nature communications

Article

https://doi.org/10.1038/s41467-026-68961-9

Copper-catalysed enantioconvergent *N*-alkylation of hydrazines with racemic α-haloamides to access enantioenriched hydrazines

Received: 25 August 2025

Accepted: 21 January 2026

Nan Li[1], Sheng-Yu He[1], Peng-Fei Wang[1], Qiang-Shuai Gu[1], Zhong-Liang Li[2], Ji-Jun Chen[1] ✉ & Xin-Yuan Liu[1] ✉

Chiral hydrazines are important building blocks in chiral drug molecules, *N*-amino peptides, and aza-heterocycles. The catalytic enantioconvergent *N*-alkylation of readily available hydrazine derivatives with various racemic alkyl halides offers a highly attractive route to chiral hydrazines. However, this process remains challenging due to the lack of efficient asymmetric catalytic systems and the difficulty in achieving regioselectivity at the N^1/N^2 positions of hydrazine derivatives. Herein, we demonstrate a general copper-catalysed enantioconvergent *N*-alkylation of hydrazine derivatives with racemic α-haloamides. This strategy provides a modular approach for the synthesis of diverse enantioenriched hydrazines with excellent regio- and enantioselectivity. The key to success lies in the development of a radical-polar crossover nucleophilic substitution process and the employment of suitable hydrazine nucleophiles. Furthermore, this method provides a versatile platform to access a series of enantioenriched aza-heterocycles through facile subsequent transformations. It also enables the stereodivergent synthesis of all four possible stereoisomers of *N*-amino dipeptides bearing two stereocenters, with excellent stereoselectivity.

Chiral hydrazines are not only prevalent in various natural products and drug molecules, but also serve as versatile chiral building blocks and catalysts in organic synthesis and asymmetric catalysis[1–6]. Specifically, the distinctive hydrazine moiety in *N*-amino peptides derived from chiral hydrazines endows these peptides with unique secondary conformations and biological activities[7,8]. Furthermore, they are also vital precursors for synthesizing a wide range of aza-heterocycles with potential pharmacological activity[9,10] (Fig. 1a). Consequently, considerable progress has been achieved in developing catalytic enantioselective approaches for their efficient preparation[11–38]. The most widely used methods are the asymmetric hydrogenation of hydrazones[16–22] and nucleophilic addition to hydrazones[23–29] (Fig. 1b, left). This is presumably due to the tunable reactivity of hydrazones and their ability to assist in the coordination of chiral catalysts. Nevertheless, the synthesis of hydrazones by condensation of hydrazine derivatives with carbonyl compounds often requires laborious separation and purification. Meanwhile, notable advances have also been made in the catalytic asymmetric electrophilic amination of carbonyl compounds with azodicarboxylates[30–38] (Fig. 1b, left). Notably, azodicarboxylates, which are derived from the oxidation of hydrazine derivatives, are explosive and necessitate careful handling. Given the importance of atom- and step-economy in constructing such

---

[1]New Cornerstone Science Laboratory, Shenzhen Grubbs Institute, Department of Chemistry, and Guangming Advanced Research Institute, Southern University of Science and Technology, Shenzhen, China. [2]Dongguan Key Laboratory of Interdisciplinary Science for Advanced Materials and Large-Scale Scientific Facilities, School of Physical Sciences, Great Bay University, Dongguan, China. ✉e-mail: chenjj@sustech.edu.cn; liuxy3@sustech.edu.cn

