# A General Copper-Box System for the Asymmetric Arylative Functionalization of Benzylic, Propargylic or Allenylic Radicals

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**ABSTRACT:** Radical-involved arylative cross-coupling reactions have recently emerged as an attractive strategy to access valuable aryl-substituted motifs. However, there still exist several challenges such as limited scope of radical precursors/acceptors, and lack of general asymmetric catalytic systems, especially regarding the multicomponent variants. Herein, we reported a general copper-Box system for asymmetric three-component arylative radical cross-coupling of vinylarenes and 1,3-enynes, with oxime carbonates and aryl boronic acids. The reactions proceed under practical conditions in the absence or presence of visible-light irradiation, affording chiral 1,1-diarylalkanes, benzylic alkynes and allenes with good enantioselectivities. Mechanistic studies imply that the copper/Box complexes play a dual role in both radical generation and ensuing asymmetric cross-coupling. In the cases of 1,3-enynes, visible-light irradiation could improve the activity of copper/Box complex toward the initial radical generation, enabling better efficiency match between radical formation and cross-coupling.

## INTRODUCTION

Chiral aryl-substituted motifs are not only prevalent in natural products and pharmaceuticals, but they are also versatile synthons and are present in catalysts/ligands, such as chiral 1,1-diarylalkanes,[1] benzylic alkynes,[2] and axially chiral allenes (Figure 1A).[3] As demonstrated by chiral 1,1-diarylalkane-based drugs, the subtle variation in the (hetero)aryl pharmacophore can often lead to variations in biological activity. Consequently, the development of efficient and practical catalytic strategies to streamline the installation of different aryl and heteroaryl motifs is an important endeavour for academic and industrial applications.[4] Transition-metal-catalyzed asymmetric arylations based on an ionic mechanistic pathway currently provide the most robust method for introducing an aryl- or heteroaryl- group into a specific substrate.

In contrast, the two-component enantioselective cross-coupling of $sp^3$-hybridized electrophiles with various arylation reagents, which is catalyzed by transition metals such as nickel, cobalt, and iron, has emerged as a powerful alternative, particularly for the construction of challenging C($sp^3$)-C($sp^2$) bonds. Representative strategies include Fu's seminal studies on the Ni-catalyzed asymmetric Negishi arylation of alkyl electrophiles,[5] in addition to the Ni-, Co-, and Fe-catalyzed Kumada arylation of *α*-bromoketones, *α*-bromo esters, and *α*-chloroesters that have been independently reported by Fu, Zhong/Bian, and Nakamura (Figure 1B, a).[6] Alternatively, the Ni-catalyzed enantioselective reductive cross-electrophile coupling provides a promising paradigm for arylation of $sp^3$-hybridized electrophiles by using another electrophilic aryl halides, in the presence of stoichiometric organic or metal reductants, and thereby circumventing the use of sensitive organometallic reagents.[7] A range of studies from Doyle,[8a] Wang,[8b] Lei/Gong,[9a] Reisman,[9b] Shi,[9c] and Wang[9d] demonstrate that styrenyl aziridines, $CF_3$-substituted alkyl bromides, *α*-chlorosulfones, *α*-chloroesters, benzylic chlorides, and propargylic chlorides undergo chiral nickel/bisoxazoline-catalyzed asymmetric cross-electrophile couplings to afford the chiral arylated products with high enantioselectivity (Figure 1B, b). Moreover, Doyle[10a] and Mei[10b] have successfully merged asymmetric nickel catalysis with photoredox catalysis or paired electrolysis to provide milder enantioselective reductive cross-coupling processes for the arylation of styrene oxides and *α*-chloroesters. It has been accepted that many of these Ni-catalyzed cross-coupling processes of alkyl halides involve oxidative addition via a radical mechanism. This unique blueprint lays the foundation for the development of an asymmetric three-component arylative cross-coupling of alkenes using aryl bromides or two distinct $Csp^2$- and $Csp^3$-halides, as demonstrated by elegant recent examples independently reported by Diao, Nevado, and Chu.[11]

Pioneered by Molander and MacMillan,[12,13] many groups have reported a range of redox-active precursors that are amenable to single-electron-transfer (SET) oxidation to form alkyl carbon radicals, which serve as formal nucleophiles to participate in two-[9d,14] and three-component[15] arylative radical cross-couplings under synergistic photoredox and nickel catalysis (Figure 1B, c). Owing to the redox-neutral conditions, these approaches provide wider substrate scope for the construction of diverse chiral molecules that feature (hetero)aryl-substituted stereogenic centers without the necessity for an external reductant. Consequently, a range of groups have reported the asymmetric copper-catalyzed cross-couplings of readily available and stable aryl boronic acids, organoboronate esters and azoles with benzylic radicals and *α*-amide radicals derived from alkylarenes, benzylic halides, or Katritzky salts (Figure

1B, d).[16] These two-component Suzuki-Miyaura-type radical cross-couplings provide access to a wide range of valuable enantioenriched compounds bearing (hetero)aryl-substituted stereocenters in a mild and efficient manner. In an adaptation to this approach, several groups have recently disclosed a range of three-component variants using styrene derivatives, *α*-substituted acrylamides, *N*-vinylbenzamides, and *tert*-butyl acrylate to relay the initially formed carbon radicals.[17] Remarkably, Liu, G.,[17a-c] Liu, X.-Y.,[17d] Maruoka,[17e] and Zhang[17f] have achieved outstanding examples of copper-catalyzed highly enantioselective three-component asymmetric (hetero)arylative radical cross-couplings of vinylarenes or α-substituted acrylamides. Quite recently, Nevado[17g] and Mei[17h] independently reported nickel-catalyzed three-component asymmetric arylative radical cross-couplings of *N*-vinylbenzamides and *tert*-butyl acrylates under photochemical or electrochemical conditions.

Although these methods clearly afford important and convenient new methods for arylative C-C bond-formation, the catalytic asymmetric arylative radical cross-coupling is still confronted by several challenges: (a) the scope of the radical precursors is typically limited to activated alkyl halides; (b) almost all the asymmetric three-component variants involve vinylarenes as acceptors to enable the radical relay event, thereby restricting the scope of the reaction and thus its impact and utility in the context of target molecule selection; (c) Despite the fact that these mostly used chiral bisoxazoline ligands or anionic N-ligands can provide good stereocontrol in the arylation step, the inherent redox potential window of copper and nickel-based complexes poses a limitation on the scope of radical precursor. In accord with our work on developing light-mediated copper-catalyzed cross-coupling reactions,[18] we reasoned that ligand tunability and/or visible light irradiation would probably provide new opportunities for developing generally applicable copper catalytic system for multicomponent arylative radical cross-coupling (Figure 1C).[19] This enabling catalytic system would allow to address the inherent complexities associated with balancing efficiency of each step and chemo- and stereoselectivity control.

