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Copper-Catalyzed Enantioconvergent Radical *N*-Alkylation of Diverse (Hetero)aromatic Amines

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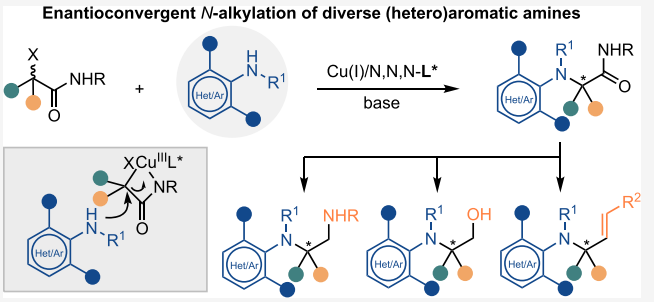
ABSTRACT: The 3d transition metal-catalyzed enantioconvergent radical cross-coupling provides a powerful tool for chiral molecule synthesis. In the classic mechanism, the bond formation relies on the interaction between nucleophile-sequestered metal complexes and radicals, limiting the nucleophile scope to sterically uncongested ones. The coupling of sterically congested nucleophiles poses a significant challenge due to difficulties in transmetalation, restricting the reaction generality. Here, we describe a probable outer-sphere nucleophilic attack mechanism that circumvents the challenging transmetalation associated with sterically congested nucleophiles. This strategy enables a general copper-catalyzed enantioconvergent radical *N*-alkylation of aromatic amines with secondary/tertiary alkyl halides and exhibits catalyst-controlled stereoselectivity. It accommodates diverse aromatic amines, especially bulky secondary and primary ones to deliver value-added chiral amines (>110 examples). It is expected to inspire the coupling of more nucleophiles, particularly challenging sterically congested ones, and accelerate reaction generality.



INTRODUCTION

Transition metal-catalyzed cross-coupling reactions have revolutionized the way chemists construct complex molecules from simple feedstocks on both benchtop and industrial scales.[1] Compared with the blooming development in cross-coupling of aryl/alkenyl halides to form sp^2-hybridized carbon−carbon/heteroatom bonds, the coupling of alkyl halides to create more commonly existing sp^3-hybridized carbon centers is less recognized.[2] This lagged development stems from a cognition that the coupling with alkyl halides suffers from relatively difficult oxidative addition and β-H elimination of alkyl metal complexes.[2] Particularly, strategies are even less focused on enantioconvergent cross-coupling of racemic alkyl halides to generate chiral three-dimensional molecules of importance in drug discovery and material science (Scheme 1A). In this aspect, 3d transition metal catalysis provides an ideal tool for enantioconvergence by converting a pair of racemic alkyl halides into the same prochiral alkyl radical via a single electron transfer (SET) process.[3] Although great efforts have been devoted to this field in the past two decades, extension to a general strategy is still a long-standing goal due to the restriction on the scope of coupling reagents. Recent advances in catalyst design have expanded the electrophile scope from well-established secondary alkyl halides to sterically hindered tertiary ones.[4] Meanwhile, the development of copper catalysis has extended the scope of nucleophiles from carbon[3c,5] to heteroatom ones,[4a,6] rendering the cross-coupling more robust in asymmetric synthesis. In broad strokes, three fundamental steps are involved in the classic catalytic cycle: (i) transmetalation (ligand exchange) to afford a nucleophile-sequestered Nu−M^n**L*** complex, (ii) SET to afford a prochiral alkyl radical, and (iii) the interaction of Nu−M^{n+1}**L*** **I** and radical to form a new chiral bond (Scheme 1B). Conceptually, the scope of nucleophiles is predominantly restricted to sterically uncongested ones since the steric encumbrance could significantly affect the transmetalation step under the classic catalytic cycle.[6b,7] Therefore, the design of a fundamentally distinct catalytic cycle to expand the scope of nucleophiles and reinforce the arsenal of cross-coupling is highly desirable.

Apart from the Nu−M**L*** complex-involved bond formation (Scheme 1B), outer-sphere nucleophilic attack enables another mechanistic paradigm in which the nucleophile directly attacks the alkyl ligand of transition metal complex **II** (Scheme 1C).[8] This strategy would probably overcome the inherently limited nucleophile scope in the classic mechanism and allow the coupling of diverse nucleophiles as demonstrated in asym-

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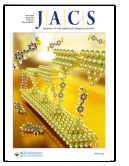

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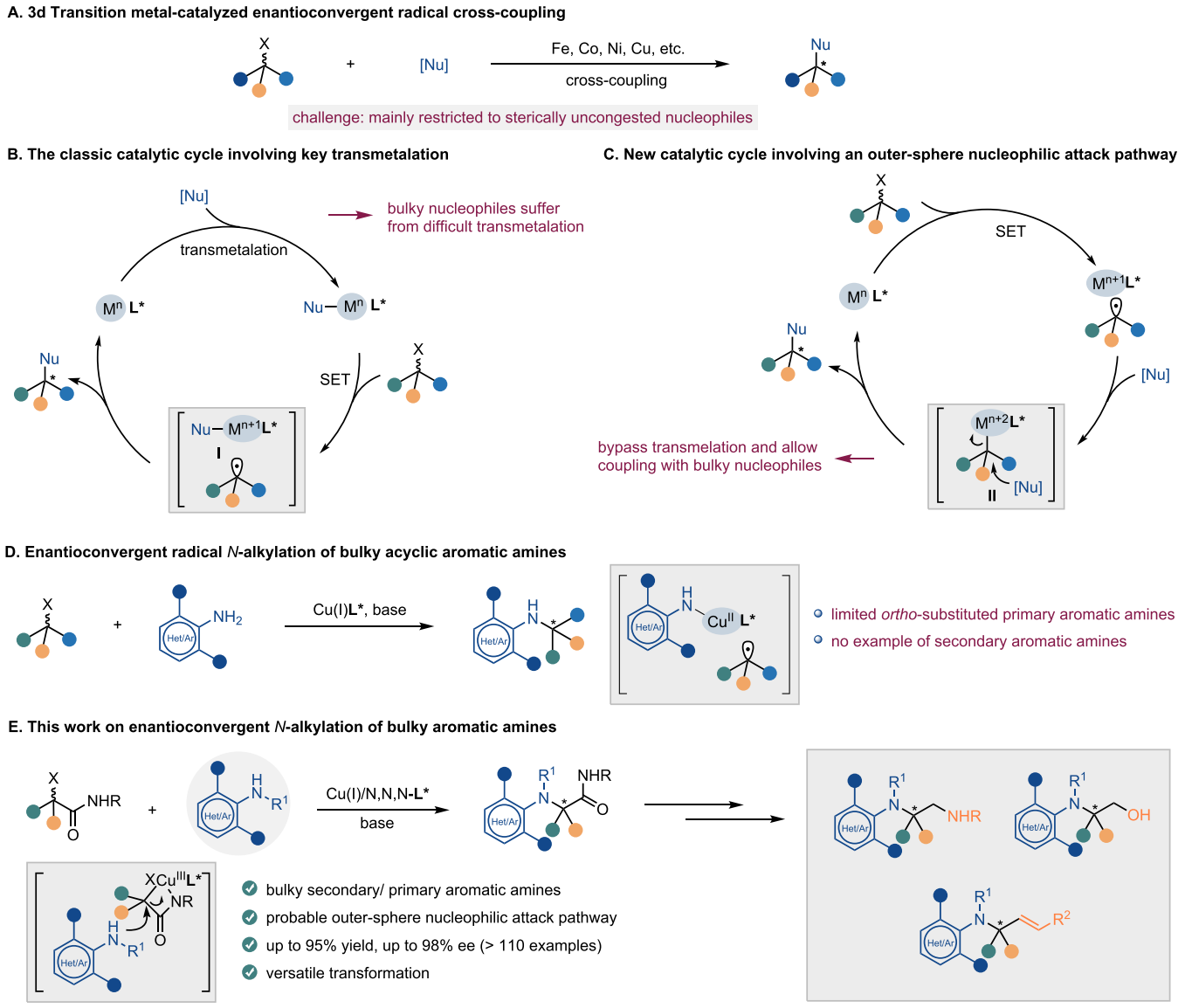
Scheme 1. Development of Enantioconvergent Radical *N*-Alkylation of Aromatic Amines via Outer-Sphere Nucleophilic Attack



