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# Enantioconvergent Cu-Catalyzed Radical C–N Coupling of Racemic Secondary Alkyl Halides to Access α-Chiral Primary Amines

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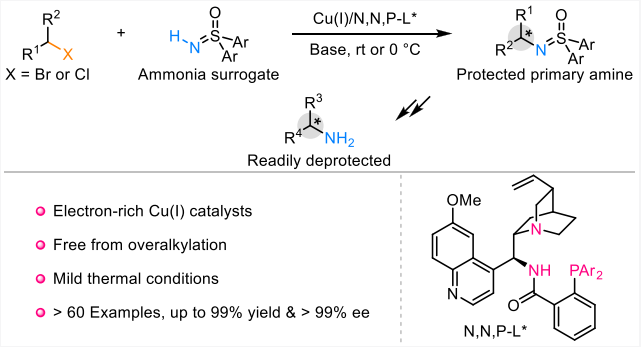
**ABSTRACT:** α-Chiral alkyl primary amines are virtually universal synthetic precursors for all other α-chiral N-containing compounds ubiquitous in biological, pharmaceutical, and material sciences. The enantioselective amination of common alkyl halides with ammonia is appealing for potential rapid access to α-chiral primary amines, but has hitherto remained rare due to the multifaceted difficulties in using ammonia and the underdeveloped C($sp^3$)–N coupling. Here we demonstrate sulfoximines as excellent ammonia surrogates for enantioconvergent radical C–N coupling with diverse racemic secondary alkyl halides (>60 examples) by copper catalysis under mild thermal conditions. The reaction efficiently provides highly enantioenriched *N*-alkyl sulfoximines (up to 99% yield and >99% ee) featuring secondary benzyl, propargyl, α-carbonyl alkyl, and α-cyano alkyl stereocenters. In addition, we have converted the masked α-chiral primary amines thus obtained to various synthetic building blocks, ligands, and drugs possessing α-chiral N-functionalities, such as carbamate, carboxylamide, secondary and tertiary amine, and oxazoline, with commonly seen α-substitution patterns. These results shine light on the potential of enantioconvergent radical cross-coupling as a general chiral carbon–heteroatom formation strategy.




## INTRODUCTION

Chiral N-containing moieties featuring an α-stereocenter are important chiral building blocks in organic synthesis and key structural elements in a variety of natural products, pharmaceuticals, agrochemicals, and functional materials (Figure 1A, bottom).[1] For example, they are ubiquitous in numerous chiral organocatalysts and ligands as well as auxiliaries in asymmetric synthesis.[2] They are also essential characteristics of proteins, one major class of biological macromolecules,[3] and alkaloids, one large and important family of natural products.[4] At least one such motif is present in roughly 40% of the top-selling 200 FDA approved small-molecule drugs in 2019.[5] Among others, α-chiral alkyl primary (1°) amines are of particular importance since besides their immediate applications[1,2,5] they are also vital synthetic precursors to most other α-chiral N-containing compounds (Figure 1A, top).[1a] Consequently, their efficient and practical preparation by catalytic enantioselective methods constitutes a long-standing prominent objective in chemical research.[6]

The direct *N*-alkylation of ammonia with secondary alkyl halides is a conceptually simple approach for the apparently straightforward preparation of α-chiral secondary alkyl primary amines given the ready availability of ammonia (Figure 1B, left). However, this approach has seldom been utilized in the literature: on one hand, the generally enantiospecific $S_N2$ mechanism of this reaction necessitates the use of highly enantiopure alkyl halides as substrates, of which the synthesis is not trivial;[7] on the other hand, the moderate nucleophilicity of neutral ammonia most often renders the reaction susceptible to overalkylation as well as undesired elimination of alkyl halides to alkenes.[8] In this vein, the transition metal-catalyzed enantioconvergent radical[9] cross-coupling of ammonia[10] with racemic secondary alkyl halides, if established, would provide a more practical method toward α-chiral alkyl primary amines (Figure 1B, right) since both of the coupling partners are readily available. Nonetheless, to the best our knowledge, this method has so far not been realized despite that the related C($sp^3$)–N radical coupling reactions of racemic alkyl halides with other N nucleophiles have recently been emerging.[11,12] Particularly, Fu, Peters, and their co-workers have pioneered copper-catalyzed enantioconvergent radical C($sp^3$)–N coupling of racemic tertiary α-aminocarbonyl alkyl chlorides with indole-type N-nucleophiles under visible light irradiation