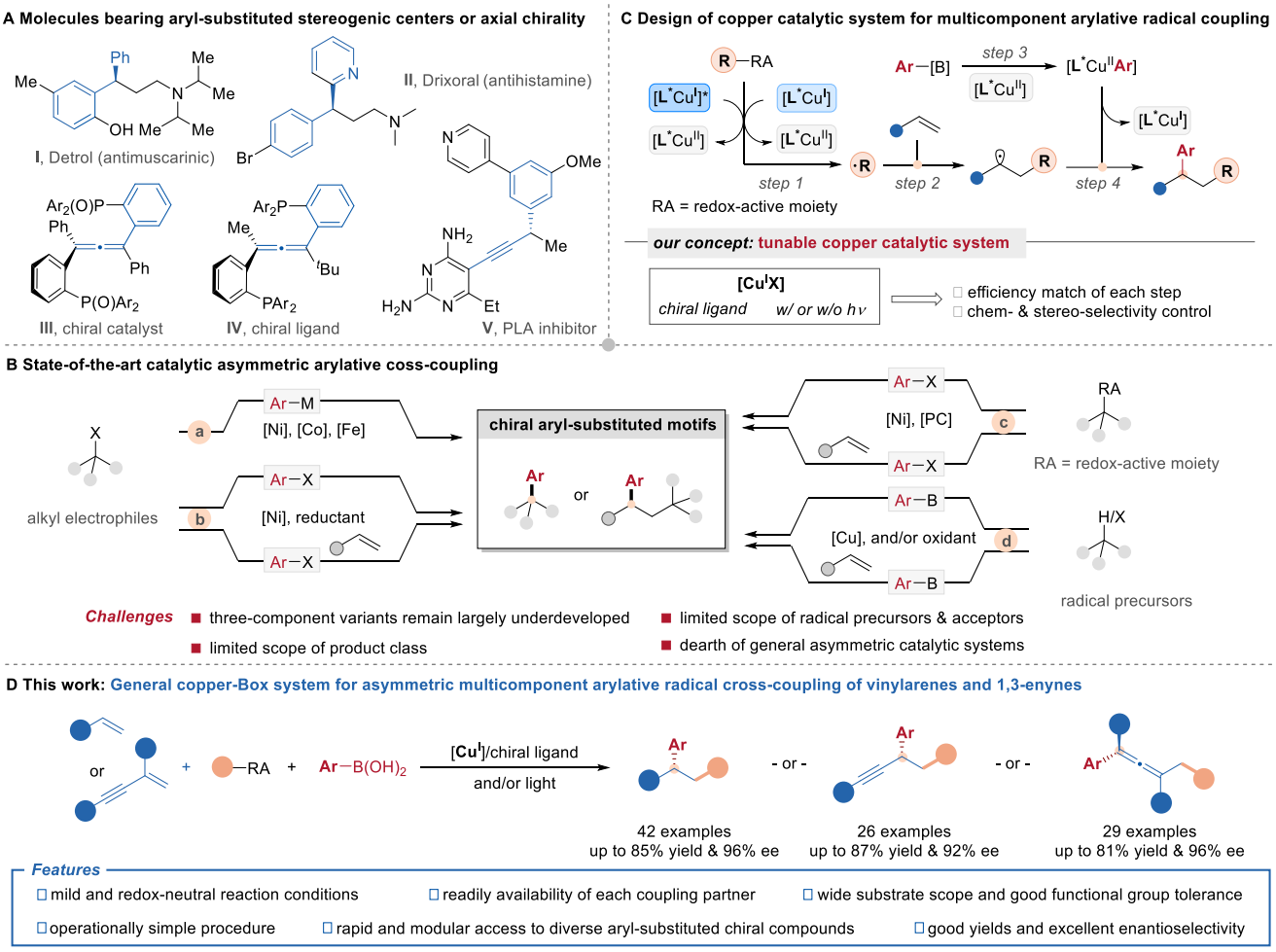



**Figure 1.** Background, envisaged catalytic strategy, and new reaction design. (**A**) Representative bioactive compounds or catalysts containing aryl-substituted stereogenic centers or axial chirality. (**B**) State-of-the-art catalytic asymmetric arylative cross-couplings. (**C**) Our concept of general and tunable copper catalytic system. (**D**) This work.

Herein, we disclose the implementation of this design strategy into an experimental reality, by developing a general copper/bisoxazoline catalytic paradigm to enable the enantioselective three-component arylative radical cross-coupling of vinylarenes and 1,3-enynes (Figure 1D). This protocol features redox-neutral conditions, excellent substrate scope of readily available starting

materials and high functional group tolerance to provide facile and divergent access to a variety of enantioenriched and high-value (hetero)aryl-substituted molecules. Note that our arylative protocol provides the first example of 1,3-enyne-based asymmetric arylative radical cross-coupling.

## RESULTS AND DISCUSSION

**Reaction Optimization.** At the outset of the study, we were particularly interested in exploiting aryl boronic acids as arylating reagents, given that they represent a large class of commercially available stable aryl building blocks. Given the significance of cyanoalkyl motifs in medicinal chemistry,[20] we considered using oximes as precursors to cyanoalkyl radicals given their ease of preparation. It is important to note that our previous work has demonstrated photoinduced copper-catalyzed radical cross-coupling of benzylic radicals with boronic acids;[21] however, this strategy is restricted to achiral 2,2'-bipyridyl-type ligand for catalytic activity. To this end, the reaction of 2-vinylnaphthalene **1a** with O-aroyl oxime **2a'** and phenylboronic acid **3a** using the chiral complex with the chiral bisoxazoline (Box) ligand **L0** gave the three-component cross-coupled product **4a** in only 6% yield and with no enantioselectivity (Table 1A), along with the formation of the undesired two-component cross-coupled byproduct from carboxylate and cyanoalkyl radical and some other unidentified byproducts.

Then, we reasoned that variation of the ligand structure would not only allow to tune the reducing ability of copper catalyst, but also provide effective enantio-differentiating environment for radical cross-coupling.[19] Therefore, according to our design plan (Fig. 1C), we hypothesized that structural modification of ligand and/or light involvement may offer a solution to addressing the issues of poor efficiency, chemo- and enantioselectivity for this transformation.

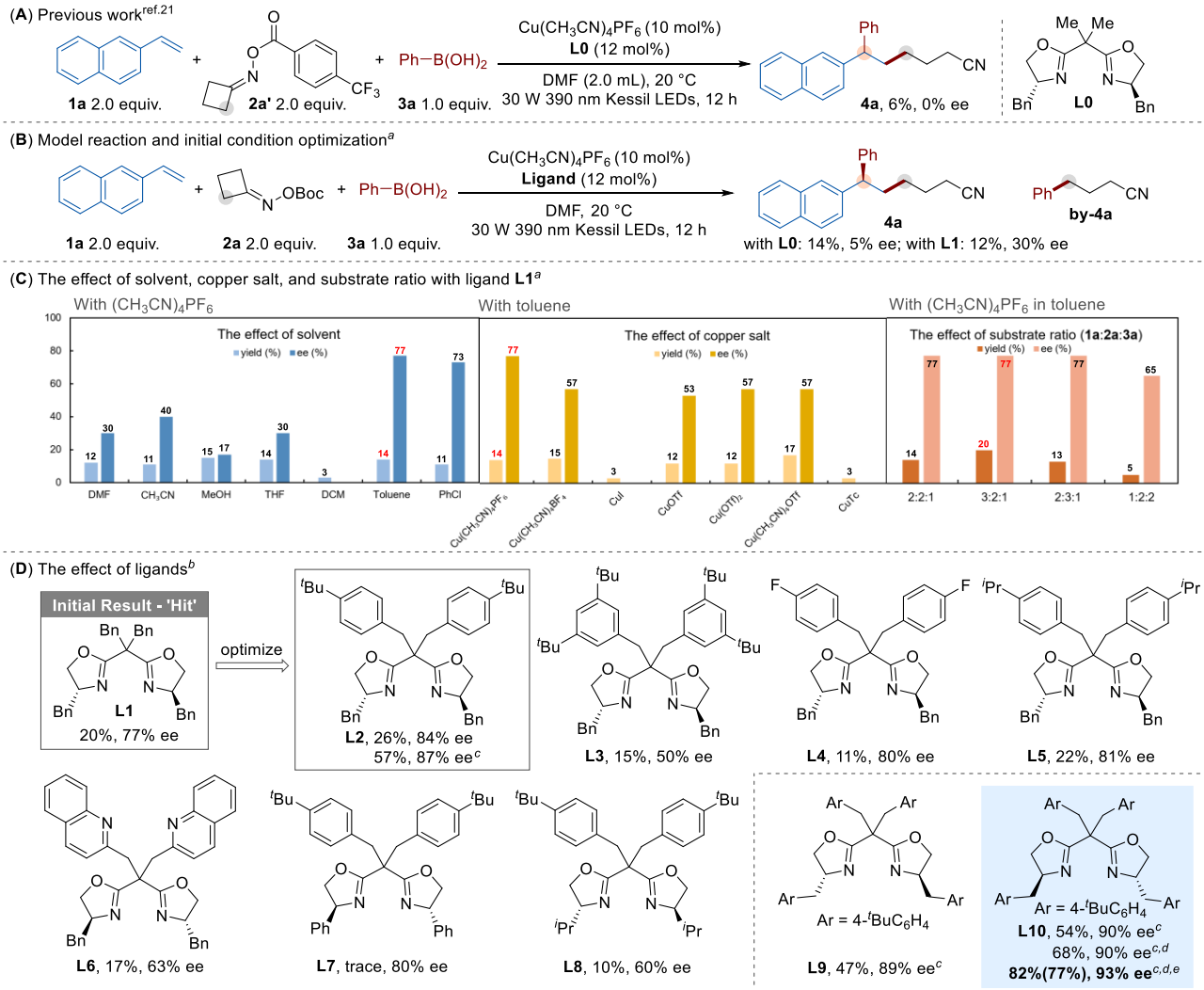
Based on these observations and the fact that the radical precursor is another important design consideration, we attempted to employ oxime carbonate **2a** as a radical precursor. We hypothesized that during the formation of the corresponding radical, the resulting *tert*-butoxy anion (*tert*-$BuO^-$) might not only avoid the competitive reaction of leaving group, but also act as a Lewis base to activate phenylboronic acid **3a** towards transmetalation with the copper catalyst to form a phenyl-bound copper complex, and thereby avoid the addition of an exogenous base.[23] Therefore, we started our study by investigating the enantioselective three-component arylative radical cross-coupling of 2-vinylnaphthalene **1a** with oxime carbonate **2a** and phenylboronic acid **3a** with a 2:2:1 molar ratio under visible light-induced copper catalysis (Table 1B).[22] Preliminary studies demonstrated the feasibility of the three-component reaction, affording product (*R*)-**4a** in 14% NMR yield and with 5% ee, using a combination of $Cu(CH_3CN)_4PF_6$ (10 mol %) and chiral Box ligand **L0** (12 mol %) under irradiation of a purple LEDs at room temperature for 12 hours in DMF. However, in this process the by-product **by-4a** resulting from two-component coupling of **2a** with **3a** could also be detected. Encouraged by this preliminary result, we performed the first round of extensive ligand screening to identify an optimal ligand (Table S1). Specifically, ligand **L1** that features gem-dibenzyl groups in the backbone and benzyl groups in the oxazoline scaffold substantially increased the enantioselectivity to 30% ee, albeit with similar reaction efficiency. With ligand **L1**, we briefly screened a range of solvents and copper salts to enhance the reaction efficiency and enantioselectivity (Table 1C), which revealed that both reaction parameters markedly influence on the reaction. Notably, the enantioselectivity was significantly improved to 77% ee in toluene, but the yield still remained low. Screening of a range of common copper salts, inorganic and organic bases (Table S3-S4), revealed that $Cu(CH_3CN)_4PF_6$ was the optimal candidate and that base is not required. Additional experiments investigated the feed ratio using $Cu(CH_3CN)_4PF_6$ in toluene (Table S5), indicating that a 3.0/2.0/1.0 ratio afforded (*R*)-**4a** in 20% yield with no loss of enantioselectivity.