metric allylic substitution.[8] Specifically, the alternative mechanism paradigm would open a new avenue for the coupling of challenging sterically congested nucleophiles. In this sense, we anticipate that the reaction could be initiated by the SET process of alkyl halides with **L***M^n in the absence of transmetalation, followed by a radical rebound to afford complex **II** (Scheme 1C). Nonetheless, the identification of an appropriate transition metal catalyst system is essential for the SET process since the reducing capability of transition metal gets much weaker without transmetalation. As our continuous interest in copper/anionic ligand-catalyzed enantioconvergent radical cross-coupling,[3b,4d,f,5e,6a,c] we have recently coupled racemic alkyl halides with aliphatic amines by using the outer-sphere nucleophilic attack model.[9] We surmise that the combination of the strongly reducing copper catalyst and the bond formation model could provide a uniform platform for more enantioconvergent radical cross-coupling reactions. Particularly, it could offer an opportunity for the coupling of challenging sterically congested nucleophiles, thus largely enriching the nucleophile scope in this field.

Chiral aromatic amines are valuable building blocks in organic synthesis and important structural motifs in natural products, pharmaceuticals, and agrochemicals (Figure S1 in the Supporting Information).[10] The asymmetric transformation of aromatic amines offers a straightforward approach to accessing chiral aromatic amines.[8b,d,11] In this context, Fu and Peters have pioneered the enantioconvergent radical *N*-alkylation of *N*-heterocycles and primary aromatic amines with readily available racemic alkyl halides.[4a,c,6d,e] Very recently, our group has also realized an enantioconvergent radical *N*-alkylation of primary aromatic amines.[6c] Despite these advances, the *N*-alkylation of bulky primary aromatic amines (with *ortho* substitution) has only met with limited success.[6e] Moreover, the *N*-alkylation of bulky acyclic secondary aromatic amines has not been disclosed (Scheme 1D). In particular, we and others have shown that the classic mechanism is unfeasible for the coupling of bulky secondary aromatic amines in recent studies.[6c,12] As such, we wondered whether the above-mentioned pathway could realize the coupling of aromatic amines, particularly diverse bulky ones, by employing the

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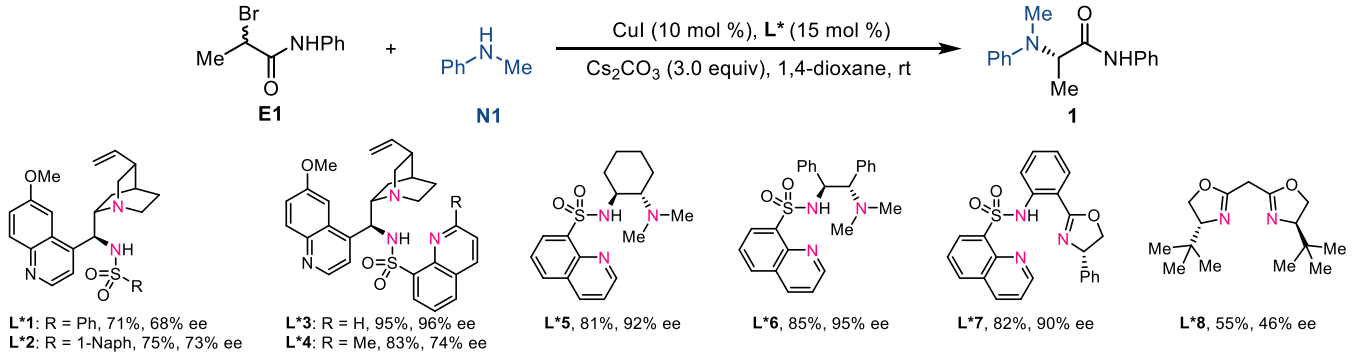
Table 1. Ligand Effect in the Model Reaction[a]



[a]Reaction conditions: racemic alkyl bromide **E1** (0.075 mmol, 1.5 equiv), aromatic amine **N1** (0.050 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 3 d (days) under argon; yield of **1** is based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; Ee values were based on chiral high-performance liquid chromatography (HPLC) analysis.

unique outer-sphere nucleophilic attack (Scheme 1C). However, the *N*-alkylation of aromatic amines was more challenging compared with the aliphatic ones because aromatic amines, particularly bulky ones, possess much weaker nucleophilicity than aliphatic ones.[9] The weak nucleophilicity might retard key C−N bond formation via the outer-sphere nucleophilic attack pathway. Here, we demonstrate a general and powerful copper/chiral anionic *N,N,N*-ligand-catalyzed enantioconvergent radical *N*-alkylation of aromatic amines with racemic alkyl halides via outer-sphere nucleophilic attack (Scheme 1E). This strategy provides a significant expansion in the nucleophile scope, enabling the successful coupling of various (hetero)aromatic amines with different electronic and steric properties. Especially, the current approach could couple the challenging bulky *ortho*-substituted or 2,6-disubstituted primary aromatic amines and even secondary acyclic ones that have not been disclosed to access higher-order tertiary aromatic amines. The scope of electrophile covers not only secondary alkyl halides but also sterically hindered tertiary ones, thus allowing the easy accommodation of both sterically congested coupling reagents and showing an important complementary strategy to the existing radical C−N formation protocols.[4c,6c,f] The catalytic system showed a strong catalyst control that can entirely override chiral substrate control. The remarkably broad scope (>110 examples) and functional group tolerance ensure the reaction generality of the enantioconvergent *N*-alkylation reactions. More importantly, this strategy provides expedient access to a wide range of synthetically valuable chiral amine building blocks when allied with follow-up manipulation of the amide moiety. The mechanistic study reveals that the C−N formation probably proceeds via an outer-sphere attack of the Cu complex by aromatic amines. We expect that the catalytic system would also provide a general strategy to enable the coupling of other sterically congested nucleophiles and further strengthen the generality of enantioconvergent cross-coupling.

