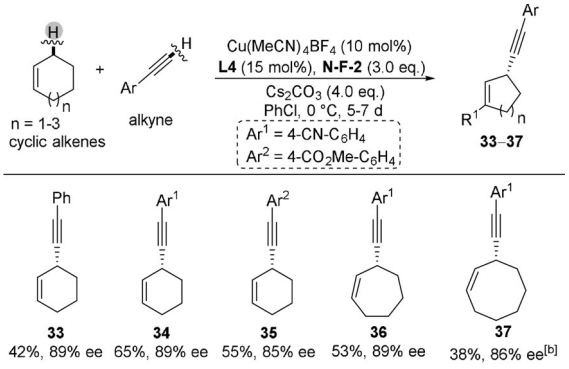
of alkylbenzenes also reacted well. A range of substituents (OMe, Br, Ph, pyrazole) regardless of their position on the phenyl rings were well-tolerated and delivered **10**–**14** in yields of 47–84 % and 77–90 % *ee*. Competition experiments demonstrated that an ethylbenzene substrate with an electron-donating group has higher reactivity than that with an electron-withdrawing group (Scheme S3). Alkylbenzenes bearing diverse functional groups (ester, halide, and azide) on the alkyl chain could be employed for this reaction to yield **15**–**17** with good to excellent enantioselectivity. 2-/1-Ethylnaphthalenes and 9-ethylphenanthrene were also suitable for the reaction and afforded **18**–**22** with 83–92 % *ee*. The absolute configuration of **20** was determined to be *R* by comparing its HPLC spectrum with that reported in the literature.[10c] Various heteroarenes are well-tolerated under

the present reaction conditions, and **23**–**25** can be obtained with good enantioselectivity. Notably, cyclic benzylic halides and benzyl halides with strong electron-donating functional groups (OMe) at the *para*-positions of the phenyl rings are inapplicable in our previous Sonogashira $C(sp^3)$–$C(sp)$ coupling with alkyl halides (Scheme S4).[10c] Hence, the current asymmetric alkynylation of $C(sp^3)$–H bonds provides a vital complementary approach to our previous cross-coupling reaction. As for the scope of alkynes, many (hetero)aryl, alkyl, and silylated alkynes reacted, with **26**–**32** obtained with up to 92% *ee*, and an aldehydic C–H bond with low bond disassociation energy was also well-tolerated.[14] It is noteworthy that moderate yields of **27** and **28** could be obtained when reducing the amount of the C–H substrates to 3.0 equiv. Generally, the alkyl alkynes gave rise to the coupling product (**32**) less efficiently and with a lower *ee* value.

Inspired by the successful alkynylation of benzylic C–H bonds, we next explored the feasibility of allylic C–H bonds in the reaction, which could provide access to synthetically useful chiral 1,4-enynes building blocks.[15] The cyclic allylic C–H bonds underwent the asymmetric alkynylation to afford the corresponding chiral 1,4-enynes **33**–**37** with good enantioselectivity when CuTc was switched to $Cu(MeCN)_4BF_4$ (Table 3). The absolute configuration of **33** was determined to be *R* by comparing its optical rotation with that reported in the literature.[15c] Competition experiments demonstrated that cyclic allylic C–H substrates show higher reactivity than the benzylic C–H substrates (Scheme S3).

