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Copper-Catalyzed Enantioconvergent Radical C(sp^3)−N Cross-Coupling of Activated Racemic Alkyl Halides with (Hetero)aromatic Amines under Ambient Conditions

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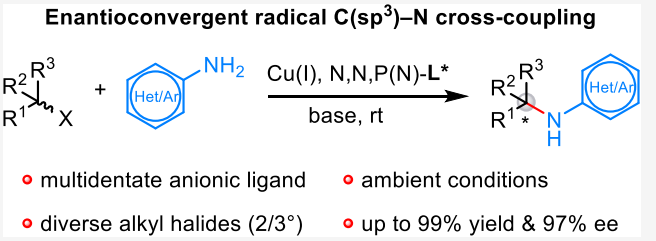
ABSTRACT: The enantioconvergent C(sp^3)−N cross-coupling of racemic alkyl halides with (hetero)aromatic amines represents an ideal means to afford enantioenriched *N*-alkyl (hetero)aromatic amines yet has remained unexplored due to the catalyst poisoning specifically for strong-coordinating heteroaromatic amines. Here, we demonstrate a copper-catalyzed enantioconvergent radical C(sp^3)−N cross-coupling of activated racemic alkyl halides with (hetero)aromatic amines under ambient conditions. The key to success is the judicious selection of appropriate multidentate anionic ligands through readily fine-tuning both electronic and steric properties for the formation of a stable and rigid chelating Cu complex. Thus, this kind of ligand could not only enhance the reducing capability of a copper catalyst to provide an enantioconvergent radical pathway but also avoid the coordination with other coordinating heteroatoms, thereby overcoming catalyst poisoning and/or chiral ligand displacement. This protocol covers a wide range of coupling partners (89 examples for activated racemic secondary/tertiary alkyl bromides/chlorides and (hetero)aromatic amines) with high functional group compatibility. When allied with follow-up transformations, it provides a highly flexible platform to access synthetically useful enantioenriched amine building blocks.



INTRODUCTION

Chiral *N*-alkyl (hetero)aromatic amines featuring an *α*-stereocenter represent key structural elements in natural products, pharmaceuticals, agrochemicals, and functional materials. Moreover, they play essential roles in organic synthesis, for instance, serving as not only important chiral building blocks but also ligands, catalysts, auxiliaries, or resolving reagents for diverse asymmetric transformations (Scheme 1A).[1,2] Consequently, their synthesis has long been recognized as a pre-eminent goal for organic synthesis in both laboratory scales and industrial processes.[1−3]

As a topic of long-standing interest in synthetic chemistry, catalytic enantioconvergent aminations of racemic alkyl electrophiles with (hetero)aromatic amines are an efficient means of preparing chiral *N*-alkyl (hetero)aromatic amines.[4] This is based on the fact that (hetero)aromatic amines are one of the largest groups of commercially available feedstock chemicals, natural products, and drug molecules.[5] Various methods have been successfully developed, including Tsuji−Trost-type allylic aminations of secondary allylic electrophiles,[6] propargylic aminations of secondary propargylic carbonates,[7] (dynamic) kinetic resolution *N*-alkylation by secondary alkyl halides,[8] catalytic asymmetric amination reactions of racemic 3-bromooxindoles,[9] and others. On the other hand, great efforts have recently been dedicated to the development of chiral earth-abundant first-row transition-metal catalysts, which could provide a suitable mechanism for enantioconvergence by converting the racemic alkyl halides to prochiral radicals via a single-electron reduction process.[10,11] In this content, Fu, Peters, and their co-workers have pioneered the copper-catalyzed enantioconvergent radical C(sp^3)−N coupling of racemic alkyl halides with *N*-nucleophiles under visible light irradiation.[12,13] Particularly, they have utilized anilines as the nucleophiles in the enantioconvergent coupling of alkyl halides to access chiral *N*-tertiary-alkyl anilines under photochemical conditions at −78 °C (Scheme 1B).[13d,14] Despite this advance, the development of more catalytic systems is still highly desirable to realize the coupling of diverse alkyl halides and

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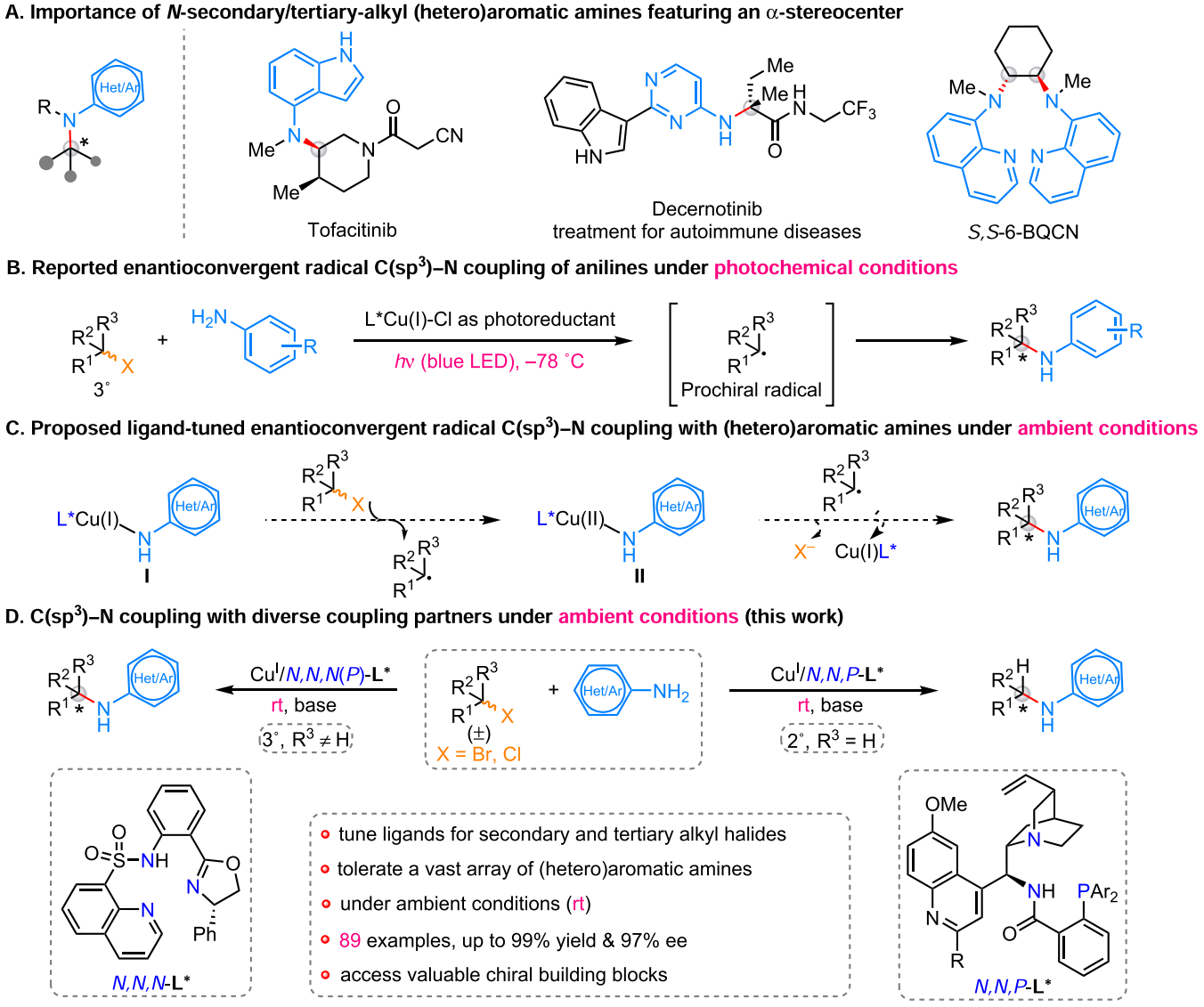
Scheme 1. Design of Copper-Catalyzed Enantioconvergent Radical C(sp^3)–N Cross-Coupling under Ambient Conditions