At this stage, we proceeded to evaluate a range of other substituted chiral Box ligands with the parent core structure similar to the ligand **L1** with 3.0:2.0:1.0 substrate ratio in toluene. The key results are highlighted in Table 1D (Table S6), which indicated that structural variations in each benzyl group significantly impact their performance. For instance, ligand **L2** with a *tert*-butyl group in the *para*-position of the gem-dibenzyl moiety slightly increased the yield, while remarkably improved the enantioselectivity of the product (*R*)-**4a** to 84% ee, whereas the more sterically demanding ligand **L3** furnished (*R*)-**4a** with diminished enantioselectivity (50% ee). Replacing the *tert*-butyl group with fluorine atom (**L4**) or *iso*-propyl group (**L5**) slightly decreased the enantioselectivity compared to ligand **L2**. In the case of ligand **L6** featuring a gem-di(2-quinolyl)methyl group, an obvious decrease of enantioselectivity was observed (63% ee). As shown in the cases of ligand **L7** and **L8**, the benzyl groups in the oxazoline scaffold are critical to the reaction efficiency. With ligand **L2**, we further explored the effects of the co-solvents, concentration, catalyst loading, and light source (Table S8-S11). It was established that product (*R*)-**4a** was formed in 57% yield with 87% ee, when using $Cu(CH_3CN)_4PF_6$ (5 mol%) and ligand **L2** (6mol%) in a mixed solvent of toluene and $CH_3CN$ under irradiation of 10 W purple LEDs.

Finally, we hypothesized that the introduction of another steric factor onto the benzylic aromatic ring of the oxazoline moiety may further change the asymmetric environment surrounding the coordinating nitrogen atoms and thus improve asymmetric induction.

Interestingly, ligand **L9** that incorporates a *tert*-butyl group at the *para*-position of the phenyl ring of the oxazoline scaffold afforded (*R*)-**4a** in 47% yield with slightly improved enantioselectivity (89% ee). Use of ligand **L10**, the enantiomer of **L9**, could also furnish the cross-coupled product (*S*)-**4a** with analogous results. Finally, control experiments confirmed that no desired three-component cross-coupling reaction occurred in the absence of copper catalyst or ligand (Table S12). Interestingly, the reaction still proceeded smoothly to afford (*S*)-**4a** in slightly improved the yield without erosion of the enantiopurity without visible light irradiation (68% yield, 90% ee). Finally, the reaction efficiency and enantioselectivity were significantly improved at 0 °C, affording (*S*)-**4a** in 77% isolated yield with 93% ee. When using the optimal ligand **L10**, the number of equivalents of 2-vinylnaphthalene **1a** and oxime carbonate **2a** relative to phenylboronic acid **3a** have somewhat influence on the ratio of desired product (*S*)-**4a** and byproduct **by-4a**. The substrate ratio of **1a**/**2a**/**3a** as 3.0:2.0:1.0 was still the best of choice (Table S13). To gain some insight into this interesting phenomenon, we performed time-course studies on the model reaction with and without visible light irradiation using a combination of $Cu(CH_3CN)_4PF_6$ and **L10** at 0 °C (Table S14 and Fig. S2). Notably, under visible light irradiation the radical precursor oxime carbonate **2a** reacted faster, and a larger amount of by-product **by-4a** was formed, compared to the reaction performed in dark. Moreover, after 4 hours, **2a** was completely consumed, thus leading to no further formation of desired product **4a**. In contrast, there was a significant amount of the oxime carbonate **2a** still present without visible light irradiation after 4 hours, which allowed the three-component cross-coupling to proceed further. These results suggest that rate matching between radical generation and cross-coupling is essential for the desired intermolecular three-component reaction.