RESULTS AND DISCUSSION

Reaction Development. Considering that acyclic secondary aromatic amines have not been used in the enantioconvergent radical *N*-alkylation to access valuable high-order tertiary chiral amines, we first chose *N*-methylaniline **N1** as the nucleophile. We investigated the *N*-alkylation of **N1** with racemic α-carbonyl alkyl chloride, which performed the best in our previous work.[9] A preliminary result revealed that the conversion of 2-chloro-*N*-phenylpropanamide **E1′** is low in the presence of CuI, **L*1**, and Cs_2CO_3 in 1,4-dioxane (Table S1 in the Supporting Information). We then switched to more reactive 2-bromo-*N*-phenylpropanamide **E1** as the electrophile, and the yield of *N*-alkylation product **1** was greatly enhanced to 71% with a similar ee (68%) even at room temperature (rt) (Table 1). Replacement of the phenyl group with a 1-naphthyl group (**L*2**) did not significantly improve the efficiency and enantioselectivity. We speculated that tridentate *N,N,N*-ligands could enhance the reducing capability of copper catalyst, which would be beneficial to the reaction efficiency. We then investigated the performance of cinchona alkaloid-derived tridentate anionic *N,N,N*-ligand **L*3**[9,13] and found that the efficiency and enantioselectivity of **1** were substantially enhanced to 95 and 96%, respectively. Installation of a methyl group at the *ortho* position of the binding quinoline moiety (**L*4**) resulted in a diminished yield and ee, indicating that the binding affinity of the quinoline moiety of **L*4** is probably weaker than that of **L*3**. The comparison of ligands **L*1**−**L*4** suggested that a strong binding tridentate ligand is vital to the reaction efficiency and enantioselectivity (Table 1). The pivotal role of the tridentate anionic *N,N,N*-ligand was also supported by changing the chiral skeleton from cinchona alkaloid to cyclohexyl- (**L*5**) and 1,2-diphenyl ethyl diamine (**L*6**) or even oxazoline (**L*7**): all of the reactions with **L*5**−**L*7** gave rise to **1** in good yields with excellent ee. However, the bisoxazoline ligand[6e] **L*8**, the optimal ligand in Fu's *N*-alkylation of primary aromatic amines, generated **1** with only moderate yield and ee. Further investigation of the other reaction parameters (Tables S2−S4 in the Supporting Information) led us to identify the optimal conditions as follows: the reaction of **N1** and **E1** (1.5 equiv) in the presence of CuI (10 mol %), **L*3** (15 mol %), and Cs_2CO_3 (3.0 equiv) in 1,4-dioxane at rt for 3 days under argon gave rise to **1** in 95% yield with 96% ee (Table 1).

Scope of (Hetero)aromatic Amines. Having established the optimal conditions, we evaluated the generality of this enantioconvergent *N*-alkylation (Table 2). With regard to the scope of aromatic amines, a wide array of acyclic secondary aromatic amines with alkyl (**1**−**7**), phenyl (**8**), alkenyl (**9**), alkynyl (**10**), ether (**11**), and ester (**12**) groups on the aliphatic chain of amines were well compatible with the reaction to afford chiral tertiary amines in good yields with excellent ee

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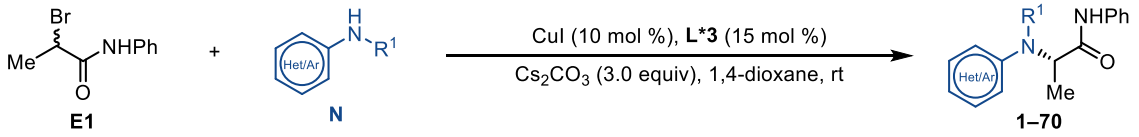
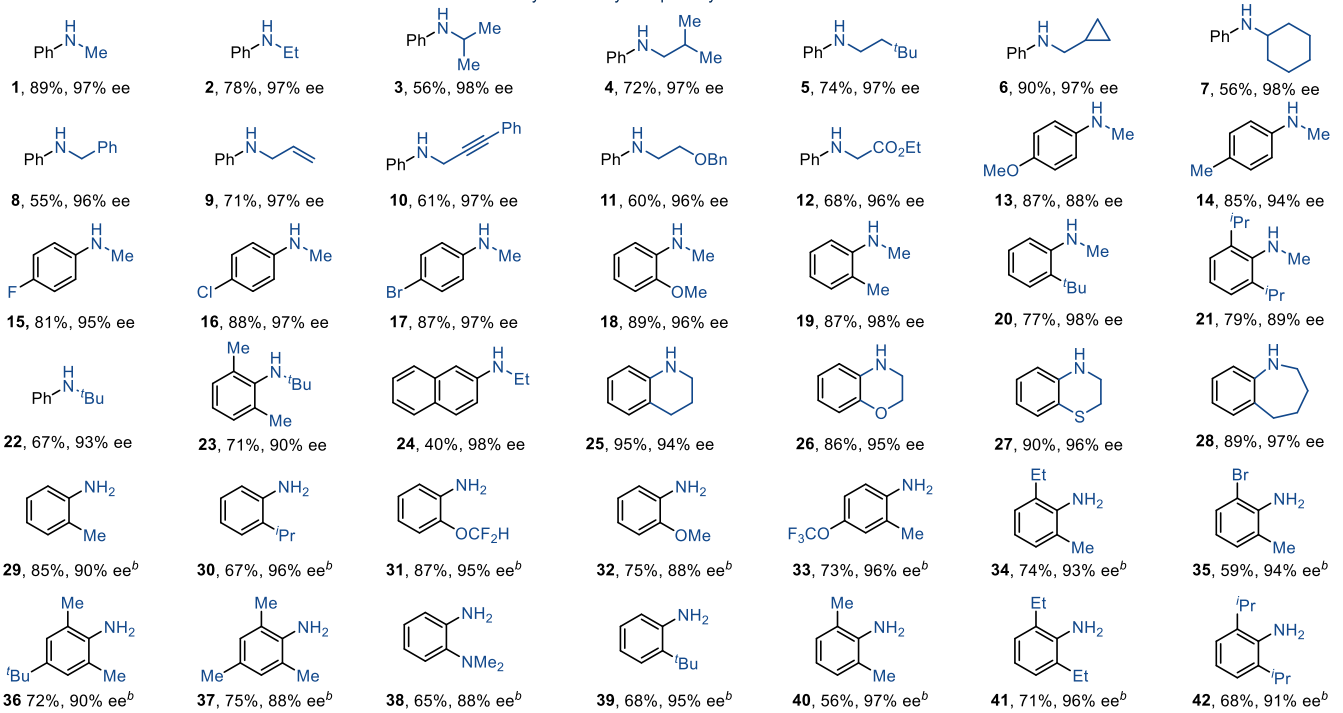
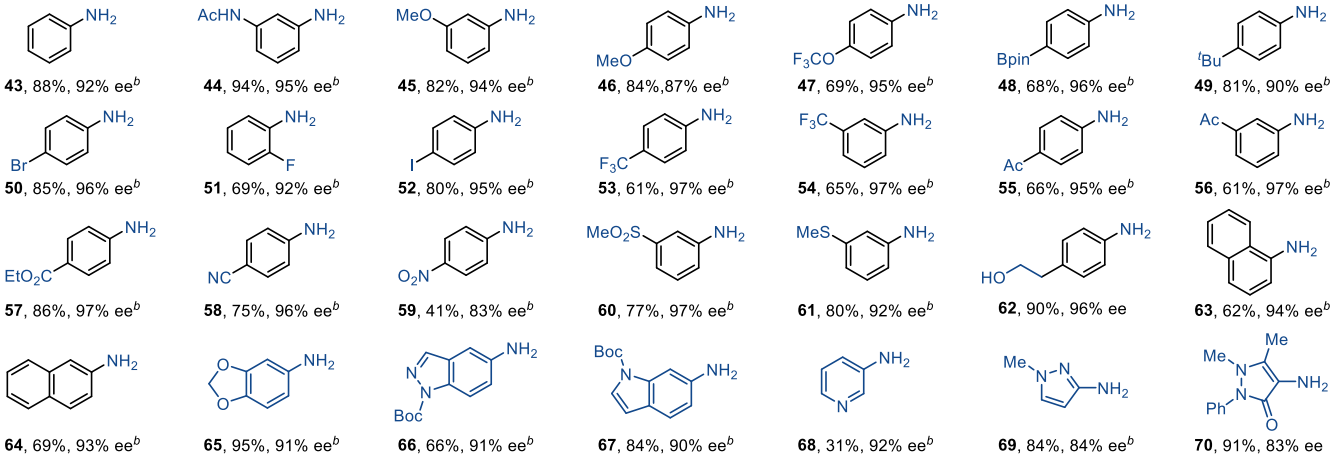
Table 2. Substrate Scope of (Hetero)aromatic Amines[a]