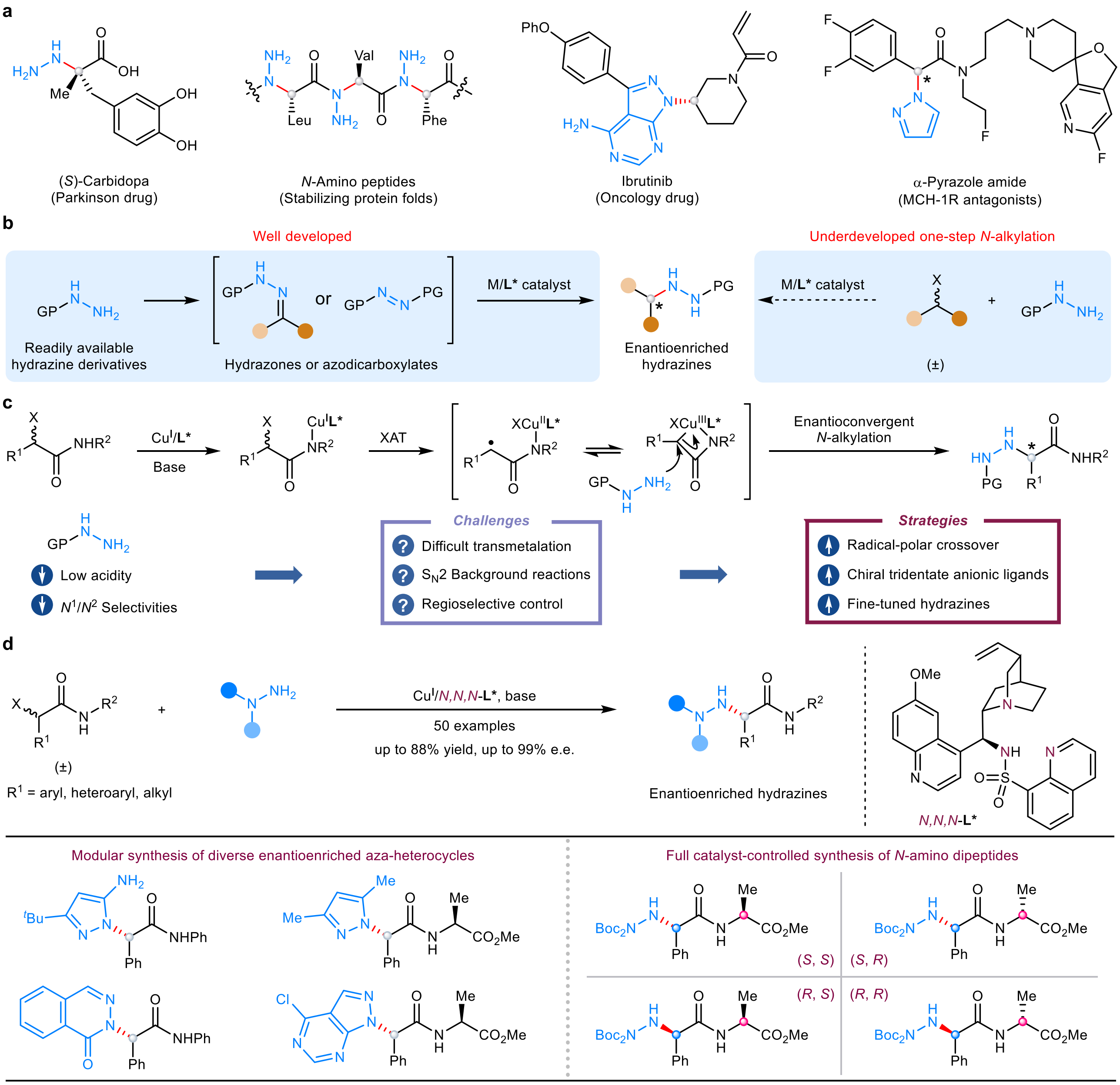

Fig. 1 | Motivation and design of copper-catalysed enantioconvergent *N*-alkylation of hydrazines to access enantioenriched hydrazines. **a** Importance of chiral hydrazines and hydrazine-based aza-heterocycles. **b** Challenges for the synthesis of enantioenriched hydrazines from hydrazine derivatives. **c** Proposed enantioconvergent *N*-alkylation of hydrazines via a radical-polar crossover approach. **d** This work: copper-catalysed enantioconvergent *N*-alkylation of hydrazines with racemic α-haloamides. Me methyl, Leu leucine, Val valine, Phe phenylalanine, PG protecting group, M metal, XAT halogen atom transfer, ᵗBu *tert*-butyl, Boc *tert*-butoxycarbonyl.

valuable enantioenriched hydrazines, the development of a new asymmetric catalytic system to directly access these skeletons from readily available and inexpensive hydrazine derivatives remains highly desirable.

In this context, the catalytic enantioconvergent *N*-alkylation of simple hydrazine derivatives with various racemic alkyl (pseudo) halides would provide a general method for accessing enantioenriched hydrazines, as these two classes of starting materials are easily available and widely applied in industry and academia (Fig. 1b, right). As a notable precedent, Carreira and co-workers pioneered an iridium-catalysed asymmetric allylic substitution of racemic allylic alcohols with hydrazine derivatives[39]. Subsequently, Zhou[40] and Xu[41] independently reported copper-catalysed asymmetric propargylic substitutions of propargylic alcohol derivatives with hydrazine derivatives. Nevertheless, these reactions are confined to allylic and propargylic electrophiles, which are well-established as versatile coupling partners in asymmetric catalysis. On the other hand, Fu[42–46] and our group[47–51] have respectively developed the enantioconvergent radical cross-coupling of racemic alkyl halides with nitrogen-containing nucleophiles using chiral copper catalysts. Such catalytic systems offer an alternative route to access enantioenriched hydrazines, albeit through multistep transformations. However, to the best of our knowledge, the direct cross-coupling of racemic alkyl halides with hydrazine derivatives for the synthesis of enantioenriched hydrazines remains unreported. A critical obstacle is the inherently low acidity of hydrazine derivatives (e.g., pK_a = 8.07 for NH_2NH_2 in H_2O)[52], which impedes the transmetalation step required for forming the key hydrazine-sequestered Nu–M^n**L*** complex intermediate (Fig. 1c). Clearly, the design of a conceptually distinct catalytic system is highly desirable to overcome the challenges posed by this nucleophile and enable enantioconvergent *N*-alkylation with a broad scope of racemic electrophiles, which, if successful, would complement the previously reported approaches[39–41].

