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Copper-Catalyzed Enantioselective Radical 1,4-Difunctionalization of 1,3-Enynes

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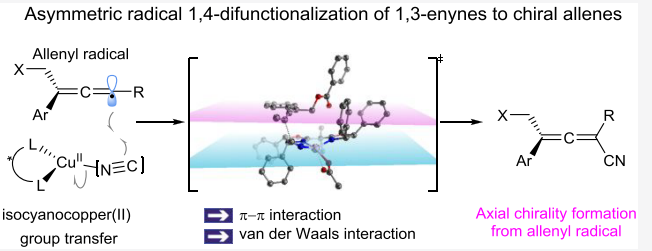
ABSTRACT: Chiral allenes are important structural motifs frequently found in natural products, pharmaceuticals, and other organic compounds. Asymmetric 1,4-difunctionalization of 1,3-enynes is a promising strategy to construct axial chirality and produce substituted chiral allenes from achiral substrates. However, the previous state of the art in 1,4-difunctionalization of 1,3-enynes focused on the allenyl anion pathway. Because of this, only electrophiles can be introduced into the allene backbones in the second functionalization step, consequently limiting the reaction and allene product types. The development of asymmetric 1,4-difunctionalization of 1,3-enynes via a *radical* pathway would complement previous methods and support expansion of the toolbox for the synthesis of asymmetric allenes. Herein, we report the first radical enantioselective allene formation via a group transfer pathway in the context of copper-catalyzed radical 1,4-difunctionalization of 1,3-enynes. This method addresses a longstanding unsolved problem in asymmetric radical chemistry, provides an important strategy for stereocontrol with free allenyl radicals, and offers a novel approach to the valuable, but previously inaccessible, chiral allenes. This work should shed light on asymmetric radical reactions and may lead to other enantioselective group transfer reactions.



INTRODUCTION

Chiral allenes are important structural motifs found frequently in natural products, pharmaceuticals, and organic compounds. They possess unique structural characteristics, biological activities, and chemical reactivities.[1,2] The development of methods for catalytic asymmetric allene synthesis has attracted increasing attention from the organic and medicinal chemistry fields in the last two decades, and as a result, some classical methods have been developed involving allenyl cations,[3] allenyl anions,[4−11] molecular rearrangements,[12,13] deracemization of racemic allenes,[14] and other pathways.[15−20] Among these, the asymmetric 1,4-difunctionalization of 1,3-enynes pioneered by Hayashi[4] is considered to be one of the best ways to construct chiral allenes, because this strategy utilizes achiral starting materials and is more efficient because two functionalities are installed in a single step (Figure 1A). Recently, the groups of Hoveyda,[8] Ge,[10,21] Engle,[9] and Buchwald[11] developed the Cu-catalyzed asymmetric 1,4-hydroboration or semireduction of 1,3-enynes via Cu−H chemistry, respectively. More recently, Liao et al. reported the enantioselective 1,4-arylboration of 1,3-enynes through a synergic catalysis by Cu/Pd.[22] Despite such breakthroughs in this area, all of the established asymmetric 1,4-difunctionalizations of 1,3-enynes proceed through an allenyl anion pathway in which only electrophiles can be introduced into allene backbones in the second functionalization step. Other useful

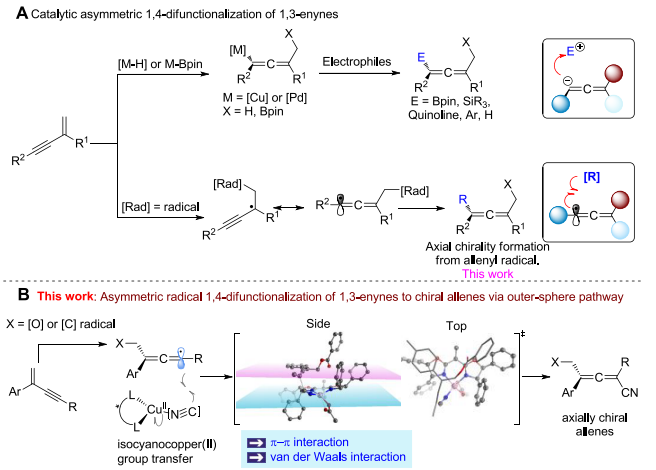


Figure 1. Catalytic asymmetric 1,4-difunctionalization of 1,3-enynes: (A) state of the art in asymmetric 1,4-difunctionalization of 1,3-enynes and possible radical pathways for catalytic asymmetric allene synthesis; (B) this work, enabling the enantioselective radical 1,4-difunctionalization of 1,3-enynes via an outer-sphere pathway.