**Table 1. Optimization of the Reaction Conditions**



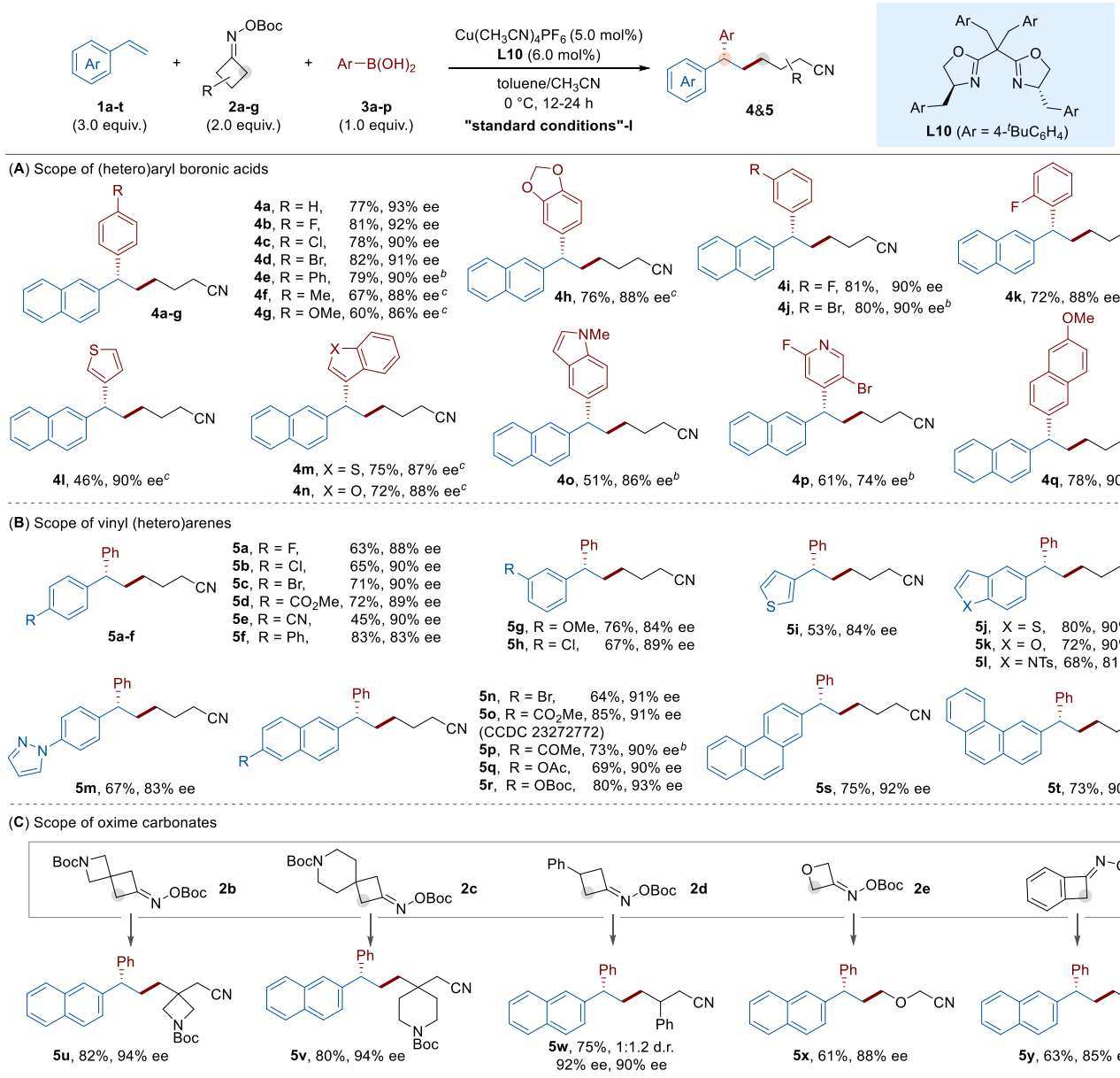

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), **3a** (0.1 mmol, 1.0 equiv.), copper salt (10 mol %), chiral ligand (12 mol %), solvent (2.0 mL), 30 W purple LEDs ($\lambda_{max}$ = 390 nm), 20 °C. Yields were determined by $^1$H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. Value in parentheses is isolated yield. The ee values were determined by chiral HPLC analysis. [b]With **1a** (0.3 mmol), **2a** (0.2 mmol), and **3a** (0.1 mmol), toluene (2.0 mL), 30 W purple LEDs ($\lambda_{max}$ = 390 nm), 20 °C. [c]With $Cu(CH_3CN)_4PF_6$ (5 mol %) and chiral ligand (6 mol %), a mixed solvent of toluene and $CH_3CN$ (1.5 mL/0.1 mL), and 10 W purple LEDs. [d]Without light irradiation. [e]Performed at 0 °C. Boc = *tert*-butyloxycarbonyl.

**Substrate Scope of Asymmetric Arylative Radical Cross-Coupling of Vinylarenes, Oxime Carbonates and Boronic Acids.** With the optimized reaction conditions, we investigated the generality of this asymmetric three-component arylative radical cross-coupling reaction by examining a representative range of commercially available boronic acids with 2-vinylnaphthalene **1a** and oxime carbonate **2a** (Table 2A). The scope appears to be relatively general in the context of the boronic acids. In addition to the parent boronic acid **3a**, the array of aryl boronic acids **3b-h** bearing electron-withdrawing (e.g., F, Cl, Br) or electron-donating (e.g., Ph, Me, OMe) substituent at the para-position of the phenyl ring all participated in the cross-coupling reaction, affording the corresponding products **4b-h** in moderate to very good yields (60-82%) and with high enantioselectivities (86-92% ee) using either 5 or 10 mol% catalyst. In the cases of electron-rich aryl boronic acids such as **3f** and **3g**, the yields are slightly diminished due to formation of small amounts of two-component coupling byproducts of aryl boronic acids with oxime carbonate **2a**. As shown in the reactions of **3i-k**, variations in the substitution pattern of the phenyl group have no deleterious influence on both reaction efficiency and enantioselectivity, with the products **4i-k** being obtained in 72-81% yields with 88-90% ee. Once again, boronic acids with *S*- (**3l**, **3m**), *O*- (**3n**), *N*-heteroaromatic (**3o**, **3p**), and fused aromatic (**3q**) ring all participated in the reaction smoothly to afford the desired cross-coupled products **4l-q** in yields ranging from 46-78% with 74-90% ee.

Next, we turned our attention to exploring the substrate scope of vinylarenes by reacting with the oxime carbonate **2a** and phenylboronic acid **3a** (Table 2B). Notably, the majority of these vinylarenes are commercially available materials or easily prepared. First, a range of challenging styrene derivatives **1b-g** with a halogen atom (e.g., F, Cl, Br), cyano, ester, or a phenyl group at the *para*-position of the aromatic ring were examined, which gave the desired products **5a-f** with high yields (45-83%) and good enantioselectivities (83-90% ee). Moreover, the reactions of vinylarenes substituted by OMe or Cl at the *meta*-position of the phenyl ring furnished products **5g** and **5h** with good results (84-89% ee). (Hetero)arenes that having *S*-, *O*-, and *N*-heteroaromatic ring also underwent the arylative cross-coupling smoothly, with the corresponding products **5i-m** being obtained in 53-80% yields with 81-90% ee. Remarkably, this protocol can be successfully extended to 2-vinylnaphthalene derivatives, in which the reaction efficiency and enantioselectivity are relatively independent of the stereoelectronic nature of the aromatic ring. For instance, an array of 2-vinylnaphthalene derivatives bearing bromo, ester, ketone, including Ac and Boc-protected hydroxyl groups at the 6-position undergo the cross-coupling reaction to furnish products **5n-r** in satisfactory yields with high enantioselectivities (90-93% ee). Markedly, a range of other easily prepared polyaromatic substrates with extended aromatic systems, such as 2-vinyl-, and 3-vinyl-subsituted phenanthrenes, were also compatible with the three-component cross-coupling, as exemplified with the preparation of **5s** and **5t** in good yield with 92% and 90% ee, respectively. The absolute configuration of products **5n** and **5o** were determined by chiroptical methods and X-ray crystallographic analysis, respectively (see Supporting Information, section 7). Other chiral 1,1-diarylalkane products were assigned by analogy. Unfortunately, our effort to expand the catalytic system to sterically more hindered 1,1- and 1,2-disubstited styrene derivatives met failure, with only two-component cross-coupling byproducts being observed (see Supporting Information, section 5).

Finally, we briefly examined the generality of this protocol by reacting a representative set of oxime carbonates with **1a** and **3a** (Table 2C). These redox-active oxime carbonates were easily prepared from the cyclobutanone precursors.[24] Importantly, variations in the substituents in the parent scaffold has no obvious deleterious effect on the reaction. For example, the more sterically encumbered 3,3-disubstituted oxime carbonates **2b** and **2c** participate in the reaction to furnish the expected products **5u** and **5v** with high yields (80-82%) and enantioselectivity (94% ee). The reaction of sterically less bulky 3-phenyl-substituted oxime carbonate **2d** afforded product **5w** with good yield and enantioselectivity, but as a mixture of diastereomers (1:1.2 d.r.) because of an initial unselective radical addition. Oxime carbonate **2e** derived from oxetan-3-one was also suitable for the reaction, with the desired product **5x** being isolated with synthetically useful yields and enantioselectivity. Moreover, benzocyclobutenone-derived oxime carbonate **2f** is a viable substrate, affording **5y** in modest yield and with 85% ee. Collectively, the broad generality and scope render this protocol to be convenient and practical process to prepare a variety of chiral cyano-alkylated 1,1-diarylalkanes.