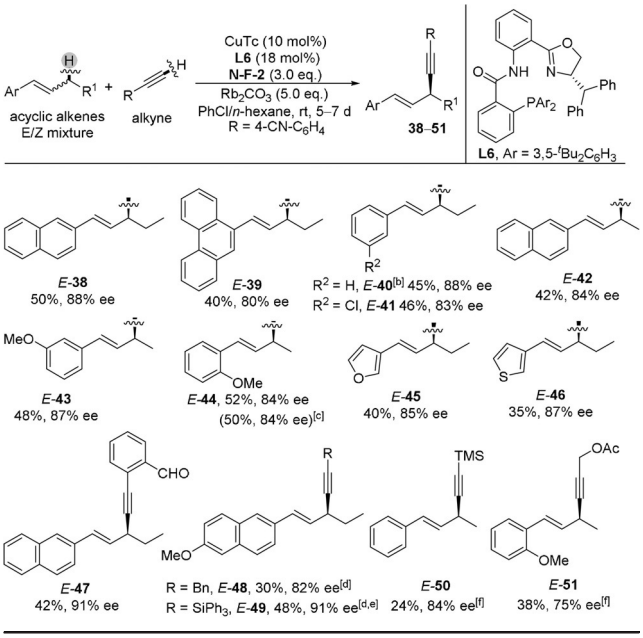
To further extend the application of the reaction, we turned our attention to acyclic allylic C–H bond substrates.[16] Unfortunately, the optimal conditions for benzylic C–H alkynylation were not applicable, only leading to a trace amount of the desired product with poor enantioselectivity. After systematic screening of reaction parameters and modifying the chiral ligands (Table S3), the alkynylated product **38** could be obtained in 50% yield and 88% *ee* by using Rb_2CO_3 as the base and **L6** as the ligand. Many aryl and heteroaryl substituents on the alkene moiety and diverse alkynes were amenable to the reaction, with **38**–**51** obtained

Table 3: Substrate scope of cyclic alkenes.[a]



[a] Reaction conditions: cyclic alkenes (1.0 mmol), alkyne (0.10 mmol), $Cu(MeCN)_4BF_4$ (10 mol%), **L4** (15 mol%), Cs_2CO_3 (0.40 mmol), and **N-F-2** (0.30 mmol) in dry PhCl (0.8 mL) at 0 °C for 5–7 days. Yield of isolated product based on alkyne is given. *ee* values are based on HPLC analysis. [b] CuTc (10 mol%) at rt.

Table 4: Substrate scope of acyclic alkenes.[a]

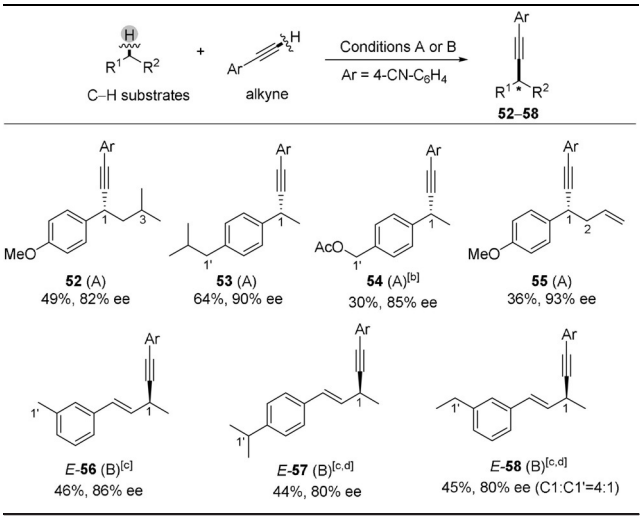


[a] Reaction conditions: acyclic alkenes (1.0 mmol), alkyne (0.10 mmol), CuTc (10 mol%), **L6** (18 mol%), Rb_2CO_3 (0.50 mmol), and **N-F-2** (0.30 mmol) in dry PhCl/*n*-hexane (v/v = 3:1, 0.8 mL) at rt for 5–7 days. Yield of isolated product based on the alkyne is given. *ee* values are based on HPLC analysis. [b] *E* isomer of the alkene substrate was used. [c] **L7** (18 mol%) was used. [d] Alkene (7.5 equiv), CuTc (15 mol%), **L6** (20 mol%), and Rb_2CO_3 (0.60 mmol) were used. [e] Yield was based on recovered alkyne. [f] $Cu(MeCN)_4BF_4$ (15 mol%) and **L6** (20 mol%) were used.

in moderate yields and 75–91% *ee* (Table 4). With phosphine oxide **L7** as the ligand, product **44** could also be obtained in a comparable manner (Scheme S5). The absolute configuration of **50** was determined to be *S* by comparing its HPLC spectrum with that reported in the literature.[17] Notably, all the chiral 1,4-enynes **38**–**51** were obtained as single *E* isomers either from the mixtures of the *E*- and *Z*-isomeric allylic C–H substrates or the single *E* isomer, while only a moderate *E*/*Z* ratio was obtained with the previously reported methods for the cross-coupling of allylic halides.[10c]