aromatic amines to access more *N*-alkyl aromatic amines under ambient conditions.

As part of our continuous interest in asymmetric radical reactions,[10e,f,15] we have found that multidentate anionic ligands can remarkably enhance the reducing capability of Cu(I) catalysts for facile radical generation from alkyl halides under ambient conditions. Accordingly, a series of enantioconvergent radical cross-coupling reactions have been established.[15] In particular, we have recently disclosed an enantioconvergent *N*-alkylation of aliphatic amines to provide *α*-chiral aliphatic amines via a mechanistic outer-sphere amine attack of the Cu(III) intermediate.[16] Given the importance of chiral *N*-alkyl (hetero)aromatic amines, we were then intrigued to explore an enantioconvergent radical C(sp^3)–N coupling of (hetero)aromatic amines. Since the acidity of aromatic amines is stronger than that of aliphatic amines, we theorized that the Cu(I)-amino complex with aromatic amines should be easily formed. As such, we assumed that the transformation of aromatic amines might proceed in a mechanistically different strategy from that of aliphatic amines.[16] Thus, the in situ-generated **L***Cu(I)-amido complex would reduce racemic alkyl halides to generate the prochiral alkyl radical. The subsequent enantioselective C(sp^3)–N coupling of the prochiral alkyl radical with the thus-oxidized **L***Cu(II)-amido complex afforded the coupling products (Scheme 1C). We envisaged that the key to success is the selection of chiral ligands for not only enhancing the reducing capability of a copper catalyst to initiate the radical process but also achieving the challenging enantiocontrol over the highly reactive radical species. Herein, we disclose a copper-catalyzed enantioconvergent radical C(sp^3)–N cross-coupling of activated racemic alkyl halides with (hetero)aromatic amines through rationally tuning electronic and steric effects of chiral *N*,*N*,*N*(*P*)-ligands (Scheme 1D). The reaction tolerates a variety of activated secondary/tertiary alkyl bromides and chlorides, as well as aniline derivatives and even strong-coordinating heteroaromatic amines under ambient conditions. Moreover, this strategy provides a highly flexible platform to access a wide array of synthetically useful enantioenriched amine building blocks when allied with follow-up transformations.

RESULTS AND DISCUSSION

Reaction Development. Owing to the importance of morpholine-based amide motif as the diversely transformable

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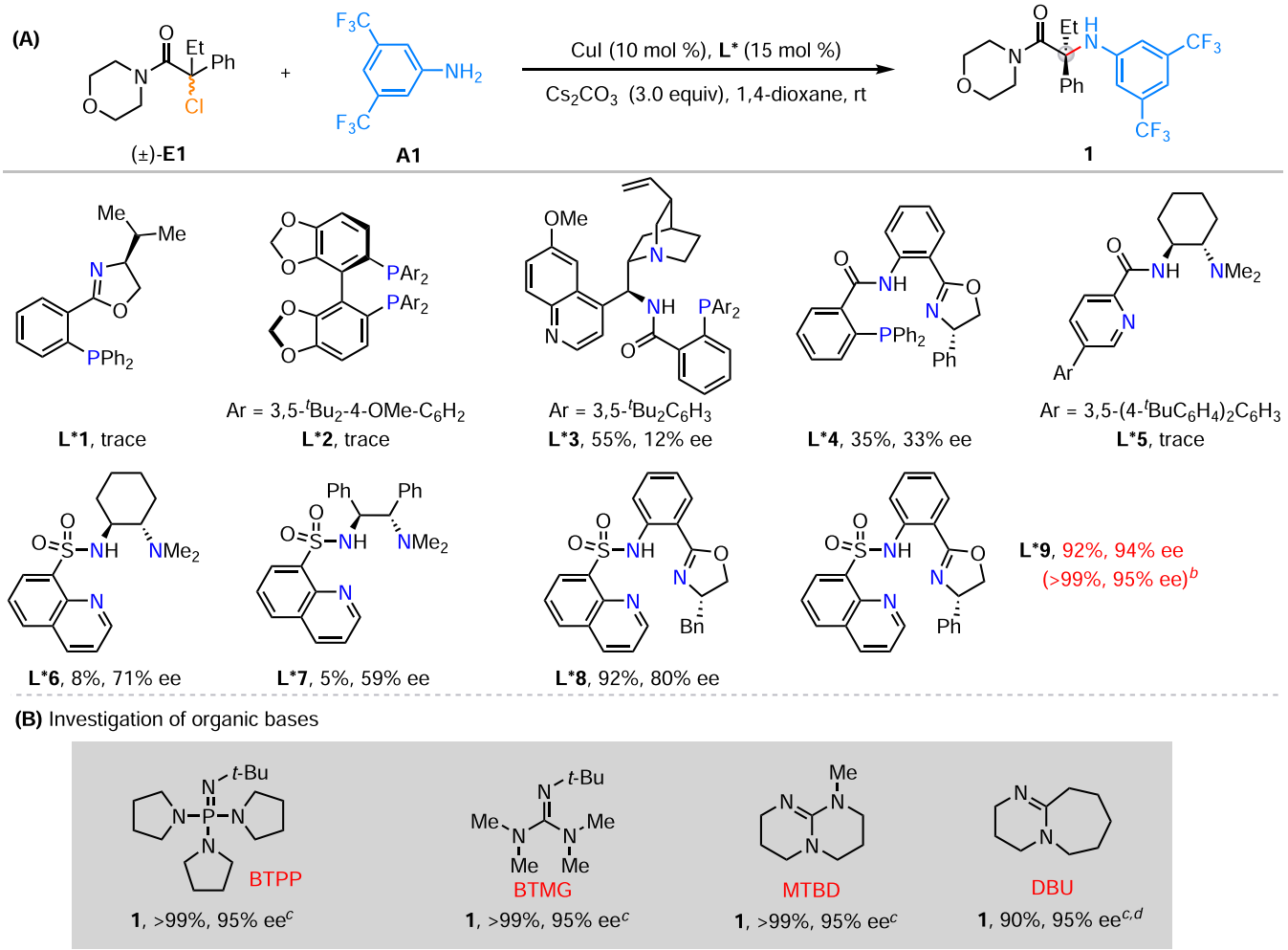
Table 1. Effect of Different Ligands in the Model Reaction and the Optimal Results[a]