**Table 2. Scope of the Copper-Catalyzed Asymmetric Arylative Radical Cross-Coupling Reaction of Vinylarenes**[a]



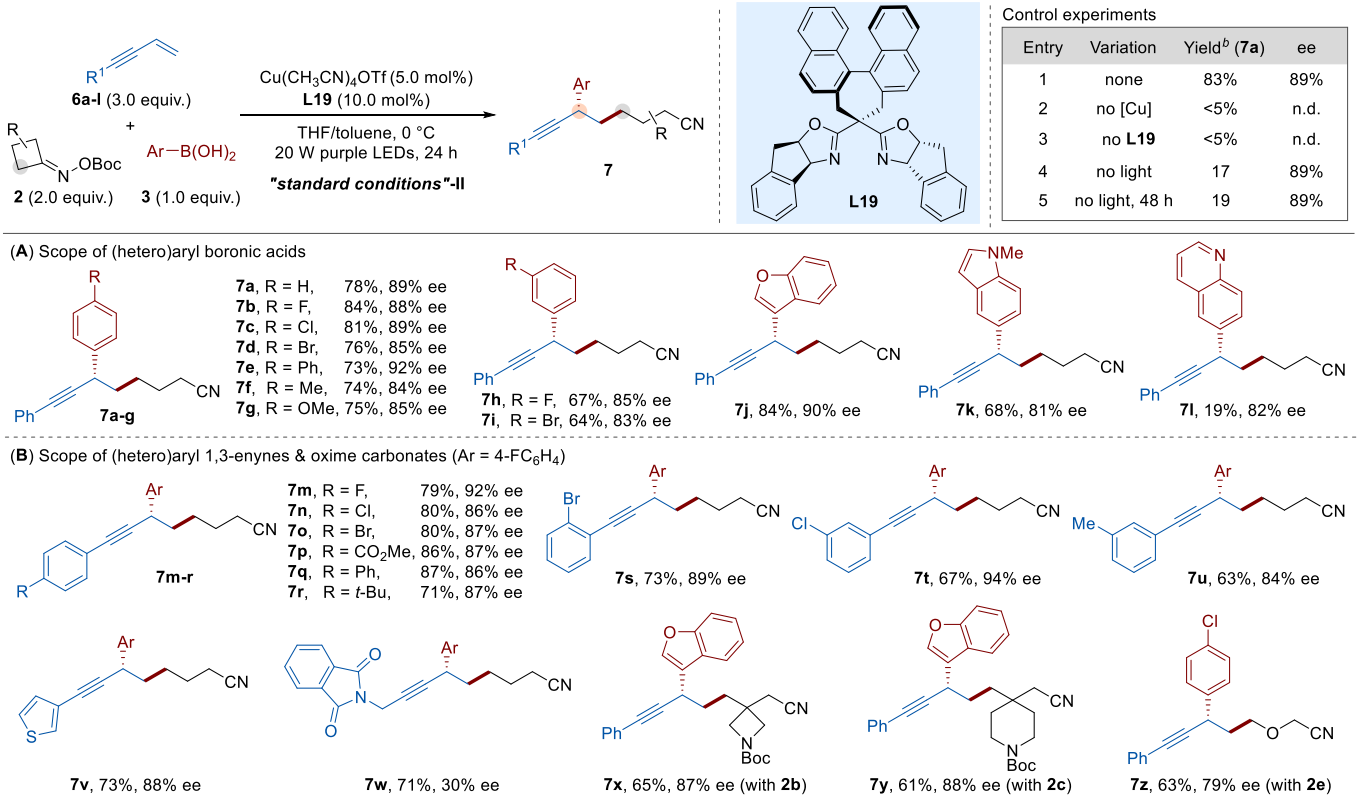

[a]Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), **3** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (5.0 mol %), **L10** (6.0 mol%), toluene/$CH_3CN$ (15/1, v/v, 1.6 mL), 0 °C, 12-24 h; isolated yield; the ee values were determined by chiral HPLC analysis. [b]24 h. [c]With $Cu(CH_3CN)_4PF_6$ (10.0 mol %), **L10** (12.0 mol%) at 0 °C for 24 h.

**Substrate Scope of Asymmetric Arylative Radical Cross-Coupling of 4-Aryl 1,3-Enynes, Oxime Carbonates and Boronic Acids.** Alkynes that contain propargylic stereogenic centers are an important class of structural scaffolds (Fig. 1A). In recent years, significant advances have been made towards the catalytic asymmetric construction of chiral benzylic alkyne derivatives, using two- or three-component cross-coupling reactions of benzylic radicals with nucleophilic alkynes.[25-27] Notably, the groups of Xiao, Lu, and Lan, disclosed the first example of asymmetric cyanation of propargyl ester-derived propargylic radical with TMSCN as cyanide source by a synergetic photoredox and copper catalysis.[28] Recently, Wang et al. reported an elegant two-component nickel-catalyzed asymmetric reductive cross-coupling of propargylic chlorides and aryl iodides, which provides practical access to chiral benzylic alkynes.[9d] Encouraged by the success of our asymmetric three-component arylative cross-coupling of styrene derivatives, we envisioned that this strategy could be extended to 1,3-enynes. The successful outcome of this process would, for the first time, provide a modular and alternative method for construction of cyano-alkylated chiral benzylic alkynes under redox-neutral conditions.

We systematically surveyed the reaction conditions by varying the copper salts, the ligands, the solvents, the light sources, and the temperatures (see Supporting Information, section 3.2). The optimal conditions were established to be irradiating (purple LEDs) a THF/toluene solution of 4-phenyl-1,3-enyne **6a**, oxime carbonate **2a**, and phenylboronic acid **3a** in the presence of $Cu(CH_3CN)_4OTf$ (5 mol%), and bisoxazoline ligand **L19** (10 mol%) at 0 °C (Table 3). Gratifyingly, the reaction proceeded in a highly chemo- and regioselective manner to afford the desired cross-coupled product **7a** in 78% isolated yield with 89% ee. A range of control

experiments performed in the absence of the copper salt, ligand, and light irradiation confirmed that these parameters are essential for this transformation (Table S26). In contrast, when the reaction was performed using ligand **L10** in the presence of absence of irradiation of purple LEDs, lower yields and only moderate enantioselectivity were observed (Table S37). Moreover, we carried out time-course studies on the reaction of **6a**, **2a**, and **3a** using ligand **L19** with or without visible light irradiation. It was found that the combination of $Cu(CH_3CN)_4OTf$/**L19** and visible light plays an important on the conversion of oxime carbonate **2a** into the relative cyanoalkyl radical, as large amount of **2a** remained intact when omitting visible light irradiation (Table S28 and Figure S3). These results implied that visible-light excited copper(I)/**L19** under purple LED irradiation enabled better efficiency match between cyanoalkyl radical generation and radical addition, and ensuing arylative cross-coupling with propargylic radical. Meanwhile the sterically more encumbered scaffold of **L19** allowed higher enantioselectivity.

**Table 3. Scope of Photoinduced Copper-Catalyzed Asymmetric Arylative Radical Cross-Coupling of 4-Aryl 1,3-Enynes**[a]



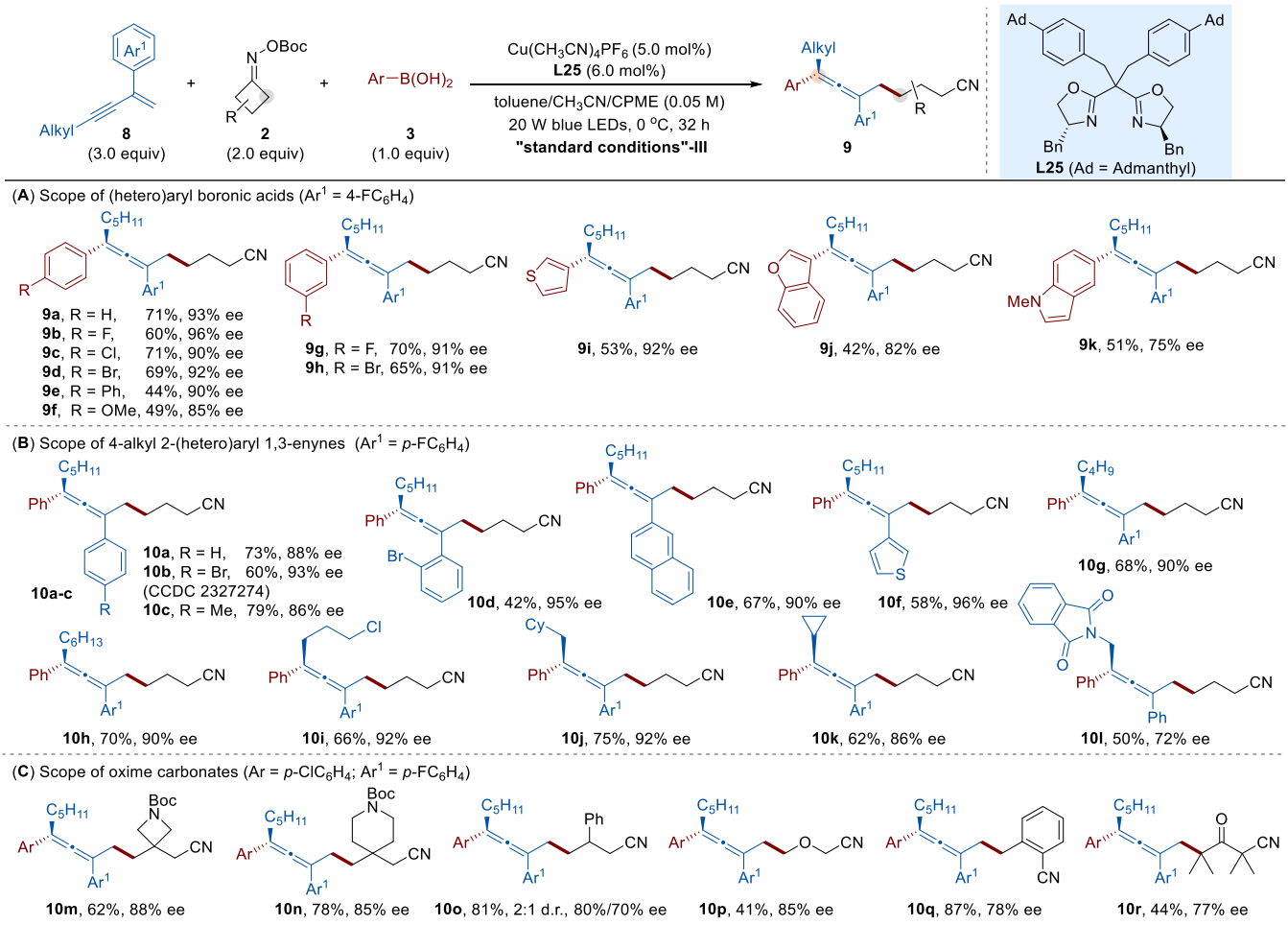

[a]Reaction conditions: **6** (0.3 mmol), **2** (0.2 mmol), **3** (0.1 mmol), $Cu(CH_3CN)_4OTf$ (5.0 mol %), chiral ligand **L19** (10.0 mol %), mixed solvent of THF/toluene (6.5/1, v/v, 1.5 mL), 20 W purple LEDs ($\lambda_{max}$ = 390 nm), 0 °C, 24 h; isolated yield; the ee values were determined by chiral HPLC analysis. [b]Yields were determined by $^1H$ NMR analysis with 1,3,5-trimethoxybenzene as the internal standard.