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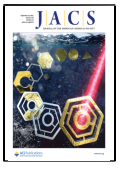







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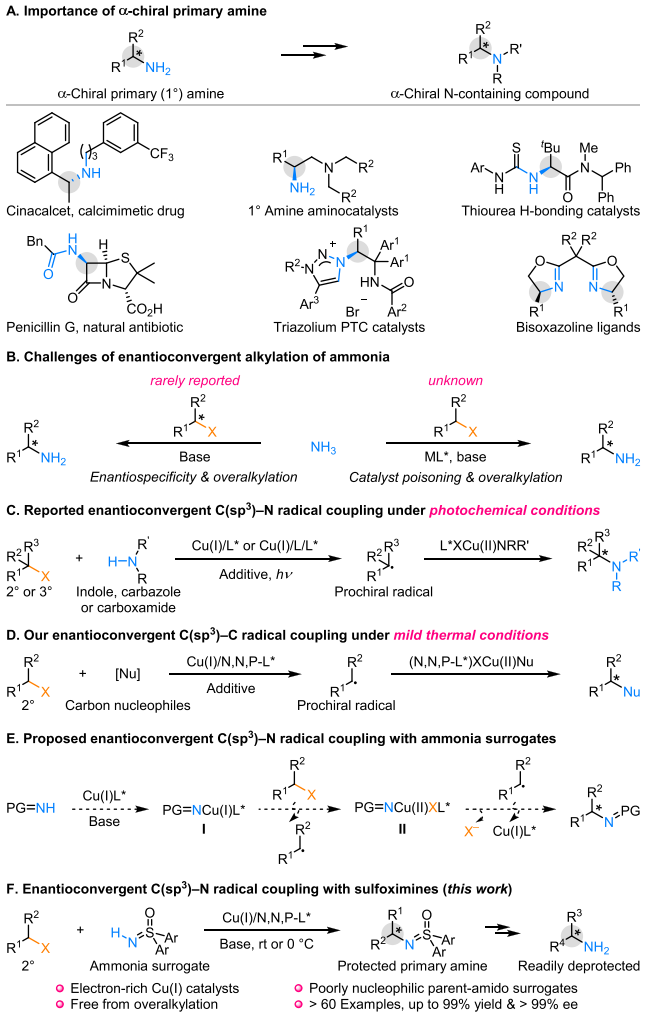


**Figure 1.** Challenges and development of enantioconvergent *N*-alkylation with racemic alkyl halides for the synthesis of α-chiral primary amines.

(Figure 1C).[12a] More importantly, during the preparation of this article, they have just made another breakthrough in this field by accomplishing the directed enantioconvergent radical coupling of racemic unactivated secondary alkyl bromides or iodides with carboxamides by copper catalysis in the presence of a mixed ligand system under photochemical conditions.[12b] The key to their chemistry is the strategical recruitment of photoactivatable Cu(I) species for the efficient reduction of racemic alkyl halides to prochiral alkyl radicals in the presence of visible light. In this regard, we have recently found that electron-rich multidentate anionic N,N,P-ligands can remarkably enhance the reducing capability of Cu(I) catalysts for facile alkyl radical generation from a range of alkyl halides under mild thermal conditions. Accordingly, a series of enantioconvergent radical C($sp^3$)–C(sp/$sp^2$) coupling reactions have been established (Figure 1D).[13] Given the importance of α-chiral alkyl primary amines, we were then intrigued to explore an enantioconvergent radical C($sp^3$)–N coupling reaction with our Cu(I)/N,N,P-ligand catalysts, which, if achieved, would provide an excellent complementary approach to those known methods.[6,12b]

However, ammonia is an excellent Lewis base that readily forms stable Lewis base–acid complexes with transition metals,[14] leading to catalyst poisoning and/or chiral ligand displacement (Figure 1B, right).[15] In addition, the low acidity of ammonia also renders the formation of amido complexes with transition metals through deprotonation difficult.[16] More importantly, the overalkylation issue also has to be dealt with, as the more nucleophilic alkyl amine products may still be competitive.

