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Copper-Catalyzed Asymmetric Radical 1,2-Carboalkynylation of Alkenes with Alkyl Halides and Terminal Alkynes

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Cite This: J. Am. Chem. Soc. 2020, 142, 9501−9509
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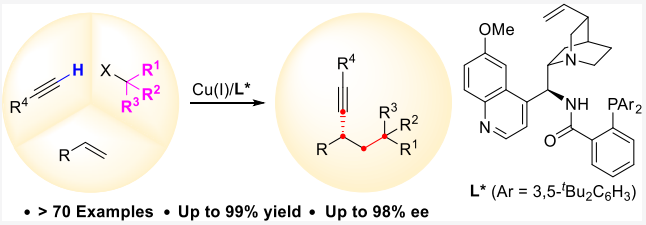
ABSTRACT: A copper-catalyzed intermolecular three-component asymmetric radical 1,2-carboalkynylation of alkenes has been developed, providing straightforward access to diverse chiral alkynes from readily available alkyl halides and terminal alkynes. The utilization of a cinchona alkaloid-derived multidentate N,N,P-ligand is crucial for the efficient radical generation from mildly oxidative precursors by copper and the effective inhibition of the undesired Glaser coupling side reaction. The substrate scope is broad, covering (hetero)aryl-, alkynyl-, and aminocarbonyl-substituted alkenes, (hetero)aryl and alkyl as well as silyl alkynes, and tertiary to primary alkyl radical precursors with excellent functional group compatibility. Facile transformations of the obtained chiral alkynes have also been demonstrated, highlighting the excellent complementarity of this protocol to direct 1,2-dicarbofunctionalization reactions with C(sp^2/sp^3)-based reagents.



INTRODUCTION

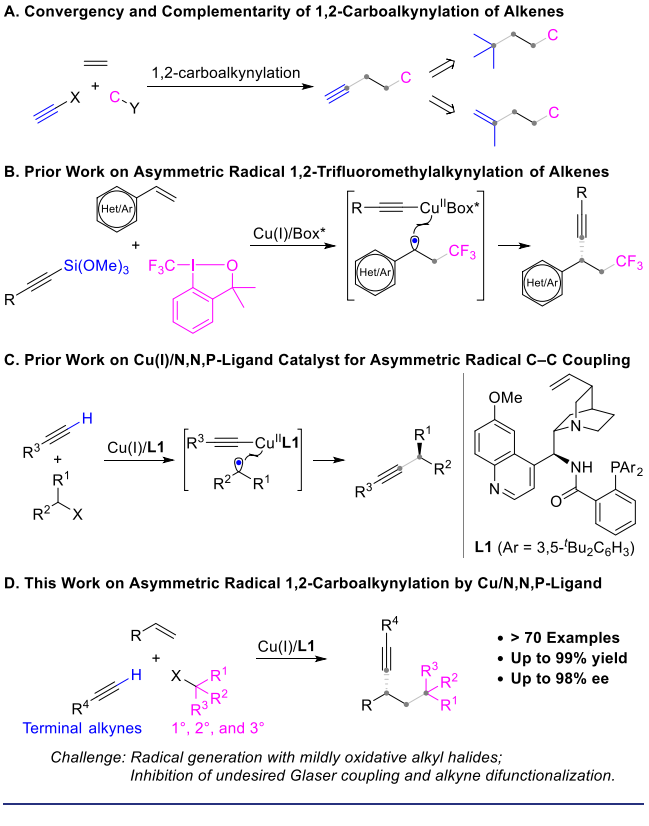
The intermolecular three-component asymmetric 1,2-dicarbofunctionalization of alkenes has recently attracted increasing attention owing to its high synthetic convergency with readily available starting materials for rapid assembly of carbon skeletons (Scheme 1A).[1,2] Given the fact that chiral alkynes are versatile synthons for many other C(sp^2/sp^3)-based functionalities,[3] the enantioselective 1,2-carboalkynylation of alkenes represents a useful and appealing strategy in asymmetric organic synthesis. However, this strategy has been significantly underdeveloped and only recently did Liu et al. achieve an asymmetric 1,2-trifluoromethylalkynylation of alkenes (Scheme 1B).[4] In this work, the efficient trap of an *in-situ* generated benzylic radical with chiral Box(bisoxazoline)-Cu^{II}−alkynyl species is crucial for subsequent enantioselective C−C bond formation, which represents a general strategy pioneered by Fu and others.[5] Notably, the reaction was demonstrated to be compatible with only the $(MeO)_3Si$-prefunctionalized alkynes and Togni's reagent as the nucleophiles and the radical precursor, respectively,[4] the cost and availability of which arguably impede its wide application in asymmetric synthesis. Therefore, the development of robust catalyst for a broadly applicable atom- and step-economic asymmetric 1,2-carboalkynylation of alkenes from readily available building blocks is highly desirable.