[a]Reaction conditions: (±)-**E1** (0.05 mmol), **A1** (0.06 mmol), CuI (10 mol %), **L*** (15 mol %), and Cs_2CO_3 (3.0 equiv) in 1,4-dioxane (1.0 mL) at room temperature (rt) for 72 h under argon; yield of **1** was based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; the ee value was based on HPLC analysis. [b]Reaction conditions: (±)-**E1** (1.2 equiv), **A1** (1.0 equiv), CuI (10 mol %), **L*9** (15 mol %), and Cs_2CO_3 (3.0 equiv) in benzene (1.0 mL) at rt for 72 h. [c]Organic base (3.0 equiv) was used in benzene at rt for 72 h. [d]For 144 h.

functional group, we first selected a racemic tertiary α-chloroamide **E1** bearing a morpholine moiety as the model substrate. To investigate the ligand effect on the proposed enantioconvergent radical process, various types of ligands were exhaustively screened with CuI/Cs_2CO_3 in 1,4-dioxane (Table 1A). Neutral bidentate ligands such as *N,P*-ligand **L*1** and DTBM-SEGPHOS **L*2** failed to initiate the single-electron reduction of **E1** under ambient conditions. In contrast, the use of cinchona-alkaloid-derived/oxazoline-derived tridentate anionic *N,N,P*-ligand **L*3**[15b,17] and **L*4**[15f] could initiate this reaction, respectively, to deliver the desired product **1** in moderate yield, albeit with poor enantioselectivity. It is interestingly found that the ligand **L*4** bearing an oxazolinyl phenylamine moiety delivered better enantioselectivity in comparison with that of **L*3** bearing a tertiary amine moiety. These results are clearly in support of our proposal that multidentate anionic ligands could enhance the reducing capability of Cu(I) catalysts to reduce racemic alkyl halides under ambient conditions. To further improve the reaction efficiency and enantioselectivity, we proceeded to evaluate other types of tridentate anionic ligands. Unfortunately, chiral diamine-derived amide *N,N,N*-ligand **L*5** with a long spreading side arm[15i] failed to competently initiate this reaction. To our surprise, replacing the picolinamide fragment with a quinoline-8-sulfonamide moiety could afford **1** with good enantioselectivity (71% and 59% ee for **L*6** and **L*7**, respectively).[15k] Inspired by these promising observations, we hypothesized that the utility of a new ligand in cooperation with the privileged chiral oxazolinyl phenylamine framework with a quinoline-8-sulfonamide motif could remarkably improve enantioselectivity. To our delight, the newly synthesized oxazoline-derived sulfonamide *N,N,N*-ligand **L*9** not only delivered an obviously enhanced enantioselectivity (94% ee) but also afforded excellent efficiency (92% yield). After further optimization of reaction parameters, including the copper catalysts, the molar ratio of the reactants, reaction temperature, reaction time, solvents, and inorganic bases (Tables S1−S4 in the Supporting Information), we identified the optimal conditions as follows: 1.2 equiv **E1**, 1.0 equiv **A1**, 10 mol % CuI, 15 mol % **L*9**, and 3.0 equiv Cs_2CO_3 in benzene at room temperature for 72 h.[18] Under the optimal conditions, the desired product **1** was obtained in >99% yield with 95% ee (Table 1A).