Bulky secondary and primary aromatic amines



Other primary aromatic amines



[a]Reaction conditions: racemic alkyl bromide **E1** (0.30 mmol, 1.5 equiv), (hetero)aromatic amines **N** (0.20 mmol), CuI (10 mol %), **L*3** (15 mol %), and Cs_2CO_3 (3.0 equiv) in 1,4-dioxane (4.0 mL) at rt (room temperature) for 3 d (days) under argon; isolated yield is shown; and ee values were based on chiral HPLC analysis. [b]**E1** (0.20 mmol) and **N** (0.30 mmol, 1.5 equiv) were used.

(>95%). Notably, the sterically hindered isopropyl (**3**) and isobutyl (**4**) substituents were also tolerated. As for the aryl ring, both electron-donating or -withdrawing groups at the *para* positions of secondary aromatic amines were well tolerated to provide **13**–**17** in good yields with high ee. More importantly, secondary aromatic amines with *ortho*- and 2,6-disubstituted aryl rings (**18**–**21**) and sterically hindered *t*-butyl (**22**, **23**) chains were competent substrates, providing the desired products in good yields with excellent ee. Furthermore, naphthyl and cyclic secondary aromatic amines reacted as well to afford **24**–**28** with 94–98% ee. We then examined the scope of bulky primary aromatic amines. A broad series of *ortho*- or 2,6-disubstituted aromatic amines were suitable for the reactions to deliver **29**–**42** in good yields with high ee. Even, the bulky *tert*-butyl group at the *ortho* position (**39**) and the isopropyl group at 2,6-positions (**42**) of the aryl ring were tolerated. In addition to bulky amines, other primary amines possessing electron-donating or -withdrawing groups at different positions of the aryl ring and even naphthyl amines could also participate in the reaction to give rise to **43**–**64** in

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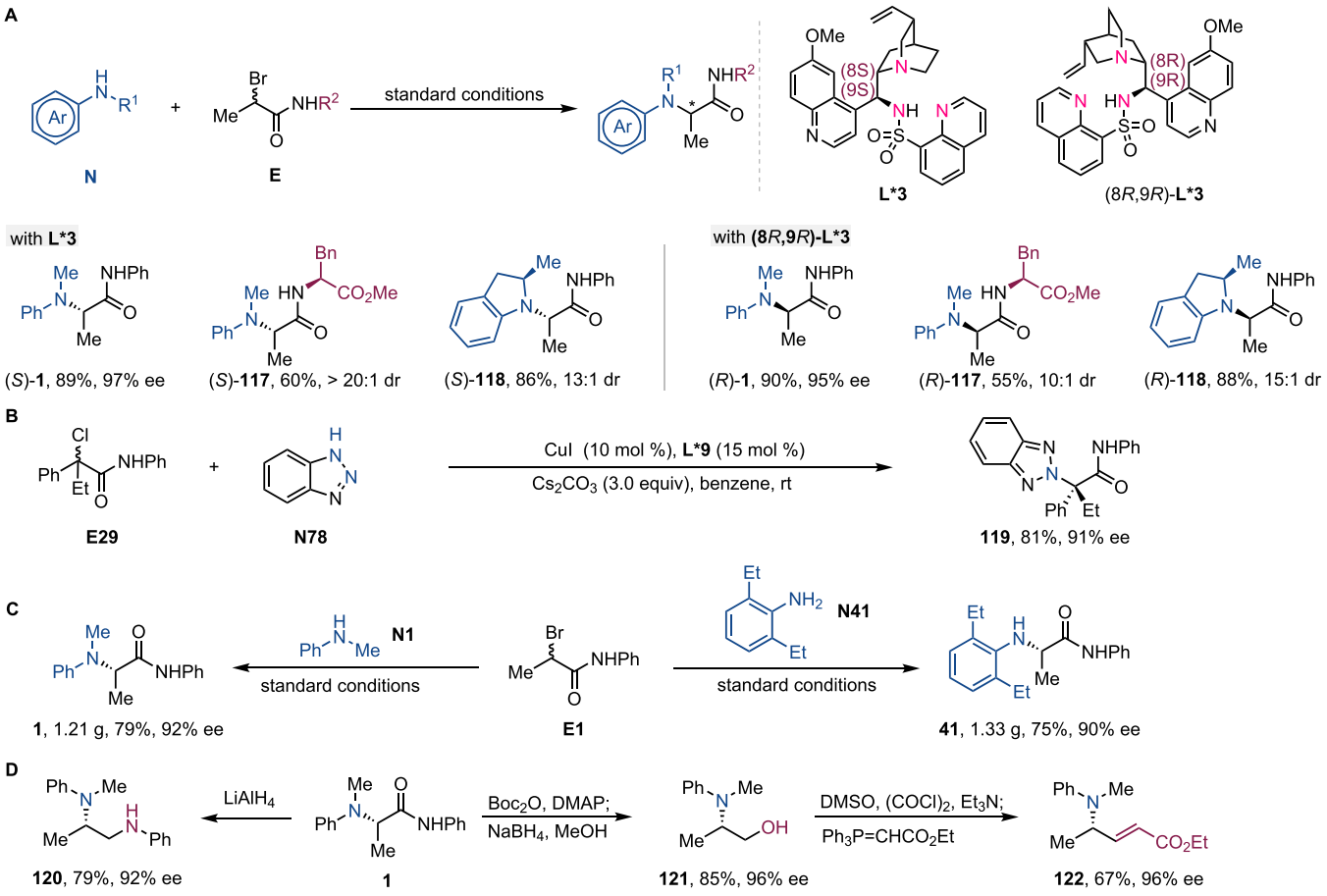
Scheme 2. Synthetic Utility