To overcome the difficulties aforementioned, we envisioned an ammonia surrogate[6c,17] with enhanced N–H acidity, diminished Lewis basicity, and preferably a single substitutable N–H bond (Figure 1E). Thus, this surrogate might undergo facile deprotonation and readily coordinate with Cu(I). Next, complex **I** would reduce an alkyl halide via a single-electron-transfer process to generate prochiral alkyl radicals.[9b–e] Last, enantioselective C($sp^3$)–N coupling by the reaction of alkyl radicals with the thus-oxidized Cu(II) complex **II** might preferably occur. Overall, this process could ideally be enantioconvergent and free from overalkylation. More importantly, there would be added benefits for the synthesis of complex α-chiral N-containing molecules in multiple steps:[18] the thus-obtained latent α-chiral alkyl primary amines could be more readily tolerated with higher operational simplicity than their free forms in early stage manipulations, which would be strategically and conveniently unmasked where appropriate. Nonetheless, two challenges still exist in order for successful implementation of such a process: (i) the deprotonated form of the surrogate and its complex with Cu(I) might be prone to $S_N2$ alkylation with secondary alkyl halides[12c,19] likely with no or low enantiocontrol; (ii) the enantiocontrol of intermolecular transformations involving highly reactive radical species, such like the one proposed above, is challenging,[20] particularly when the mode of the envisioned final reductive elimination lacks well-defined precedents.[11c,12a]

To this end, herein we report our efforts in identifying diaryl sulfoximines as excellent ammonia surrogates with acidities comparable to water (p$K_a$ about 15 in water) (Figure 1F).[21] More importantly, they possess poor Lewis basicity and nucleophilicity even when deprotonated[22] and are also important pharmacophores in their own right.[23] In addition, we have also found that our recently developed Cu(I)/N,N,P-ligand catalysts[13] readily engage in the expected transformation described above under mild thermal conditions (Figure 1F). Thus, an enantioconvergent C($sp^3$)–N coupling reaction has been successfully developed, providing enantioenriched α-chiral sulfoximines with secondary benzyl and propargyl as well as α-carbonyl and α-nitrile alkyl stereocenters. Further follow-up transformations of these products have led to a range of common chiral N-containing compounds, such as carbamates, carboxylamides, secondary and tertiary amines, and an oxazoline, with most common substitution types of α-stereocenters present in useful synthetic building blocks, ligands, and drugs via corresponding α-chiral alkyl primary amines, demonstrating the synthetic utility and adaptability of this methodology.

## RESULTS AND DISCUSSION

**Reaction Development.** Our initial investigation revealed that only the electron-rich multidentate anionic N,N,P-ligand **L*3** delivered the desired product **1**, albeit in low yield with moderate enantioselectivity, from racemic benzyl bromide **E1** and sulfoximine **N1** in the presence of a Cu(I) salt under ambient thermal conditions (Scheme 1; for results of other common ammonia surrogates under the same conditions, see


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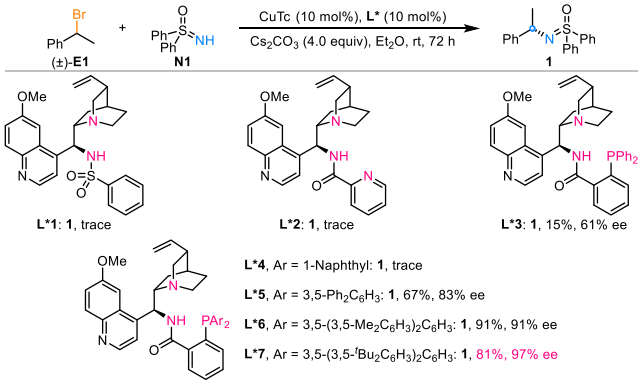
**Scheme 1. Results of Ligand Screening**[a]

