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Asymmetric Catalysis

# Copper-Catalyzed Enantioconvergent Radical C($sp^3$)–N Cross-Coupling: Access to α,α-Disubstituted Amino Acids

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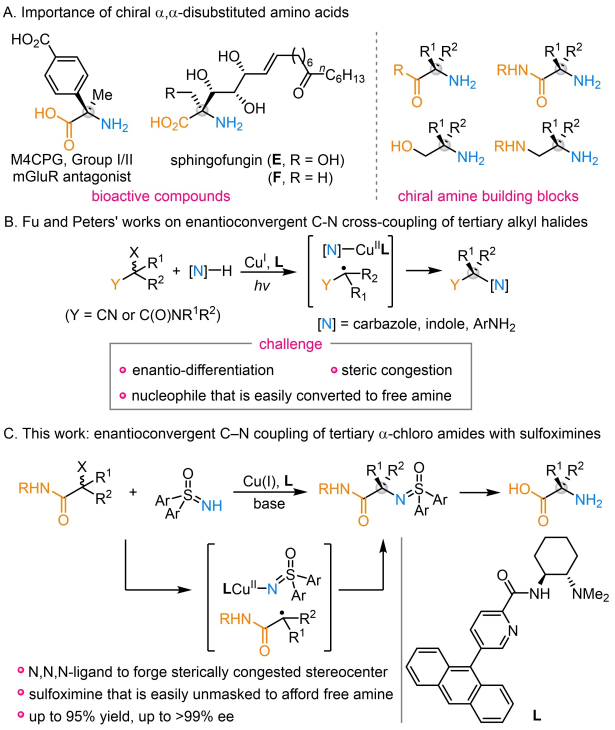
*Dedicated to Professor Dawei Ma on the occasion of his 60th birthday*

**Abstract:** Transition-metal catalyzed enantioconvergent cross-coupling of tertiary alkyl halides with ammonia offers a rapid avenue to chiral unnatural α,α-disubstituted amino acids. However, the construction of chiral C–N bonds between tertiary-carbon electrophiles and nitrogen nucleophiles presented a great challenge owing to steric congestion. We report a copper-catalyzed enantioconvergent radical C–N cross-coupling of alkyl halides with sulfoximines (as ammonia surrogates) under mild conditions by employing a chiral anionic N,N,N-ligand with a long spreading side arm. An array of α,α-disubstituted amino acid derivatives were obtained with good efficiency and enantioselectivity. The synthetic utility of the strategy has been showcased by the elaboration of the coupling products into different chiral α-fully substituted amine building blocks.

## Introduction

Unnatural α,α-disubstituted amino acids are structural motifs found in many biologically active natural products and are highly valued in modern drug discovery.[1] The incorporation of these building blocks can alter molecular conformation and enhance the resistance of peptide-related compounds against chemical and enzymatic degradation.[2] In chemical synthesis, they serve as vital synthons for the preparation of numerous chiral building blocks (Scheme 1A). This relevance has motivated considerable synthetic efforts to establish the efficient synthesis of enantioenriched α,α-disubstituted amino acids.[3–6] Among them, the catalytic enantioselective construction of C($sp^3$)–C bonds has been one of the predominant approaches, such as the well-established nucleophilic addition of ketimines and electrophilic alkylation of α-amino acid derivatives.[3,4] On the other hand, the enantioselective construction of C($sp^3$)–N bonds offers an appealing alternative to synthesize enantioenriched α,α-disubstituted amino acid derivatives but this route has not been explored as thoroughly.[5] The development could be impeded by several synthetic hurdles: (i) the difficult enantio-differentiation of three carbon substituents; (ii) the steric congestion encountered in constructing a fully substituted stereocenter;[6] (iii) the identification of a suitable nitrogen nucleophile that could be conveniently unmasked to release the primary amine entity (Scheme 1B). Consequently, developing new methods for the direct construction