good yields with 87−97% ee. Many reactive functional groups, such as amidyl (**44**), methoxyl (**45**, **46**), trifluoromethoxyl (**47**), pinacolborato (**48**), halo (**50**−**52**), trifluoromethyl (**53**, **54**), carbonyl (**55**, **56**), ethoxylcarbonyl (**57**), cyano (**58**), nitro (**59**), sulfonyl (**60**), thioether (**61**), and free alcohol (**62**), were compatible with the mild reaction conditions. Moreover, amines containing many medicinally relevant heterocycles, such as indazole, indole, pyridine, and pyrazole, were viable substrates to give **65**−**70** in moderate to good yields with a high ee.

Scope of Secondary Alkyl Halides. As for the scope of secondary alkyl halides, owing to the increased steric hindrance in the alkyl chain, the chiral ligand was further modified to get high efficiency and enantioselectivity and we finally identified cyclohexane-1,2-diamine-derived *N*,*N*,*N*-ligand **L*5** as the best one (Tables S5−S7 in the Supporting Information). Many secondary alkyl bromides with diverse substituents on the aliphatic chain were suitable for the reaction to provide **71**−**80** in good yields with high ee. Even bulky isopropyl (**73**), and *tert*-butyl (**74**) groups were tolerated. A gamut of functional groups, such as imidyl (**76**), ether (**77**, **78**), thioether (**79**), and ester (**80**) were left unscathed under the reaction conditions. More importantly, the substrate bearing an *α*-phenyl group underwent the reaction smoothly to result **81** in 81% yield with 94% ee. Regarding the *N*-substituents of alkyl bromides, the aryl group with different steric and electronic properties (**81**−**83**), alkyl group (**84**), and even primary amide (**85**) were all easily accommodated to furnish the desired products with excellent ee. In addition to *N*-methylaniline **N1**, the primary aniline was also feasible for the *N*-alkylation with alkyl bromides other than **E1** to give **86** in 66% yield with 95% ee.

Scope of Tertiary Alkyl Chlorides. The coupling of tertiary alkyl halides is difficult due to the large steric hindrance.[4] The outer-sphere nucleophilic attack model inspired us to investigate the *N*-alkylation of bulky aromatic amines with tertiary alkyl chlorides. Unfortunately, the attempts to afford the desired product **87** from the corresponding tertiary alkyl chloride using chiral diamine-derived anionic ligands (**L*1**, **L*3**, and **L*5**) met with only marginal enantioselectivity albeit with good yield (Table S8 in the Supporting Information). This result arose mainly from the large steric nature of tertiary alkyl chlorides, and the chiral ligands needed to be modified to achieve effective enantiocontrol. After investigating other ligands and reaction parameters, we found that the anionic *N*,*N*,*N*-ligand[9,14] **L*9** was an effective ligand for the *N*-alkylation with tertiary alkyl chlorides to provide **87** with high ee (Table S8 in the Supporting Information). Under the optimal conditions, an array of secondary amines reacted well to provide **87**−**96** in good yields with high ee as shown in Table 4. Moreover, bulky primary amines underwent the reaction smoothly to afford **97**−**105** with a high ee. Other primary amines with different substituents at the *meta* or *para* positions (**106** and **107**) of the aryl ring are also amenable to the standard conditions. More significantly, tertiary alkyl chlorides with diverse functional groups at the aliphatic chain or aryl ring worked well under

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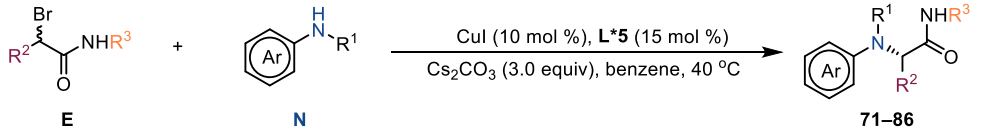
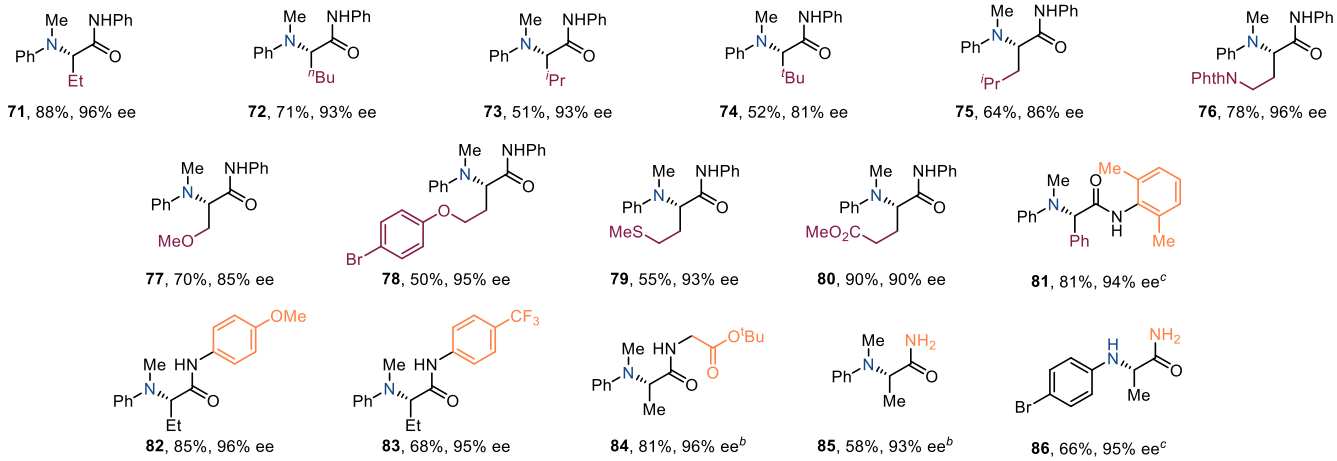
Table 3. Substrate Scope of Secondary Alkyl Halides[a]