We proceeded to examine the generality and functional group compatibility of this protocol by initially examining the scope of the boronic acids using 1,3-enyne **6a** with oxime carbonate **2a** (Table 3A). In addition to the parent phenylboronic acid **3a**, a series of aryl boronic acids with different functionalities, including halides (e.g., F, Cl, Br), phenyl, methyl, methoxy at the para- and meta-positions are all suitable substrates in the reaction. The corresponding cross-coupled products **7b-i** were isolated in modest to good yields (64-84%) with high enantioselectivities (83-92% ee). The reaction of the benzofuran-substituted boronic acid was also suitable for the reaction, which gave product **7j** in 84% yield with 90% ee. Notably, 1-methyl-1*H*-indol-5-boronic acid and quinoline-6-boronic acid that feature biologically important *N*-heterocycles have also proven to be suitable for the reaction, affording **7k** and **7l** with good enantioselectivities. The low yield of **7l** was ascribed to its poor solubility in the reaction system.

Additional studies explored the substrate scope of 4-aryl-1,3-enynes by reacting with oxime carbonate **2a** and 4-F-substituted-phenylboronic acid **3b** (Table 3B). Aside from the parent 1,3-enyne **6a**, a series of 4-aryl-1,3-enyne derivatives **6b-g** bearing an electron-withdrawing (e.g., F, Cl, Br, $CO_2Me$) and electron-donating (e.g., Ph, *t*-Bu) group at the para-position of the aromatic ring all furnished the desired products **7m-r** in high yields (71-86%) and enantioselectivities (86-92% ee). Moreover, as shown in the reactions of 4-aryl-1,3-enynes **6h-j**, variation of the substitution pattern of the aromatic rings was also accommodated, with the desired products **7s-u** being obtained with good results. Notably, heteroaromatic 1,3-enyne **6k** is also a suitable substrate, affording product **7v** in modest yield with 88% ee. Note that 4-alkyl 1,3-enyne **6l** having phthalimide moiety at the alkyl chain could also participate in the

reaction to furnish the propargyl arylation product **7w** in modest yield, though the enantioselectivity awaits further optimization. Additional studies examined the scope of oxime carbonates, wherein reactions of sterically congested 3,3-disubstituted oxime carbonates **2b** and **2c**, as well as sterically less hindered oxetan-3-one-derived oxime carbonate **2e** all proceed smoothly to give the corresponding products **7x-z** with satisfactory results. Notably, all these examples display exclusive 1,2-regioselectivity in the addition to 1,3-enynes, although there are two possible sites for the addition. The absolute configuration of **7q** was determined by chiroptical methods (see Supporting Information, section 7).

**Table 4. Scope of Photoinduced Copper-Catalyzed Asymmetric Arylative Radical Cross-Coupling of 4-Alkyl 1,3-Enynes**[a]




[a]Reaction conditions: **8** (0.3 mmol), **2** (0.2 mmol), **3** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (5.0 mol %), chiral ligand **L25** (6.0 mol %), toluene/$CH_3CN$/CPME (1.9/0.5/0.5, v/v/v, 2.0 mL), 20 W blue LEDs ($\lambda_{max}$ = 456 nm), 0 °C, 32 h; isolated yield; the ee values were determined by chiral HPLC analysis. CPME = Cyclopentyl methyl ether.

**Substrate Scope of Asymmetric Arylative Radical Cross-Coupling of 4-Alkyl 1,3-Enynes, Oxime Carbonates and Boronic Acids.** Given the extensive applications of the axially chiral allenes in many disciplines, numerous elegant strategies have been developed for the assembly of chiral di- and trisubstituted allenes.[29] The majority of these methods typically proceed through ionic pathways, and only a limited number of catalytic systems have been disclosed for the synthesis of tetrasubstituted chiral allenes. Recently, some inspiring studies from several groups have demonstrated the enantioselective cross-coupling of allenyl radicals with nucleophilic trimethylsilyl cyanide, terminal alkynes, or aldehydes provide a robust strategy for the construction of tetrasubstituted chiral allenes.[30,31] However, further exploration of the scope of radical precursors and coupling partners is still highly desirable.

Previous studies have established the intermediacy of propargylic radicals during the radical addition of 1,3-enynes.[25] We envisioned that introduction of an aryl group at the propargylic position can also access the allenyl radicals through resonate; the subsequent asymmetric arylative cross-coupling with boronic acids would offer a novel approach toward challenging and previously inaccessible chiral tetrasubstituted allenes. Based on this design plan, and using the model three-component cross-coupling of 2-phenyl-1,3-enyne **8a** with oxime carbonate **2a** and phenylboronic acid **3a**, we performed a systematic investigation of the concentration, solvent, and ligand (see Supporting Information, section 3.3). The optimization studies indicate that a combination of 5 mol% of $Cu(CH_3CN)_4PF_6$ and 6 mol% of chiral bisoxazoline ligand **L25** as the catalyst, in a mixed solvent system of toluene/$CH_3CN$/CPME with irradiation of visible light using a 20 W blue LEDs at 0 °C is optimal for this process (Table 4). Under these

conditions, the desired product **9a** was isolated in 71% isolated yield and with excellent enantioselectivity (93% ee).

Next, we briefly investigated the substrate scope of boronic acids (Table 4A), which again demonstrated that a myriad of aryl and heteroaryl boronic acids were applicable to the reaction to provide the corresponding chiral allenes **9b-9j** in 42-71% yields with 82-96% ee. A range of electron-withdrawing and electron-donating substituents, such as halogen atoms (**9b-d**, **9g-h**), phenyl (**9e**), and methoxy (**9f**) at the *para*- or *meta*-position of the phenyl ring are tolerated under the standard conditions. More importantly, heteroaryl boronic acids having heterocycles that are present in a range of important therapeutics-such as thiophene and benzo[b]furan-are also suitable for the cross-coupling and furnish the desired products **9i** and **9j** with 92% and 82% ee, respectively. Furthermore, 1-methyl-1*H*-indol-5-boronic acid could also participate in the reaction to afford cross-coupled product **9k** with modest yield and enantioselectivity.