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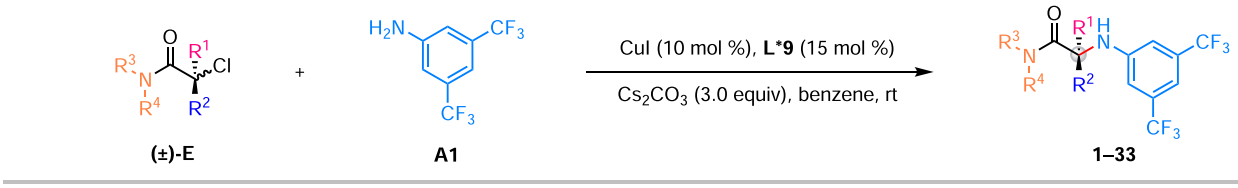
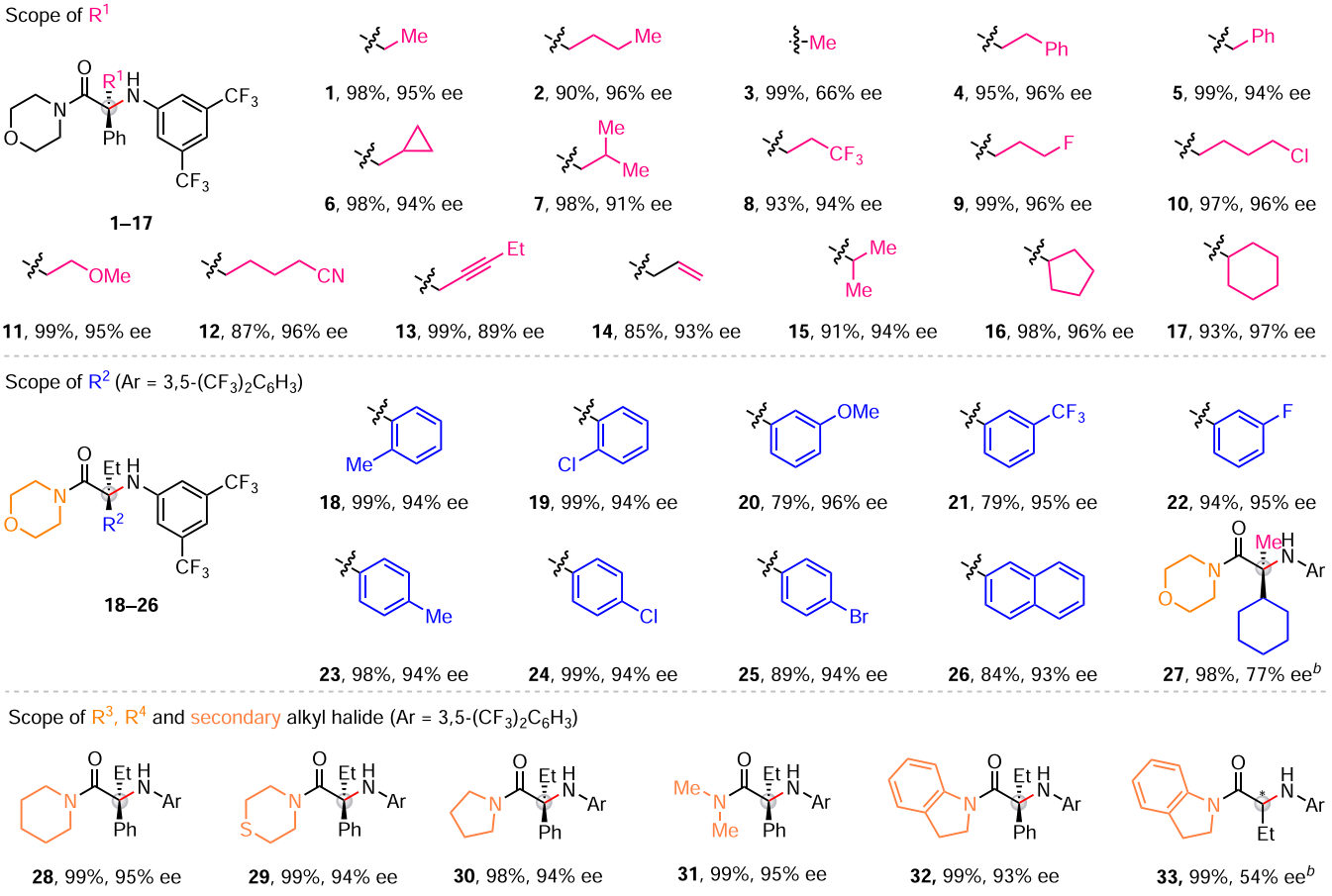
Table 2. Scope of Racemic Tertiary Alkyl Chlorides[a]





[a]Reaction conditions: (±)-**E** (1.2 equiv), **A1** (0.20 mmol), CuI (10 mol %), **L*9** (15 mol %), and Cs_2CO_3 (3.0 equiv) in benzene (4.0 mL) at rt for 72 h under argon; yields were isolated ones; ee values were determined by HPLC analysis. [b]Alkyl bromide was used.

The commercially available organic bases, such as BTPP (*tert*-butylimino-tri(pyrrolidino)phosphorane), BTMG (2-*tert*-butyl-1,1,3,3-tetramethylguanidine), MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene), and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) facilitate the cross-coupling as well to deliver **1** with good yield and ee (Table 1B). Clearly, the current homogeneous C−N cross-coupling approach in combination with other established C−N coupling methods[8b,13d] would have the potential to enable the high-throughput reaction screening settings, continuous flow chemistry, and microfluidic screening platforms.[19]

Scope of Tertiary Alkyl Halides and (Hetero)aromatic Amines. With the optimal reaction conditions in hand, we examined the scope of tertiary α-chloroamides (Table 2). With regard to the α-alkyl substituent (R^1 group in the substrate), many substrates bearing simple unfunctionalized aliphatic side chains or those functionalized with phenyl, cyclopropyl, trifluoromethyl, fluoro, chloro, ether, nitrile, alkynyl, and alkenyl groups were all well accommodated in this process to deliver **1**−**14** in 85−99% yields with 66−96% ee. Importantly, it was found that steric hindrance around the chiral center bearing *iso*-propyl, cyclopentyl, and cyclohexyl groups did not greatly affect the reaction efficiency and enantioselectivity to provide **15**−**17**. Moreover, a panel of α-phenyl rings with electron-donating or -withdrawing groups at different positions as well as an α-naphthyl ring were compatible with the reaction conditions to afford **18**−**26** with 93−96% ee. In addition, an α,α-dialkyl-substituted bromide underwent such a coupling reaction as well to deliver **27** in 98% yield with 77% ee. Besides, a variety of tertiary amides bearing piperidine, thiomorpholine, pyrrolidine, dimethylamine, and indoline were also suitable electrophilic cross-coupling partners (**28**−**32**).[20] However, secondary halo-amide only afforded the desired coupling product **33** with moderate ee. The absolute configurations of **1**, **5**, **13**, **31**, and **32** (Figures S2−S6 in the Supporting Information) were determined to be *S* by X-ray crystallographic analysis, and all other compounds were assigned by analogy accordingly.

