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Copper-Catalyzed Asymmetric Coupling of Allenyl Radicals with Terminal Alkynes to Access Tetrasubstituted Allenes

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Dedicated to the 70th anniversary of the Shanghai Institute of Organic Chemistry

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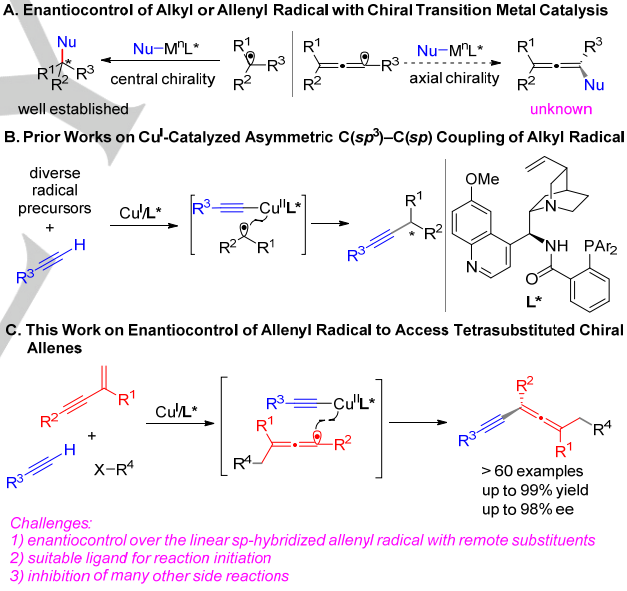
Abstract: In contrast to the wealth of asymmetric transformations for generating central chirality from alkyl radicals, the enantiocontrol over the allenyl radicals for forging axial chirality represents an uncharted domain. The challenge arises from the unique elongated linear configuration of the allenyl radicals that necessitates the stereo-differentiation of remote motifs away from the radical reaction site. We herein describe a copper-catalyzed asymmetric radical 1,4-carboalkynylation of 1,3-enynes via the coupling of allenyl radicals with terminal alkynes, providing diverse synthetically challenging tetrasubstituted chiral allenes. A chiral N,N,P-ligand is crucial for both the reaction initiation and the enantiocontrol over the highly reactive allenyl radicals. The reaction features a broad substrate scope, covering a variety of (hetero)aryl and alkyl alkynes and 1,3-enynes as well as radical precursors with excellent functional group tolerance.

In the past decades, tremendous progress has been made in the development of asymmetric catalysis to realize enantioselective radical reactions for synthesis of enantioenriched molecules.[1,2] Among innovative approaches, chiral first-row transition metal catalysis represents an appealing strategy for generating central chirality from mostly sp^2-hybridized planar alkyl radical species (Scheme 1A, left).[2] In contrast, the *sp*-hybridized allenyl radicals feature a linear geometry with two flanking substituents far away from the radical reaction sites,[3] thus rendering the enantiocontrol over such radicals to forge axial chirality difficult and significantly unexplored (Scheme 1A, right).[4,5] On the other hand, axially chiral allenes not only are important structural motifs in natural products, bioactive molecules, and functional materials, but also serve as versatile synthons, ligands, and catalysts in organic synthesis.[6] In this context, although many elegant strategies have been described for the synthesis of chiral di- and trisubstituted allenes,[7] only a limited number of approaches have been reported for the synthesis of tetrasubstituted chiral allenes based on metal catalysis[8] and organocatalysis.[9] Moreover, most of these methodologies rely on substrates with particular polar functional groups and/or kinetic resolution processes, which arguably impedes their wide applications in organic synthesis.[8,9] Therefore, the development of robust catalysts to achieve the enantiocontrol over allenyl radical species for the expedient assembly of diverse tetrasubstituted chiral allenes is still highly desirable.

