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Synthesis of Axially Chiral Vinyl Halides via Cu(I)-Catalyzed Enantioselective Radical 1,2-Halofunctionalization of Terminal Alkynes

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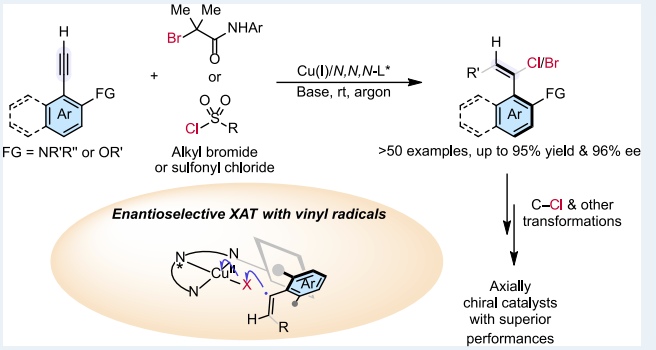
ABSTRACT: Organohalides are crucial in modern organic synthesis, thanks to their robust and versatile reactivity in cross-coupling and other key transformations. However, catalytic asymmetric methods for producing enantioenriched organohalides, particularly axially chiral vinyl halides, remain underdeveloped. Here, we present a Cu(I)-catalyzed, highly enantioselective radical alkyne 1,2-halofunctionalization, utilizing custom-designed tridentate anionic *N,N,N*-ligands with bulky peripheral substituents. This method efficiently employs (hetero)aryl and alkyl sulfonyl chlorides, as well as α-carbonyl alkyl bromides, as radical precursors and utilizes a diverse range of 2-amino and 2-oxy aryl terminal alkynes as substrates to produce highly enantioenriched axially chiral vinyl halides. The reaction is scalable to gram quantities, and the vinyl halides can be further transformed into axially chiral thiourea, pyridyl carboxamide, and quinolyl sulfonamide compounds, some of which show significant potential in asymmetric catalysis. Both experimental and theoretical mechanistic studies support an enantioselective halogen atom transfer mechanism. This method opens an avenue for accessing axially chiral organohalides, facilitating their broad applications in various related fields.



KEYWORDS: *axially chiral vinyl halides, enantioselective halogen atom transfer, copper catalysis, vinyl radicals, asymmetric 1,2-difunctionalization of terminal alkynes*

INTRODUCTION

Atom transfer, one of the prototypical and important elementary radical reactions,[1] is involved in many useful radical transformations, such as atom transfer radical addition/polymerization,[2] which has found numerous applications in organic synthesis and medicinal and material sciences (Figure 1A). Despite the recent enormous development of radical asymmetric catalysis,[3] investigations of chemocatalytic enantioselective atom transfer reactions have only met with limited success using chiral Lewis acid catalysis,[4] organocatalysis,[5] or transition metal catalysis.[3a,d,e,6] Of particular note is the incompatibility of almost all these chiral catalytic systems with vinyl radical species in spite of their excellent and well-investigated reactivity toward hydrogen,[7] halogen,[8] and chalcogen[9] atom transfer. The major challenge likely stems from their inherently much higher reactivity (corresponding C−H bond dissociation energy (BDE): ∼98−110 kcal/mol[10]) than most alkyl radicals (corresponding C−H BDE: <90 kcal/mol[10]) that have been successfully accommodated,[3k,l] which renders the stereochemical control more difficult (Figure 1A).

In this regard, radical addition to alkynes provides convenient access to vinyl radicals since direct single-electron reduction of vinyl halides is much more difficult than that of their alkyl counterparts.[11] Thus, a number of nonenantioselective radical alkyne functionalization methodologies,[12] particularly those under transition-metal catalysis,[13] have been developed for the rapid and convenient access to structurally complex and diverse molecules given the ready availability of both alkynes and various radical precursors and the usually robust radical alkyne addition.[12b] Nonetheless, enantioselective versions of these reactions have only sparsely been achieved,[14] and none of them have so far allowed for the realization of enantioselective intermolecular atom transfer