***Scheme 1.*** Development of enantioconvergent radical C($sp^3$)–N cross-coupling of tertiary alkyl halides.

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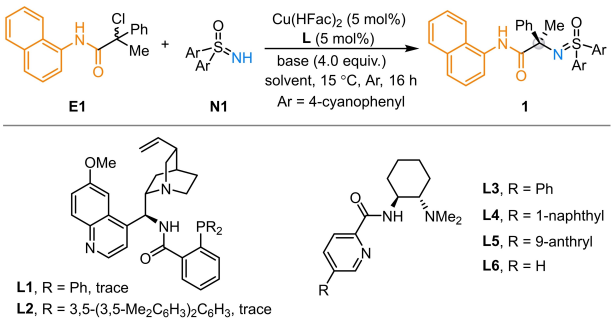
of chiral C($sp^3$)–N bonds to allow the efficient synthesis of valuable α,α-disubstituted amino acids is highly desirable.

The earth-abundant first-row transition metal-catalyzed enantioconvergent radical cross-coupling of racemic alkyl halides has recently emerged as a powerful tool in the synthesis of enantioenriched molecules.[7] Compared to well-established C($sp^3$)–C cross-coupling,[7] the C($sp^3$)–N cross-coupling of alkyl halides has been less studied.[6,8] Pioneering works by Fu and Peters have elegantly demonstrated the photoinduced enantioconvergent C($sp^3$)–N cross-coupling of tertiary α-halo amides with *N*-heterocycles/aniline derivatives to generate high-order chiral amine frameworks (Scheme 1B).[6,8] We envisioned that the employment of amine nucleophiles that could release free amines in need would expand the scope of the cross-coupling chemistry to access α,α-disubstituted amino acids. Ammonia is an ideal amine source for this purpose. However, our recent research on achieving enantioconvergent N-alkylation of ammonia with tertiary α-halo amides afforded the free α,α-disubstituted amino amide through the direct outer-sphere amine attack of $Cu^{III}$ intermediate only in 51 % yield with 85 % ee with a single example.[9] Our long-standing research interest in designing multidentate chiral anionic ligands for copper-catalyzed enantioconvergent radical cross-coupling reactions[7d,10] has recently culminated in a C($sp^3$)–N coupling of racemic secondary alkyl halides with sulfoximines.[11] Subsequently, we wondered if the same copper/N,N,P-ligand catalyst was applicable for the enantioconvergent C($sp^3$)–N coupling of tertiary α-halo amides by sulfoximines and furnished enantioenriched α,α-disubstituted amino acid derivatives. In theory, the $Cu^{I}$ complex would stimulate the generation of prochiral alkyl radicals from alkyl halides through single electron transfer, followed by enantioselective C($sp^3$)–N coupling between the alkyl radical and the thus-oxidized N-sequestered copper(II) complex. Unfortunately, our preliminary endeavors with the model coupling reaction of α-halo amide **E1** and sulfoximine[12] **N1** showed that the Dixon's ligand[13] **L1** or the best-performing N,N,P-ligand **L2** in the coupling of secondary alkyl halides[11] afforded almost no desired product **1** (Table 1, entries 1 and 2; see also Scheme S1 in the Supporting Information). We reasoned that the steric bulk of a tridentate N,N,P-ligand might be incompatible with the construction of a congested tetrasubstituted carbon stereocenter. Herein, we present a copper-catalyzed enantioconvergent C($sp^3$)–N cross-coupling of tertiary α-halo amides with sulfoximines to afford a