In continuation of our research interest in copper-catalyzed asymmetric radical reactions,[6] we have recently developed a copper-catalyzed enantioconvergent Sonogashira C(sp^3)−C(sp) coupling reaction.[7] Critical to the success of the reaction is the development of a chiral alkaloid-derived multidentate N,N,P-ligand for both enhancing the reducing capability of a copper catalyst and inhibiting the Glaser coupling side reaction (Scheme 1C).[8] Thus, mildly oxidative alkyl halides and side-reaction-prone terminal alkynes were highly enantioselectively coupled together via trapping alkyl radicals with the presumed chiral Cu^{II}−alkyne complex. Since alkyl halides and terminal alkynes[9] both are widespread building blocks in organic synthesis, we envisioned a copper-catalyzed asymmetric radical 1,2-carboalkynylation of alkenes directly with these two readily available reagents (Scheme 1D). The success of this method would not only allow expeditious access to diverse chiral alkynes but also offer complementary approaches to direct asymmetric 1,2-dicarbofunctionalization of alkenes using C(sp^2/sp^3)-based reagents. Several factors have thwarted the development of such a strategy: (1) the relatively difficult radical generation from alkyl halides by copper catalysts with most common chiral ligands;[10] (2) the inhibition of easily occurring copper-catalyzed Glaser homocoupling of terminal alkynes;[8] (3) the problematic chemoselectivity between radical addition to terminal alkenes and alkynes owing to the inherently high reactivity of radical species.[11] Herein, we describe the development of a mild copper(I)/cinchona alkaloid-derived N,N,P-ligand catalytic

Received: March 21, 2020
Published: April 25, 2020

https://dx.doi.org/10.1021/jacs.0c03130
J. Am. Chem. Soc. 2020, 142, 9501−9509

Scheme 1. Intermolecular 1,2-Carboalkynylation of Alkenes



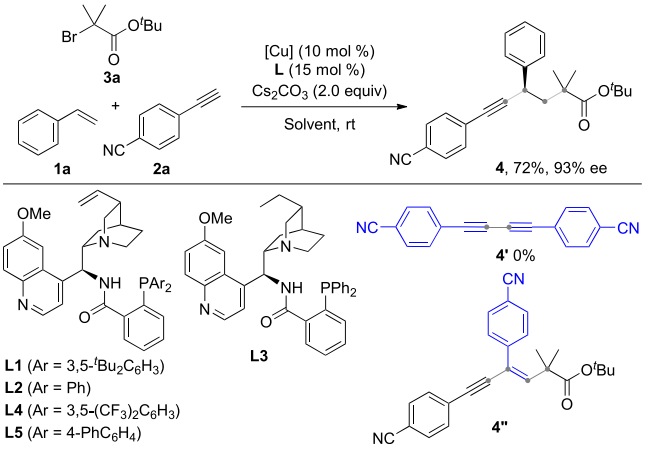
system for a general asymmetric intermolecular three-component radical 1,2-carboalkynylation of alkenes with alkyl halides and terminal alkynes.

RESULTS AND DISCUSSION

Reaction Development. Based on the above-mentioned proposal, we began to investigate the three-component asymmetric reaction of easily available styrene **1a**, alkyne **2a** and *tert*-butyl α-bromoisobutyrate **3a** (Table 1). After extensive screening of reaction conditions, we were pleased to find that the chiral cinchona alkaloid-derived N,N,P-ligands were remarkably effective in radical generation and inhibition of the Glaser coupling side reaction leading to **4′** (Table 1). In addition, the desired reaction was disfavored with ligands bearing electron-deficient *P*-aryl rings and the most sterically bulky ligand **L1** gave rise to the highest enantioselectivity. In contrast, the enantioselectivity only slightly changed among different solvents or copper salts. Notably, the reaction solvent significantly affected the ratio between the desired alkene addition product **4** and the undesired alkyne addition product **4′′** and 1,4-dioxane gave the highest ratio. We finally identified the best reaction conditions in terms of cost efficiency as follows: the reaction of **1a**, **2a**, and **3a** in a molar ratio of 1.5:1.0:1.2 in the presence of 7.5 mol % CuOAc and 7.5 mol % **L1** provided **4** in 72% yield and 93% ee in 1,4-dioxane at room temperature (Table 1, entry 15).

With the optimized reaction conditions in hand, the substrate scope of alkenes for this asymmetric transformation was then investigated (Table 2). Various styrene-type alkenes, including those having monosubstituted phenyl rings with electron-neutral, -rich, or -deficient functional groups at different positions (*ortho*, *meta*, or *para*) and a disubstituted phenyl ring, were suitable for this reaction to afford the desired

Table 1. Screening of Reaction Conditions for Model Reaction[a]



Entry	[Cu]	L	Solvent	Yield (%)[b] 4	4′′	Ee (%)[c]
1	CuI	**L2**	Et_2O	42	16	72
2	CuI	**L2**	CH_3CN	31	43	69
3	CuI	**L2**	EtOAc	45	20	74
4	CuI	**L2**	1,4-dioxane	50	12	70
5	CuI	**L3**	1,4-dioxane	52	14	70
6	CuI	**L4**	1,4-dioxane	20	15	77
7	CuI	**L5**	1,4-dioxane	68	18	77
8	CuI	**L1**	1,4-dioxane	66	32	94
9[d]	CuI	**L1**	1,4-dioxane	67	27	94
10[e]	CuI	**L1**	1,4-dioxane	76	8	94
11[e]	CuBr	**L1**	1,4-dioxane	71	12	93
12[e]	CuTc	**L1**	1,4-dioxane	67	8	94
13[e]	$Cu(CH_3CN)_4PF_6$	**L1**	1,4-dioxane	70	15	93
14[e]	CuOAc	**L1**	1,4-dioxane	76	4	94
15[e,f]	**CuOAc**	**L1**	**1,4-dioxane**	**72**	**4**	**93**