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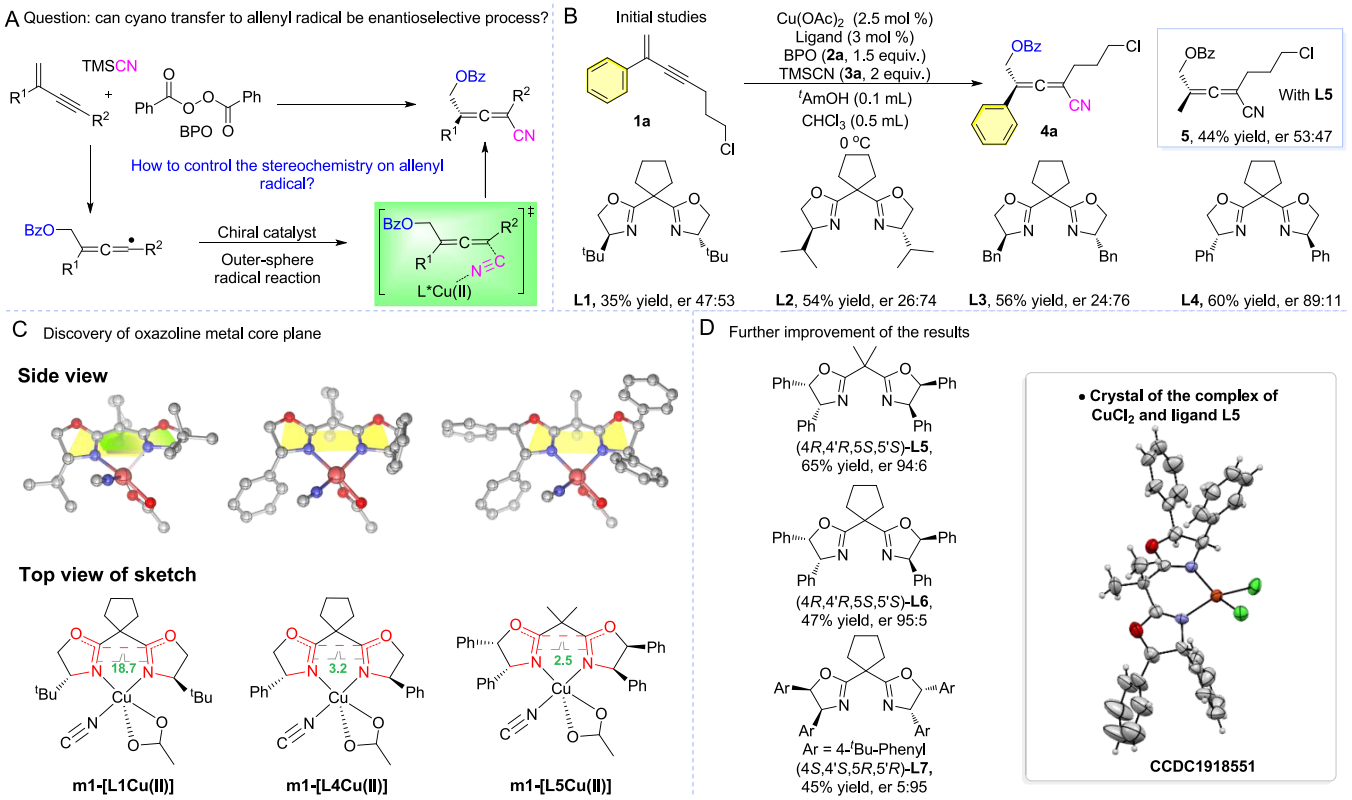