We next evaluated the scope of aromatic amines (Table 3). A wide range of strongly electron-withdrawing substituents (F, NO_2, CN, CF_3, CO_2Me, SO_2Me) at different positions of the phenyl rings were tolerated to provide **34**−**45** in 91−99%

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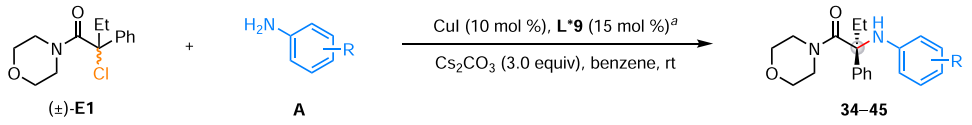
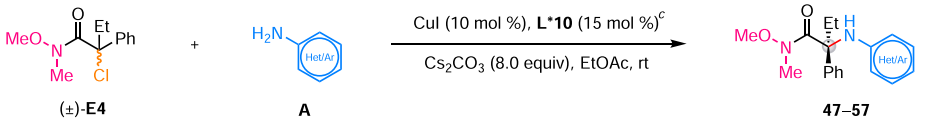
Table 3. Scope of Aromatic Amines



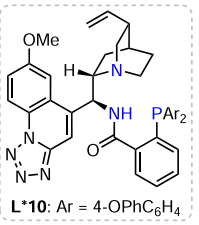
(±)-**E1** + **A** → **34–45**

34, 95%, 90% ee[b] | **35**, 99%, 87% ee[b] | **36**, 98%, 94% ee | **37**, 97%, 91% ee | **38**, 97%, 88% ee | **39**, 99%, 87% ee

40, 94%, 87% ee | **41**, 99%, 82% ee | **42**, 91%, 94% ee[b] | **43**, 98%, 88% ee | **44**, 99%, 88% ee[b] | **45**, 96%, 88% ee[b] | **46**, 0%



(±)-**E4** + **A** → **47–57**



Scope of amines

47, 99%, 81% ee (96%, 16% ee)[a] | **48**, 93%, 85% ee (98%, 8% ee)[a] | **49**, 80%, 78% ee (92%, 27% ee)[a] | **50**, 81%, 84% ee (96%, 12% ee)[a] | **51**, 93%, 74% ee (80%, 39% ee)[a] | **52**, 92%, 76% ee | **53**, 88%, 69% ee

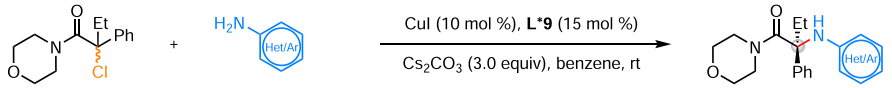
54, 64%, 81% ee | **55**, 74%, 80% ee | **56**, 63%, 68% ee (99%, 68% ee)[a] | **57**, 96%, 83% ee

Scope of racemic tertiary alkyl chlorides (Ar = 4-BrC6H4)

58, 89%, 84% ee[c] | **59**, 88%, 83% ee[c] | **60**, 97%, 80% ee[c]

[a]Reaction conditions: (±)-**E1** (1.2 equiv), **A** (0.20 mmol), CuI (10 mol %), **L*9** (15 mol %), and Cs_2CO_3 (3.0 equiv) in benzene (4.0 mL) at rt for 72 h under argon; yields were isolated ones; ee values were determined by HPLC analysis. [b]In THF (4.0 mL) at 10 °C. [c]**L*10** (15 mol %) and Cs_2CO_3 (8.0 equiv) in EtOAc (4.0 mL).

Table 4. Scope of Heteroaromatic Amines[a]



(±)-**E1** + **A** → **61–77**

61, 64%, 87% ee | **62**, 98%, 92% ee | **63**, 79%, 93% ee | **64**, 85%, 92% ee | **65**, 96%, 91% ee | **66**, 99%, 95% ee | **67**, 99%, 94% ee | **68**, 91%, 94% ee | **69**, 93%, 94% ee

70, 99%, 92% ee | **71**, 45%, 89% ee | **72**, 81%, 91% ee | **73**, 99%, 89% ee[b] | **74**, 88%, 82% ee | **75**, 96%, 74% ee | **76**, 70%, 83% ee | **77**, 91%, 80% ee

[a]Reaction conditions: (±)-**E1** (1.2 equiv), **A** (0.20 mmol), CuI (10 mol %), **L*9** (15 mol %), and Cs_2CO_3 (3.0 equiv) in benzene (4.0 mL) at rt for 72 h under argon; yields were isolated ones; ee values were determined by HPLC analysis. [b]In THF (4.0 mL) at 10 °C.

yields with 82−94% ee. Notably, the reaction was sensitive to the steric effect at the *ortho* position of aromatic amines. While the less sterically crowded methoxyl group (**38** and **40**) was tolerated, the bulkier methyl substituents (**46**) were not applicable. Moreover, aromatic amines with slightly electron-withdrawing and electron-donating groups led to poor ee (16−39% ee). To further extend the scope of aromatic amines, we rescreened different types of ligands and reoptimized the reaction conditions (see Tables S6−S8 in the Supporting Information). We identified that the cinchona-alkaloid-derived *N,N,P*-ligand **L*10** provided the best reactivity and enantioselectivity (99% yield and 81% ee for **47**) with 8.0 equiv Cs_2CO_3 as the base for the reaction of **E34** and 4-bromoaniline. Aniline and a series of aniline derivatives with slightly electron-withdrawing/donating groups at different positions were viable substrates to afford **47−60** with good