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), **3a** (0.12 mmol), [Cu] (10 mol %), **L** (15 mol %), and Cs_2CO_3(2.0 equiv) in solvent (1.0 mL) at room temperature for 24 h under argon. [b]Yields of **4** and **4′′** were based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard, and that of **4′** was based on GC-MS analysis. [c]Ee values based on HPLC analysis. [d]**1a** (0.12 mmol), **2a** (0.10 mmol), **3a** (0.12 mmol). [e]**1a** (0.15 mmol), **2a** (0.10 mmol), **3a** (0.12 mmol). [f]CuOAc (7.5 mol %), **L** (7.5 mol %).

products **4**–**25** in good yields and excellent ee. Many functional groups, such as methoxyl (**5**–**7**), phenoxyl (**8**), acetoxyl (**9**), halo (**15**–**19**), trifluoromethyl (**20**), cyano (**21**), formyl (**22**), acetyl (**23**), and methoxylcarbonyl (**24**) groups, were well tolerated under the reaction conditions. Furthermore, alkenes bearing polycyclic aryl rings were also compatible with the reaction to give **26**–**28** in moderate to good yield with excellent enantioselectivity. Noteworthy is that many alkenes that contain medicinally relevant heterocycles, such as benzo[*d*][1,3]dioxole, pyrazole, furan, benzofuran, thiophene, benzo[*b*]thiophene, pyridine, quinoline, and thiazole, all underwent the current reaction smoothly to deliver the corresponding products **27**–**35**, respectively, in 46–91% yields with 83–96% ee. Interestingly, besides (hetero)aryl alkenes, the reaction of an aminocarbonyl-substituted alkene also proceeded to provide the corresponding product **36** in 20% yield and 81% ee. More significantly, the conjugated eneyne was also a suitable substrate to afford

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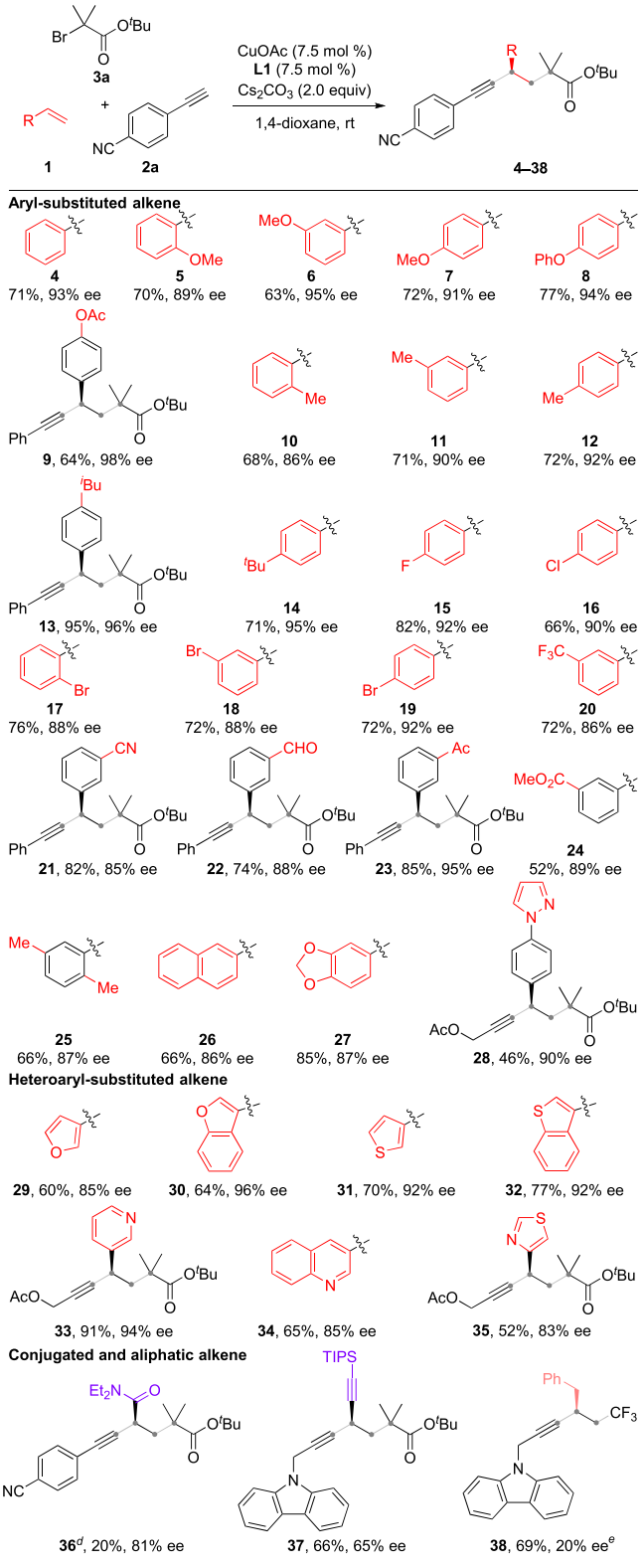
Table 2. Substrate Scope of Alkene[a,b,c]