Figure 2. Rational initial design and ligand screening: (A) design of an outer-sphere asymmetric radical pathway; (B) initial studies; (C) discovery of an oxazoline metal core plane; (D) further development of the results.

functional groups such as CN, NR_2, and OR cannot be incorporated into allene backbones through this allenyl anion pathway. This limited mechanism type restricts the successful reaction types and thus limits the diversity of products. The development of new enantioselective 1,4-difunctionalization of 1,3-enynes via other pathways and the corresponding new stereocontrol models are highly desired, as these will significantly expand the reaction types by trapping the reactive allenyl intermediates not only with electrophiles but also with nucleophiles and radicals.

Radical chemistry has seen much activity over the past two decades. The newly developed radical reactions and classical radical reactions have rendered chemistry with open-shell intermediates even more powerful in organic synthesis.[23,24] Among these, several radical 1,4-difunctionalizations of 1,3-enynes to allene syntheses have been reported recently by Liu,[25,26] Wang[27] and our group[28] and have diversified the allene syntheses. Notwithstanding the significant advances in asymmetric radical reactions,[29−67] the stereoselective formation of a new chemical bond on a free (untethered) and unstrained radical is still extremely difficult. There are a few examples of building *center chirality* on free radicals[59−67] but the enantioselective creation of allenyl *axial chirality* on a free radical is still unknown. The asymmetric radical 1,4-difunctionalization of 1,3-enynes which requires enantioselective installation of groups on the allenyl radical is likewise unprecedented. The underlying reasons for this lack of development are presumably due to the inherent high reactivity of radicals, the structural characteristics of free allenyl radicals, i.e., longer distance from C3 substituents, and the absence of moderate/strong interactions between radicals and catalysts. Despite these challenges, the development of asymmetric radical 1,4-difuntionalization of 1,3-enynes is highly sought after, as it could provide a novel approach to the creation of axial chirality and ignite a fast expansion of the toolbox for asymmetric allene synthesis to afford previously inaccessible chiral allenes.

Previously, we reported the 1,4-carbocyanation of 1,3-enynes via allenyl radical intermediates. An isocyanocopper(II) species was identified as the key intermediate, and an outer-sphere cyanation pathway (group transfer) was also demonstrated (Figure 1B).[28] It is noteworthy that the amination of benzyl radicals employing Cu(II)NR_2 species[68,69] and fluorination of alkyl radicals by Cu(II)F complexes[70] have also been established through an outer-sphere pathway. Inspired by these reactions and the only example of asymmetric radical atom transfer reaction of untethered radical discovered by Ready et al.,[63] we wondered whether an outer-sphere radical 1,4-difunctionalized cyanation reaction could be made enantioselective and, if so, how to control the stereochemistry on the allenyl radical (Figure 2A). We have conducted extensive studies to address these questions, and here, we report the first radical enantioselective 1,4-oxycyanation of 1,3-enynes, affording chiral allenes which otherwise are not easily accessible (Figure 1B).[28]

RESULTS AND DISCUSSION

We chose the unprecedented 1,4-oxycyanation of 1,3-enynes as the model reaction and initiated the studies with a conjugate 1,3-enyne (**1a**), benzoyl peroxide (**2a**, BPO), and trimethylsilyl cyanide (**3a**, TMSCN). The combination of copper acetate and a chiral bisoxazoline ligand (BOX) was chosen as an asymmetric catalytic system. When the chiral BOX ligand was switched from **L1** to **L4**, a clear increase in enantioselectivity of