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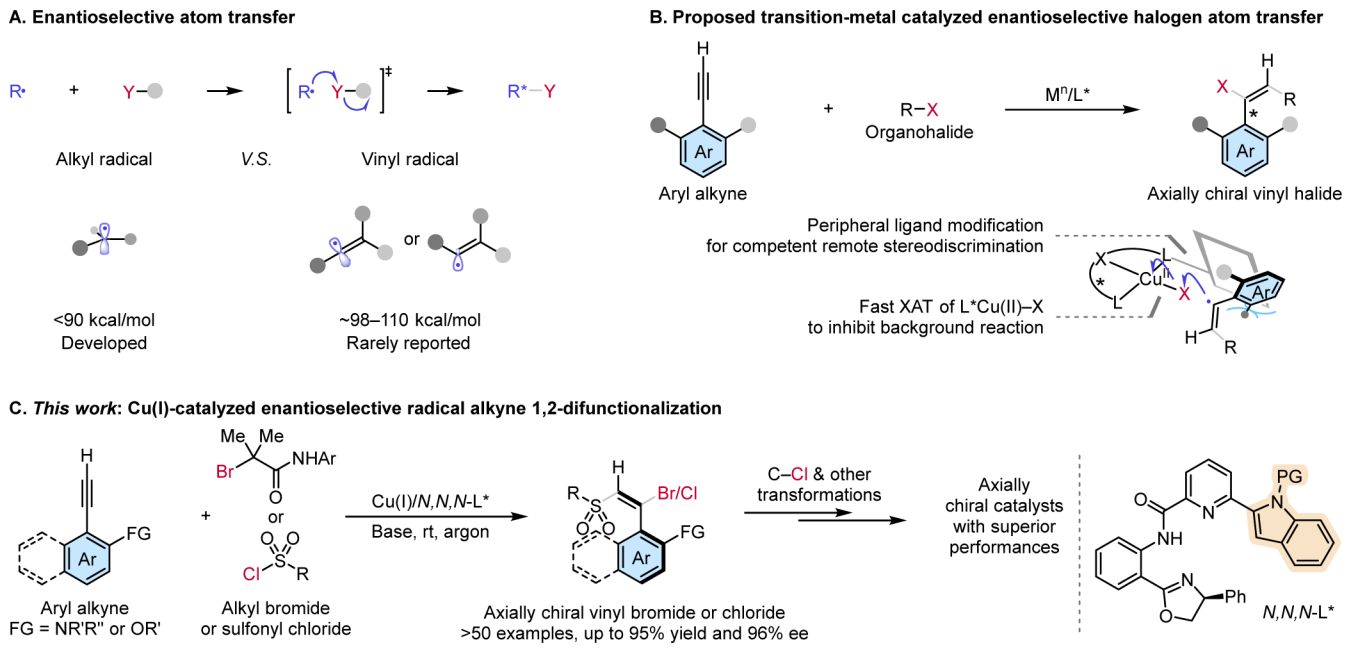
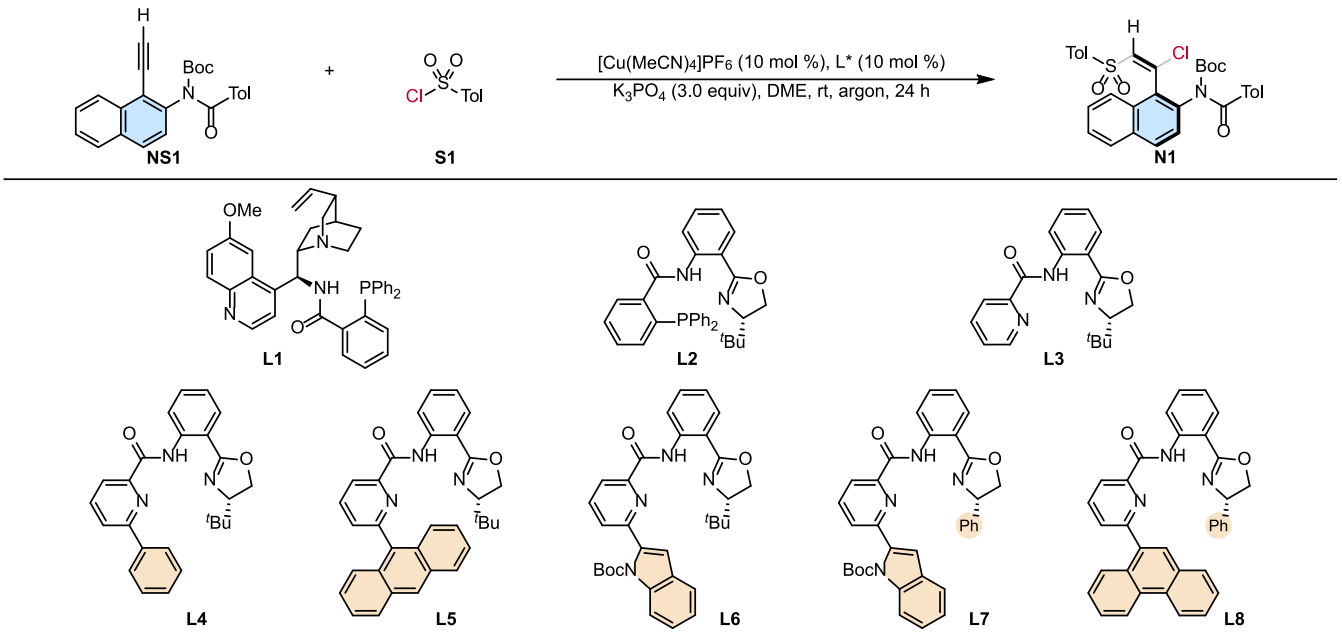


Figure 1. Motivation and development of Cu(I)-catalyzed enantioselective radical 1,2-halofunctionalization of terminal alkynes. Ar, aryl; XAT, halogen atom transfer; rt, room temperature; ee, enantiomeric excess; and PG, protecting group.

Table 1. Effect of Chiral Ligands[a]



Entry	L*	Yield (%)	Ee (%)
1	**L1**	10	5
2	**L2**	40	20
3	**L3**	21	28
4	**L4**	35	40
5	**L5**	47	77
6	**L6**	45	93
7	**L7**	68	94
8[b]	**L7**	80	93

[a]Reaction conditions: **NS1** (0.050 mmol), **S1** (1.5 equiv), $[Cu(MeCN)_4]PF_6$ (10 mol %), **L*** (10 mol %), and K_3PO_4 (3.0 equiv) in DME (1.0 mL) at rt for 24 h under argon. Yield of **N1** is based on ^1H NMR analysis of the crude products using dibromomethane as an internal standard; Ee of **N1** is based on chiral HPLC analysis. [b]**NS1** (0.20 mmol) in DME/MTBE (v/v 1/3, 4.0 mL) for 5 d. Boc, *tert*-butyloxycarbonyl; Tol, *p*-tolyl; DME, 1, 2-dimethoxyethane; MTBE, methyl *tert*-butyl ether.