As part of our continuous interest in asymmetric radical reactions[53–58], we have recently developed a general radical-polar crossover nucleophilic substitution platform: a chiral copper catalyst promotes the single-electron reduction of racemic α-haloamides to generate Cu^{II}-bonded prochiral alkyl intermediates. This intermediate then undergoes intramolecular radical rebound to form a Cu^{III} intermediate, which subsequently undergoes polar outer-sphere nucleophilic attack by various nucleophiles[59–61] (Fig. 1c). This radical-polar crossover platform offers an alternative mechanistic paradigm, in which nucleophiles can directly attack the highly reactive hypervalent transition metal complex. This provides an opportunity for the coupling of challenging nucleophiles such as aliphatic amines, bulky aromatic amines, and alcohols, thereby significantly expanding the scope of nucleophiles in this field. Inspired by these observations and aiming to address the aforementioned challenges associated with using hydrazine derivatives as nucleophiles, we sought to determine whether enantioenriched hydrazines could be accessed through the direct enantioconvergent *N*-alkylation of readily available and inexpensive hydrazine derivatives with racemic α-haloamides under mild conditions. However, even though the transmetalation hurdles for hydrazine derivatives in the aforementioned classic cross-coupling reactions[42–51] have been overcome, several additional challenges still need to be well addressed: (1) the non-stereoselective background nucleophilic substitution between hydrazine derivatives and α-haloamides occurs via an aziridinone intermediate in the presence of an inorganic base[62] due to the strong nucleophilic properties of hydrazine derivatives (e.g., nucleophilicity $N = 16.45$ for NH_2NH_2 in CH_3CN)[63]; (2) the high Lewis basicity of hydrazine derivatives (e.g., $pK_{aH} = 16.61$ for NH_2NH_2 in CH_3CN)[64] would probably cause transition-metal catalyst poisoning—a problem analogous to that observed with our previously reported aliphatic amines[59]; and (3) most importantly, the regioselective control between the N^1 and N^2 positions of protected hydrazines presents an additional synthetic challenge[65–68], contrasting with the reported aliphatic amine, aniline, and alcohol nucleophiles[59–61]. To address these challenges, we envisaged that: (1) chiral tridentate anionic ligands with strong binding affinities to copper catalysts could not only enhance the reducing capability of copper, thereby accelerating the radical process and outcompeting non-stereoselective background reactions, but also overcome catalyst poisoning; and (2) the selection of suitable hydrazine derivatives with readily removable protecting groups could not only enable regioselective alkylation but also provide access to enantioenriched unprotected hydrazines through simple deprotection (Fig. 1c). Herein, we demonstrate a general copper/chiral anionic *N,N,N*-ligand-catalysed enantioconvergent *N*-alkylation of hydrazine derivatives with racemic α-haloamides, providing a modular approach for the synthesis of diverse enantioenriched hydrazines with excellent regio- and enantioselectivity (Fig. 1d). The key to success lies in the development of a radical-polar crossover nucleophilic substitution process and the employment of hydrazine derivatives bearing easily removable protecting groups as nucleophiles. This method can accommodate a broad range of readily accessible racemic α-haloamides, including those with (hetero)aryl or alkyl substituents at the α-carbon center, as well as aryl, alkyl, and amino acid motifs as *N*-substituents. The synthetic utility of this method is demonstrated by the synthesis of enantioenriched *N*-amino dipeptides and azaheterocycles. Furthermore, this reaction can produce all four possible stereoisomers of *N*-amino dipeptides bearing two chiral centers, demonstrating high catalyst-controlled stereoselectivity that overrides the influence of substrate chirality.