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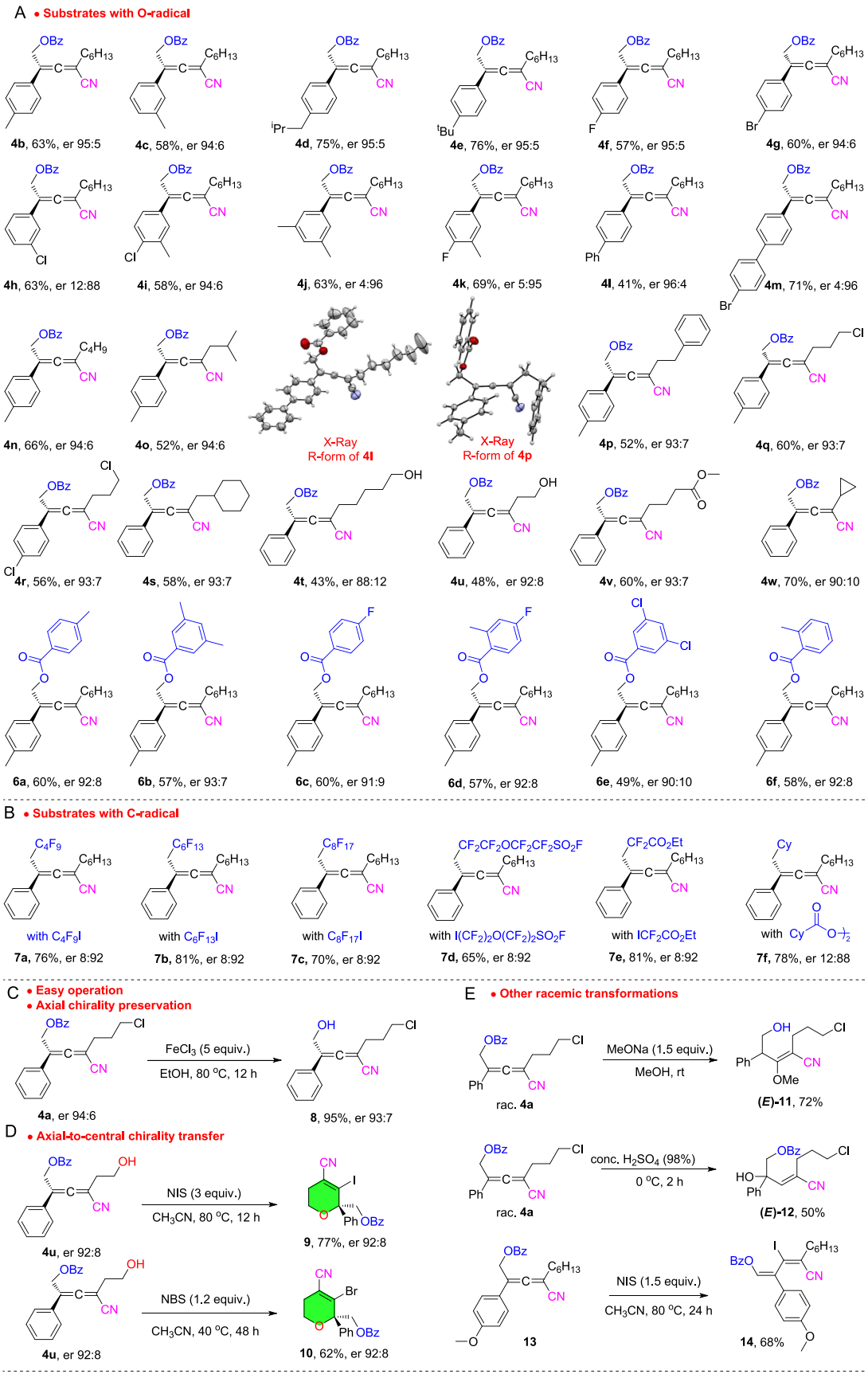

Figure 3. Substrate scope, further transformations, and synthetic applications: (A) asymmetric allene synthesis with oxygen radicals, with products **4h,j,k,m** processed with **L7**; (B) asymmetric allene synthesis with carbon radicals; (C) removal of the benzoyl group with ferric chloride; (D) axial to central chirality transfers with *N*-iodo- and *N*-bromosuccinimide; (E) other racemic transformations of allenes.