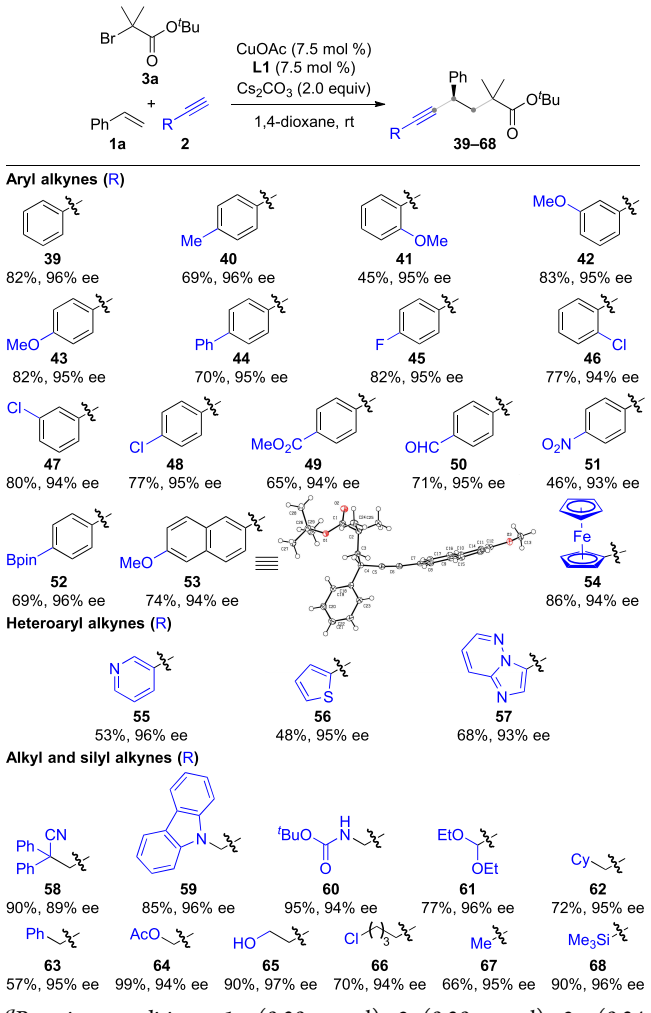


[a]Reaction conditions: **1** (0.30 mmol), **2a** (0.20 mmol), **3a** (0.24 mmol), CuOAc (7.5 mol %), **L1** (7.5 mol %), and Cs_2CO_3 (0.40 mmol) in 1,4-dioxane (2.0 mL). [b]Isolated yield. [c]The ee value was determined by HPLC. [d]*N*,*N*-Diethylacrylamide (0.80 mmol) was used as the alkene substrate. [e]Togni's reagent **3h** was used as the radical precursor.

the carboalkynylation product **37** in 66% yield and 65% ee. With regard to the unactivated aliphatic alkene, the reaction also worked with Togni's reagent **3h** (Table 2) as the radical precursor to afford the product **38** in good yield, albeit with low ee. These results are currently under further optimization in our lab. Unfortunately, the 1,1- and 1,2-disubstituted alkenes are currently inapplicable to the carboalkynylation (see Scheme S1 in the Supporting Information).

Encouraged by the above results, we next switched our attention to evaluate the scope of alkynes (Table 3). Thus,

Table 3. Substrate Scope of Alkyne[a,b,c]



[a]Reaction conditions: **1a** (0.30 mmol), **2** (0.20 mmol), **3a** (0.24 mmol), CuOAc (7.5 mol %), **L1** (7.5 mol %), and Cs_2CO_3 (0.40 mmol) in 1,4-dioxane (2.0 mL). [b]Isolated yield. [c]The ee value was determined by HPLC.

under the standard conditions, a series of aryl alkynes possessing phenyl rings with distinct electronic and steric properties and a naphthalene ring as well as a ferrocene ring all worked well to give **39**−**54** in moderate to good yield with excellent ee. Many functional groups, such as methoxyl (**41**−**43**), halo (**45**−**48**), methoxylcarbonyl (**49**), formyl (**50**), nitro (**51**), and pinacolborato (**52**), survived the reaction conditions. The absolute configuration of **53** was determined to be *R* by X-ray crystallographic analysis (Table 3 and Figure S1 in the Supporting Information). Furthermore, heteroaryl alkynes, such as 3-pyridinyl-, 2-thiophenyl-, and 3-imidazo[1,2-*b*]-

https://dx.doi.org/10.1021/jacs.0c03130
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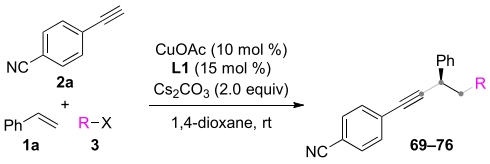
pyridazinyl-substituted acetylenes, were also viable substrates for this reaction to deliver **55**−**57** in 48−68% yield with 93−96% ee. Notably, a series of alkyl alkynes underwent the current reaction smoothly to give products **58**−**67** in good yield and high ee. And a wide range of functional groups, such as cyano (**58**), carbazole (**59**), carbamate (**60**), acetal (**61**), ester (**64**), primary alcohol (**65**), and even primary chloride (**66**), at different distances away from the reacting alkynes were compatible with the reaction conditions. Most importantly, the industrially relevant propyne, one key component of the readily available MAPP (methylacetylene-propadiene propane) welding gas, was also a suitable substrate to give the desired product **67** in 66% yield and 95% ee. Furthermore, trimethylsilyl acetylene also worked well to provide **68** in 90% yield and 96% ee. As for the scope of alkyl radical precursors (Table 4), tertiary alkyl bromide **3b** and chloride **3c**