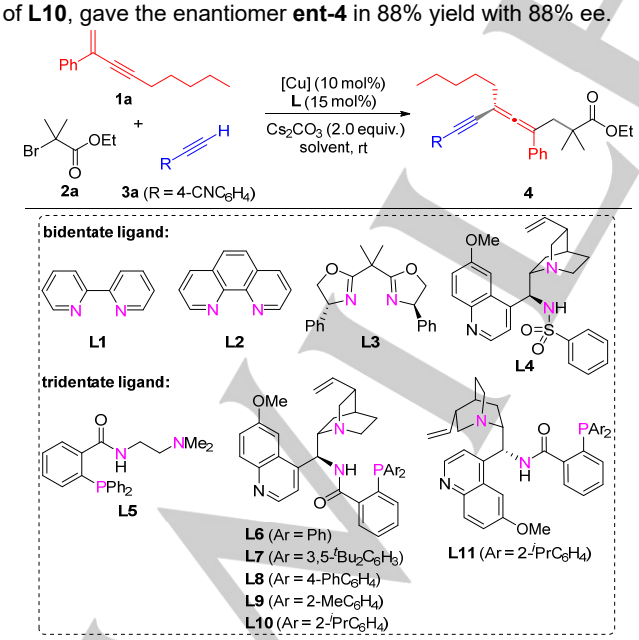


Scheme 1. Motivation and design of enantioselective alkynylation of allenyl radicals to access tetrasubstituted chiral allenes.

As our continuous efforts in copper-catalyzed asymmetric radical reactions,[2e,2f,10] we have demonstrated that a copper/chiral N,N,P-ligand catalyst is robust for the enantiocontrol over sp^2-hybridized alkyl radicals to construct chiral C(sp^3)–C(sp) bonds with terminal alkynes (Scheme 1B).[11] We speculated that such a strategy might also be suitable for the enantiocontrol over the *sp*-hybridized allenyl radicals to construct tetrasubstituted chiral allenes. Given the easy availability of alkyl halides and terminal alkynes, along with the ubiquity of 1,3-enynes,[5] we targeted the development of an asymmetric radical 1,4-difunctionalization of 1,3-enynes with alkyl halides as the radical precursors and terminal alkynes as

the nucleophiles (Scheme 1C). However, several challenges have to be solved: (1) the aforementioned unexplored enantiocontrol over the highly reactive allenyl radicals; (2) the identification of a suitable ligand to initiate the reaction; (3) the inhibition of easily occurring side reactions, such as the Glaser homocoupling of terminal alkynes,[12] the cross-coupling of alkyl halides with terminal alkynes,[11a] and 1,2-carboalkynylation of alkynes.[13] Herein, we describe the development of a copper-catalyzed three-component asymmetric radical 1,4-carboalkynylation of 1,3-enynes, providing straightforward access to diverse tetrasubstituted chiral allenes.

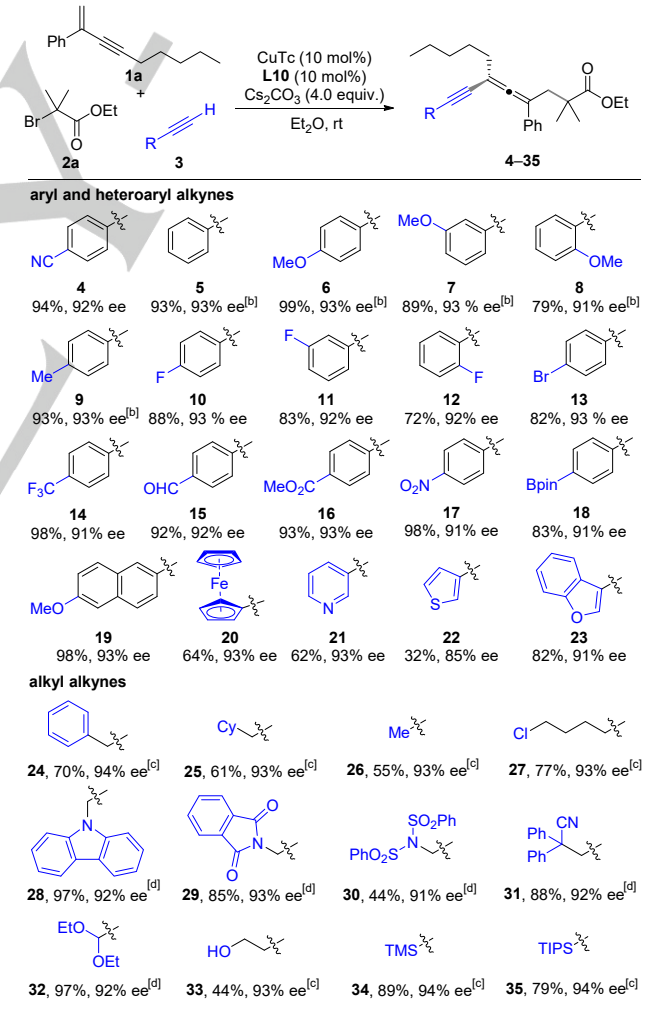
We initiated our investigation by searching for a suitable ligand for the 1,4-carboalkynylation of 2-phenyl-1,3-enyne **1a** with alkyne **3a** and ethyl α-bromoisobutyrate **2a**. A screening of bidentate ligands (**L1–L4**) with CuTc as the catalyst indicated very low reaction efficiency, presumably due to the insufficient reducing capability of the copper complex (Scheme 2 and Table S1, entries 1–5). Thus, we next examined the more electron-rich N,N,P-tridentate ligand **L5** and found that the reaction provided product **4** in 61% yield, along with side products **4'** and **4''** (Scheme 2 and Table S1, entry 6).[14] We then evaluated a series of chiral cinchona alkaloid-derived N,N,P-ligands (**L6–10**) with diverse substituents at different positions of the P-phenyl rings and found that **L10** with an isopropyl group on the *ortho* position proved to be the best (Scheme 2 and Table S1, entries 7–11). The ratios of starting materials also affected the ratio between the desired product and side products and the reaction of **1a**, **2a,** and **3a** in a molar ratio of 1.5:1.2:1.0 gave the sole product **4** with excellent enantioselectivity (Table S1, entry 12). Further evaluation of different copper salts, solvents, and catalyst loadings led to the discovery of the optimal conditions as follows: the reaction in the presence of 10 mol% CuTc and **L10** with 4.0 equivalents of Cs_2CO_3 in Et_2O at room temperature for 24 h provided **4** in 98% yield and 92% ee (Table S1, entry 20). An experiment with the **L11**, which is the pseudoenantiomer of **L10**, gave the enantiomer **ent-4** in 88% yield with 88% ee.