E N 71–86



71, 88%, 96% ee; **72**, 71%, 93% ee; **73**, 51%, 93% ee; **74**, 52%, 81% ee; **75**, 64%, 86% ee; **76**, 78%, 96% ee; **77**, 70%, 85% ee; **78**, 50%, 95% ee; **79**, 55%, 93% ee; **80**, 90%, 90% ee; **81**, 81%, 94% ee[c]; **82**, 85%, 96% ee; **83**, 68%, 95% ee; **84**, 81%, 96% ee[b]; **85**, 58%, 93% ee[b]; **86**, 66%, 95% ee[c]

[a]Reaction conditions: racemic alkyl bromides **E** (0.24 mmol, 1.2 equiv), aromatic amines **N** (0.20 mmol), CuI (10 mol %), **L*5** (15 mol %), and Cs_2CO_3 (3.0 equiv) in benzene (4.0 mL) at 40 °C for 3 d under argon; isolated yield is shown; and ee values were based on chiral HPLC analysis. [b]**E** (0.30 mmol, 1.5 equiv) and **N** (0.20 mmol) in 1,4-dioxane (4.0 mL) at rt. [c]**E** (0.20 mmol) and **N** (0.30 mmol, 1.5 equiv) in 1,4-dioxane (4.0 mL) at rt. Phth, phthalimidyl.

standard conditions to provide **108**−**116** in moderate to good yields with 86−95% ee (Table 4).

Synthetic Utility. The antipode of (*S*)-**1** was easily prepared by using the pseudoenantiomer of ligand **L*3** ((8*R*,9*R*)-**L*3**) in good yield and excellent ee (Scheme 2A). Given the abundance of chiral amines bearing multiple chiral centers in organic synthesis and based on the outer-sphere nucleophilic attack pathway, we surmised that the current catalytic system could result in high enantioselectivity via the full catalyst control regardless of the pre-existing stereocenters in chiral substrates. To our delight, we found that both the installation of the chiral amine motif in racemic alkyl halides and the direct use of chiral amine as the nucleophile gave rise to desired products **117** and **118** in high diastereoselectivity in the presence of **L*3** (Scheme 2A). Replacing **L*3** with its pseudoenantiomer (8*R*,9*R*)-**L*3** generated the other diastereomer of **117** and **118**, respectively (Scheme 2A). These results demonstrate that this methodology has broad application in the synthesis of stereochemically complex molecules. In addition, we also successfully realized the *N*-alkylation of benzotriazole to afford **119** in 81% yield with excellent regio- and enantioselectivity, suggesting that the current methodology is also applicable to *N*-heterocycles (Scheme 2B). The absolute configurations of **58**, **71**, and **119** (Figures S2−S4 in the Supporting Information) were determined to be *S* by X-ray crystallographic analysis, and all other compounds were assigned by analogy accordingly. The reaction was also conducted on a gram scale to access desired products **1** and **41** without a significant decrease in reaction efficiency and enantioselectivity (Scheme 2C). Notably, the amide moiety is a valuable synthon in organic chemistry that can be easily converted to other useful chiral building blocks. The synthetic application of this strategy is first demonstrated in the facile conversion of product **1** to chiral 1,2-diamine **120** and amino alcohol **121** (Scheme 2D). Most importantly, the amide moiety can be used in the construction of new carbon−carbon bonds via a one-pot Swern oxidation/Wittig sequence from **121** to afford carbon chain-elongated building blocks, such as **122** without loss of enantiopurity. These results demonstrate the practicality of this methodology in synthesizing chiral complex molecules.

Mechanistic Studies. We have previously reported the tridentate binding mode of these *N*,*N*,*N*-ligands in copper catalysts by X-ray structural analysis of a Cu(II)**L*5** complex.[9] In order to gain more insight into the nature of the reaction, we carried out a series of control experiments. A catalytic amount of the Cu(II)**L*5** complex afforded the desired *N*-alkylation product **71** with yield and ee similar to that under the standard conditions (Table 3 and Scheme 3A). In addition, a linear relationship between the catalyst and product ee values was observed, indicating a likely 1:1 copper-to-ligand ratio in the enantioselectivity-determining transition states (Scheme 3B). These results collectively demonstrated that the mononuclear copper species coordinated with one chiral ligand was probably the active catalyst. The subsequent radical clock experiment with alkyl bromide **E30** bearing an α-cyclopropyl substituent predominantly afforded ring-opening products **124** and **125** under the standard reaction conditions, supporting the involvement of alkyl radicals in the reaction (Scheme 3C). Regarding the radical generation, the reaction of **E30** without amine **N1** also yielded ring-opening products **124** and **125** (Scheme 3C). Further control experiments performed in deuterated tetrahydrofuran (THF-d_8) solvent without any amine nucleophiles resulted in an 8% yield of reduced alkyl electrophile **126**-*d* (Scheme 3D), likely via deuterium atom transfer. Further, the control experiment utilizing DMPO (5,5-dimethyl-1-pyrroline-*N*-oxide) produced trapped radical product **127**, confirmed by EPR (electron paramagnetic resonance) analysis (Scheme 3E). These findings were in agreement with our initial hypothesis presented in Scheme 1C that the copper

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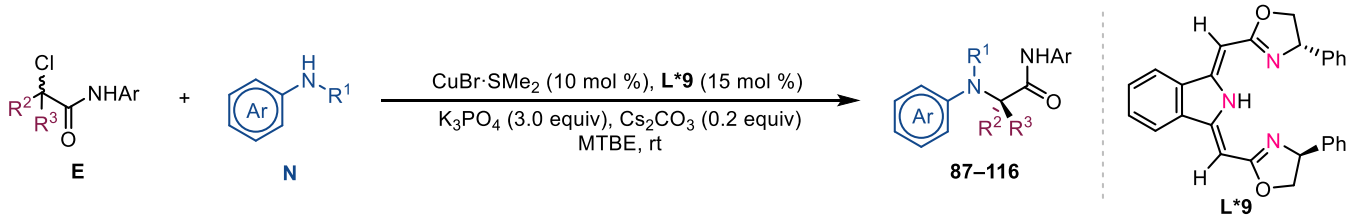
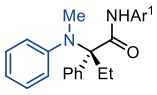
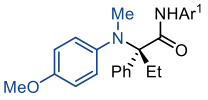
Table 4. Substrate Scope of Tertiary Alkyl Chlorides[a]

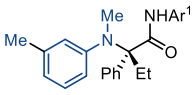


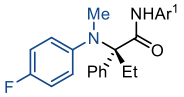
Aromatic amines scope

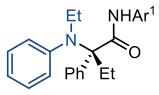
(Ar^1 = 3,5-$Cl_2C_6H_3$, Ar^2 = 4-$CF_3C_6H_4$)