***Table 1:*** Screening of reaction conditions.[a]




| Entry | L | Base | Solvent | Yield [%] | Ee [%] |
|---|---|---|---|---|---|
| 1 | **L1** | $Cs_2CO_3$ | $Et_2O$ | Trace | – |
| 2 | **L2** | $Cs_2CO_3$ | $Et_2O$ | Trace | – |
| 3 | **L3** | $Cs_2CO_3$ | $Et_2O$ | 71 | 71 |
| 4 | **L4** | $Cs_2CO_3$ | $Et_2O$ | 95 | 84 |
| 5 | **L5** | $Cs_2CO_3$ | $Et_2O$ | 92 | 92 |
| 6 | **L6** | $Cs_2CO_3$ | $Et_2O$ | 60 | 2 |
| 7 | **L5** | $K_2CO_3$ | $Et_2O$ | 28 | 95 |
| 8 | **L5** | $K_3PO_4$ | $Et_2O$ | 73 | 93 |
| 9 | **L5** | NaOH | $Et_2O$ | 50 | 93 |
| 10 | **L5** | LiO$^t$Bu | $Et_2O$ | 78 | 93 |
| **11**[b] | **L5** | **$K_3PO_4$** | **$Et_2O$** | **93** | **92** |
| 12 | **L5** | $Cs_2CO_3$ | $^iPr_2O$ | 39 | 95 |
| 13 | **L5** | $Cs_2CO_3$ | toluene | 25 | 91 |
| 14 | **L5** | $Cs_2CO_3$ | THF | 82 | 87 |
| 15 | **L5** | $Cs_2CO_3$ | EtOAc | 87 | 90 |
| 16 | **L5** | $Cs_2CO_3$ | DCM | 24 | 76 |
| 17[c] | **L5** | $Cs_2CO_3$ | $Et_2O$ | 78 | 92 |
| 18[d] | **L5** | $Cs_2CO_3$ | $Et_2O$ | 59 | 90 |

[a] Reaction conditions: **E1** (0.05 mmol), **N1** (0.05 mmol), Cu(HFac)$_2$ (5 mol%), **L** (5 mol%), and $Cs_2CO_3$ (4.0 equiv) in $Et_2O$ (1.0 mL) at 15 °C for 16 h under argon; yield of **1** was isolated one; ee was determined by analysis of chiral HPLC measurement. [b] $Cs_2CO_3$ (10 mol%), $K_3PO_4$ (4.0 equiv) [c] Conducted under air. [d] Cu(HFac)$_2$ (2 mol%), **L5** (2 mol%). THF, tetrahydrofuran. DCM, dichloromethane. HFac, hexafluoroacetylacetonate. Me, methyl.

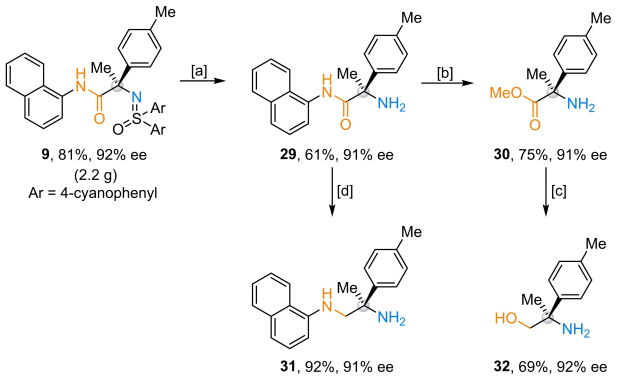
collection of enantioenriched α,α-disubstituted amino acids (Scheme 1C). The success of this strategy relies on the utilization of an N,N,N-ligand with small-sized coordinating atoms and a long spreading side arm,[10e] which enables the efficient formation of the highly congested carbon stereocenter under mild conditions (Scheme 1C). The sulfoximines serve as one kind of ideal amine nucleophiles that could be released to free amines when necessary. Moreover, the downstream transformation of the C–N coupling products allows direct access to numerous synthetically valuable chiral α-fully substituted amine building blocks, including 1,2-diamines and amino alcohols.