Achieving high levels of site selectivity while maintaining good reactivity and enantioselectivity in intermolecular asymmetric C–H bond functionalization remains a great challenge.[18] To survey the site selectivity of the reaction, substrates incorporating more than one potentially reactive C–H bond were investigated (Table 5 and Scheme S6). The reaction shows unique benzylic site selectivity to afford **52** with 82% *ee*, with no alkynylation occurring on the tertiary C–H bond. In substrates containing multiple benzylic C–H bonds, a bias for the less sterically hindered and more electron-rich site was observed, as illustrated in the formation of **53** and **54**. Interestingly, the alkynylation occurred exclusively at the benzylic site in the presence of an allylic C–H bond to yield the product **55** with 93% *ee*. In comparison, the alkynylation occurred more easily on the conjugated allylic sites than the benzylic positions to deliver **56**–**58**. Collectively, these results highlight the high sensitivity of this reaction to

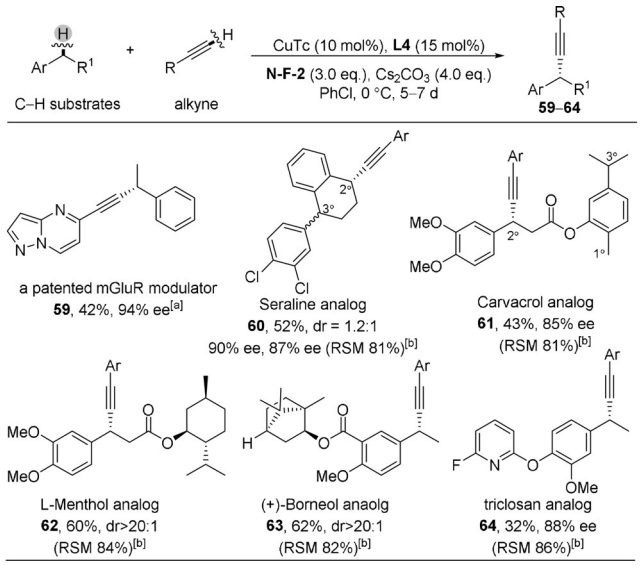
Table 5: The site selectivity of C(sp^3)–H bonds.[a]



[a] Conditions A: C–H substrates (1.0 mmol), alkyne (0.10 mmol), CuTc (10 mol%), **L4** (15 mol%), Cs_2CO_3 (0.40 mmol), and **N-F-2** (0.30 mmol) in dry PhCl (0.8 mL) at 0°C for 5–7 days. Conditions B: C–H substrates (1.0 mmol), alkyne (0.10 mmol), CuTc (10 mol%), **L6** (18 mol%), Rb_2CO_3 (0.50 mmol), and **N-F-2** (0.30 mmol) in dry PhCl/*n*-hexane (v/v = 3:1, 0.8 mL) at rt for 5–7 days. [b] Reaction was run at rt. [c] From an *E*/*Z* mixture of alkene substrates. [d] CuTc (15 mol%) and **L6** (20 mol%) were used.

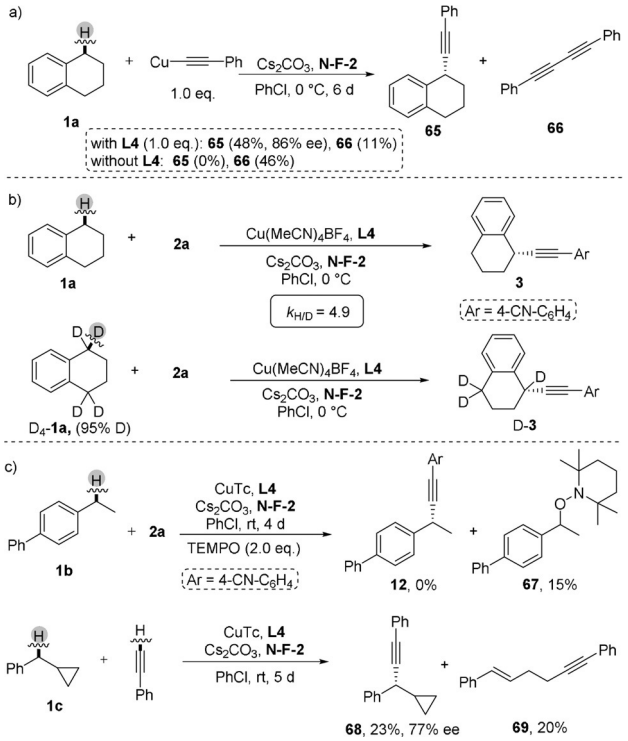
the electronics and steric environment of C–H bonds, likely by virtue of the electrophilic and bulky properties of the imidyl radical derived from **N-F-2**.[6c]