Results

Reaction development

Considering the significant influence of hydrazine substituents on reactivity and selectivity, we initially investigated the enantioconvergent *N*-alkylation of various hydrazine derivatives with racemic α-chloroamide **E1** using CuTc as the catalyst and our previously reported anionic *N,N*-ligand **L*5**[59] as the ligand (Fig. 2). As anticipated, the results revealed that the structure of hydrazine derivatives has a significant effect on the reaction efficiency and enantioselectivity. When *N*-phenyl hydrazine **N1** was employed, the corresponding hydrazine **1a** was obtained in 8% yield and 3% e.e., accompanied by side product **1a'** formed in 7% yield through the rapid oxidation of the freshly generated **1a**[67,69]. Subsequently, the evaluation of *N*-sulfonyl hydrazine **N2** and benzoyl hydrazine **N3**, which had previously been utilized in propargylic substitution reactions[40], revealed that **E1** was completely consumed without the formation of any corresponding hydrazines. Considering the widespread application of the Boc group in hydrazine protection, utilization of *N*-Boc hydrazine **N4** as the substrate afforded the desired hydrazine **1 d** in 30% yield and 8% e.e. However, the byproduct **1 d'** was also formed in 16% yield, likely attributed to the relatively high acidity of the N–H bond adjacent to the Boc moiety. To enhance product stability and reaction efficiency, we hypothesized that introducing an additional substituent into *N*-Boc hydrazine **N4** would suppress side reactions and improve the stability of the resulting product. Encouragingly, the use of *N*-Me-*N*-Boc hydrazine **N5** significantly improved reaction efficiency, thus affording the desired product **1e** with 80% yield and 71% e.e. Similarly, other alkyl-substituted *N*-Boc hydrazines were evaluated, and they exhibited comparable reactivity and stereoselectivity (Supplementary Fig. 1). Furthermore, motivated by the urgent need for unprotected chiral hydrazines in versatile synthesis, the potential of *N*-aminophthalimide **N6** was investigated. Unfortunately, this reaction afforded **1 f** in only 28% yield with 62% e.e. In order to balance practicability and reaction efficiency, *N,N*-bis-Boc hydrazine **N7** was subsequently used. To our delight, this reagent provided the corresponding hydrazine **1** with a comparable yield (49%) and excellent enantioselectivity (82% e.e.), outperforming both **N5** and **N6** in overall synthetic utility. Consequently, *N,N*-bis-Boc hydrazine **N7** was identified as the optimal hydrazine source for this synthetic strategy, given its unique ability to enable regioselective alkylation while serving as a viable source for synthesizing enantioenriched unprotected hydrazines.

Having identified *N,N*-bis-Boc hydrazine **N7** as the optimal hydrazine source, we then systematically screened various ligands to improve the yield and enantioselectivity of **1**. Our investigations commenced with neutral ligands, including *N,N*-ligand **L*1,** *N,P*-ligand **L*2**, DTBM-SEGPHOS **L*3**, and *N,N,N*-ligand **L*4**. Although these ligands could furnish the desired product **1** with 20–40% yield, negligible enantiomeric excess (<5% e.e.) was consistently observed. This strongly indicates that these neutral ligands failed to trigger the proposed radical pathway, instead undergoing non-stereoselective background nucleophilic substitution via an aziridinone intermediate[61]. In order to promote the proposed radical-polar crossover pathway[59–61], we hypothesized that chiral tridentate anionic ligands with strong binding affinity to copper catalysts could not only enhance the reducing capability of copper to accelerate the radical process over non-stereoselective background reactions, but also stabilize the highly active Cu^{III} intermediate by forming a coordinatively saturated intermediate, thereby suppressing side processes. Gratifyingly, the tridentate anionic ligand **L*6**, which incorporates an additional nitrogen-coordinating site based on **L*5**, significantly increased the yield to 75% and the enantioselectivity to 95%. To further clarify the role of the tridentate *N,N,N*-ligand, we synthesized **L*7** by introducing a methyl group at the α-position of the nitrogen-coordinating moiety, observing a decrease in both yield and e.e. The importance of the tridentate anionic *N,N,N*-ligand was further validated by replacing the cinchona