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the product (**4a**) was observed, suggesting that the phenyl group of the BOX ligand affects the stereochemistry (Figure 2B). When the reaction was performed with 7-chloro-2-methylhept-1-en-3-yne (**1x**), which lacks an aryl substituent, a product (**5**) was isolated with almost no enantiomeric excess. These results suggest the possibility of a $\pi-\pi$ interaction between the allenyl radical and the aryl ring of the BOX ligand. Consequently, we performed density functional theory (DFT) calculations at the B3LYP-D3(SMD)/Def2-TZVP//B3LYP-D3/Def2-SVP level of theory to examine the structures of chiral catalysts (see more details in the Supporting Information). Isocyanocopper(II) complexes with ligands **L1** and **L4** were selected as representatives containing alkyl and aryl substituents, respectively.

The optimized structures of isocyanocopper(II) intermediates **m1**-[**L1Cu(II)**] and **m1**-[**L4Cu(II)**] with ligands **L1** and **L4** are shown in Figure 2C. The planarities of the oxazoline moiety in **m1**-[**L1Cu(II)**] and **m1**-[**L4Cu(II)**] are significantly different. The dihedral angle between the two oxazoline rings *D*(N1−C2−C2′−N1′) are 18.7 and 3.2° in **m1**-[**L1Cu(II)**] and **m1**-[**L4Cu(II)**], respectively. These geometrical parameters are similar to those in the relevant crystal structure of a dichlorocopper(II) complex (cf. Table S10 and Figure S1).[71] We hypothesized that this planarity of the oxazoline−metal complex is critical in the stereocontrolling step and that a variation of the substituents on the oxazolines might further improve the enantioselectivity. Therefore, we carried out further DFT calculations on some isocyanocopper(II) complexes and found that **m1**-[**L5Cu(II)**], which bears two aryl substituents, has the smallest dihedral angle (2.5°). A reaction with ligand **L5** was conducted. The enantioselectivity was indeed drastically improved to er = 94:6. Ligands **L6** and **L7** were also tested, and similar enantioselectivities and lower yields were observed (Figure 2D). **L5** was therefore chosen for further investigation. These results of the planarity correlated to the enantioselectivity fit to the strategy of a quantitative structure selective relationship (QSSR), which is a useful tool in the development of asymmetric catalytic reactions.[72]

The substrate scope of conjugate 1,3-enynes in the reaction was examined under the optimized conditions (Figure 3A). Electron-rich alkyl-substituted aryl groups with primary and tertiary alkyl groups afforded the corresponding products in good yields with a high er, and substrates bearing halogenated aromatic substituents were compatible with the reaction conditions. The long alkyl chain in the 1,3-enyne substrates can be replaced by short alkyl chains or haloalkyl chains, a free alcohol group, a cyclopropyl group, or an ester group. Due to the utilization of (4*S*,4′*S*,5*R*,5′*R*)-**L7**, which has the opposite absolute configuration in comparison to **L5** and **L6**, the opposite enantiomer for products **4h,j,k,m** can be obtained. The absolute configuration of the products (*R* forms of **4l,p**) was confirmed by X-ray single-crystal diffraction. The successful preparation of highly enantioenriched tetrasubstituted allenes with the established catalytic system prompted us to study the use of other peroxides. For phenyl-substituted peroxides, both electron-donating and electron-withdrawing phenyl groups were tolerated under the standard reaction conditions, affording the corresponding chiral allenes in high yields and enantioselectivities. This enantioselective radical 1,4-difunctionalization of 1,3-enynes can also be successfully achieved with carbon-centered radicals. As shown in Figure 3B, perfluoroalkyl iodides, ethyl difluoroiodoacetate, and cyclohexanecarboxylic peroxyanhydride engaged in the asymmetric radical 1,4-carbocyanation of 1,3-enynes, affording the corresponding allenes in good yields and with high er.

Although some racemic allenyl cyanides have been synthesized previously, the generation of enantioenriched allenyl cyanides and their stereoselective transformations has not been reported. Accordingly, we explored their stereoselective transformations and synthetic utility (Figure 3C,D). The construction of chiral quaternary carbon centers is a major challenge in synthetic chemistry, and the development of methods for the formation of such chiral centers is an important goal. In the presence of $FeCl_3$, the benzoyloxy group of **4a** can be easily converted into a free alcohol group and the allenyl alcohol (**8**) can be produced quantitatively without loss of enantiomeric excess (Figure 3C).