Table 4. Substrate Scope of Alkyl Radical Precursors[a,b,c]



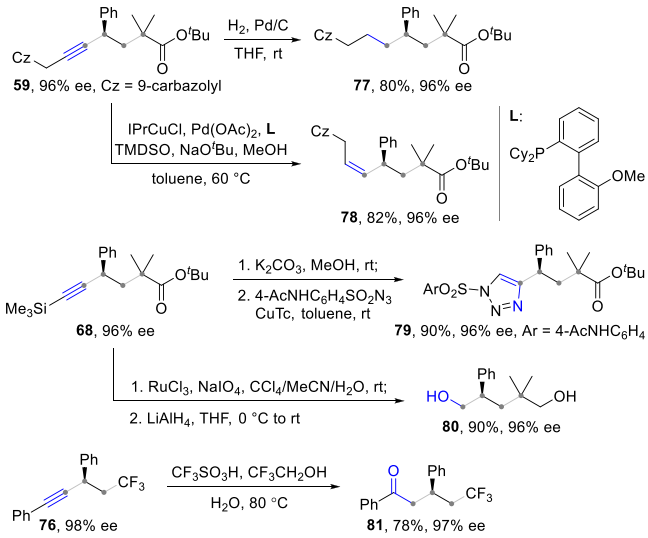
R−X	Product	R−X	Product
Br, OEt, O	OEt, O — **69**[d], 78%, 93% ee	Me, Cl, CN — **3f**	Me, CN — **73**, 40%, 1.3/1 dr 91%/94% ee
Cl, OMe, O — **3c**	OMe, O — **70**[d], 51%, 93% ee	Br, CN — **3g**	CN — **74**[e], 70%, 95% ee
Br, N, OMe, O — **3d**	N, OMe, O — **71**, 74%, 94% ee	F_3C, I, O, O — **3h**	CF_3 — **75**, 71%, 96% ee
F, F, Br, OEt, O — **3e**	F, F, OEt, O — **72**[e], 53%, 92% ee	F_3C, I, O, O — **3h**	Ph, CF_3 — **76**, 69%, 98% ee

[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.20 mmol), **3** (0.24 mmol), CuOAc (10 mol %), **L1** (15 mol %), and Cs_2CO_3 (0.40 mmol) in 1,4-dioxane (2.0 mL). [b]Isolated yield. [c]The ee value was determined by HPLC. [d]CuOAc (7.5 mol %), **L1** (7.5 mol %). [e]Yield was based on recovered **2a**.

that are α to ester functional groups were suitable radical precursors to afford **69** and **70**, respectively, in excellent ee. The structurally similar Weinreb amide-type tertiary alkyl bromide **3d** also delivered product **71** in 74% yield and 94% ee, of which the amide moiety is readily amenable to facile synthesis of carbonyl compounds. In addition, the fluoro-containing tertiary alkyl bromide **3e** was applicable to this transformation too, providing the enantioenriched product **72** with the pharmacologically important difluoromethylene moiety.[12] Importantly, the secondary alkyl chloride **3f** gave the desired product **73** as a 1.3:1 mixture of diastereomers with 91% and 94% ee, respectively. Furthermore, the asymmetric reaction proceeded smoothly on primary alkyl bromide **3g** to give **74** in 70% yield and 95% ee. Interestingly, the Togni's reagent **3h** was also a viable radical precursor to afford **75** and **76** in good yield and excellent ee. Noteworthy is that the thus-incorporated trifluoromethyl units are particularly important in the development of many pharmaceuticals and agricultural chemicals.

Synthetic Utility. To demonstrate the synthetic utility of this method, we carried out further transformations of the prepared chiral alkynes. As shown in Scheme 2, the complete

Scheme 2. Synthetic Applications



hydrogenation of chiral alkyne **59** provided **77** featuring a saturated aliphatic chain. On the other hand, a highly stereoselective partial hydrogenation of this chiral alkyne afforded *Z*-alkene **78**. Besides, the trimethylsilyl group of chiral alkyne **68** was readily removed to provide the corresponding terminal alkyne, which further underwent copper-catalyzed azide−alkyne cycloaddition (CuAAC) reaction to provide 1-sulfonyl-1,2,3-triazole **79** in 90% yield and 96% ee. In addition, direct oxidation of alkyne **68** to the corresponding carboxylic acid followed by reduction with $LiAlH_4$ successfully gave the chiral 1,5-diol **80**. Moreover, straightforward hydration of chiral alkyne **76** furnished ketone **81** characterized by a β-chiral stereocenter. It is noteworthy that no apparent loss of enantiopurity was observed during all these transformations. Thus, this asymmetric radical 1,2-carboalkynylation of alkenes—when combined with one- or two-step further manipulations—provides practical and excellent complementary approaches to direct asymmetric 1,2-dicarbofunctionalization of alkenes using C(sp^2/sp^3)-based reagents.