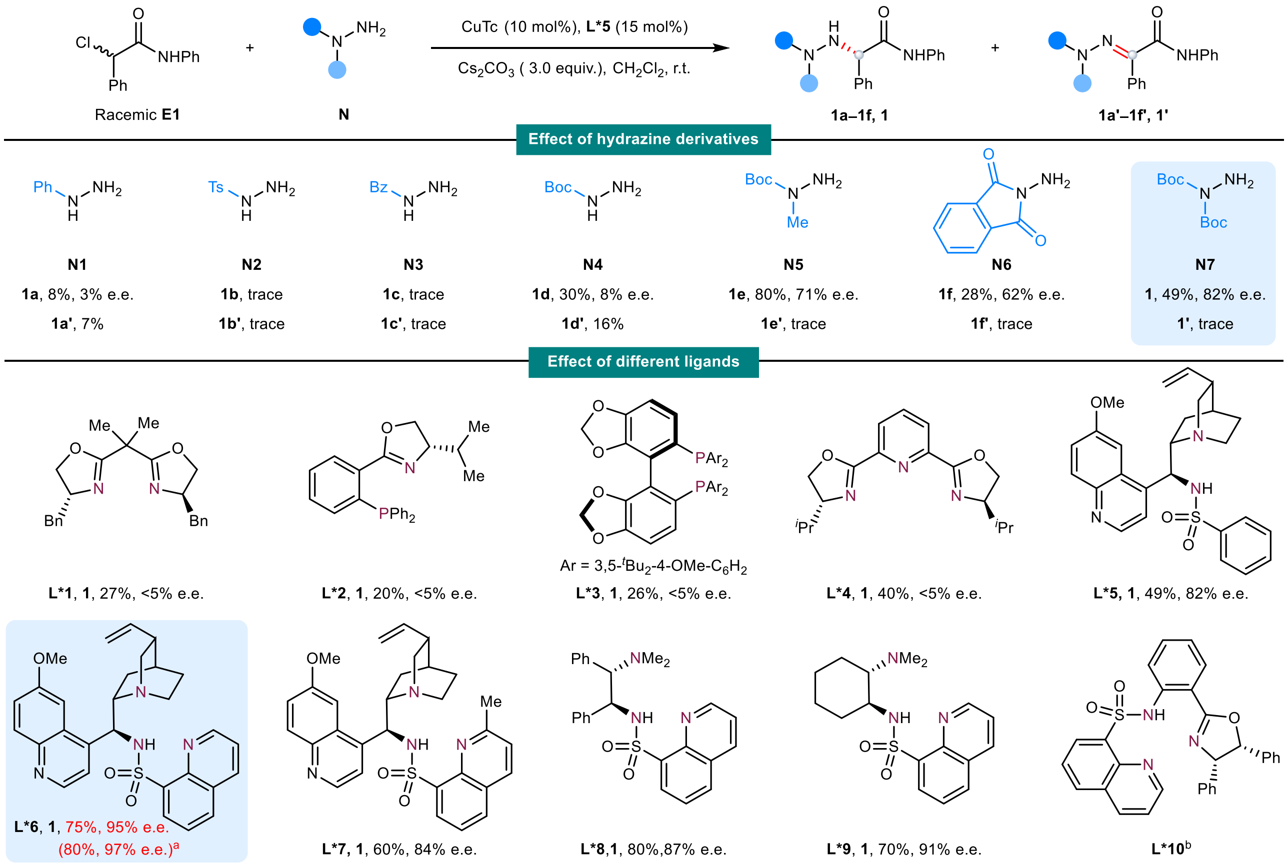

Fig. 2 | Reaction discovery and optimization. Reaction conditions: racemic **E1** (0.05 mmol), **N** (1.2 equiv.), CuTc (10 mol%), **L*** (15 mol%), and Cs_2CO_3 (3.0 equiv.) in CH_2Cl_2 (1.0 mL) at r.t. for 48 h under argon. Yields were based on ^1H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; e.e. values were based on chiral HPLC analysis. [a]$Cu(OAc)_2$ (10 mol%) at 10 °C. [b]The optimal ligand for α-methyl haloamide. Tc thiophene-2-carboxylate, CH_2Cl_2 dichloromethane, Ts *p*-toluenesulfonyl, Bz benzoyl, Bn benzyl, ^{i}Pr *iso*-propyl, OAc acetate, r.t. room temperature.

alkaloid chiral skeleton with 1,2-diphenyl-ethyl-diamine (**L*8**) and cyclohexyl-diamine (**L*9**). Notably, reactions with **L*8** and **L*9** afforded **1** in good yields with excellent e.e. These results highlight the importance of the chiral tridentate anionic *N,N,N*-ligand in forming a coordinatively saturated Cu^{III} intermediate, which plays a crucial role in improving enantioselectivity and reactivity. After further optimization of reaction parameters, including copper catalysts, solvents, inorganic bases as well as reaction temperature (Supplementary Tables 1–3 for the results of condition screening), we identified the optimal conditions as follows: 1.0 equiv. **E1**, 1.2 equiv. **N7**, 10 mol% $Cu(OAc)_2$, 15 mol% **L*6**, and 3.0 equiv. Cs_2CO_3 in CH_2Cl_2 at 10 °C for 48 h. Under the optimal conditions, the desired enantioenriched hydrazine **1** was obtained in 80% yield with 97% e.e.