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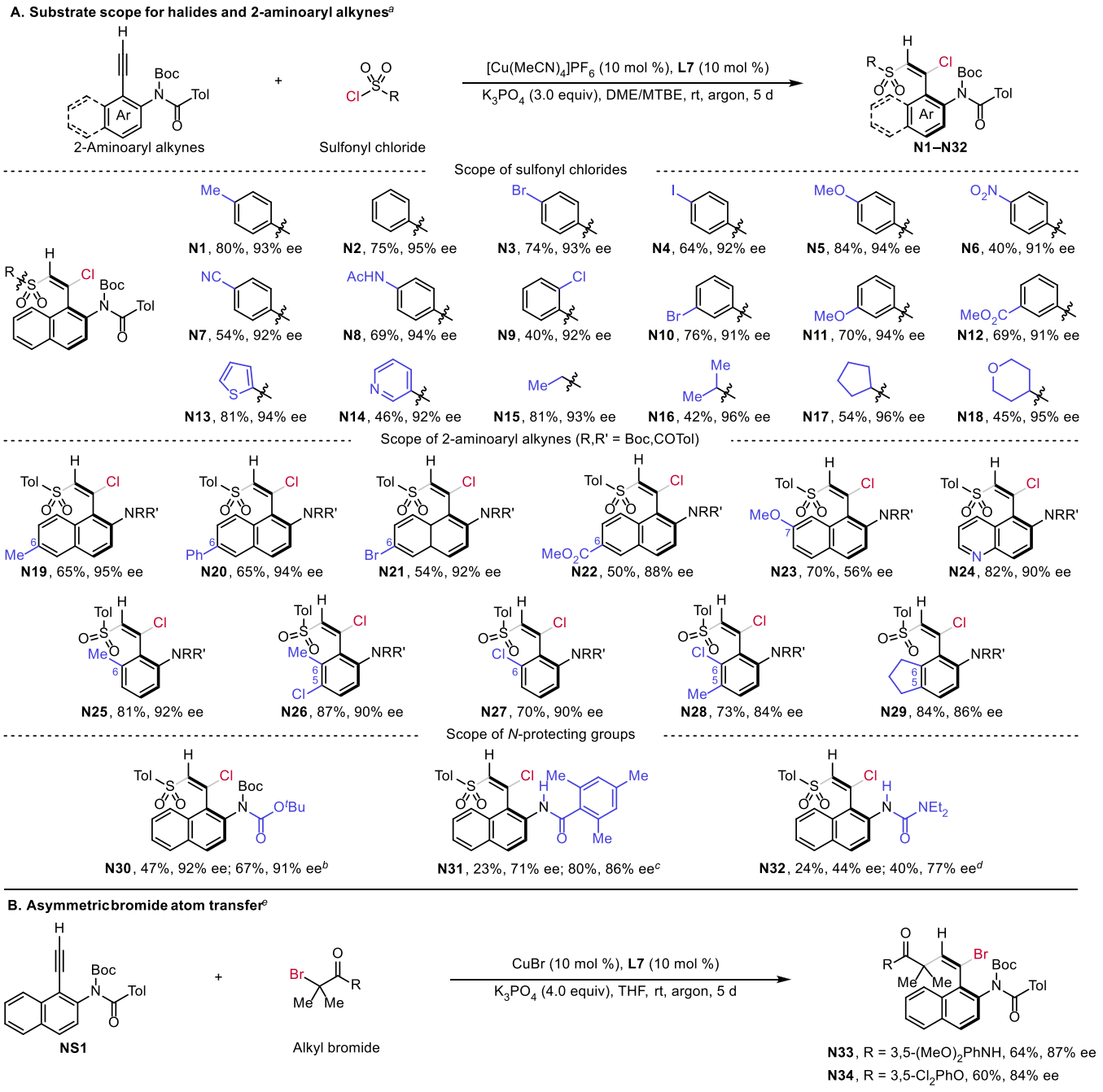

Figure 2. Substrate scope for halides and 2-aminoaryl alkynes. [a]Standard reaction conditions: 2-aminoaryl alkyne (0.20 mmol), sulfonyl chloride (1.5 equiv), $[Cu(MeCN)_4]PF_6$ (10 mol %), **L7** (10 mol %), and K_3PO_4 (3.0 equiv) in DME/MTBE (v/v = 1/3, 4.0 mL) at rt for 5 days under argon. [b]CuCl (10 mol %), 2-(diphenylphosphaneyl)pyridine (10 mol %), and **L8** (10 mol %) were added to THF (4.0 mL) at 0 °C. [c]**L6** (10 mol %) in DCM/toluene (v/v = 1/3, 4.0 mL) at −10 °C. [d]**L6** (10 mol %) in DCM (4.0 mL). [e]Reaction conditions: **NS1** (0.20 mmol), alkyl bromide (1.5 equiv), CuBr (10 mol %), **L7** (10 mol %), and K_3PO_4 (4.0 equiv) in THF (4.0 mL) at rt for 5 days under argon. Isolated yields are shown; Ee is based on chiral HPLC analysis. Ac, acetyl; THF, tetrahydrofuran; DCM, dichloromethane.

reactions with vinyl radicals. Thus, the development of a novel catalytic system is highly desirable and is in great demand.

Our group has long been investigating asymmetric radical reactions using chiral copper catalysis.[15] Recently, we disclosed the development of tailor-made *N,N,N*-ligands for copper-catalyzed enantioselective alkynyl-group transfer by tertiary alkyl radicals.[16] Long-spreading side arms are deliberately introduced to these ligands to elicit highly efficient stereo-discrimination of motifs in tertiary radicals, which are remote from the copper center in the key enantioselective homolytic radical substitution-type C−C bond coupling. These results prompted us to investigate whether this strategy would generally be applicable to transition metal-catalyzed atom transfer reactions, particularly with the highly reactive vinyl radicals (Figure 1B). To this end, we first envisioned that radical addition to *ortho*-substituted aryl alkynes would generate vinyl radicals and subsequent enantioselective halogen atom transfer[6a,b,g] from chiral metal complexes by these vinyl radicals might provide axially chiral vinyl halides.[17−23] In this scenario, the use of copper catalysts