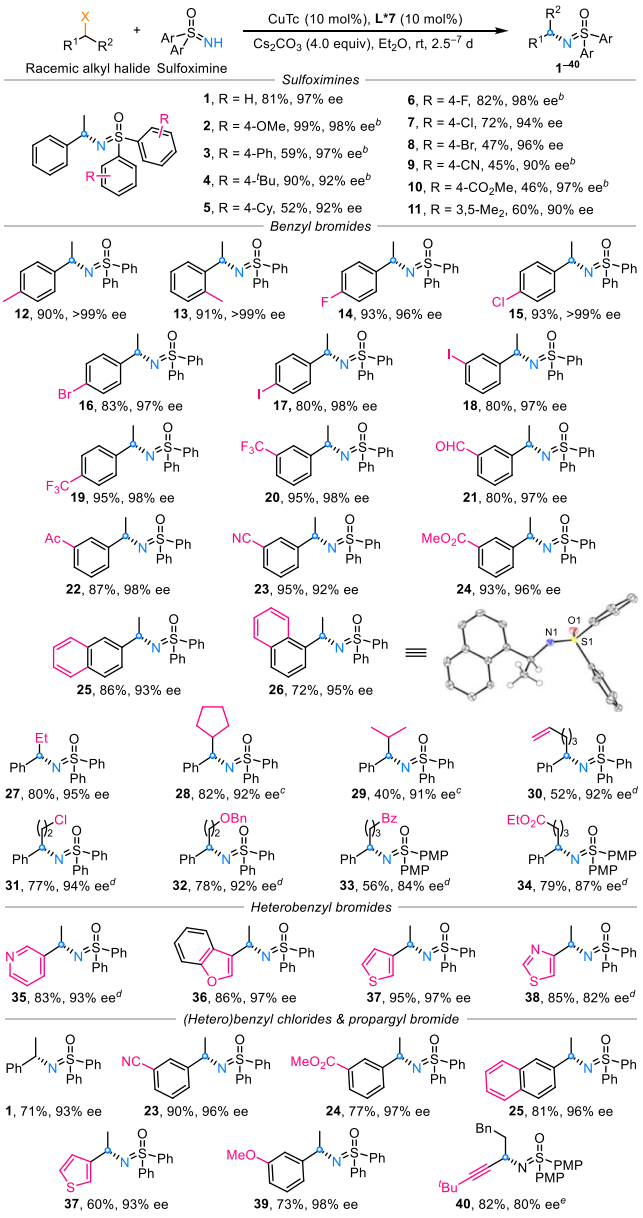



[a]Reaction conditions: (±)-**E1** (0.025 mmol), **N1** (1.0 equiv), CuTc (10 mol %), **L*** (10 mol %), and $Cs_2CO_3$ (4.0 equiv) in $Et_2O$ (0.5 mL) at room temperature (rt) for 72 h under argon; yield of **1** was isolated one; ee was determined by analysis of chiral HPLC measurement. Tc, thiophene-2-carboxylate.

Scheme S1). One major side product was 2,3-diphenylbutane (~13% yield, Table S1), possibly originating from homocoupling of the generated benzyl radicals. In contrast, other less electron-rich anionic ligands such as N,N-ligand **L*1** and N,N,N-ligand **L*2** even failed to competently initiate the single-electron reduction of **E1** under otherwise the same conditions, as evidenced by the much less or no formation of either **1** or the homocoupling side product (Table S1). These results are in accord with the usually low capability of Cu(I) catalysts to undergo oxidative addition to alkyl halides under ambient thermal conditions, and alternative photoactivation conditions,[11a−f,12a,b] very reactive alkyl iodide substrates,[12c] or indirect halogen-atom abstraction[11g,h] has previously had to be invoked to cross this hurdle. Further investigation (Table S1 for other details) on the substitution effect of the phosphine moieties in the N,N,P-ligands indicated that both the reaction efficiency and enantioselectivity were greatly affected, and the most sterically bulky ligand **L*7** gave the highest enantioselectivity. Thus, the optimal conditions are equal amounts of **E1** and **N1** in the presence of 10 mol % CuTc, 10 mol % **L*7**, and 4.0 equiv of $Cs_2CO_3$ in $Et_2O$ at room temperature for 72 h (for a time-course profile, see Figure S1), providing **1** in 81% yield with 97% ee.