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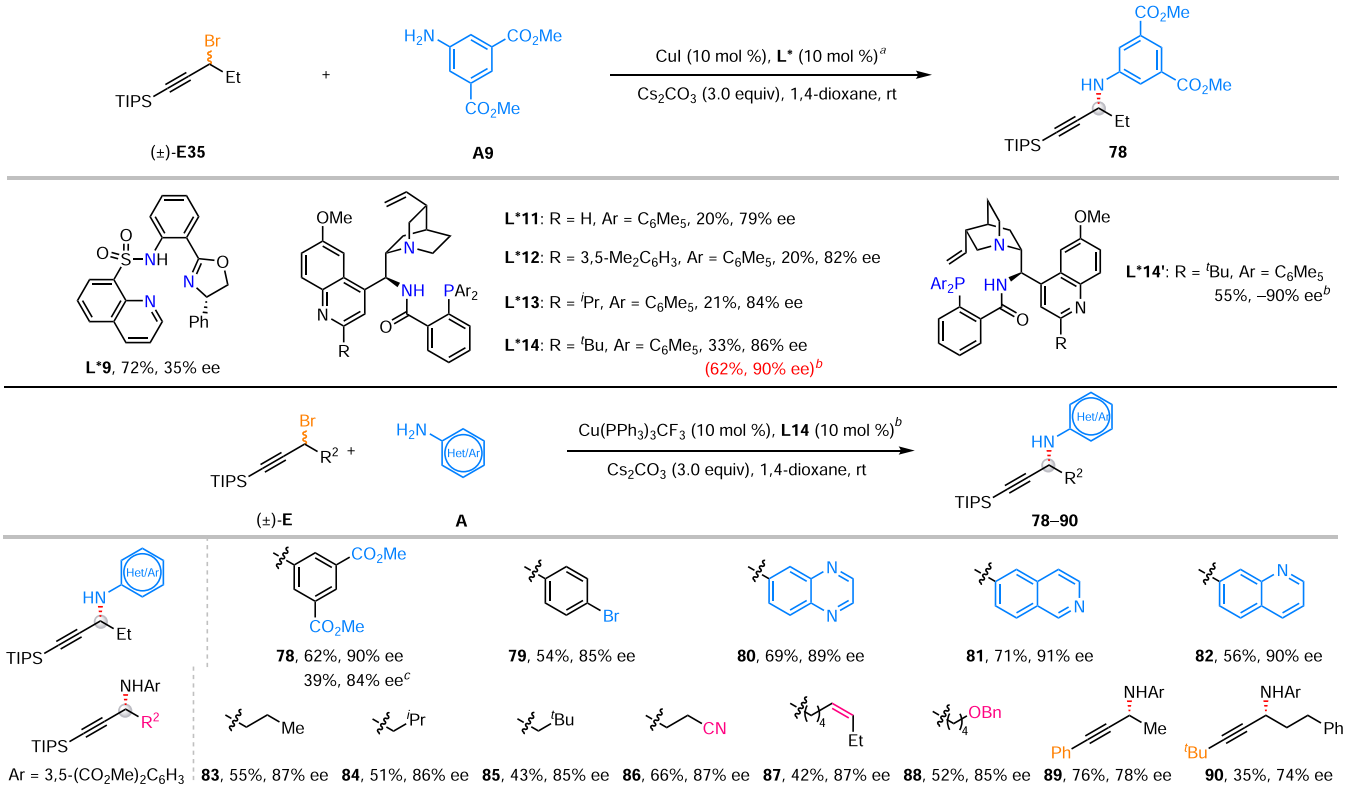
Table 5. Reaction Development and Scope of Secondary Propargyl Bromides and (Hetero)aromatic Amines



[a]Reaction conditions: (±)-**E35** (0.05 mmol), **A9** (1.5 equiv), CuI (10 mol %), **L*** (10 mol %), and Cs_2CO_3 (3.0 equiv) in 1,4-dioxane (0.5 mL) at rt for 48 h under argon; yield of **78** was based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; the ee value was based on HPLC analysis. [b]Reaction conditions: (±)-**E** (0.1 mmol), **A** (1.5 equiv), $Cu(PPh_3)_3CF_3$ (10 mol %), **L*14** (10 mol %), and Cs_2CO_3 (3.0 equiv) in 1,4-dioxane (1.0 mL) at room temperature for 120 h under argon; isolated yields. [c]Alkyl chloride was used.

enantioselectivity, which is currently under further optimization in our laboratory. The absolute configuration of **53** (Figure S7 in the Supporting Information) was determined to be *S* by X-ray crystallographic analysis, and all other compounds were assigned by analogy accordingly. These results emphasize the high diversity of aromatic amines. Unfortunately, secondary aromatic amines were not applicable probably due to the steric congestion in the C(sp^3)–N formation process, indicating the sensitivity of the strategy toward the steric effect of aromatic amines (see Figure S1 in the Supporting Information).

To further extend the substrate scope of this process, the reaction was evaluated with respect to the heteroaromatic amines owing to the importance of the obtained enantioenriched chiral *N*-alkyl heteroaromatic amines in pharmaceutical and catalysis fields. Compared with that of aromatic amines, the coupling of such nucleophiles remains more challenging due to the strong chelating effect of heteroaromatic amines with transition metals, therefore leading to catalyst poisoning and/or chiral ligand displacement.[21] To our delight, a wide range of heteroaromatic amines all worked well to give **61**–**77** in 45–99% yields with 74–95% ee under the standard conditions in the presence of **L*9** (Table 4). The success might be attributed to the formation of stable and rigid anionic sulfoamido-chelating Cu complex with **L*9** during the catalytic course due to a strong chelating effect (such complex **CatA** as shown in Scheme 3A). This stable coordination would avoid the additional coordination with other coordinating heteroatoms at the heteroaromatic ring, thereby overcoming catalyst poisoning and/or chiral ligand displacement. Accordingly, a gamut of medicinally relevant heterocycles such as pyridines (**61**–**63**), pyrazines (**64**–**66**), pyrimidines (**67**–**71**), quinoxalines (**72** and **73**), (iso)quinolines (**74** and **75**), thiazole (**76**), and thiophene (**77**) were well tolerated. Noteworthy is that the enantioenriched *N*-tertiary-alkyl pyrimidine **71**, a moiety existing in decernotinib (Scheme 1A), could be easily constructed by coupling the corresponding amine with electrophile **E1**. All of these results highlight the potential of our methodology in the process of further drug optimization.

Scope of Secondary Alkyl Halides and (Hetero)-aromatic Amines. To further demonstrate the generality of this process, we switched our attention to secondary propargyl halides, considering that the alkynyl group would be readily converted to many other functional groups.[7] Unfortunately, **L*9** led to poor enantioselectivity (35% ee for **78**) from the corresponding propargyl bromide **E35** and 3,5-diester-aniline **A9** under the standard conditions (Table 5). After screening other types of anionic ligands **L*11**–**L*14** and systematic optimization of reaction parameters (see Tables S9 and S10 in the Supporting Information), we found that a modified cinchona-alkaloid-derived *N*,*N*,*P*-ligand **L*14** provided the best efficiency and enantioselectivity (62% yield and 90% ee). Replacing **L*14** with its pseudoenantiomer **L*14′** gave rise to the enantiomer of (*S*)-**78** in 55% yield with 90% ee under otherwise identical conditions. The corresponding propargyl chloride only afforded **78** with lower yield and ee under the standard conditions. As for the substrate scope, many amines worked well to give **78**–**82** in good yields with good to