Scheme 2. The effect of different ligands for model reaction.

With the optimal reaction conditions established, the substrate scope of alkynes was then investigated. As shown in Table 1, a number of aryl alkynes were applicable to the reaction, providing the chiral allenes **4–20** in 64–99% yields with 91–93% ee. A myriad of electron-donating or -withdrawing substituents, such as methoxyl (**6–8**), halo (**10–13**), trifluoromethyl (**14**), formyl (**15**), methoxylcarbonyl (**16**), nitro (**17**), and pinacolborato (**18**), at *para*, *meta*, or *ortho* positions of the phenyl rings were tolerated under the standard conditions. The aryl alkynes with a naphthalene ring (**19**) and a ferrocene ring (**20**) were also amenable to the 1,4-carboalkynylation reaction. More importantly, heteroaryl alkynes containing heterocycles commonly existing in therapeutics—such as pyridine, thiophene and benzo[*b*]furan—were suitable for the reaction to afford the desired products **21**–**23** with 85–93% ee. Notably, many alkyl alkynes with aliphatic chains or a series of functionalities, such as chloride, carbazole, imide, sulfonimide, nitrile, acetal, free alcohol as well as silicon, underwent the reaction smoothly to deliver **24**–**35** in good to excellent yields with excellent ee.

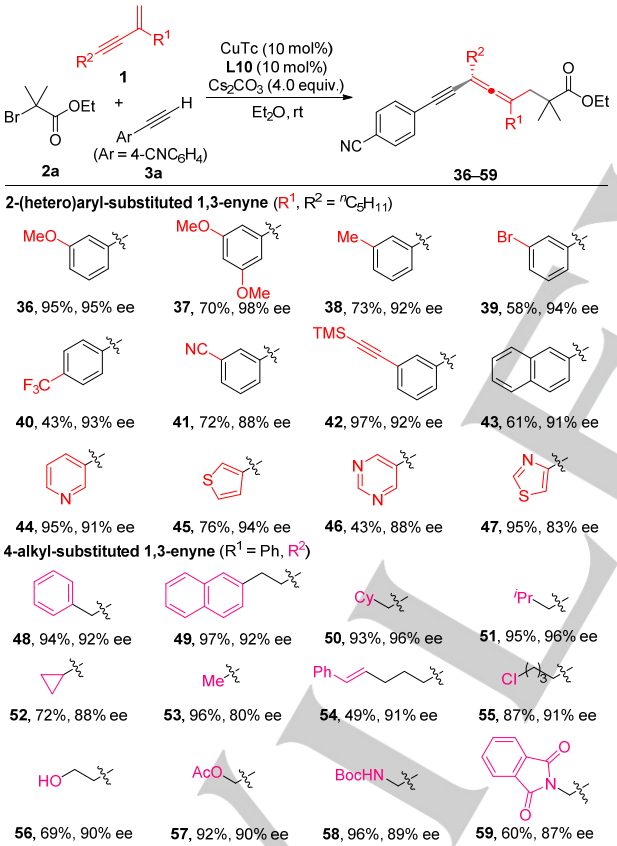
Table 1. Substrate scope of alkynes.[a]



[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.24 mmol), **3** (0.20 mmol), CuTc (10 mol%), **L10** (10 mol%), and Cs_2CO_3 (4.0 equiv.) in Et_2O (4.0 mL) at room temperature for 24 h under argon; the yields are isolated and the ee values were determined by HPLC. [b] Cs_2CO_3 (6.0 equiv.). [c] CuTc (15 mol%), PPh_3 (45 mol%). [d] CuTc (15 mol%).