## Results and Discussion

As the preliminary investigation has informed about the detrimental effect of bulky N,N,P-ligands (**L1**, **L2**) in current molecular setting, the study continued with an assessment of alternative categories of chiral ligands for suitable reactivity (Table 1, entries 1 and 2; see also Scheme S1 in the Supporting Information). We resorted to our recently developed chiral anionic N,N,N-ligands that possess small-sized coordinating atoms and a long spreading side arm.[10e] The screening revealed ligand **L3** with a *meta*-phenyl substituent on the pyridyl group gave the desired coupling product **1** in 71 % yield with 71 % ee (Table 1, entry 3). The subsequent modification of this substituent proved to be fruitful: the replacement of the phenyl ring by a bulkier 1-naphthyl group (**L4**) enhanced the product yield (95 %) and ee (84 %) (Table 1, entry 4). The equipment of 9-anthryl group (**L5**) with a much larger steric size further improved the product ee (92 %) while the high product yield (92 %) was maintained (Table 1, entry 5). A control experiment using N,N,N-ligand (**L6**) with an unelaborated pyridine moiety led to a completely diminished enantioselectivity, indicating the substantial role of the large side arm in stereochemical control of this reaction (Table 1, entry 6). Subsequently, a systematic investigation of other reaction parameters was conducted. First, different bases exhibited significant differences in the reaction efficiency but had less impact on the ee value (Table 1, entries 7–11). Second, although both ether and benzene solvents exhibited better performance in terms of enantioselectivity, only $Et_2O$ (diethyl ether) was able to achieve a high yield (Table 1, entries 5, 12–16). The reaction efficiency decreased slightly when it was carried out under an air atmosphere and product **1** was obtained in 78 % yield with 92 % ee (Table 1, entry 17). A more notable decrement of yield (59 %) was observed when a lower catalyst loading of 2 mol % was used, although the product ee was minimally changed to 90 % (Table 1, entry 18). The results of optimization showed that the selection of copper salts, bases, and solvents could significantly influence the reaction efficiency, but have less detrimental impact on enantioselectivity (Table 1; see also Tables S1–S3 in the Supporting Information). We finally concluded the optimal reaction conditions as follows: a 1:1 stoichiometric amount of **E1** and **N1** reacted in the presence of 5 mol % copper hexafluoroacetylacetonate ($Cu(HFac)_2$), 5 mol % **L5**, 10 mol % $Cs_2CO_3$ and 4.0 equiv of $K_3PO_4$ in $Et_2O$ at 15 °C for 16 h, generating **1** in 93 % yield with 92 % ee (Table 1, entry 11).