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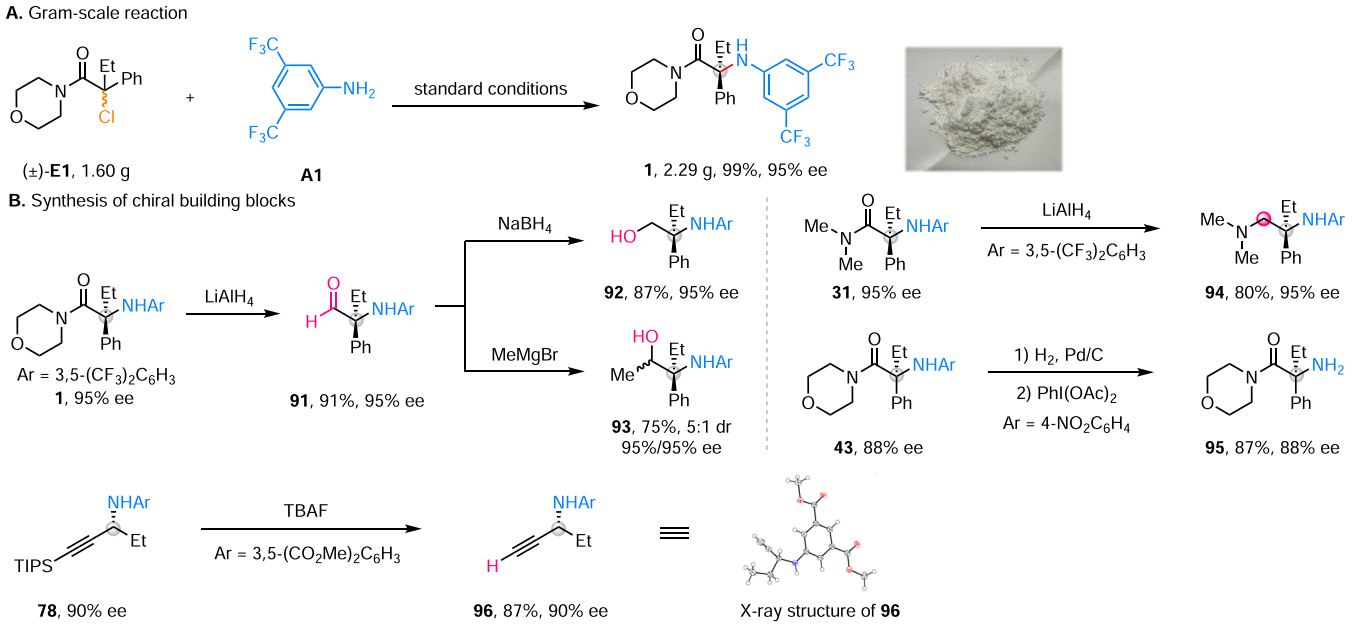
Scheme 2. Synthetic Utility



excellent enantioselectivity. With respect to the alkyl side chain of propargyl bromides, simple unfunctionalized linear and branched alkyl chains (**83**−**85**) and functionalized alkyl chains (**86**−**88**), such as nitrile, alkene, and ether, were tolerated. In addition to the triisopropylsilyl (TIPS) group, the aryl and alkyl substituents on the alkynyl moiety were tolerated as well to give the desired products **89** and **90**.

Synthetic Utility. To demonstrate the practicality of this methodology, a gram-scale reaction was first carried out, and the coupling product **1** was readily obtained with high efficiency and high enantioselectivity (Scheme 2A). It is well-known that α-aminoamides with an α-chiral center are important not only as endpoints but also as key intermediates in the synthesis of valuable chiral building blocks. To demonstrate the synthetic utility of the obtained enantioenriched α-aminoamides, facile transformations of morpholine-based amide motifs were performed to convert them to other chiral scaffolds, such as amino aldehyde **91**, amino alcohols **92** and **93**, and diamine **94**. In addition, the conversion of the aromatic amine motif to α-chiral primary amine **95** was achieved using a sequential reduction and oxidation (Scheme 2B). More importantly, product **78** underwent the deprotection smoothly to generate propargylamine **96** bearing a terminal alkyne (the absolute configuration was determined to be *R* by X-ray crystallographic analysis, and the propargyl products **78**−**90** were assigned by analogy accordingly), which could serve as precursors for alkenes, alkanes, etc.[7] Noteworthy is that no obvious loss of enantiopurity was observed during all of these transformations, thus demonstrating the practicality of this method as a robust complementary approach to reported strategies.[6−8,13d]

Mechanistic Studies. A series of control experiments were conducted to gain insights into the reaction mechanism. The complex **CatA** was easily obtained by mixing **L*9** with $CuBr_2$, on which the X-ray structural analysis clearly indicated an anionic tridentate coordination mode of the ligand (Scheme 3A and Figure S9 in the Supporting Information). It was observed that complex **CatA** and the CuI/**L*9** catalyst gave **1** with similar results under the otherwise identical reaction conditions (Scheme 3B). Additionally, the observed linear relationship between the enantiopurities of the products and the corresponding ligands indicates the probable involvement of one single chiral ligand in the enantioselectivity-determining transition states (Scheme 3C). These results supported a monomeric copper species tridentately coordinated by the *N*,*N*,*N*-ligand as the active catalyst in this process.

Second, no apparent enantioenrichment of the recovered **E1** was observed in the reactions, ruling out a possible kinetic resolution of **E1** (Scheme 3D). The observed product ee values at different time intervals remained nearly constant, supporting the involvement of a uniform mechanism throughout the reaction course (Scheme 3D). In addition, we observed an induction period in the time course experiment (Scheme 3D). Interestingly, the induction period could be suppressed by premixing CuI, **L*9**, base, and amine **A1** at 50 °C (Scheme 3E, gray spots). It was probable that chiral ligand-chelated **L***Cu(I)-amido complex was the active catalytic species, the formation of which was possibly a slow step. We were also surprised to observe that **CatA** showed a different kinetic profile: no induction period and slow reaction rate (Scheme 3E, blue spots). We theorized that the copper(II) complex **CatA** reacted very quickly with amine **A1** to form a resting-state **L***Cu(II)-amido complex,[22] but only part of the resting-state Cu(II) complex was reduced to the active **L***Cu(I)-amido complex by amine/base.[23] The rapid formation of the **L***Cu-amido complex with **CatA** helped to suppress the induction period, while the partial conversion to active catalyst accounted for the slow reaction rate for **CatA**.

Third, the reaction of radical clock substrates **E44** and **E45** gave rise to the corresponding cyclization products **97** and **99**, respectively, under the typical conditions in addition to the cross-coupling products **98** and **100**, arguing for the formation of alkyl radical intermediates (Scheme 3F). The electron paramagnetic resonance (EPR) experiment revealed that the persistent nitroxyl radical **101** trapped by an oxygen-centered radical, which would be isomerized from in situ-generated tertiary carbon-centered radical, was formed in the presence of 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) (Scheme 3G).