Substrate scope

With the optimal reaction conditions in hand, we examined the reaction's generality. Concerning the scope of α-aryl haloamides (Fig. 3), a panel of α-phenyl rings bearing electron-neutral, -donating or -withdrawing groups were well-tolerated under these conditions, delivering products **1**–**14** in 42–82% yields and 88–99% e.e. α-Phenyl rings with diverse functional groups, such as halogens (**2**–**8**), methyl (**9**–**11**), methoxyl (**12**), trifluoromethyl (**13**) were all compatible with the reaction conditions. Notably, the reaction was sensitive to the steric effect at the *ortho*-position of the aromatic ring. While the less sterically hindered *ortho*-fluoro and *ortho*-methyl substituents (**4** and **11**) were well tolerated, the bulkier *ortho*-phenyl substituent (**15**) was incompatible with the reaction conditions. Furthermore, 2-naphthyl, 1-naphthyl and thienyl-substituted substrates were also viable, yielding products **16**–**18** with moderate yields and good enantioselectivity. Notably, substrates bearing a complex moiety derived from the bioactive molecule isoxepac could also be used in this reaction, delivering the desired product **19** with 96% e.e., albeit in a moderate yield. In addition, α-aryl haloamides bearing various *N*-aryl (**20**–**24**) and *N*-alkyl (**25**) groups, as well as the bioactive molecule amlodipine (**26**), could be employed in the reaction with good results.

To further enhance the synthetic utility of this method, we investigated the enantioconvergent *N*-alkylation of α-alkyl haloamides. Unfortunately, *N,N*-bis-Boc hydrazine **N7** showed low reactivity in the *N*-alkylation of α-ethyl haloamide **E27**, affording the desired product in only 5% yield (Supplementary Table 4). This result highlights the critical impact of hydrazine derivatives in reaction efficiency. To address this limitation, we further modified hydrazine derivatives and reoptimized the reaction conditions (Supplementary Tables 4–5 for condition optimizations). Gratifyingly, the combination of 1,1-diphenylhydrazine hydrochloride **N8** with ligand **L*9** afforded the optimal reactivity and enantioselectivity, delivering product **27** in 62% yield and 87% e.e. Regarding the scope of α-alkyl haloamides (Fig. 4), a wide range of substrates bearing simple unfunctionalized aliphatic chains, as well as those functionalized with phenyl, ether, thioether, trifluoromethyl, ester, alkenyl, and imidyl groups, afforded products **27**–**41** in 51–71% yields and 79–93% e.e. Notably, sterically hindered isobutyl or isopropyl groups did not significantly diminish the reaction efficiency or enantioselectivity, and products **31**–**32** were obtained with comparable results. Furthermore, for the reaction of *N,N*-bis-Boc hydrazine **N7** with α-methyl haloamide **E28**, we rescreened different types of ligands and reoptimized the reaction conditions (see