Mechanistic Studies. To gain insights into the reaction mechanism, control experiments were conducted. First, the reaction of copper phenylacetylide, **1a**, and **3a** proceeded smoothly in the presence of **L1** to provide **39** in 80% yield and 96% ee, while no reaction occurred in the absence of **L1** (Scheme 3A). Thus, the ligand-coordinated copper acetylide is likely the reductant of alkyl halides for reaction initiation. The radical clock substrate **82** led to the ring-opening product **83** under the standard reaction conditions (Scheme 3B). Thus, a radical pathway was likely involved, which was further supported by the radical inhibition experiment with TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) (Scheme 3C).

To investigate the possible binding mode of the N,N,P-ligand with Cu^I, we carried out the NMR experiments (Figure 1). The **L2**Cu^I complex was synthesized by mixing CuI and **L2** in a 1:1 ratio in $CDCl_3$ at room temperature. Its ^{1}H NMR

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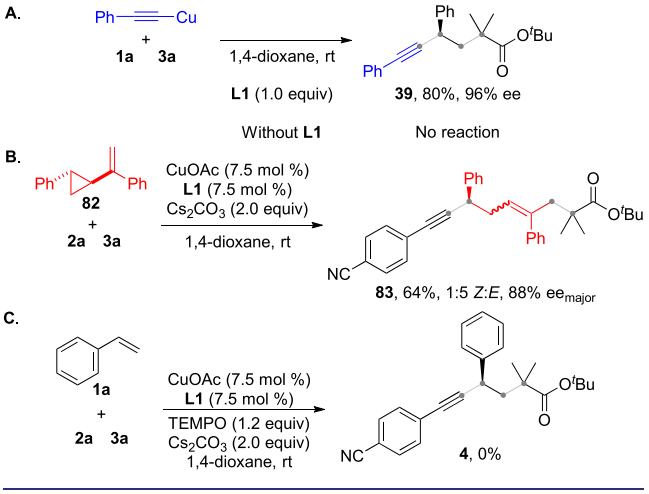
Scheme 3. Control Experiments



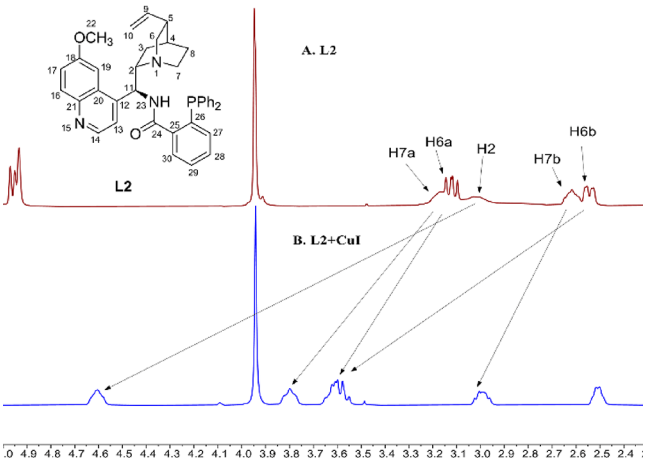


Figure 1. ^{1}H NMR Studies of the **L2** Cu^I Complex. Red: ^{1}H NMR of **L2**. Blue: ^{1}H NMR of **L2** Cu^I.

spectrum revealed apparent downfield shifts of protons adjacent to the quinuclidine nitrogen compared with those of **L2**, indicating probable binding of Cu^I with the quinuclidine moiety **L2** in solution (see full NMR analysis in the Supporting Information). The ^{31}P NMR experiments also showed an apparent downfield shift (+2.4 ppm relative to that of **L2**), supporting probable binding of Cu^I with the phosphine moiety in **L2** in solution (see Figure S2 in the Supporting Information). The complex formation was further supported by the observation of the signals at m/z of 674.1969 and 676.1960, corresponding to the masses of **L2**^{63}Cu^I and **L2**^{65}Cu^I, respectively (see Figure S3 in the Supporting Information). However, we cannot obtain further information on other binding sites in **L2** with Cu^I from the NMR experiments.

A series of cyclic voltammogram (CV) experiments were performed to investigate the influence of the N,N,P-ligand on the redox potential of Cu^I catalyst utilizing CuBr as the copper salt. The CV of CuBr showed a quasi-reversible couple at +0.6 V (Figure 2). The complex of **L2**CuBr was prepared by mixing CuBr, **L2**, and Cs_2CO_3 in a 1:1:1 ratio, and the CV experiment showed a quasi-reversible couple at −0.1 V, corresponding to the Cu^I/Cu^{II} redox couple (Figure 2). These experiments support our hypothesis that the multidentate N,N,P-ligand could enhance the reducing capability of copper catalyst.

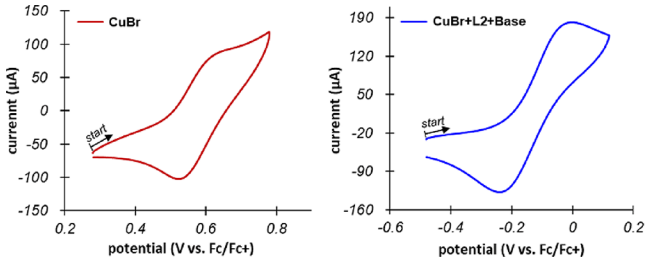


Figure 2. Cyclic voltammograms of CuBr (red) and the **L2** CuBr complex (blue). Conditions: 10 mM in CH_3CN with 0.1 M Bu_4NPF_6 as electrolyte and a 100 mV/s scan rate using a glassy carbon working electrode and a Pt counter electrode. Potentials were calibrated with Fc as an internal standard.