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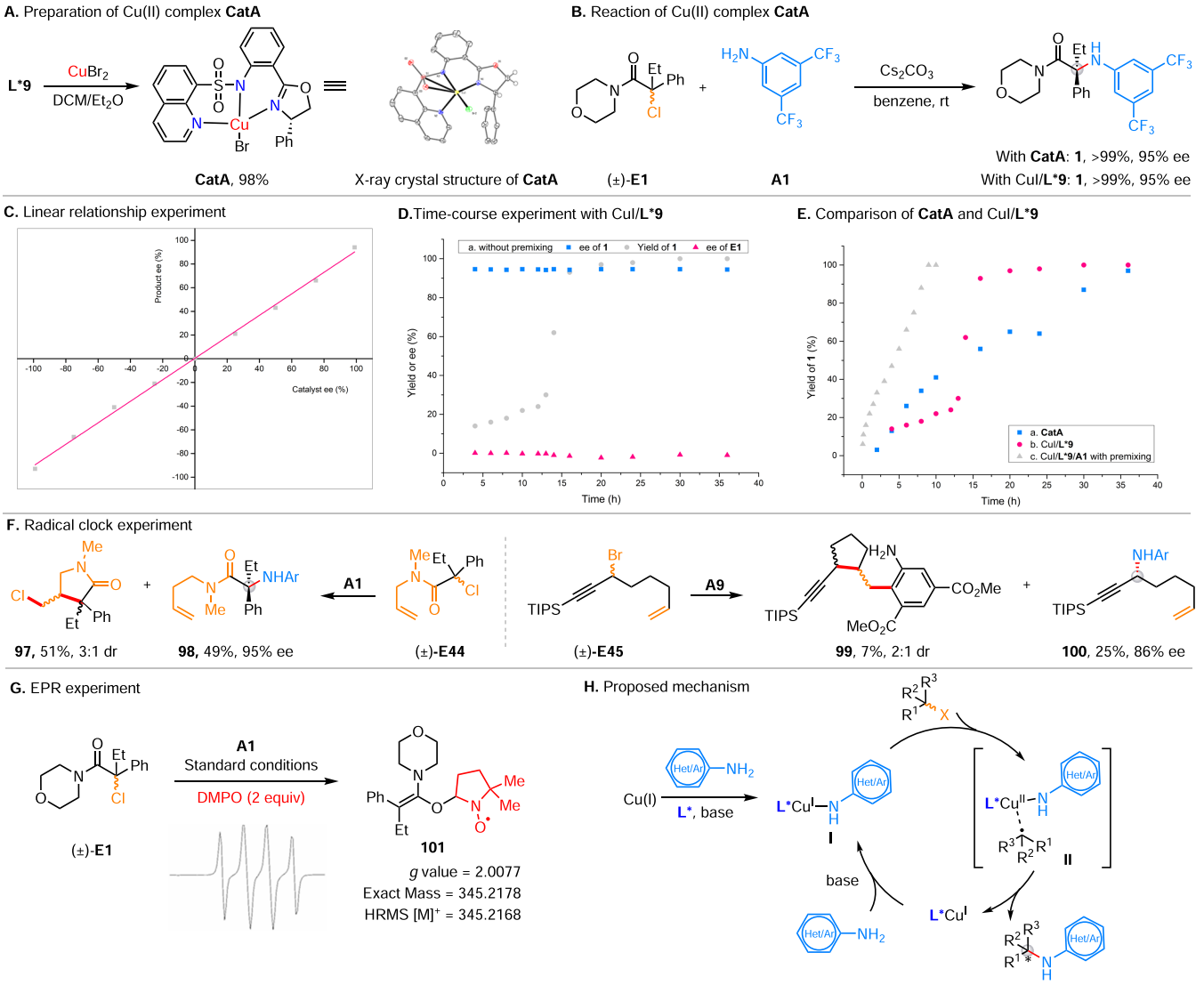
Scheme 3. Mechanistic Investigation and Mechanistic Proposal



These observations together favor the formation of alkyl radical species from alkyl halides via a single-electron reduction process with the **L***Cu(I)-amido complex. Of particular note, the strategy was mechanistically distinct from our reported *N*-alkylation of aliphatic amines, which proceeds via a direct outer-sphere amine attack of the Cu(III) intermediate.[16]

On the basis of the abovementioned mechanistic results, we propose a possible mechanism (Schemes 3H and 1C). The reaction starts with the formation of **L***Cu^{I}-amido complex **I** through facile deprotonation of aryl amine in the presence of a base. Although there is an induction period, it can be suppressed by premixing Cu, **L***, base, and amine. Subsequently, complex **I** would reduce racemic alkyl halides via a single-electron reduction process to generate the prochiral alkyl radical **II**. Next, enantioselective C(sp^3)−N bond coupling via either a Cu(III) intermediate or radical addition to the Cu−N bond[15] would give rise to the enantioenriched product and **L***Cu^{I} complex, which would undergo ligand exchange with amine to regenerate **I** for the next catalytic cycle. Further experimental and computational studies are underway in our laboratory to delineate the mechanistic details.

CONCLUSIONS

In summary, we have established a copper-catalyzed enantioconvergent radical C(sp^3)−N cross-coupling of activated racemic alkyl halides with (hetero)aromatic amines under ambient conditions. This coupling exhibits a broad scope (89 examples) in both reaction partners, covering a variety of activated secondary/tertiary alkyl bromides/chlorides and (hetero)aromatic amines. Moreover, this strategy provides a highly flexible platform to access diverse synthetically useful enantioenriched amine building blocks when allied with follow-up transformations. The key to success is the judicious selection of appropriate multidentate anionic ligands through rationally tuning electronic and steric effects. Thus, this kind of ligand could not only enhance the reducing capability of a copper catalyst to favor an enantioconvergent radical pathway but also avoid the additional coordination with other coordinating heteroatoms at the heteroaromatic amines, thereby overcoming catalyst poisoning and/or chiral ligand displacement. Further efforts will focus on the development of the enantioconvergent radical carbon−heteroatom cross-coupling of alkyl halides with more heteroatomic nucleophiles under ambient conditions.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c02387.

Experimental procedures; characterization of compounds; reaction condition optimization; and crystallographic data of **1**, **5**, **13**, **31**, **32**, **53**, **96**, and **CatA** (PDF)

Accession Codes

CCDC 2245320−2245324, 2246040, and 2261401−2261402 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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