The transfer of axial chirality to central chirality was also studied. For example, the chiral allenyl cyanide **4u** smoothly reacted with *N*-iodosuccinimide (NIS) or *N*-bromosuccinimide (NBS) to produce the enantioenriched 3,6-dihydro-2*H*-pyrans **9** and **10** with a chiral quaternary carbon center via a cyclization process (Figure 3D). Moreover, *E*/*Z* selective transformations corresponding to the *E*-selective vinyl cyanides (*E*)-**11** and (*E*)-**12** were accessed upon treatment of the racemic allene **4a** under basic or acidic reaction conditions (Figure 3E). Treatment of the allenyl cyanide **13** with NIS led to a practical synthesis of the highly substituted conjugated cyanide **14**, which is a versatile building block.

Control experiments were conducted to further probe the mechanism of this radical reaction (Figure 4). The addition of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) inhibited the formation of the desired product, suggesting that the reaction could involve a radical pathway (Figure 4A). The observation of the BHT·OBz adduct supports the formation of a benzoyloxyl radical, and the detection of trimethylsilyl benzoate indicates an interaction of the benzoyloxyl group with TMSCN (see the Supporting Information). On the other hand, the CH_3OH adduct **15**, whose appearance would suggest the formation of the allenyl cation, was not observed (Figure 4B). The presence of the radical adduct and the absence of cation adducts indicate that the allenyl radical pathway is more likely to be adopted rather than the allenyl cation pathway. Although only a low yield was obtained, the formation of the cyclized product **17** strongly suggests that an allenyl radical is indeed generated *in situ* (Figure 4C). A linear correlation between the ee of ligand **L5** and the ee of **4a** was observed (Figure 4D), indicating that the active catalytic species is a monomeric copper complex bearing a single chiral ligand.

DFT calculations on the asymmetric radical 1,4-oxycyanation of 1,3-enynes were performed to elucidate the key factors of stereocontrol in this reaction. The mechanism is similar to that in our previous case.[28] In addition, an inner-sphere pathway via Cu(III) intermediates has also been considered, but no transition states for reductive elimination could be located, which is similar to the very recent study by Lin, Liu, et al.[73] Therefore, we focused on the enantiodetermining step.

With a comprehensive conformational search of radical trapping transition states (TSs), **TS-L5-R1** and **TS-L5-S1** were found to be the lowest enthalpic conformers leading to the products of *R* and *S* enantiomers, respectively (Figure 4E; see the Supporting Information for more computational details of the conformational search). **TS-L5-R1** is preferred with an enthalpy difference of 1.7 kcal/mol, consistent with exper-