**Substrate Scope.** The subsequent survey on the scope of sulfoximines revealed excellent tolerance of a panel of functional groups with different electronic and steric properties on the *S*-aryl rings (**1**−**11**, 45−99% yield with 90−98% ee; Scheme 2). With regard to benzyl bromides (Scheme 2), phenyl rings possessing slight electron-donating methyl groups or a broad series of electron-withdrawing substituents at different (*ortho*, *meta*, or *para*) positions and bicyclic naphthalene rings all were compatible with the reaction conditions to deliver **12**−**26** in 72−95% yield with 92 to >99% ee. In addition, a range of linear or *β*-branched alkyl side chains did not greatly affect the enantioselectivity (**27**−**34**). However, an acyclic *β*-branched isopropyl side chain led to diminished yield. Importantly, a gamut of labile functional groups toward nucleophiles, such as halo (**15**−**18** and **31**), formyl (**21**), ketone (**22** and **33**), nitrile (**23**), ester (**24** and **34**), terminal olefin (**30**), and benzyl ether (**32**), were all well tolerated under the mild reaction conditions. Besides benzyl bromides, many heterobenzyl bromides featuring medicinally relevant

**Scheme 2. Substrate Scope for Sulfoximines and (Hetero)benzyl and Propargyl Halides**[a]




[a]Standard reaction conditions: racemic alkyl halide (1.0 equiv), sulfoximine (0.20 mmol), CuTc (10 mol %), **L*7** (10 mol %), and $Cs_2CO_3$ (4.0 equiv) in $Et_2O$ (2.0 mL) under argon at rt; yields are isolated ones; ee was determined by analysis of chiral HPLC measurement. [b]Racemic alkyl halide (1.5 equiv). [c]CuTc (40 mol %) and **L*6** (40 mol %). [d]**L*6** (10 mol %) at 0 °C. [e]Racemic alkyl bromide (2.0 equiv), $Cu(PPh_3)_3Br$ (20 mol %), and **L*4** (20 mol %) were used, and the yield is based on recovered starting material (50% conversion). PMP, *para*-methoxyphenyl.

heterocycles including pyridine, benzo[*b*]furan, thiophene, and thiazole were well accommodated, providing the desired products **35**−**38** in excellent yield with excellent enantioselectivity. Further, the less reactive (hetero)benzyl chlorides were also viable substrates with comparable efficiency and enantioselectivity for the reaction (**1**, **23**−**25**, **37**, and **39**). More importantly, a racemic propargyl bromide was suitable for the reaction, too, delivering chiral propargyl sulfoximine **40** in 82% yield with 80% ee. Noteworthy is that the



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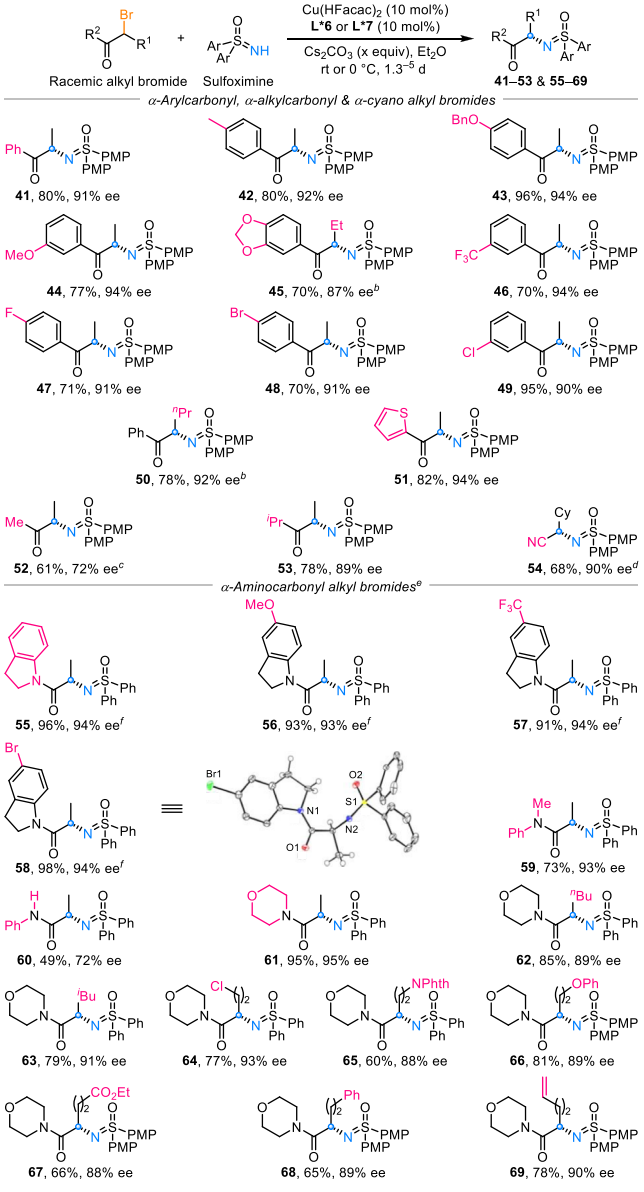
corresponding chiral propargyl amines are valuable and versatile building blocks in organic synthesis.[24]