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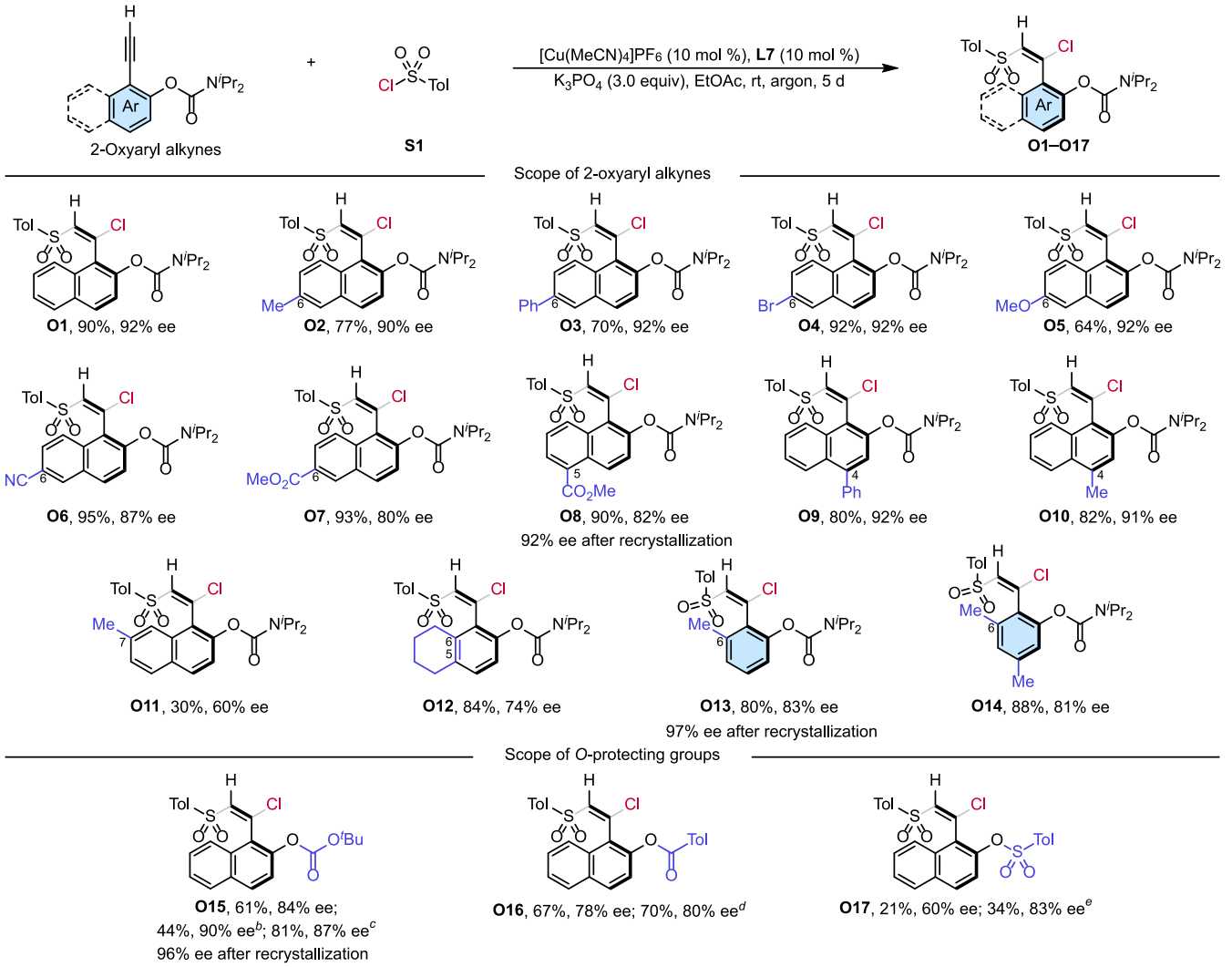
Table 2. Substrate Scope for 2-Oxyaryl Alkynes[a]



[a]Standard reaction conditions: 2-oxyaryl alkyne (0.20 mmol), **S1** (1.5 equiv), $[Cu(MeCN)_4]PF_6$ (10 mol %), **L7** (10 mol %), and K_3PO_4 (3.0 equiv) in EtOAc (4.0 mL) at rt for 5 d under argon. Isolated yields are shown; Ee is based on chiral HPLC analysis. [b]2-(Diphenylphosphaneyl)pyridine (10 mol %) and **L6** (10 mol %) in DME (4.0 mL) at 0 °C. [c]**L6** (10 mol %) in DME (4.0 mL). [d]**L6** (10 mol %). [e]**L6** (10 mol %) at 0 °C.

seemed to be privileged since copper(II) halides are reported to undergo fast halogen atom transfer (XAT), which would efficiently suppress the nonstereoselective background XAT of vinyl radicals with organohalide starting materials.[24] More importantly, we speculated that appropriate peripheral ligand modifications would be indispensable for achieving competent stereodiscrimination of the *ortho*-substituents on the aryl rings, which are far away from the copper centers.[16] Notably, chiral organohalides are well-established robust intermediates with numerous synthetic applications,[25] particularly in transition-metal-catalyzed cross-coupling reactions,[25a] and thus, the enantioselective synthesis of vinyl halides,[26,27] if successfully achieved, would provide a versatile synthetic hub for a diverse range of axially chiral alkene compounds.[19−21,23] Herein, we report our efforts in developing the copper-catalyzed enantioselective chlorine and bromine atom transfer with vinyl radicals, thus providing axially chiral vinyl chlorides and bromides from a broad range of aryl alkynes and diverse sulfonyl chlorides,[28] as well as α-carbonyl alkyl bromides, with high enantioselectivity (Figure 1C).[14e] The synthetic potential of this reaction was demonstrated by $C(sp^2)-C(sp/sp^2)$ cross-coupling of these vinyl chloride products followed by other straightforward manipulations, leading to efficient axially chiral alkene catalysts for asymmetric catalysis. Our experimental and theoretical mechanistic results supported the radical mechanism, particularly the XAT step, of the reaction.