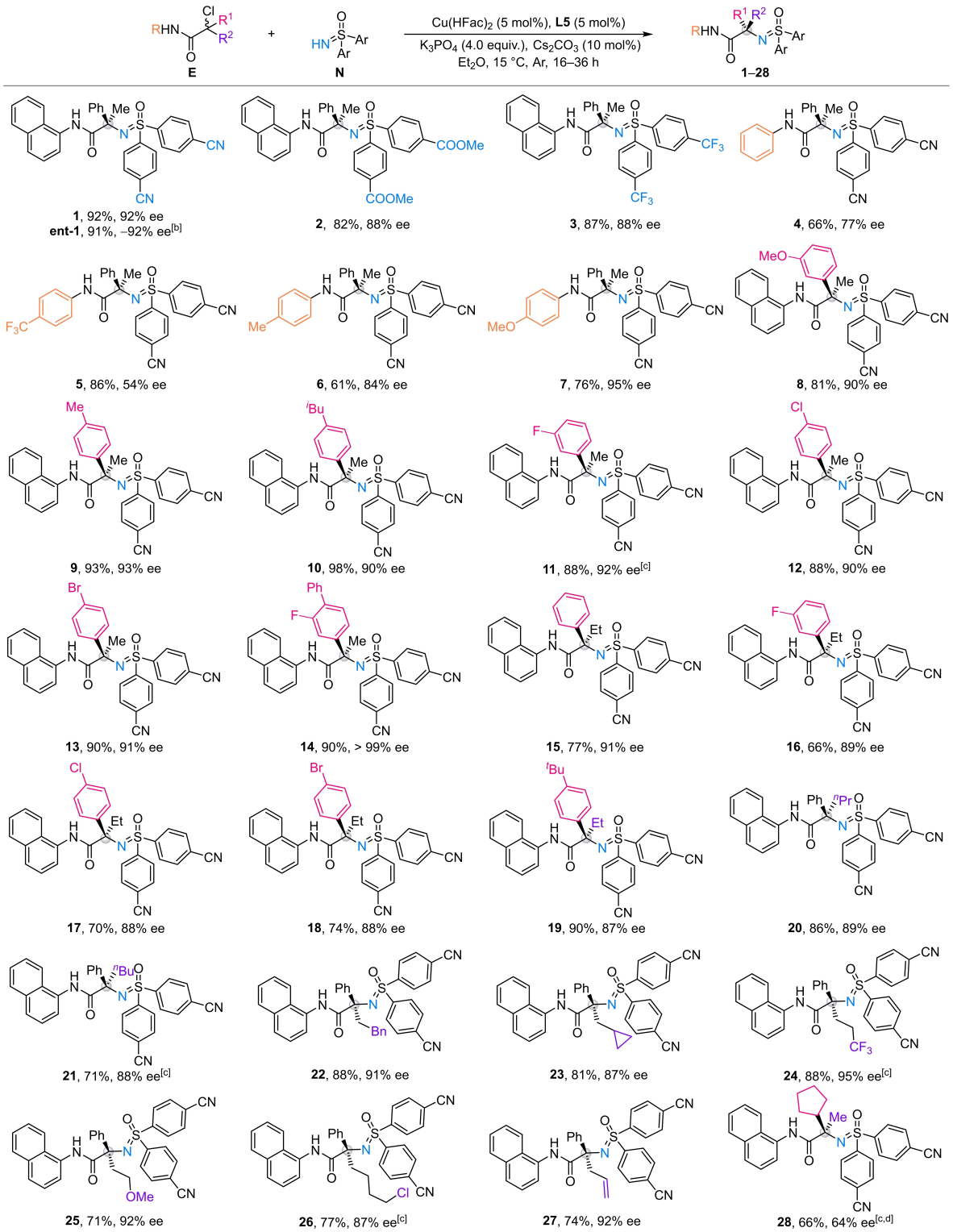
With the established optimal conditions in hand, we proceeded to investigate the scope of the coupling reaction (Table 2). The aryl rings with different substituents (–CN, –COOMe, $–CF_3$) on sulfoximines all gave the desired coupling products **1–3** in satisfactory yields (82–92 %) with 88–92 % ee. The coupling of **E1** and **N1** in the presence of the enantiomer of chiral ligand **L5** (**ent-L5**) gave rise to the enantiomer of **1** (**ent-1**) in 91 % yield with 92 % ee. The scope of the *N*-aryl substituent on the alkyl halides (**4–7**) revealed that the electronic factor greatly affected the enantioselectivity and the substrates with electron-rich substituents provided higher ee (**7**) than those with electron-deficient/neutral ones (**4–6**). A diverse array of α-aryl α-alkyl chloro amides were suitable substrates for the reaction to afford **8–19** in 66–98 % yields with 87–>99 % ee. The reaction tolerated diverse substituents with different electronic and steric properties on the aryl ring, such as MeO (**8**), Me (**9**), $^t$Bu (**10**), $^t$Bu (**19**), halogen (**11–14**, **16–18**). Furthermore, the substrate with disubstituted phenyl rings (**14**) was also amenable to the reaction. The alkyl group of the tertiary alkyl halides was not limited to the methyl group. Other simple alkyl (Et, $^n$Pr, $^n$Bu, methylenecyclopropyl) and functionalized aliphatic groups that possess $CF_3$, MeO, Cl, phenyl or alkenyl functionality were also tolerated under the standard conditions to afford amino amides **20–27** in 71–88 % yields with 87–95 % ee. In addition, an α,α-dialkyl-substituted bromide could undertake the enantioconvergent coupling as well to deliver amino amides **28**, albeit with moderate enantioselectivity. Further optimization of this reaction is still ongoing in our laboratory. The absolute configurations of the coupling products were determined with the aid of X-ray crystallographic analysis of **9**, **12**, and **15**, which have been characterized unequivocally (Figures S1–S3 in the Supporting Information).[14]

To demonstrate the preparative utility of this methodology, we first prepared **9** on a gram-scale (5.0 mmol) and observed a comparable yield and enantioselectivity (Scheme 2). The enantioenriched product **9** could be readily