We then evaluated the synthetic application of this transformation (Scheme 2). The asymmetric C–H alkynylation of ethylbenzene furnished a patented mGluR modulator **59** in a straightforward manner. In addition, the reaction took place exclusively at the less sterically hindered benzylic C–H position to provide a seraline analogue **60** in 52% yield (d.r. 1.2:1). Rapid access to bioactive analogues plays a profound part in preliminary drug discovery.[19] We sought to explore the application of the strategy in the expedient construction of bioactive analogues. An exceptional site-selectivity at the 2° benzylic site of a carvacrol analogue was observed to afford **61** with 85% *ee*. Moreover, the substrates containing L-menthol and the (+)-borneol core structure gave rise to **62** and **63** in good yields and excellent diastereoselectivity, irrespective of the presence of existing chiral centers. Furthermore, a triclosan analogue could be transformed into its chiral alkynylated derivative **64** with 88% *ee*. More than 80% of the C–H substrates could be recovered in these transformations. It should be noted that a common challenge with the intermolecular HAA process is the low efficiency for abstracting C–H bonds, which necessitates the requirement of an excess of the C–H substrates or nucleophiles.[4–7,9,20] Our further investigation on reducing the amount of C–H substrates will focus on merging the photocatalyst with our copper catalyst.[21]



Scheme 2. The synthetic application of asymmetric C(sp^3)–H alkynylation. Conditions: C–H substrate (1.0 mmol), alkyne (0.10 mmol), CuTc (10 mol%), **L4** (15 mol%), Cs_2CO_3 (0.40 mmol), and **N-F-2** (0.30 mmol) in dry PhCl (0.8 mL) at 0°C for 5–7 days. [a] Ethylbenzene (2.0 mmol) was used. [b] Data in parentheses indicate recovered C–H substrates. RSM, recovered starting material.

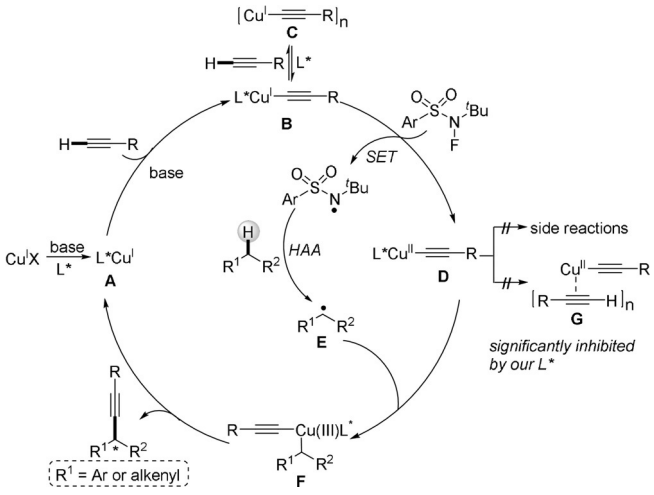
To gain some insight into the reaction mechanism, a series of control experiments were performed. Analysis of the reaction mixture by ^{31}P NMR spectroscopy showed that **L4** was quickly converted into phosphine oxide **L5** and possibly fluorine-containing phosphine ligands (Figure S4a).[22] The yield of **3** was lower than 10% after 1 h, at which time the ^{31}P NMR signal of **L4** had completely disappeared, and reached up to 60% after 5 days, which indicates the predominant contribution of phosphine oxide **L5** to the reaction conversion and yield. The *ee* value of **3** increased from an initial 89% to 93% after 18 h and then remained stable during the reaction, which suggests that **L4** or fluorine-containing phosphine ligands can also affect the enantioselectivity (Figure S4b). Collectively, these observations suggest that pentavalent phosphine oxides could be generated quickly from trivalent aryl phosphines under oxidative conditions, and these pentavalent phosphine oxides might serve as the active catalysts for this reaction. A striking ligand-accelerated catalysis phenomenon was also observed.[23] The reaction of copper acetylide and **1a** proceeded smoothly in the presence of **L4** to afford **65** in 48% yield and 86% *ee*, while only the Glaser homocoupling product **66** could be obtained without **L4** (Scheme 3a). In sharp contrast, no desired coupling product from the reaction of copper acetylide was obtained with or without the chiral BOX ligand under the conditions developed by Liu and co-workers (Scheme S7).[6d] This result indicates that copper acetylide might be an intermediate in the whole process and our N,N,P(O)-ligand not only significantly inhibits the side reaction of terminal alkyne but also promotes the formation of the C(sp^3)–C(sp) bond, likely by preventing the formation of deactivated polymeric Cu^{II}-alkynyl species. The measured intermolecular KIE data (4.9) for substrates **1a** and D_4-**1a** suggest that the intermolecular HAA process might be involved in the rate-determining step (Scheme 3b). No desired product from the reaction of substrate **1b** was detected in the presence of the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), but