We then switched our attention to the scope of substituted 1,3-enynes (Table 2). Many 1,3-enynes with 2-phenyl rings bearing functional groups, such as (bis)methoxy, bromo, trifluoromethyl, nitrile, and alkyne, at different positions and even a naphthalene ring were well compatible with the mild reaction conditions, delivering tetrasubstituted chiral allenes **36**–**43** with 88–98% ee. The 1,3-enynes containing medicinally relevant heterocycles, such as pyridine (**44**), thiophene (**45**), pyrimidine (**46**), and thiazole (**47**), were viable substrates to give the desired products with good to excellent ee. With respect to the 4-substituents, the 1,3-enynes having benzyl or purely aliphatic functional groups provided **48**–**53** in excellent yields with 80–96% ee. Notably, many functionalities, such as alkene, chloride, free alcohol, ester, amide as well as imide, at different distances away from the allenyl radicals were well tolerated to generate the chiral allenes **54**–**59** with up 91% ee. The absolute configurations of **58** have been determined by chiroptical methods (See Supporting Information for details) and other products were assigned by analogy thereafter.

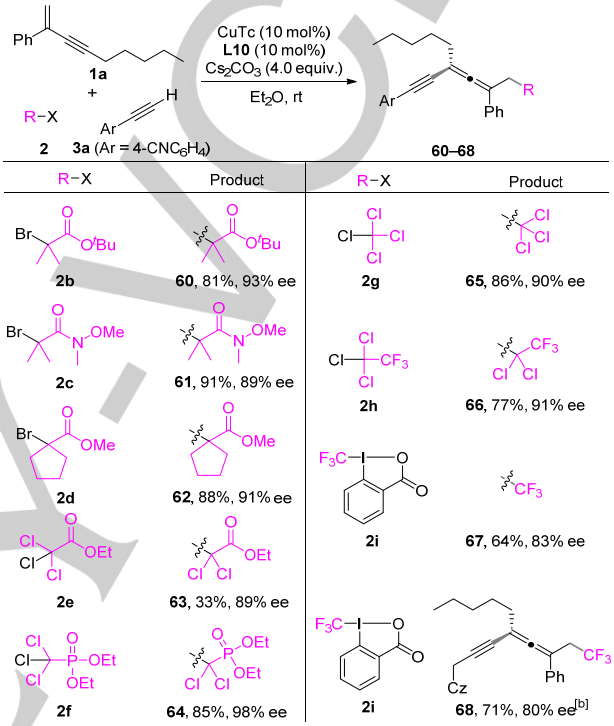
Table 2. Substrate scope of 1,3-enynes.[a]



[a] Reaction conditions: **1** (0.30 mmol), **2a** (0.24 mmol), **3a** (0.20 mmol), CuTc (10 mol%), **L10** (10 mol%), and Cs_2CO_3 (4.0 equiv.) in Et_2O (4.0 mL) at room temperature for 24 h under argon; the yields are isolated and the ee value was determined by HPLC.

These results encouraged us to investigate the scope of radical precursors (Table 3). The commercially available *tert*-butyl α-bromoisobutyrate **2b** was applicable to this transformation, furnishing **60** in 81% yield with 93% ee. Importantly, the Weinreb amide-type bromide **2c** was also suitable for the reaction to provide **61** in 91% yield with 89% ee, of which the amide group could be easily transformed to other carbonyl compounds.[15] Furthermore, with bromide **2d** as the radical precursor, the reaction proceeded smoothly to yield **62** in 88% yield with 91% ee. Importantly, alkyl chlorides **2e**–**2h** were also viable radical precursors to generate diversely functionalized chiral allenes **63**–**66** with excellent ee**.** Notably, the Togni's reagent **2i** was also a suitable radical precursor to provide **56** and **57** with a pharmaceutically important trifluoromethyl moiety.[16]