RESULTS AND DISCUSSION

Reaction Development. At the beginning of the investigation, we took 2-aminoaryl alkyne **NS1** as the model starting material, given the widely explored use of axially chiral aryl amine compounds.[29] An initial screening of ligands employed in our previous works revealed that both oxazoline-based *N,N,P*-ligand **L2**[30] (entry 2; Table 1) and *N,N,N*-ligand **L3**[31] (entry 3), but Dixon's *N,N,P*-ligand **L1**[15d,32] (entry 1), afforded low yet significant enantioselectivity (for additional ligand screening results, see Table S1). As proposed above, the introduction of a 6-phenyl ring into the pyridine motif of **L3** boosted the ee value to 40% (entry 4). Replacing the phenyl ring with a bulkier 9-anthracenyl group greatly enhanced the ee

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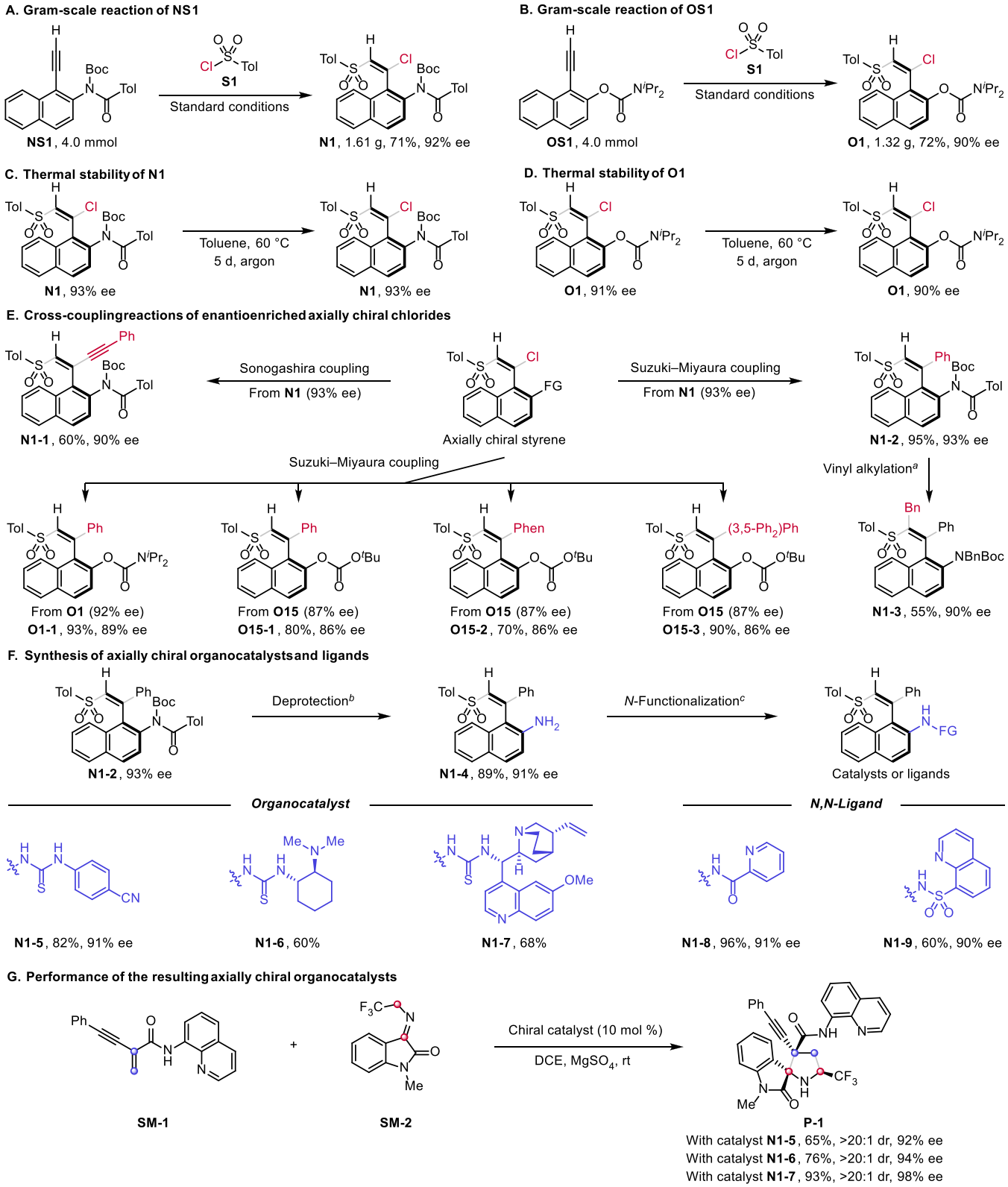
Scheme 1. Synthetic Utility for the Construction of Valuable Axially Chiral Reagent[a]



[a]The vinyl alkylation was performed after replacing the *N*-4-methylbenzoyl group with a *N*-benzyl group. [b]Conditions: (i) K_2CO_3, EtOH, 60 °C, Ar, 48 h; (ii) TFA/DCM (v/v = 1/1), rt, Ar, 12 h. [c]Conditions for **N1−5**: 4-isothiocyanatobenzonitrile, DMAP, DCM, rt, Ar, 48 h; for **N1−6** and **N1−7**: thiophosgene, pyridine, DCM, rt; then chiral amine; for **N1−8**: picolinic acid, DMAP, DCC, DCM, rt, Ar, 24 h; for **N1−9**: quinoline-8-sulfonyl chloride, DMAP, pyridine, DCM, 50 °C, Ar, 3 d. Phen, 9-phenanthryl; TFA, trifluoroacetic acid; DMAP, 4-dimethylaminopyridine; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DCE, 1,2-dichloroethane; dr, diastereomeric ratio.