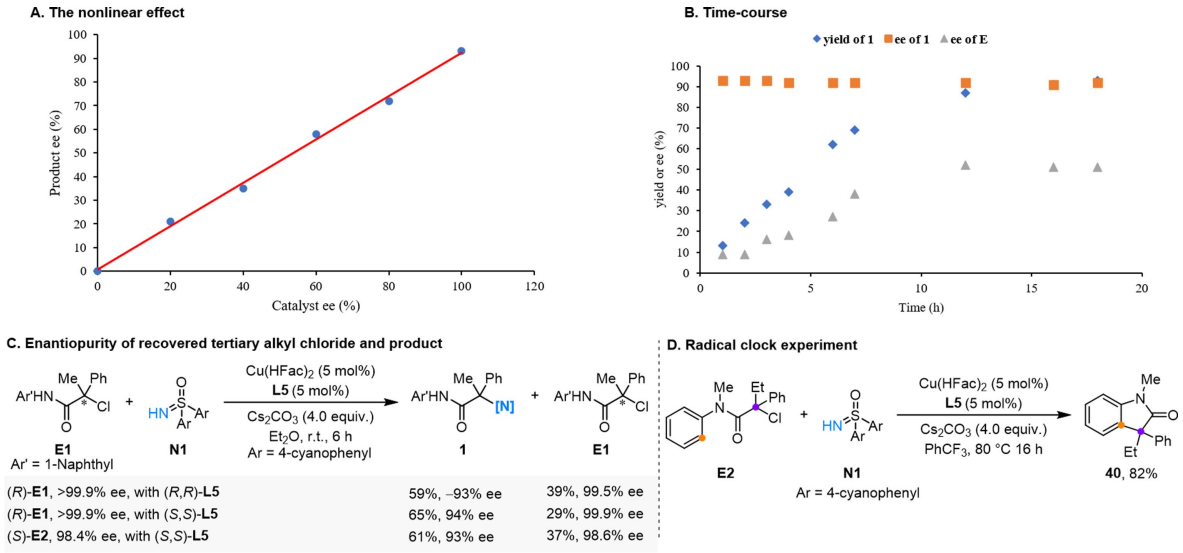

***Scheme 2.*** Synthetic utility. [a] Mg, MeOH; HCl (6 M); NaOH, rt. [b] HCl (*conc.*), reflux; NaOH; HCl in 1,4-dioxane, then $SOCl_2$, MeOH, reflux. [c] $NaBH_4$, MeOH, 0 °C. [d] $LiAlH_4$, 1,4-dioxane, 0 °C to reflux.

***Table 2:*** Scope of alkyl halides and sulfoximines.[a]




[a] Reaction conditions: **E** (0.20 mmol), **N** (0.20 mmol), $Cu(HFac)_2$ (5 mol%), **L5** (5 mol%), $Cs_2CO_3$ (10 mol%) and $K_3PO_4$ (4.0 equiv) in $Et_2O$ (2.0 mL) at 15 °C under argon; yields were isolated one; ee was determined by analysis of chiral HPLC measurement. [b] The enantiomer of **L5** (**ent-L5**) was used. [c] $Cs_2CO_3$ (4.0 equiv) and $^{i}Pr_2O$ (2.0 ml) was used. [d] Alkyl bromide was used. Et, ethyl. $^{i}$Bu, isobutyl. $^{t}$Bu, tertiary butyl. $^{n}$Pr, *n*-propyl. $^{n}$Bu, *n*-butyl. Bn, benzyl.

converted to its free amine form **29** via the Mg/MeOH reduction. A sequential hydrolysis/esterification process would furnish the amino acid ester **30** as another derivative of α,α-disubstituted amino acid. Notably, these enantioen-




***Scheme 3.*** Mechanistic investigation.

riched products also constituted a versatile platform to synthesize α-fully substituted chiral amine building blocks. As an illustration, the reduction of amino amide **29** by $LiAlH_4$ provided 1,2-diamine **31** and the $NaBH_4$-mediated reduction of amino acid ester **30** gave 1,2-amino alcohol **32**. It is noteworthy that these transformations have proceeded without apparent erosion of enantiopurity.