To further strengthen the synthetic utility of this methodology, we next reoptimized (Tables S2 and S3) the reaction conditions to extend the reaction to $\alpha$-carbonyl alkyl bromides. Thus, a panel of $\alpha$-(hetero)arylcarbonyl alkyl bromides were converted to chiral alkyl sulfoximines **41**−**51** in 70−96% yield with 87−94% ee under modified conditions (Scheme 3). In addition, the reactions of $\alpha$-alkylcarbonyl alkyl bromides proceeded efficiently, forging **52** and **53** in good yield and

**Scheme 3. Substrate Scope for $\alpha$-Carbonyl/Cyano Alkyl Bromides**[a]




[a]Standard conditions: racemic alkyl halide (0.20 mmol), sulfoximine (1.1 equiv), $Cu(HFacac)_2$ (10 mol %), **L*7** (10 mol %), and $Cs_2CO_3$ (4.0 equiv) in $Et_2O$ (4.0 mL) under argon at 0 °C; yields are isolated ones; ee was determined by analysis of chiral HPLC measurement. [b]**L*6** (10 mol %). [c]Racemic alkyl bromide (1.5 equiv) and sulfoximine (0.20 mmol). [d]$Cu(PPh_3)_3Br$ (10 mol %) and **L*7** (11 mol %). [e]Sulfoximine (1.2 equiv) and $Cs_2CO_3$ (2.5 equiv) at rt. [f]Sulfoximine (1.0 equiv) and **L*6** (10 mol %). Phth, phthalyl.

enantioselectivity. Interestingly, an $\alpha$-cyano alkyl bromide was also well applicable to this transformation, leading to sulfoximine **54** in high enantiopurity. Notably, an array of $\alpha$-aminocarbonyl alkyl bromides were viable substrates, too, and *N*,*N*-disubstituted ones (**55**−**59** and **61**, 93−95% ee) generally outcompeted an *N*-monosubstituted one (**60**, 41%, 72% ee) in terms of both reaction efficiency and enantioselectivity. More encouragingly, in regard to the alkyl branch, the reaction was well tolerant of $\beta$-branching (**63**) as well as a host of potentially interfering functional groups such as primary chloride (**64**), phthalimide (**65**), phenyl ether (**66**), ester (**67**), phenyl (**68**), and terminal alkene (**69**). The absolute configurations of **26** (Scheme 2 and Figure S2) and **58** (Scheme 3 and Figure S3) were determined by X-ray crystallographic analysis, and those of all other related compounds were assigned by analogy, accordingly.