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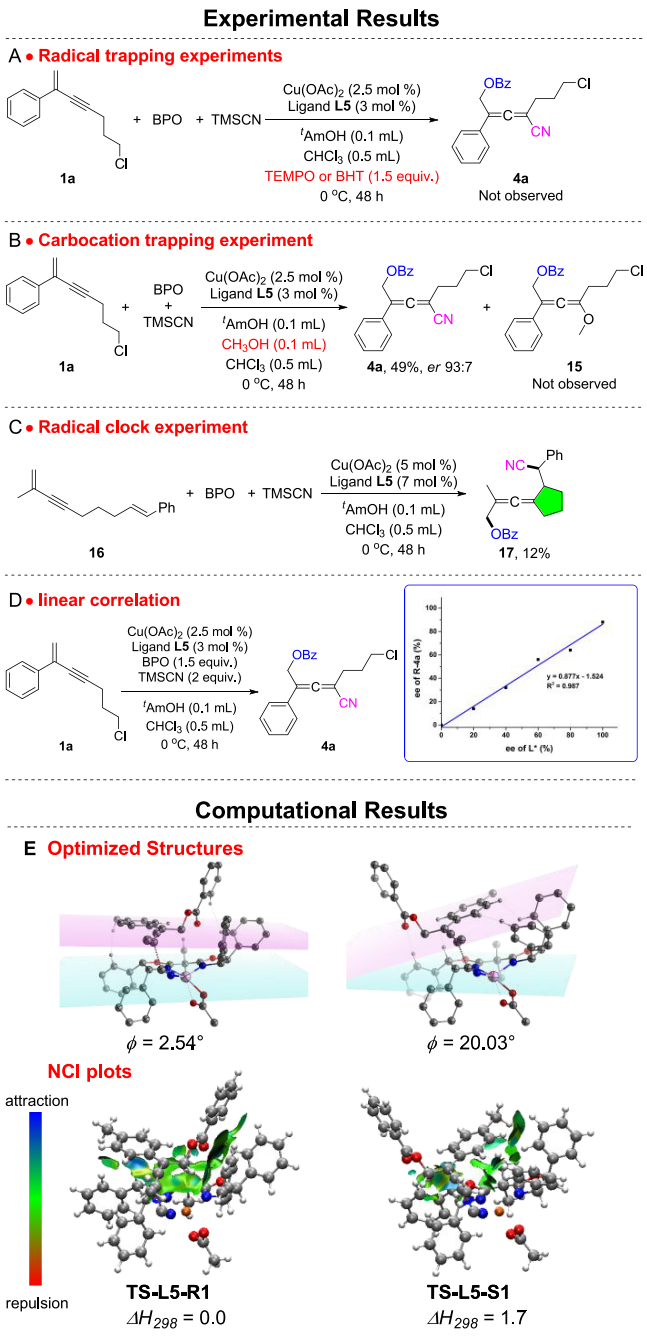

Figure 4. Mechanistic studies: (A) radical trapping experiments; (B) carbocation trapping experiment; (C) radical clock experiment; (D) linear correlation between the ee of ligand **L5** and the ee of **4a**; (E) optimized structures and NCI plots of **TS-L5-R1** and **TS-L5-S1**. For clarity, hydrogen atoms are omitted in pictures of optimized structures except for some short H−H or O−H distances. The dihedral angle between planes of the aromatic substituent (pink plane) and the oxazoline (cyan plane) is denoted as ϕ.

imental observations that the *R* enantiomer is preferred. As reflected from the dihedral angles (2.5 and 20.0°), a $\pi-\pi$ interaction between the aromatic substituent with the plane of the oxazoline-metal complex was found in **TS-L5-R1** but not in **TS-L5-S1**. An analysis of noncovalent interactions (NCI) between the allenyl radical and the ligated catalyst[74] also supported the stronger $\pi-\pi$ interactions in **TS-L5-R1**. The $\pi-\pi$ interactions in **TS-L5-S1** were weakened to avoid steric repulsion with the phenyl groups of the ligand, and the distances of the $\pi-\pi$ interaction plane are 3.47 and 4.07 Å in **TS-L5-R1** and **TS-L5-S1**, respectively. A further distortion/interaction analysis also revealed that the repulsion between the substituent of the allenyl radical and the phenyl ring on the oxazoline disturbs the $\pi-\pi$ interaction, consequently decreasing the interaction energy (see Figure S4). On the basis of these experimental and theoretical studies, the $\pi-\pi$ interaction may account for the observed enantioselective control on the allenyl radical. With this model, the low enantioselectivity in the cases with the ligands **L1**−**L3** and the substrate **1x**, in which a proper $\pi-\pi$ interaction is absent, can be understood.

CONCLUSION

In conclusion, we have developed a copper-catalyzed asymmetric radical 1,4-oxycyanation of 1,3-enynes under mild reaction conditions. This hitherto unknown method offers an efficient approach to the synthesis of a range of axially chiral allenes. Experimental and theoretical studies support that the cyanation reaction proceeds by an allenyl radical pathway rather than an allenyl cation pathway. This work may shed some light on the study of asymmetric radical reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c06177.

Experimental details and data, including NMR, HPLC spectra and crystal data, and computational methods, details and discussion, including figures, energies and geometrical coordination (PDF)

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Notes

The authors declare no competing financial interest.

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