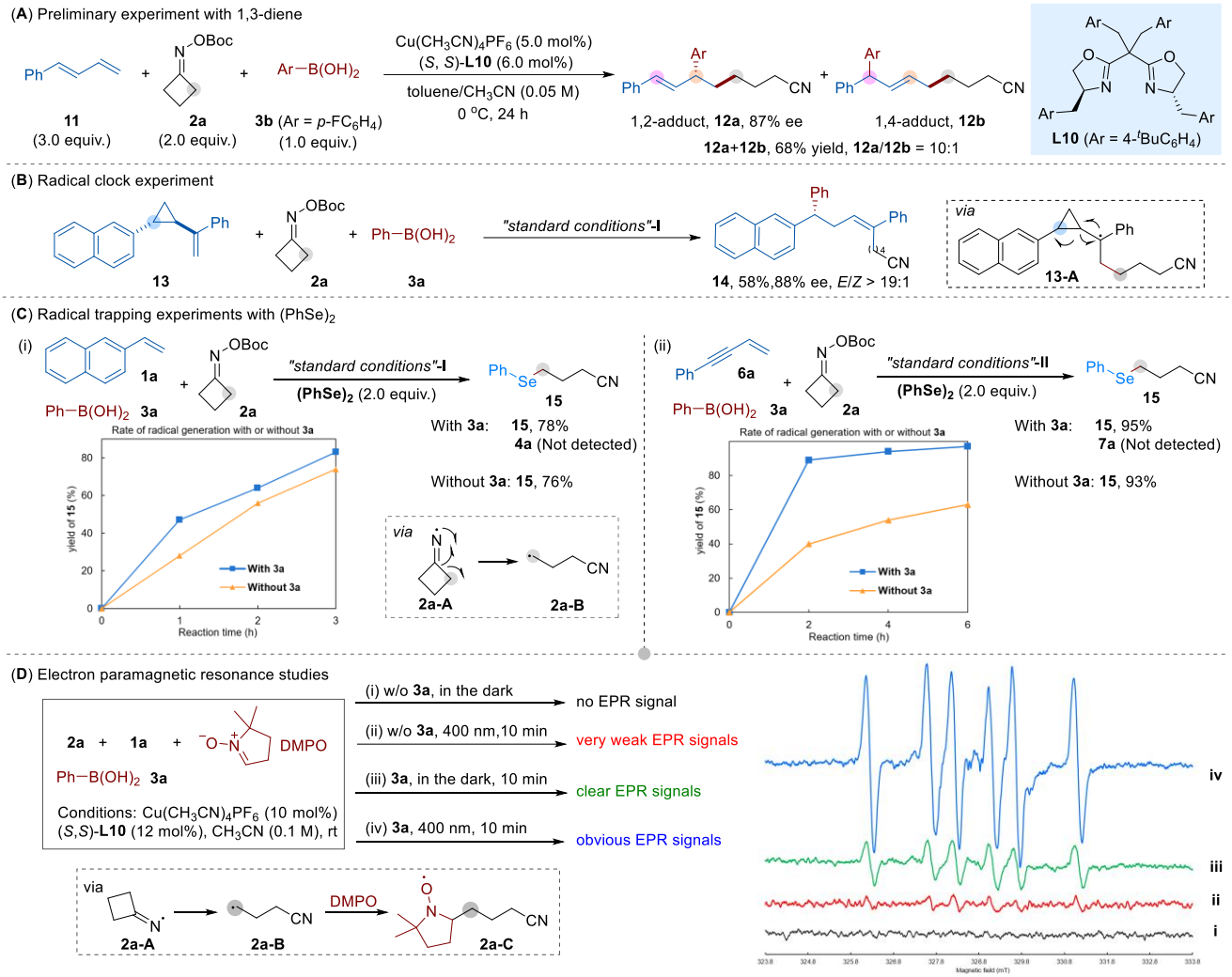



**Figure 2.** Synthetic application and mechanistic studies. (**A**) Preliminary experiment with 1,3-diene. (**B**) Radical clock experiment. (**C**) Radical trapping experiments. (**D**) EPR studies probing the role of phenylboronic acid.

Exploration of the scope of 2-(hetero)aryl-substituted 1,3-enynes (Table 4B) demonstrated that the reactions of the parent 2-phenyl-1,3-enyne and its analogues with bromo, or methyl group at the different positions, and even a naphthalene ring afforded the desired tetrasubstituted chiral allenes **10a-e** in 42-79% yields with 86-95% ee. Moreover, a 1,3-enyne with a 2-thienyl group gave product **10f** in modest yield but with 96% ee. We also evaluated the impact of 4-subsituents on the reaction. As shown in the synthesis of chiral allenes **10g** and **10h**, the 4-alkyl-1,3-enynes with longer and shorter chain lengths are accommodated and afford good results. Notably, the reactions of 1,3-enynes with 4-alkyl chain containing chloride, cyclohexyl, and cyclopropyl functionalities also furnish products **10i-k** in satisfactory yields with 86-92% ee. The reaction of 4-alkyl 1,3-enyne having phthalimide moiety at the alkyl chain could also work, giving the corresponding product **10l** with modest yield and enantioselectivity. The absolute configurations of products **10b** and **10e** were determined by X-ray crystallographic analysis and chiroptical methods (see Supporting Information, section 7), respectively.

Finally, the scope of oxime carbonates (Table 4C) was examined, wherein a representative set of sterically distinct oxime carbonates **2b-f** were compatible with the reaction. These radical precursors reacted smoothly with 1,3-enyne **8a** and boronic acid **3c**, delivering the corresponding products **10m-q** in modest to good yields with high enantioselectivities (70-88% ee). Importantly, the

sterically very demanding oxime carbonate **2g** could also participate in the cross-coupling to form the desired chiral allene **10r** in moderate yield with 77% ee.

**Synthetical Application and Mechanistic Studies.** Readily available 1,3-dienes have recently been extensively explored as radical acceptors to generate allylic radical intermediates and trigger radical cross-coupling reactions.[32] In order to further examine the potential of our catalytic system, we preliminarily attempted a three-component cross-coupling reaction between 1-phenylbutadiene **11**, oxime carbonate **2a**, and aryl boronic acid **3b** under the standard conditions of Table 2 (Figure 2A). The reaction indeed worked to afford the 1,2-adduct **12a** as the major product with high enantioselectivity (87% ee), though accompanied by small amount of 1,4-adduct **12b**, which is highly promising for the future development enantioselective arylative functionalization of 1,3-dienes.

After surveying the substrate scope of the three types of asymmetric arylative radical cross-coupling reactions, we initiated mechanistic investigations to gain some insight into the reaction. Treatment of the radical clock substrate **13** with oxime carbonate **2a** and phenylboronic acid **3a** under the standard reaction conditions afforded the ring-opening product **14** in 58% yield and 88% ee, which supported the intermediacy of a labile benzylic radical **13-A** that is prone to ring-opening (Figure 2B).

We further investigated the reaction progression of two sets of control experiments of 2-vinylnaphthalene **1a** and 4-phenyl-1,3-enyne **6a**, respectively, in the absence and presence of stoichiometric radical scavenger PhSeSePh under the standard conditions (Figure 2C). In both cases, the three-component arylative cross-coupling reactions does not proceed and radical-trapping adduct **15** was isolated in high yield, lending support for iminyl radical **2a-A** and cyanoalkyl radical **2a-B**. In these processes, only cyanoalkyl radical-trapping adduct **15** were observed. Notably, in the presence of phenyl boronic acid **3a**, a significant enhancement of formation rate of **15** was observed, implying that phenylboronic acid **3a** may facilitate the copper-catalyzed SET-reduction of oxime carbonate **2a** to the corresponding cyanoalkyl radical **2a-B** through formation of **L**Cu(I)/Ph complex via transmetalation (Figure 2C, i and ii).

To further probe the radical generation process, electron paramagnetic resonance (EPR) studies were then carried out with 5,5-dimethyl-pyrroline *N*-oxide (DMPO) as a radical trap (Figure 2D). In a solution of **1a**, **2a**, and DMPO in the presence of $Cu(CH_3CN)_4PF_6$/**L10** in the dark without **3a**, no EPR signal was observed (Figure 2D, i). Irradiation of this solution for 10 min only led to very weak EPR signals (Figure 2D, ii). In contrast, upon addition of phenylboronic acid **3a**, clear signals with six lines ($g$ = 2.0049, $A_N$ = 1.44 mT, $A_H$ = 2.05 mT) were observed and identified as EPR signals of the cyanoalkyl radical-trapping adduct **2a-C** even without irradiation (Figure 2D, iii). Notably, in the presence of **3a** under visible light irradiation, much stronger EPR signals of **2a-C** were found, probably due to the formation of **L**Cu(I)/Ph complex via transmetalation (Figure 2D, iv).

Moreover, the cyclic voltammetry experiments showed that the oxidation potential of copper catalysts can be significantly influenced by coordinating with different Box-type ligands (Supporting Information, Figure S16). Recently, the Gong group disclosed that chiral Cu(II)-Box catalyst can coordinate with imine substrates to facilitate their SET-reduction.[33] Based on these literature reports[33,34] and our mechanistic studies, we proposed that the Cu(I)/Box can work as Lewis acid to coordinate with oxime carbonate to facilitate its SET-reduction towards generation of iminyl radical and Cu(II) complex.

Then, we measured the UV/vis absorption spectra of various combinations of copper salts, phenylboronic acid **3a**, and Box ligands (**L10**, **L19**, and **L25**) (Supporting Information, Figures S7-S9). It was found that the equimolar mixtures of Cu(I)/**L10**, Cu(I)/**L19**, Cu(I)/**L25** showed absorption band around the visible region. Notably, among them, the UV/vis absorption of Cu(I)/**L19** is the strongest, and can be greatly enhanced upon addition of phenylboronic acid **3a**. This observation is also in accordance with the optimization study, wherein the reaction efficiency of Cu(I)/**L19**-catalzyed arylative radical cross-coupling of 4-aryl 1,3-enynes can be obviously improved upon purple LED irradiation.