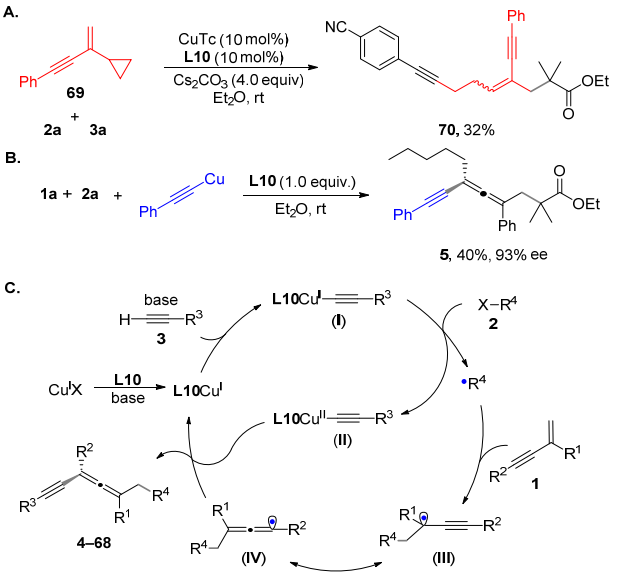
Table 3. Substrate scope of radical precursors.[a]



[a] Reaction conditions: **1a** (0.30 mmol), **2** (0.24 mmol), **3** (0.20 mmol), CuTc (10 mol%), **L10** (10 mol%), and Cs_2CO_3 (4.0 equiv.) in Et_2O (4.0 mL) at room temperature for 24 h under argon; the yields are isolated and the ee values were determined by HPLC. [b] CuTc (15 mol%).

To provide insights into the reaction mechanism, we conducted control experiments. When the radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was added, the reaction was completely inhibited, implying a possible radical pathway (Scheme S1 in Supporting Information). To probe the reaction intermediates, we carried out the radical clock experiment with substrate **69**. The reaction furnished the ring-opening product **70** in 32% yield, indicating the involvement of a propargyl radical, the resonance form of an allenyl radical, in this process (Scheme 3A). In addition, the reaction of copper phenylacetylide in the presence of **L10** proceeded as well to afford **5** in 40% yield with 93% ee, suggesting the possible intermediacy of copper acetylide (Scheme 3B). Based on the above observations and our previous reports,[11] we proposed a possible mechanism (Scheme 3C). Under basic conditions, Cu^{I}, **L10**, and alkyne reacted to afford the complex **I**, which next reduced **2**, simultaneously generating the Cu^{II} complex **II** and an alkyl radical ($\cdot R^4$). The addition of this alkyl radical to the alkene moiety of 1,3-enyne **1** provided the propargyl radical **III** and its resonance structure trisubstituted allenyl radical **IV**. Afterwards, the allenyl radical **IV** reacted with the Cu^{II} complex **II** to give rise

to the tetrasubstituted chiral allene (**4**–**68**), while the complex **I** was generated for the next catalytic cycle.



Scheme 3. Mechanistic studies and proposal.

In summary, we have described a copper-catalyzed three-component asymmetric radical 1,4-carboalkynylation of 1,3-enynes, providing an efficient tool for the construction of diverse tetrasubstituted chiral allenes from easily available starting materials. The key to the success is the strategic utilization of a cinchona alkaloid-derived N,N,P-ligand to enhance the reducing capability of copper catalyst for reaction initiation and further achieve the enantiocontrol over the structurally unique allenyl radical. A wide range of (hetero)aryl and alkyl alkynes and 1,3-enynes as well as various readily available radical precursors are easily accommodated in this reaction. Further extension of the asymmetric coupling of allenyl radicals to other nucleophiles and detailed mechanistic studies are ongoing in our laboratory.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allenes • asymmetric radical reactions • copper • 1,4-enynes • alkyl bromides

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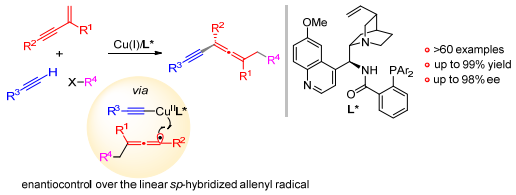

Enantiocontrol over allenyl radical: A copper-catalyzed asymmetric radical 1,4-carboalkynylation of 1,3-enynes is realized, providing diverse tetrasubstituted chiral allenes. The utilization of copper/chiral N,N,P-ligand is crucial for the enantiocontrol over the allenyl radicals, which is difficult due to their elongated linear configuration that necessitates the stereo-differentiation of remote motifs away from the reaction site.