Scheme 3. Mechanistic studies.

a 15% yield of the TEMPO-trapped adduct **67** was obtained. Moreover, a radical clock experiment showed that substrate **1c** underwent a tandem cyclopropane ring-opening/alkynylation process to provide **69** in 20% yield along with **68**. These observations indicate the involvement of benzylic radicals in this reaction (Scheme 3c).

On the basis of the experimental observations as well as prior reports,[5,6,10] a plausible mechanism was proposed (Scheme 4). Initially, $Cu^{I}L^{*}$ complex **A** might be formed with the assistance of base. It further reacts with a terminal alkyne to generate the active Cu^{I}-acetylide complex **B**, which may transform into catalytically inactive polymeric copper acetylide **C** in the presence of an excess amount of terminal alkyne,



Scheme 4. Mechanistic proposal.

thereby resulting in reaction inhibition (see Table 1, entries 15 and 16).[10c,23] The active monomeric intermediate **B** undergoes a single electron transfer process with *N*-fluoroalkylsulfonamide to form the Cu^{II}-acetylide complex **D** and the N-centered radical. Afterwards, the N-centered radical abstracts a benzylic/allylic hydrogen atom to produce the corresponding alkyl radical intermediate **E**. The intermolecular trapping of this radical intermediate by Cu^{II}-acetylide complex **D** might generate the Cu^{III} intermediate **F**,[24] which undergoes a subsequent reductive elimination to furnish enantioenriched alkynylation products and liberate the $Cu^{I}L^{*}$ complex **A**. Since the trapping of alkyl radical **E** by the Cu^{II}-acetylide complex **D** is probably a reversible process,[6,25] it is likely that the subsequent reductive elimination is the stereodetermining step. On the other hand, the Cu^{II}-alkynyl species might transform into the Glaser homocoupling side product through a dimeric intermediate[9c] (Scheme S7) or coordinate with the alkyne and be deactivated, although both competing pathways could be significantly inhibited by the multidentate N,N,P(O)-ligand.[26]

Conclusion

In summary, we have established a copper-catalyzed intermolecular asymmetric radical oxidative $C(sp^3)$–C(sp) cross-coupling of diverse benzylic and allylic C–H bonds with commercially available terminal alkynes, thereby providing a straightforward approach to chiral benzylic alkynes and 1,4-enynes, which are significant building blocks. The newly designed anionic N,N,P(O)-ligands bearing stable chiral oxazoline and pentavalent phosphine oxide could not only induce excellent enantiocontrol, but also inhibit the side reactions of terminal alkynes. The procedure highlights the exquisite site selectivity of the intermolecular HAA step with the *N*-fluoroalkylsulfonamide-derived imidyl radical and its potential application for the facile synthesis and modification of bioactive compounds. Mechanistic studies suggest the involvement of alkyl radical intermediates with intermolecular radial C–H abstraction as the rate-determining step. Moreover, we anticipate that this strategy will spur more efforts in ligand and catalyst design for the development of more asymmetric radical oxidative cross-coupling reactions of diverse $C(sp^3)$–H bonds with different types of nucleophiles.

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Conflict of Interest

The authors declare no conflict of interest.

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