**Synthetic Utility.** To demonstrate the practicality and synthetic potential of this methodology, a gram-scale reaction was first carried out, and both high efficiency and high enantioselectivity were readily obtained (Scheme 4A). To access the antipodes of products, the N,N,P-ligand **L*7** could be replaced with its pseudoenantiomer **L*7′**, leading to comparable yield and enantioselectivity (Scheme 4B; for more examples with **L*7′**, see Scheme S2). The vital important conversion of enantioenriched sulfoximines to chiral primary amines was achieved using mild reduction by Mg or stronger reduction by sodium naphthalide followed by acidic hydrolysis without remarkable losses of enantiopurity (Scheme 4C). Accordingly, the enantioenriched sulfoximine **61** was straightforwardly converted to a myriad of chiral building blocks, such as amino alcohols **73**, **77**, and **78**, diamine **75**, amino ketone **76**, $\alpha$,$\alpha$-dialkyl-substituted primary amine **79**, and natural amino acid ester **80** (Scheme 4D). Notably, the sulfoximine moiety proved to be relatively stable and, thus, could be unmasked at a late stage during multistep synthesis, as demonstrated by the synthesis of **73**. These newly obtained building blocks were further transformed to several novel ligands such as pyrox **81** and N,P-ligand **82** (Scheme 4E). More importantly, commercial drugs including cinacalcet for the treatment of hyperparathyroidism and hypercalcemia, dapoxetine for the treatment of premature ejaculation, and rivastigmine for the treatment of dementia were readily prepared in high enantiopurity (Scheme 4F) using the current methodology as the key steps. Of particular note is that no obvious loss of enantiopurity was observed during all these transformations, thus demonstrating the practicality and adaptability of this method as a robust complementary approach to reported strategies for the synthesis of an abundance of $\alpha$-chiral N-containing compounds.[1]

**Mechanistic Study.** Concerning the mechanism of this reaction, the Cu(I)-sulfoximinato complex **83** was first prepared from **N1**, and its structure was validated by NMR and X-ray analysis (one-fourth of the tetrameric complex is shown in Scheme 5A for clarity; for the full structure, see Figure S4). The stoichiometric reaction of analytically pure **83** with racemic **E1** proceeded in the presence of a catalytic amount of **L*7** to provide **1** in comparable efficiency and enantioselectivity with that in the catalytic reaction, while no reaction occurred in its absence (Scheme 5B). Thus, the sulfoximinato complex is likely the first intermediate in the catalytic cycle, which upon coordination with chiral ligand brings about the reaction with alkyl halide (for a cyclic voltammetry study on **83**, see Figure S5). This reasoning was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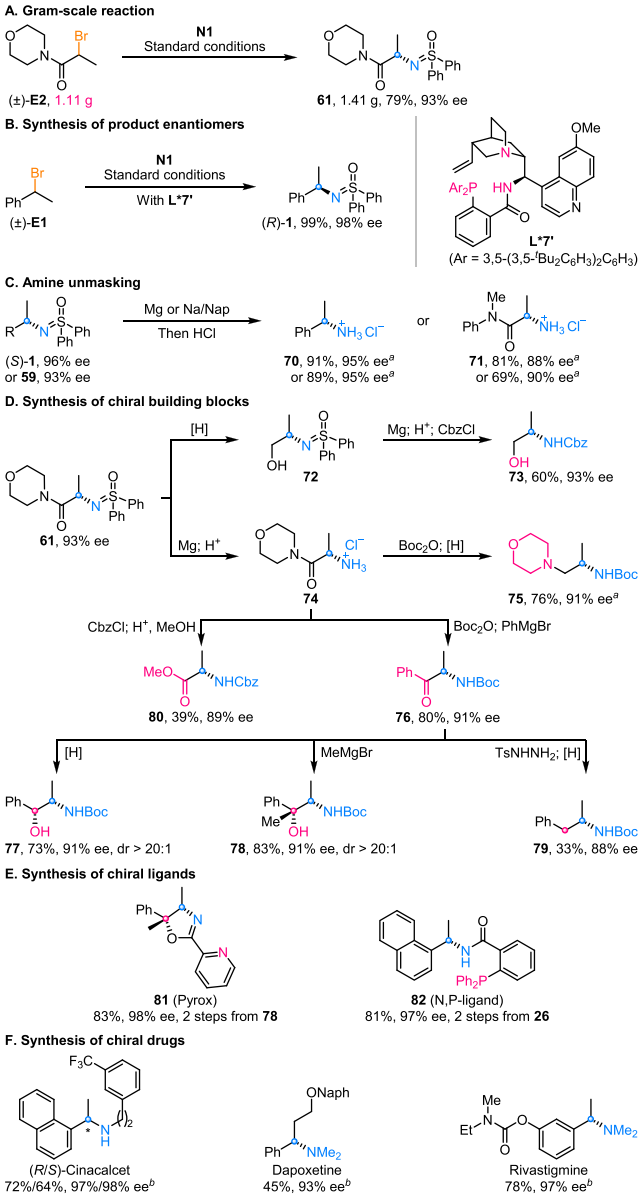
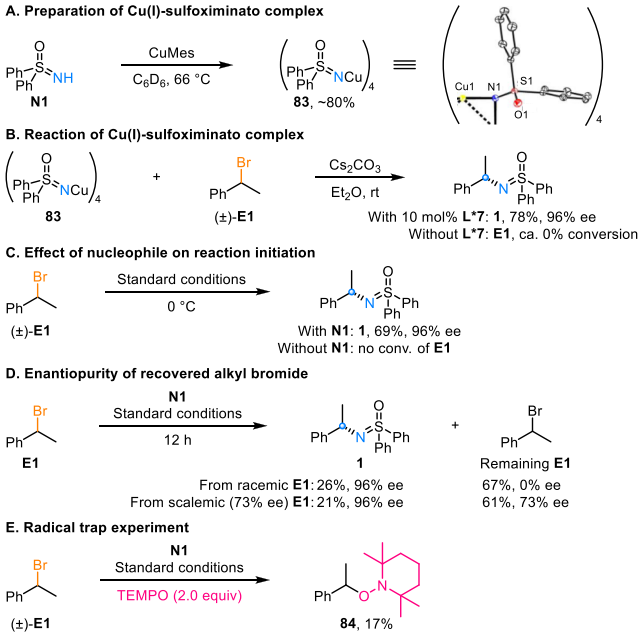
### Scheme 4. Demonstration of Synthetic Potentials