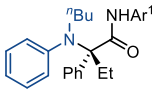

87, 79%, 88% ee

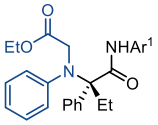

88, 63%, 85% ee

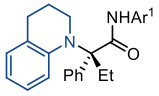

89, 75%, 90% ee

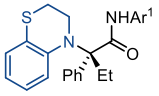

90, 58%, 88% ee

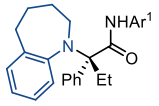

91, 61%, 87% ee

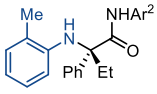

92, 52%, 87% ee

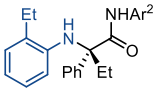

93, 51%, 91% ee

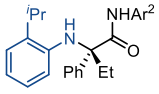

94, 71%, 90% ee

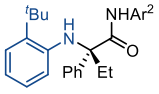

95, 65%, 87% ee

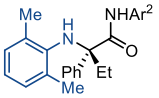

96, 55%, 90% ee

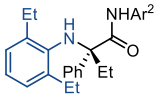

97, 54%, 92% ee[b]

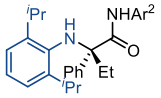

98, 63%, 90% ee[b]

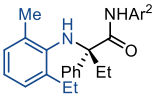

99, 55%, 83% ee[b]

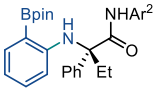

100, 50%, 90% ee[b]

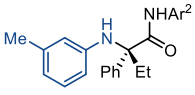

101, 66%, 90% ee[b]

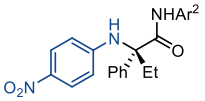

102, 73%, 90% ee[b]


103, 70%, 90% ee[b]

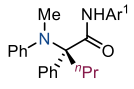

104, 63%, 88% ee[b]

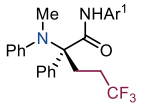

105, 43%, 82% ee[b]

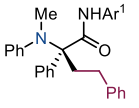

106, 53%, 88% ee[b]

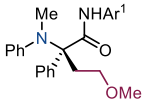

107, 43%, 88% ee[b]

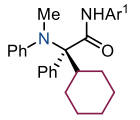
Tertiary alkyl chloride scope

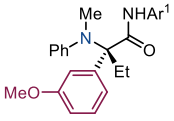

108, 66%, 90% ee

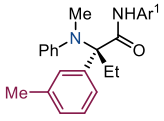

109, 59%, 88% ee

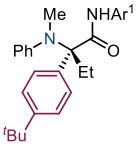

110, 61%, 86% ee

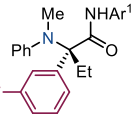

111, 54%, 88% ee


112, 69%, 95% ee


113, 64%, 92% ee


114, 51%, 90% ee


115, 63%, 86% ee


116, 58%, 90% ee

[a]Reaction conditions: racemic alkyl bromides **E** (0.24 mmol, 1.2 equiv), aromatic amines **N** (0.20 mmol), $CuBr·SMe_2$ (10 mol %), **L*9** (15 mol %), and K_3PO_4/Cs_2CO_3 (3.0 equiv/0.2 equiv) in MTBE (2.0 mL) at rt for 4 d under argon; isolated yield is shown; and ee values were based on chiral HPLC analysis. [b]**E** (0.20 mmol) and **N** (0.24 mmol, 1.2 equiv) were used. MTBE, methyl *tert*-butyl ether.

catalysts should be able to reduce alkyl halides to alkyl radicals without requiring amine coordination.

Regarding the possible Cu(III) intermediate, it is difficult to gain insights into its structure through experimental methods at this stage. But a preliminary density functional theory (DFT) study in a model system of **E1** and ligand **L*5** revealed that the N,C-bound Cu(III) intermediate **C** is the most thermostable one rather than the N,O- and O,C-bound one (for details, see Figure S5 and related discussion in the Supporting Information). Concerning the key C−N bond formation step, time-course experiments showed a significantly faster reaction rate for electron-rich *p*-anisidine compared to unsubstituted aniline (Figure S6 in the Supporting Information), indicating the participation of aromatic amines in the rate-determining step(s). Consistent with these results, competition experiments with paired aromatic amines possessing distinct electronic properties (OMe, H, and CF_3 at the *para* position) revealed the uniformly predominant formation of products from more electron-rich aromatic amines (Scheme 4A). Further KIE (kinetic isotope effect) experiments demonstrated almost the same reaction rates for deuterated and nondeuterated substrates (Scheme 4B). This finding suggested that the deprotonation was not rate-limiting, thus disproving a concerted deprotonation/nucleophilic attack mechanism via **D** (Scheme 4E). As such, the proposed outer-sphere nucleophilic attack via either **F** or **G** (Scheme 4E) might be the rate-determining step. The competing *N*-alkylation of aliphatic and aromatic amines showed excellent chemoselectivity to deliver **128** and **129** for the *N*-alkylation of aliphatic amine, which normally undergoes slower ligand exchange than the aromatic one (Scheme 4C). This experiment suggested that the ligand exchange of amines with copper