In order to gain insight into the reaction mechanism, the non-linear effect was first studied. The linear correlation between the enantiopurities of product and ligand suggested the involvement of one single chiral ligand in the enantio-determining transition state and the tridentate coordination mode of N,N,N-ligand to a monomeric copper species in this process (Scheme 3A). In addition, the ee values of product **1** remained nearly constant at different time intervals, indicating that a uniform mechanism was likely involved throughout the reaction course, rather than a kinetic resolution process, though enantio-enrichment of the recovered alkyl chloride **E1** was observed under typical conditions (Scheme 3B). Both enantiomers of tertiary chloride ((*R*)-**E1** and (*S*)-**E1**[14]) were prepared in enantiopure forms and individually subjected to reaction with **N1** under standard conditions (The X-ray crystallographic analysis of (*S*)-**E1** see Figures S4 in the Supporting Information). Upon halting the reaction at partial conversion (Scheme 3C), no enantioenrichment or enantioerosion was observed with (*R*)-**E1** or (*S*)-**E1**. Thus, the occurrence of a dynamic kinetic resolution process via fast racemization of **E1** is less likely. Furthermore, the intramolecular cyclization reaction was performed with **E2** and **N1** to give indolin-2-one **33** in 82 % yield. The electron paramagnetic resonance (EPR) and the high-resolution mass spectrometry (HRMS) analyses of the reaction indicated the possible formation of alkyl radicals (Figure S5 in the Supporting Information). Collectively, these results implied that the current enantioconvergent cross-coupling of tertiary alkyl halides occurred possibly through a single-electron-transfer process (Scheme 3D).[15] Overall, all the experimental results are in support of our original proposal outlined in Scheme 1C.

## Conclusion

In summary, a general enantioconvergent radical cross-coupling of sulfoximines with racemic tertiary alkyl halides catalyzed by copper/chiral anionic multidentate N,N,N-ligand catalyst under mild thermal conditions was described. This protocol provides an efficient and practical platform for the synthesis of α-chiral N-containing compounds, which can be further transformed into enantioenriched α,α-disubstituted amino acids. The straightforward conversion of the coupling products gives direct access to important building blocks such as α,α-disubstituted α-amino amide, amino acid ester, 1,2-amino alcohol, and 1,2-diamine in one or two steps. More importantly, the successful development of this catalytic system paves the way for discovering more enantioconvergent carbon-heteroatom cross-coupling reactions of tertiary alkyl halides with other heteroatomic nucleophiles, which have long remained underdeveloped.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are openly available in Cambridge Crystallographic Data Centre at https://www.ccdc.cam.ac.uk/structures/, reference numbers 2060748, 2243904, 2243902, and 2244868.

**Keywords:** Asymmetric Catalysis · Copper · Cross-Coupling · Tertiary Alkyl Halides · Unnatural Amino Acids

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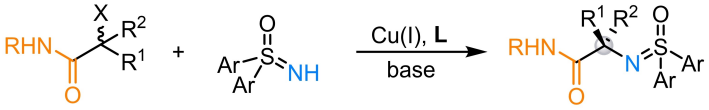
# Research Articles

## Asymmetric Catalysis

Y.-F. Zhang, J.-H. Wang, N.-Y. Yang, Z. Chen, L.-L. Wang, Q.-S. Gu, Z.-L. Li, X.-Y. Liu* e202302983

Copper-Catalyzed Enantioconvergent Radical C($sp^3$)–N Cross-Coupling: Access to α,α-Disubstituted Amino Acids

An enantioconvergent C($sp^3$)–N coupling to access α, α-disubstituted amino acids




- ligand to forge sterically congested stereocenter
- up to 95% yield, >99% ee

A copper-catalyzed enantioconvergent radical C–N cross-coupling of tertiary alkyl halides with sulfoximines (as ammonia surrogates) was realized by employing a chiral anionic N,N,N-ligand with a long spreading side arm under mild conditions. An array of valuable α,α-disubstituted amino acids could be furnished with good efficiency (up to 95% yield) and enantioselectivity (up to >99% ee).