Since Cu^{II} has a d^9 configuration, we carried out the electron paramagnetic resonance (EPR) experiment of the reaction mixture in order to support the involvement of a Cu^{II} species. The sample was prepared by taking an aliquot from the standard model reaction in glovebox. The EPR spectrum of the reaction mixture is consistent with that of a standard Cu^{II} complex, thus indicating that a Cu^{II} species is likely involved (Figure 3).

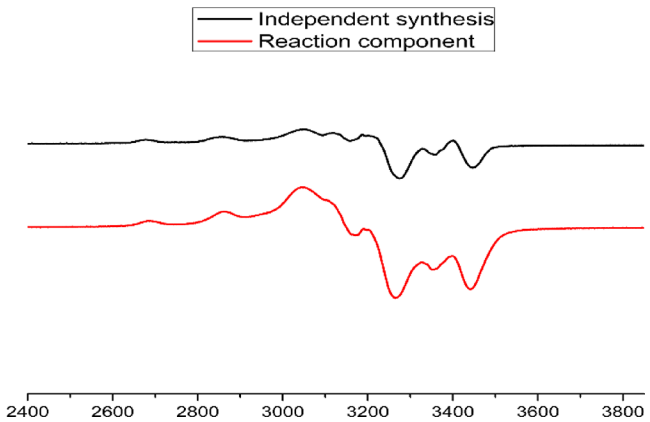


Figure 3. X-band EPR spectrum (9.26 GHz, 100 K). Black: a mixture of Cu(OAc)$_2$, **L2**, and **2a**. Red: a reaction component of the standard model carboalkynylation reaction.

Further kinetic analysis on the carboalkynylation reaction of 4-fluorostyrene **1l** was performed with alkyne **2a**, alkyl halide **3a**, CuOAc, and ligand **L2**. The reaction was found to be of first-order dependence in alkene and catalyst, respectively (Figures 4A and 4B). The rate dependence on alkyl halide was close to zeroth-order, demonstrating that the generation of radical species from alkyl halide was irrelevant to the rate-determining step(s) (Figure 4C). With regard to alkyne, the reaction rate was first increased and then decreased following the increase of its concentration, indicating its multifaceted roles in the reaction process (Figure 4D).

Based on these results and our previous reports,[6,7] we proposed a plausible reaction mechanism, shown in Scheme 4. In the presence of base, Cu^I, alkyne, and **L1** react to form a monomeric intermediate **II**. This complex may further react to afford the inactive polymeric complex **V** in the presence of excessive terminal alkyne, thus resulting in reaction inhibition.[13] The Cu^I intermediate **II** reduces alkyl halide **3** to generate a Cu^{II} complex **III** and a ·R^2 radical possibly via a single electron transfer process. The alternative halogen atom

https://dx.doi.org/10.1021/jacs.0c03130
J. Am. Chem. Soc. 2020, 142, 9501−9509

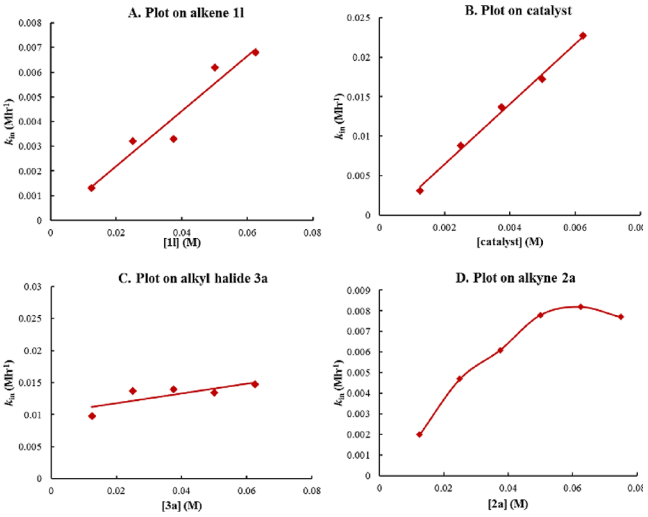
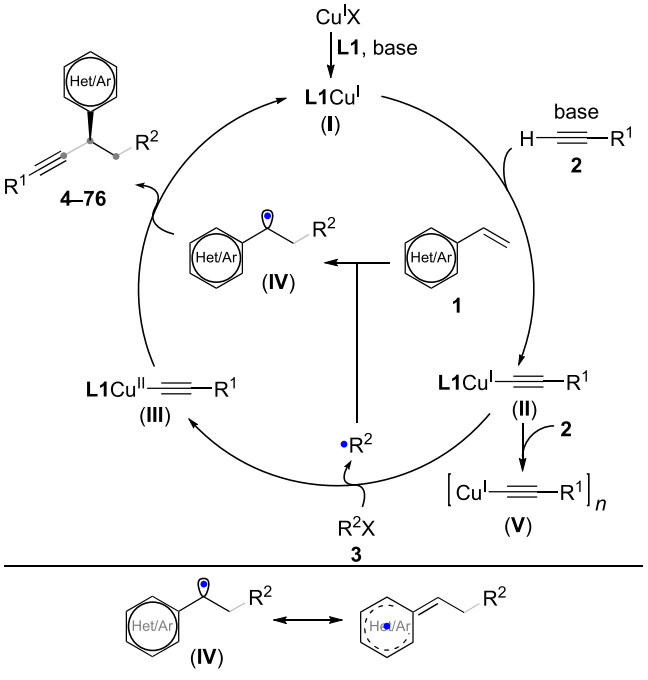