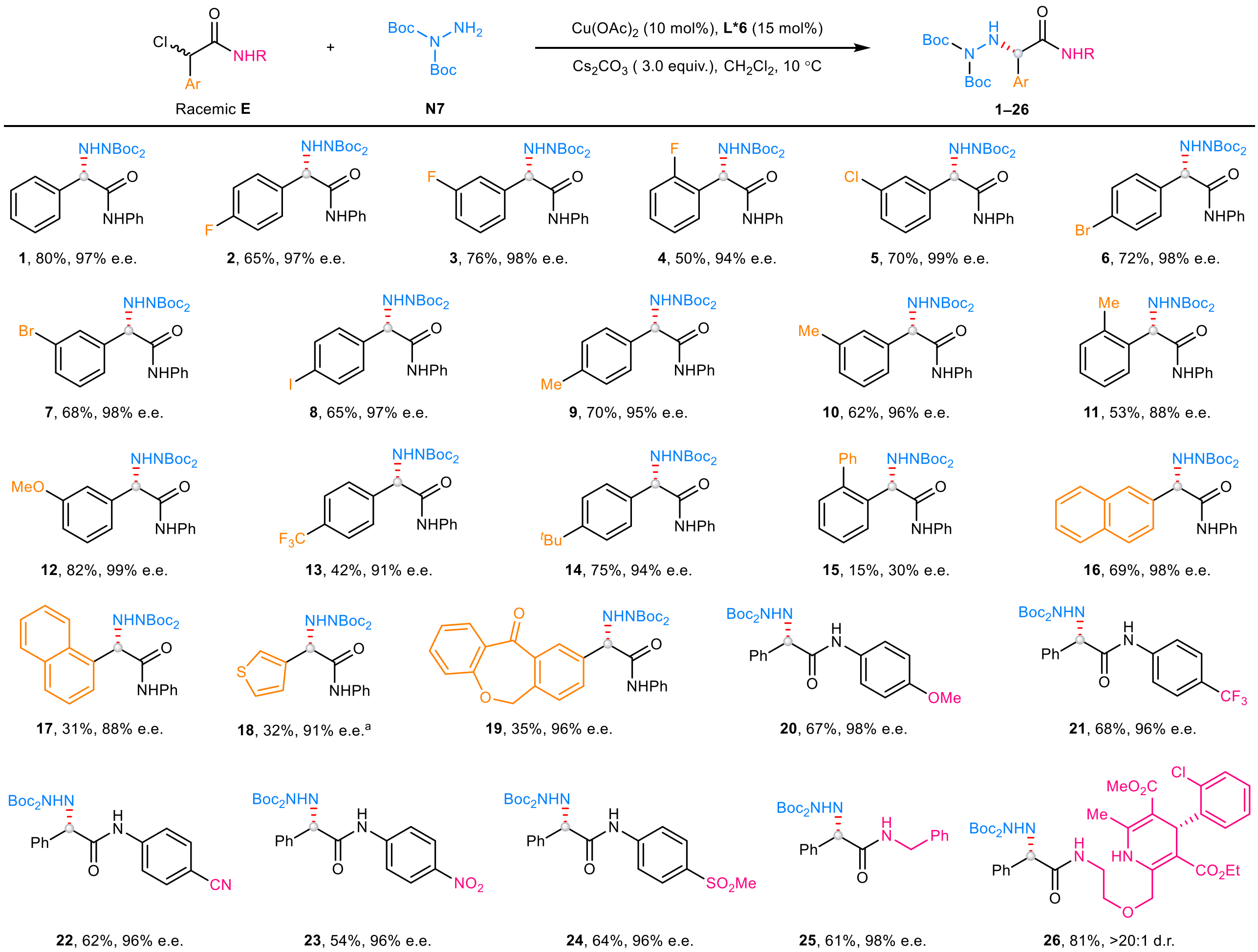

Fig. 3 | Substrate scope of α-aryl haloamides. Standard reaction conditions: racemic **E** (0.20 mmol), **N7** (1.2 equiv.), Cu(OAc)$_2$ (10 mol%), **L*6** (15 mol%), and Cs$_2$CO$_3$ (3.0 equiv.) in CH$_2$Cl$_2$ (4.0 mL) at 10 °C for 48 h under argon. Isolated yields were shown; e.e. values were based on chiral HPLC analysis; d.r. values were based on crude ^{1}H NMR analysis. ^{a}At 0 °C for 96 h. Ar aryl.

Supplementary Table 6). These efforts identified that the oxazoline-derived tridentate *N,N,N*-ligand **L*10** afforded the best reactivity and enantioselectivity (60% yield and 86% e.e. for **42**). The absolute configurations of compounds **8, 27**, and **42** were determined to be *S* by X-ray crystallographic analysis (Supplementary Fig. 2–4), and all other compounds were assigned by analogy.

Synthetic utility

It is well known that enantioenriched *N*-amino peptides play a pivotal role in the stabilization of protein secondary structures and resistance to proteolysis[7,8]. To demonstrate the synthetic potential of this method, we investigated the feasibility of constructing enantioenriched *N*-amino peptides via enantioconvergent *N*-alkylation of hydrazines with α-amino acid-derived α-chloroamides. To our delight, the reaction proceeded smoothly with glycine-derived α-chloroamide **E42** under the standard conditions, delivering the desired enantioenriched *N*-amino dipeptide **43** with 57% yield and 99% e.e. (Fig. 5a). Encouraged by this success, we wondered whether our strategy could circumvent the stereoselectivity induced by the pre-existing stereocenters in α-chloroamides to achieve full catalyst control. We found that more challenging α-chloroamides, derived from chiral amino acids (e.g., Val, Leu, Phe), could successfully furnish the corresponding *N*-amino dipeptides **44**–**49** in satisfactory yields and with high diastereoselectivity (Fig. 5a). These results highlight the compatibility and potential of this method for the late-stage functionalization of complex compounds. Furthermore, stereodivergent synthesis plays a crucial role in modern synthesis, particularly in drug discovery, since each isomer of multiple stereocenter compounds often possesses distinct physical and biological properties[70]. Leveraging our proposed radical-polar crossover pathway, we were also interested in applying this method to synthesize all possible stereoisomers of the *N*-amino dipeptide **50** from readily available starting materials. Notably, by employing the **L*6** and (8*R*,9*R*)-**L*6** ligands, the *N*-alkylation of *N,N*-bis-Boc hydrazine **N7** with *L*-alanine/*D*-alanine-derived α-chloroamides **E49**/**E49′** readily afforded all four stereoisomers of the enantioenriched *N*-amino dipeptides **50** with high catalyst-controlled stereoselectivity (Fig. 5b). These results clearly demonstrate that this method provides an efficient platform for achieving stereochemical diversity in peptidomimetics, thereby showcasing potential applications for high-throughput drug screening.