Building on these mechanistic studies and previous reports,[35,36] we proposed two plausible catalytic cycles for the model arylative radical cross-coupling reactions without or with light irradiation (Figure 3A). It was postulated that the arylative radical cross-coupling of 2-vinylnaphthalene **1a** and somewhat background reaction of 4-alkyl 1,3-enyne **8a** should proceed through non-photoinduced catalytic cycle in the absence of visible light irradiation (Figure 3A, i). Initially, the ground state **L**$Cu^{I}$ complex **A** (**L** = **L10** or **L25**) coordinates with oxime carbonate **2a** to facilitate otherwise difficult SET-reduction of **2a**, generating an iminyl radical **2a-A** together with carboxylic anion ($BocO^-$) and the **L**$Cu^{II}$ species **C**.[36] The $BocO^-$ species undergoes rapid decarboxylation to form *tert*-butoxyl anion (*tert*-$BuO^-$), which can serve as a Lewis base to activate phenylboronic acid **3a** to promote its transmetalation with **L**$Cu^{II}$ species **C** to form **L**$Cu^{II}$/Ph complex **D**. Meanwhile, the initially formed iminyl radical **2a-A** undergoes ring-opening *β*-C-C bond cleavage to form cyanoalkyl radical **2a-B**.[21] Intermolecular radical addition of **2a-B** to either 2-vinylnaphthalene **1a** or 4-alkyl 1,3-enyne **8a** generates the more stabilized benzylic radical **1a-A** or allenyl radicals **8a-B**. Finally, radical intermediates **1a-A** and **8a-B** undergo enantioselective cross-coupling with species **D** to deliver the corresponding products **4a** and **9a**, respectively, with regeneration of

the catalyst **L**Cu$^{I}$ **A**.

During the optimization studies, we found that a small background reaction of 4-phenyl 1,3-enyne **6a** also occurred to give a 17% yield of **7a** without visible light irradiation (Table 3), which implied that the catalytic cycle i should be operative to somewhat extent in this process, but not the major pathway. As for the photoinduced arylative cross-couplings of 4-phenyl 1,3-enyne **6a** and 4-alkyl 2-phenyl-1,3-enyne **8a**, we proposed that both reactions should proceed through photoinduced catalytic cycle as the major route (Figure 3B, ii). Specifically, in the presence of a small amount of *tert*-BuO$^{-}$ formed in the non-photoinduced background reaction, the ground state **L**Cu$^{I}$ complex **A** (**L** = **L19** or **L25**) first undergoes transmetalation with phenylboronic acid **3a** to form **L**Cu$^{I}$/Ph complex **E**. Then, upon visible light irradiation, complex **E** can be exited to the more reducing photoexcited state **E***, which undergoes a SET with oxime carbonate **2a** to form cyanoalkyl radical **2a-B** via iminyl radical **2a-A**, generating **L**Cu$^{II}$/Ph species **D**. Finally, enantioselective cross-coupling reactions of intermediate **D** with the propargylic radical **6a-A** and allenyl **8a-B**, formed by addition of **2a-B** to **6a** or **8a**, occur to afford the correspond products **7a** and **9a**, respectively.

As for 1,3-enynes **6a** and **8a**, we reasoned that site-selectivity can be attributed to the steric interaction during the arylative cross-coupling step. Specifically, in the case of 4-phenyl 1,3-enyne **6a**, the propargylic radical **6a-A** is sterically less encumbered and is thus prone to undergo arylative cross-coupling at the propargylic position to produce 1,2-adduct **7a**. In contrast, as for 4-alkyl 2-phenyl-1,3-enyne **8a**, the addition of cyanoalkyl radical **2a-B** to its double bond affords a pair of resonance structures, the tertiary propargylic radical **8a-A** and allenyl radical **8a-B**. The allenyl radical **8a-B** is more prone to undergo arylative cross-coupling than its resonance form, tertiary benzylic radical **8a-A**. Moreover, the 1,4-adduct allene **10k** was calculated to be significantly more stable than the 1,2-adduct **10k'** by 12.4 kcal/mol due to strong conjugation of allene with both aryl groups (Figure 3B).[22]

Remarkably, the readily accessible chiral copper catalyst works not only as photoredox catalyst for radical formation, but also as the source of stereoinduction in C(sp$^3$)-C(sp$^2$) and C(sp$^2$)-C(sp$^2$) bond-formations. As such, these cross-coupling processes are redox-neutral, and do not require external strong base to activate the boronic acids.

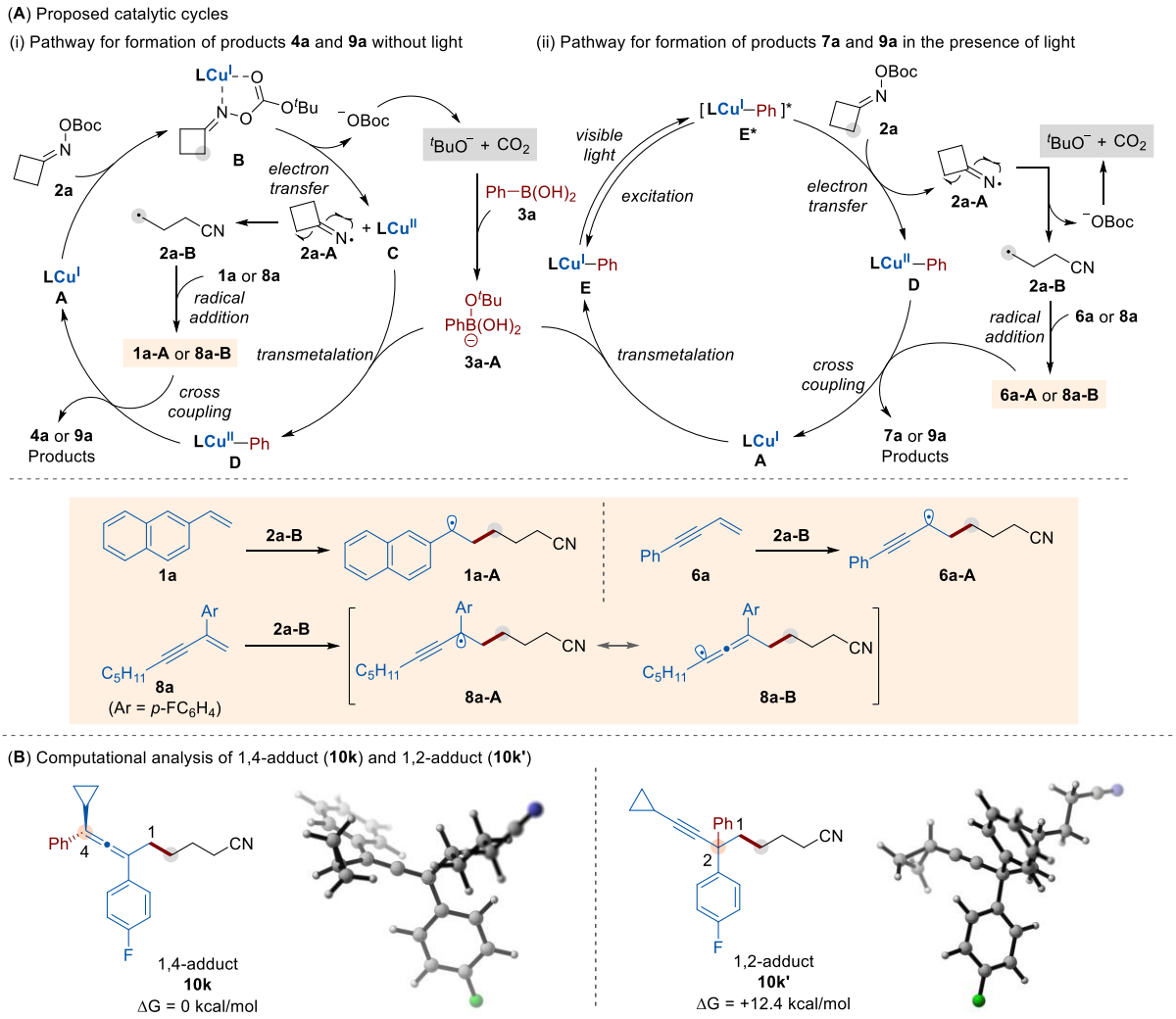



**Figure 3.** Proposed catalytic cycles and computational analysis of 1,4-adduct (**10k**) and 1,2-adduct (**10k'**)

## CONCLUSIONS

In summary, we have demonstrated a general copper catalysis system that is uniquely effective in being able to facilitate the

asymmetric multicomponent arylative radical cross-couplings of vinylarenes and 1,3-enynes, with oxime carbonates and (hetero)aryl boronic acids. The key to the success of these cross-coupling reactions lies in ready regulation of the redox potential of copper catalysts by combination of visible light activation or/and ligand-ligation, thus enabling better rate match of each step. The mild and redox-neutral catalytic systems permit a broad substrate scope and good functional group toleration, providing practical and versatile access to various enantioenriched high-value chiral 1,1-diarylalkanes, benzylic alkynes, and allenes. We believe the new asymmetric multicomponent cross-coupling reactions will provide a new vista for the use of other types of radicals and boronic acids in the development of related asymmetric radical cross-coupling reactions.

**Accession Codes**

CCDC 2327272 (**5m**) and 2327274 (**10b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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**Notes**

The authors declare no competing financial interests.

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