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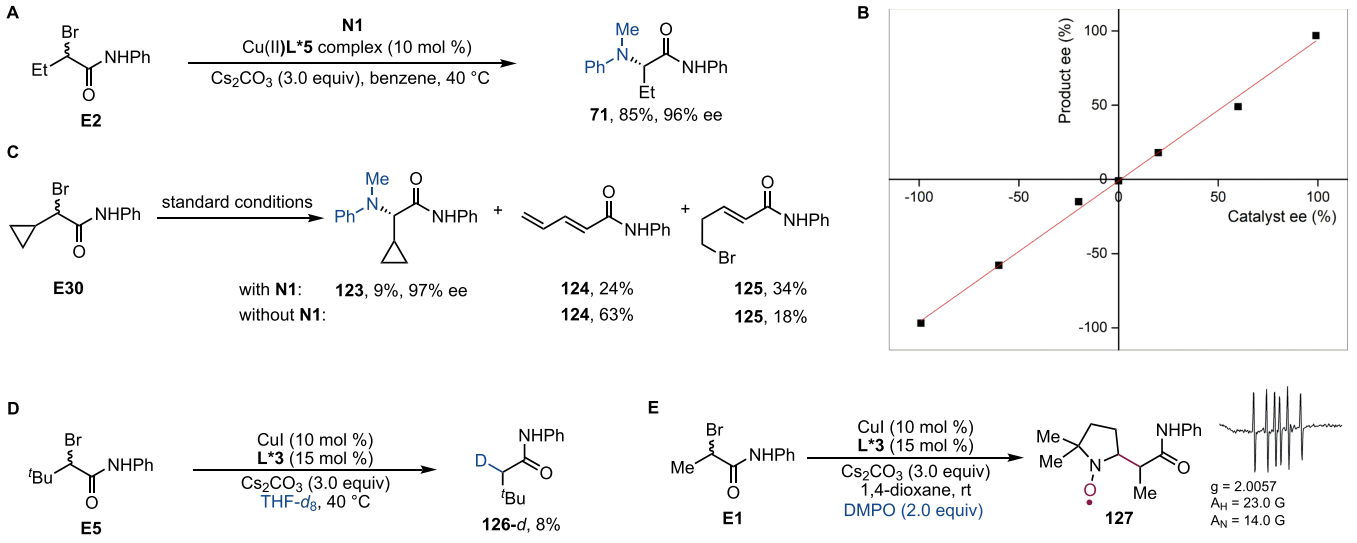
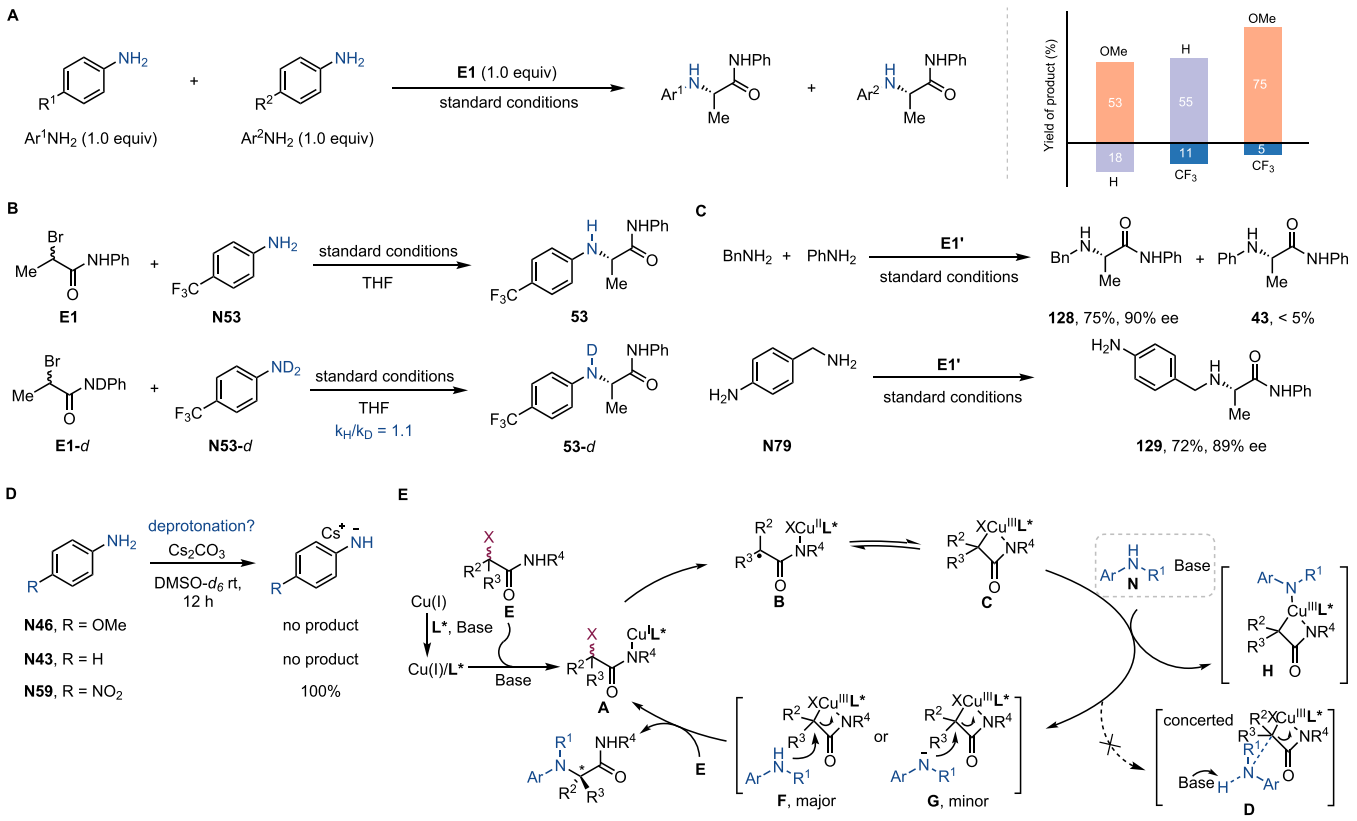
Scheme 3. Mechanistic Experiments



Scheme 4. Mechanistic Experiments



is less likely to be involved. Additional control experiments disclosed the facile deprotonation of *p*-nitroaniline, but not other aromatic amines investigated in this study by Cs_2CO_3 (Scheme 4D). Nevertheless, all of these aromatic amines participated in this reaction, delivering the corresponding desired *N*-alkylation products with high enantioselectivity (Table 2). Therefore, aromatic amines most likely underwent a stepwise nucleophilic attack/deprotonation in the C−N bond formation step (**F** in Scheme 4E). However, the reverse deprotonation/nucleophilic attack also contributed to the C−N bond formation step for strongly acidic amines (**G** in Scheme 4E), which is slightly different from that in our previous report.[9] Based on the control experiments, we proposed a plausible mechanism (Scheme 4E), whereby the Cu(I) salt, **L***, and Cs_2CO_3 reacted first to produce the Cu(I) **L*** complex. Subsequently, this complex reacted with alkyl halide **E** to generate intermediate **A**. Intramolecular oxidative addition of **A** then provided **B** and **C** in equilibrium. The outer-sphere nucleophilic attack of **C** by aromatic amine **N** via intermediate **F** or **G** followed by ligand exchange with alkyl halide **E** gave rise to the desired *N*-alkylation product along with intermediate **A** for the next catalytic cycle. However, an alternative ligand exchange of aromatic amines **N** with

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intermediate **C** followed by inner-sphere reductive elimination via **H** cannot be ruled out at this stage.

CONCLUSIONS

In summary, we have described a strategy for enantioconvergent radical *N*-alkylation of diverse aromatic amines with racemic alkyl halides using the copper/chiral anionic *N*,*N*,*N*-ligand catalyst. The key to the success is the design of an outer-sphere nucleophilic attack mechanism in the chiral bond formation process that bypasses the involvement of the nucleophile-sequestered Nu−M**L*** complex. Thus, it can override the mechanistic limitation inherent to classic enantioconvergent radical cross-coupling and allows the coupling of bulky aromatic amines, especially secondary ones that have not been previously disclosed. We anticipate that this methodology will inspire the development of general enantioconvergent coupling of more nucleophiles, particularly sterically congested ones, which remains a difficult task in classic mechanisms.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c02141.

Experimental procedures, characterization of compounds, Tables S1−S8, Figures S1−S6, and crystallographic data of **58**, **71**, and **119** (PDF)

Accession Codes

CCDC 2307252 (for **58**), 2307253 (for **71**), and 2307254 (for **119**) contain supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 441223 336033.

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Author Contributions

#X.-Y.D., J.-H.F., J.-J.C., and B.S. contributed equally to this work. The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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