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value to 77% (entry 5), and further switching to a nonsymmetrically bulky 2-indolyl group ultimately gave excellent enantioselectivity (entry 6). Nonetheless, the reaction efficiency was generally low with these tested ligands (entries 1−6), likely due to the steric congestion around the copper center caused by the bulky *tert*-butyl group on the oxazoline ring (see Figures S1 and S2 for X-ray structures of **L6** and **L7**). Accordingly, a phenyl ring in place of this *tert*-butyl group resulted in a substantially increased yield with almost unaltered enantioselectivity (entry 7). Additional condition optimizations in terms of copper salts, base additives, and solvents (Table S1) revealed the optimal conditions (entry 8) as follows: **NS1** (0.20 mmol) and **S1** (1.5 equiv) in the presence of $[Cu(MeCN)_4]PF_6$ (10 mol %), **L7** (10 mol %), and K_3PO_4 (3.0 equiv) in mixed DME/MTBE (v/v 1/3, 4.0 mL) at rt for 5 d under argon, giving **N1** in 80% yield with 93% ee. The amount of the base additive was found to be critical for reaction efficiency (entries 23−27). This is likely due to its dual role in facilitating the coordination of copper salts with chiral ligands to form the active catalyst and in neutralizing acidic side products generated from sulfonyl chloride.

Substrate Scope. We first investigated the scope of sulfonyl chlorides and found excellent tolerance of unsubstituted phenyl sulfonyl chlorides and those bearing a wide range of functional groups with different electronic properties on the *para*-, *meta*-, or *ortho*-position (**N1**−**N12**; Figure 2A). Particularly, reactive halides (**N3**, **N4**, **N9**, and **N10**) and acidic acetamides (**N8**) were well-tolerated, and nitro (**N6**) and cyano (**N7**) groups, which are usually problematic in copper-catalyzed radical transformations, were also compatible with this reaction. In addition, 2-thiophenyl (**N13**) and 3-pyridyl (**N14**)-substituted heteroaryl sulfonyl chlorides were applicable to this transformation. Notably, primary (**N15**) and secondary (**N16**−**N18**) alkyl sulfonyl chlorides were viable radical precursors for this reaction. More importantly, besides sulfonyl chlorides, alkyl bromides—but not iodides and chlorides (Scheme S4)—also worked well under very similar reaction conditions, delivering products **N33** and **N34** with good efficiency and stereoselectivity (Figure 2B; see Table S2 for the results of condition screening). By contrast, tosyl bromide provided only low enantioselectivity (Scheme S1), likely due to its relatively strong nonstereoselective background bromine atom transfer.[33] As for the scope of 2-aminoaryl alkynes (Figure 2A; see Scheme S2 for results of aryl alkynes bearing other *ortho*-functionalities), a series of 6-substituted naphthyl rings (**N19**−**N22**) were readily accommodated in this reaction, while a 7-methoxyl group (**N23**) led to greatly diminished enantioselectivity. Interestingly, a heteroaromatic quinoline-derived alkyne proved to be effective in this reaction, yielding **N24** with excellent enantioselectivity. Furthermore, various 5- and/or 6-substituted phenyl rings also performed well, producing **N25**−**N29** in high yields and excellent enantioselectivity. Regarding the 2-amino group, both two imide substrates (**N1** and **N30**; see Table S3 for condition optimizations of **N30**) delivered higher enantioselectivity than an amide one (**N31**; see Table S4 for condition optimizations), which in turn performed better than a urea substrate (**N32**).

Considering the high utility of axially chiral phenol compounds,[29] we next investigated the reaction with 2-oxyaryl alkynes. Fortunately, excellent enantioselectivity of product **O1** was observed under the aforementioned optimal conditions, albeit with only a low yield (46% yield, 92% ee; Table S5, entry 3). These results encouraged us to further examine the effects of ligands, solvents, and copper sources, during which a straightforward solvent change to ethyl acetate led to not only high reaction efficiency but also outstanding enantioselectivity (90% yield; 92% ee; Table S5, entry 15). Accordingly, we next explored the scope of 2-oxyaryl alkynes and found that a range of naphthyl rings without or with additional substituents at the 4-, 5-, and 6-positions were well-tolerated (**O1**−**O10**, Table 2). In accord with the results of 2-aminoaryl alkynes (Figure 2A), the 7-substitution of 2-oxyaryl substrates also resulted in a greatly decreased enantioselectivity (**O11**). Likewise, good tolerance of 5- and/or 6-substitution of 2-oxyphenyl alkyne substrates was also observed (**O12** and **O13**). In addition, 4,6-disubstituted 2-oxyphenyl alkynes were applicable to this reaction, affording good enantioselectivity with high yield (**O14**). As for the 2-oxy functionality, carbamate (e.g., **O1**) and carbonate (**O15**; see Table S6 for condition optimizations), as well as carboxylic (**O16**) and sulfonyl ester (**O17**) groups, proved to be workable in this reaction, providing the desired products in high enantioselectivity with varied yield. Unfortunately, internal alkynes were found to be unsuitable for this reaction (Scheme S5). Notably, some well-crystallized products with initially low enantioselectivity, such as **O8**, **O13**, and **O15**, achieved significantly higher ee values (>92%) after recrystallization (Scheme S6). The absolute structures of products **N1** (Figure S3), **N31** (Figure S4), and **O1** (Figure S5) were all determined to be *Ra* by X-ray structural analysis, and those of other products were assigned by analogy.