[a]The ee value was determined using a derivative compound. [b]The drugs were prepared from corresponding alkyl bromides in three steps, and the yields were calculated over three steps. Nap, naphthalene; [H], hydride reagents; Naph, 1-naphthalenyl.

### Scheme 5. Mechanistic Investigations




further supported by the nearly zero conversion of **E1** in the absence of **N1**, while good yield of **1** was obtained in its presence under the standard conditions at 0 °C (Scheme 5C). Additionally, no enantioenrichment or enantioerosion was observed with **E1** in the reactions starting from racemic or scalemic **E1**, respectively, of which both were stopped at partial conversion. Thus, the kinetic resolution or dynamic kinetic resolution via fast racemization of **E1** is unlikely (Scheme 5D). Further a radical trap experiment with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) indicated complete reaction inhibition for the formation of **1**, and a possible radical-trapped product **84** was isolated instead (Scheme 5E). In addition, three radical clock halide substrates bearing $\alpha$-cyclopropyl substituents all underwent ring-opening and C−N bond formation to afford corresponding *N*-primary alkyl sulfoximines under typical reaction conditions (Scheme S3). These observations together favor the formation of alkyl radical species from alkyl halides via a single-electron-transfer process. Overall, all these experimental results are in support of our initial proposal, as shown in Figure 1E.

## CONCLUSION

In summary, we have described a general radical enantioconvergent *N*-alkylation of sulfoximines with racemic secondary alkyl halides catalyzed by copper/chiral anionic multidentate N,N,P-ligand catalysts under mild thermal conditions. This protocol provides an efficient and practical platform to access diverse types of valuable enantioenriched $\alpha$-chiral N-containing compounds via the corresponding $\alpha$-chiral alkyl primary amines. With the operational simplicity, efficacy, generality, and practicality, this strategy is expected to find widespread use among practitioners across academia and industry settings. More importantly, the successful development of this catalytic system paves the way for discovering more enantioconvergent carbon−heteroatom cross-coupling reactions of alkyl halides with other heteroatomic nucleophiles, which have long remained underdeveloped.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07726.

Experimental procedures, characterization of compounds, Tables S1−S3, Schemes S1−S3, Figures S1−S3, and crystallographic data of **26**, **58**, and **83** (PDF)

### Accession Codes

CCDC 2060739, 2060741, and 2060750 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 interest.

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