Figure 4. Kinetic analysis of the 1,2-carboalkynylation of alkenes. (A) Initial rate plot for determining the order in alkene. (B) Initial rate plot for determining the order in catalyst. (C) Initial rate plot for determining the order in alkyl halide. (D) Initial rate plot for alkyne.

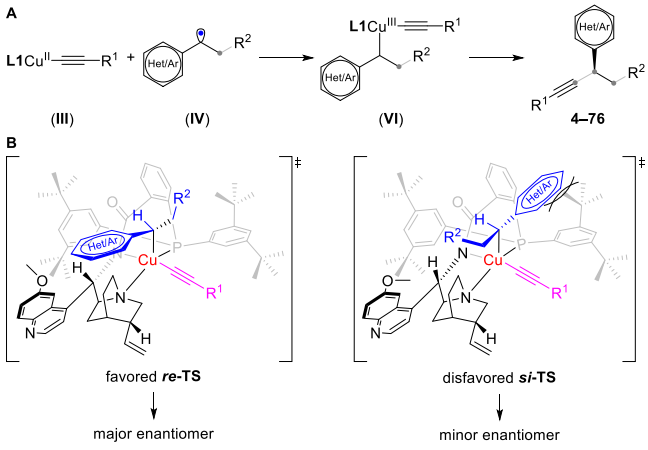
Scheme 4. Proposed Mechanism



transfer process is less likely based on the fact that **3b** and **3c** have led to the same enantioselectivity (Table 4).[14] Next, the ·R^2 radical selectively adds to alkene **1** to provide a prochiral alkyl radical **IV**, which was stabilized by delocalization of the unpaired electron into the adjacent (hetero)aromatic ring. Finally, radical **IV** and the Cu^{II} complex **III** undergo C(sp^3)−C(sp) bond formation to deliver the enantioenriched products **4**−**76**, while releasing the **L1**Cu^{I} complex **I** for the next catalytic cycle. Notably, the direct coupling reaction between the tertiary ·R^2 radical and the Cu^{II} complex **III** was not observed, probably due to the steric hindrance in the construction of quaternary carbon centers.

As for the enantiodetermining C(sp^3)−C(sp) bond formation, we have tentatively proposed the formation of Cu(III) species **VI** and its subsequent reductive elimination[15] (Scheme 5A; also see Scheme S2 in the Supporting Information for

Scheme 5. Proposed Mechanism



alternative possible pathways). Accordingly, two enantiodiscrimination transition states of pentacoordinated Cu(III) complexes[15] leading to enantiomers of **4**−**76**, respectively, were deduced, as shown in Scheme 5B. The steric clash between the relatively bulky (hetero)aryl group in substrate and the *P*-3,5-di-*tert*-butylphenyl group in the ligand renders the *si*-**TS** unfavorable. Thus, the favorable *re*-**TS** leads to the formation of products of an *R* absolute configuration as experimentally observed. Nonetheless, we currently have no solid evidence to support this proposed enantiodiscrimination mechanism and, thus, are carrying out further experimental and theoretical studies on this reaction.

CONCLUSION

In summary, we have developed a copper-catalyzed intermolecular three-component asymmetric radical 1,2-carboalkynylation of alkenes for expedited synthesis of structurally diverse chiral alkynes. One striking feature of this method is the ready accommodation of easily available terminal alkenes ((hetero)aryl-, alkynyl-, and aminocarbonyl-substituted) and alkynes ((hetero)aryl, alkyl, and silyl) as well as various alkyl radical precursors (3°, 2°, and 1°). A multidentate cinchona alkaloid-derived N,N,P-ligand was strategically employed to enhance the reducing power of copper. Thus, a variety of mildly oxidative alkyl halides could be used as radical precursors and the Glaser coupling side reaction was effectively inhibited. Importantly, this reaction provides a general strategy for asymmetric 1,2-dicarbofunctionalization with not only chiral C(sp^3)−C(sp) but also chiral C(sp^3)−C(sp^2/sp^3) bond formations when allied with follow-up transformations. Further efforts for exploration of this catalyst system in asymmetric radical reactions are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c03130.

Experimental procedures, characterization of compounds, Schemes S1 and S2, Figures S1−S3 (PDF)
Crystallographic data for **53** (CIF)

https://dx.doi.org/10.1021/jacs.0c03130
J. Am. Chem. Soc. 2020, 142, 9501−9509

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (Nos. 21722203, 21831002, and 21801116), Natural Science Foundation of Guangdong Province (No. 2018A030310083), Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), Guangdong Innovative Program (2019BT02Y335), Shenzhen Special Funds (No. JCYJ20180302180235837), Shenzhen Nobel Prize Scientists Laboratory Project (No. C17783101), and SUSTech Special Fund for the Construction of High-Level Universities (No. G02216303).

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