Synthetic Utility. To demonstrate the synthetic potential of these axially chiral vinyl halide products, we first carried out gram-scale reactions of both 2-aminoaryl and 2-oxyaryl alkyne substrates **NS1** (Scheme 1A) and **OS1** (Scheme 1B) and still obtained good yields with excellent enantioselectivity. Next, we examined their thermal stability and observed marginal racemization up to 60 °C (Scheme 1C,D; see Tables S7 and S8 for more details). Accordingly, we managed to perform Sonogashira and Suzuki−Miyaura coupling reactions with these axially chiral vinyl chlorides at or below 60 °C, which generally yielded the corresponding products **N1**−**1**, **N1**−**2**, **O1**−**1**, and **O15**−**1**−**3** with highly retained enantiopurity (Scheme 1E). The sulfonyl alkene was also amenable to further manipulations, delivering axially chiral tetrasubstituted alkene **N1**−**3**. In addition, subsequent straightforward deprotection and *N*-functionalization of **N1**−**2** gave rise to axially chiral thioureas **N1**−**5**−**7**, pyridinyl carboxamide **N1**−**8**, and quinolyl sulfonamide **N1**−**9** (Scheme 1F), which are promising organocatalysts[34] or *N*,*N*-bidentate ligands.[15b] Accordingly, purely axially chiral thiourea **N1**−**5** delivered good diastereoselectivity and enantioselectivity in the tandem Michael addition and cyclization reaction of enynamide **SM-1** and ketimine **SM-2**,[35] and the presence of additional chiral amine moieties in **N1**−**6** and **N1**−**7** further enhanced the stereoselectivity while greatly improving the reaction efficiency (Scheme 1G). Notably, the stereointegrity was generally maintained throughout the manipulation processes, thus showcasing the high utility and versatility of our reaction as a competent synthetic hub in preparing axially chiral alkene reagents for asymmetric catalysis and synthesis.

Mechanistic Investigation. Control experiments in the absence of the copper salt, chiral ligand, or base additive confirmed that all of these components were indispensable for the reaction (Tables S9 and S10; see Figure S6 for catalyst-controlled regioselectivity). In the presence of either BHT (butylated hydroxytoluene; Scheme 2A and Table S11) or

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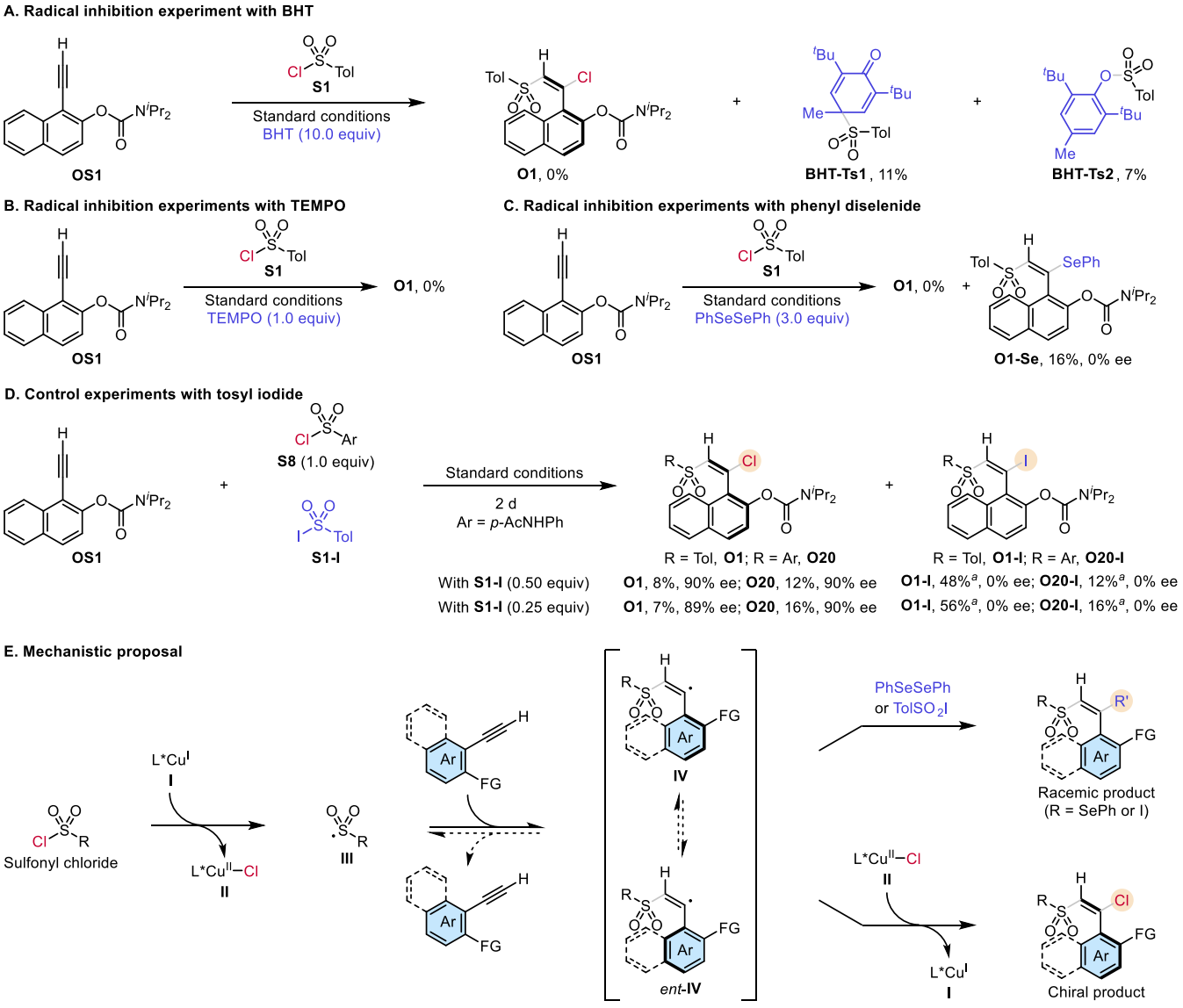
Scheme 2. Mechanistic Experiments and Proposal[a]



[a]The yield was calculated based on the amount of **S1**–**I**. To express the yield relative to OS1, the value should be divided by 2 or 4 for reactions using 0.50 or 0.25 equiv of **S1**–**I**, respectively. BHT, butylated hydroxytoluene; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; Ar, *p*-acetylaminophenyl; FG, functional group.

TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl; Scheme 2B and Table S10), the reaction was completely shut down. Additionally, sulfonyl radical-trapped products **BHT-Ts1** and **BHT-Ts2** were isolated in the reaction with BHT (Scheme 2A and Table S11). Furthermore, the addition of another radical trapper, phenyl diselenide, led to the formation of vinyl radical-trapped product **O1**–**Se** (Scheme 2C). These results supported the proposed formation of sulfonyl radicals and their subsequent addition to alkynes, generating vinyl radicals. Notably, vinyl radical-trapped product **O1**–**Se** was racemic (Scheme 2C). More importantly, the addition of tosyl iodide, a known fast iodine-atom-transfer donor,[33] also resulted in racemic iodination products **O1**–**I** and **O20**–**I**, while the simultaneously formed chlorination products **O1** and **O20** were highly enantioenriched (Scheme 2D; see Scheme S3 for additional results and discussions). These results together strongly indicated that the in situ-formed vinyl radicals were racemic and that the C–Cl bond coupling proceeded enantioselectively (Scheme 2E). Subjecting racemic product **N1** to the standard conditions resulted in no enantioenrichment (Scheme S7), ruling out the possibility of its kinetic resolution through reversible chlorine atom transfer. Regarding the key C–Cl bond formation, our preliminary density functional theory (DFT) calculations revealed that the presumed chlorine atom transfer pathway is energetically more favorable than that involving the formation of Cu(III) species[14e] and subsequent reductive elimination (Figure S8). In addition, chlorine atom transfer involving TsCl proceeds through an energetically unfavorable transition state.

Based on these mechanistic results, as well as others in literature,[36] we proposed a possible mechanism shown in Scheme 2E. The reaction starts with the single-electron reduction of sulfonyl chloride with Cu(I) species **I**, generating Cu(II) chloride **II** and sulfonyl radical **III** (for the electrochemical analysis of radical precursors employed in this study, see Figure S7). Then, **III** undergoes addition to the aryl alkyne,

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forming vinyl radical **IV** and its enantiomer *ent*-**IV**. Finally, one of the two vinyl radical enantiomers selectively abstracts a chlorine atom from the chiral Cu(II) chloride complex **II**, leading to the axially chiral chloride product and regenerating Cu(I) catalyst **I**. The remaining vinyl radical enantiomer likely transforms to its antipode via direct epimerization or reversible β-elimination and subsequent readdition.

CONCLUSIONS

In summary, we have successfully tailored tridentate anionic *N,N,N*-ligands to realize highly enantioselective chlorine or bromine atom transfer with very reactive vinyl radicals under copper catalysis. The installation of sterically bulky groups at the peripheral positions of these *N,N,N*-ligands to elicit competent stereodiscrimination of remote motifs of the vinyl radicals has been experimentally proven to be essential for attaining high enantioselectivity. The reaction readily affords an abundance of valuable enantioenriched vinyl chlorides and bromides, thus providing a robust platform for expedient access to a myriad of axially chiral acyclic styrene compounds. Notably, some of these compounds exhibited superior performance in a demonstration reaction in terms of both the reaction efficiency and stereoselectivity, showcasing the great potential of these axially chiral molecules in asymmetric catalysis. These results highlight the great potential of strategically devised multidentate anionic ligands for the development of asymmetric radical reactions of highly reactive carbon radicals using transition-metal catalysis, particularly copper catalysis.

METHODS

General Procedure for 2-Aminoaryl Alkynes. A flame-dried Schlenk tube equipped with a magnetic stir bar was charged with $Cu(CH_3CN)_4PF_6$ (7.45 mg, 0.020 mmol, 10 mol %), **L7** (11.2 mg, 0.020 mmol, 10 mol %), alkyne (0.20 mmol, 1.0 equiv), sulfonyl chloride (0.30 mmol, 1.5 equiv), and K_3PO_4 (127.4 mg, 0.60 mmol, 3.0 equiv). The tube was evacuated and backfilled with argon three times. Anhydrous DME (1.0 mL) and MTBE (3.0 mL) were then added to the mixture, and the reaction mixture was stirred at room temperature for 5 d. Upon completion, the precipitate was filtered off and washed with DCM. The filtrate was evaporated, and the residue was purified by column chromatography on silica gel to afford the desired product.

General Procedure for 2-Oxyaryl Alkynes. A flame-dried Schlenk tube equipped with a magnetic stir bar was charged with $Cu(CH_3CN)_4PF_6$ (7.45 mg, 0.020 mmol, 10 mol %), **L7** (11.2 mg, 0.020 mmol, 10 mol %), alkyne (0.20 mmol, 1.0 equiv), sulfonyl chloride (0.30 mmol, 1.5 equiv), and K_3PO_4 (127.4 mg, 0.60 mmol, 3.0 equiv). The tube was evacuated and backfilled with argon three times. Anhydrous EtOAc (4.0 mL) was then added to the mixture, and the reaction mixture was stirred at room temperature for 5 d. Upon completion, the precipitate was filtered off and washed with DCM. The filtrate was evaporated, and the residue was purified by column chromatography on silica gel to afford the desired product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c06672.

Additional experimental and theoretical results, experimental procedures, characterization of compounds, computational details, NMR spectra, and HPLC traces (PDF)
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Accession Codes

CCDC 2259801−2259805 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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Notes

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