To further demonstrate the synthetic utility of this method, a gram-scale reaction (3.5 mmol) was successfully performed, yielding product **1** with comparable yield and enantioselectivity. Subsequently, the enantioenriched product **1** was efficiently deprotected with HCl in 1,4-dioxane to produce the corresponding hydrazine hydrochloride salt **51** (Fig. 6a). Meanwhile, the scale-up reaction of enantioenriched hydrazine **50** also provided consistent yield and diastereoselectivity, followed by efficient deprotection to yield the corresponding hydrazine hydrochloride salt **52**. Notably, the synthetic potential of this strategy is enhanced by the readily available unprotected hydrazine

https://doi.org/10.1038/s41467-026-68961-9

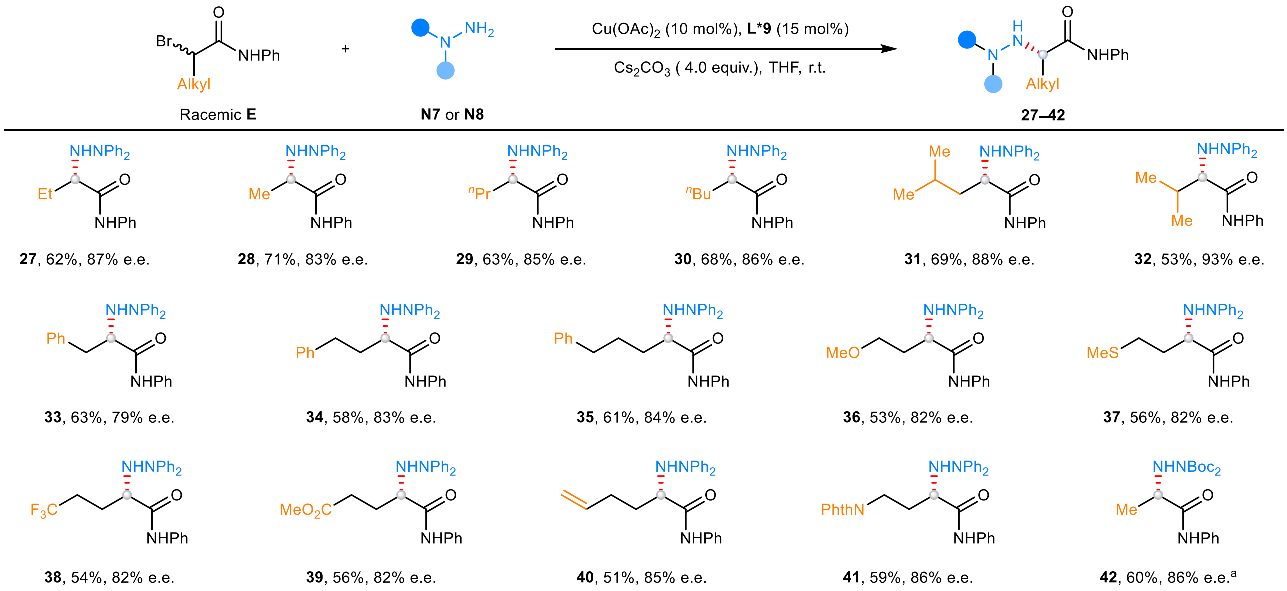

Fig. 4 | Substrate scope of α-alkyl haloamides. Standard reaction conditions: racemic **E** (0.20 mmol), **N8** (1.2 equiv.), $Cu(OAc)_2$ (10 mol%), **L*9** (15 mol%), and Cs_2CO_3 (4.0 equiv.) in THF (4.0 mL) at r.t. for 72 h under argon. Isolated yields were shown; e.e. values were based on chiral HPLC analysis. [a]**E28** (1.5 equiv.), **N7** (0.20 mmol), CuI (10 mol%), **L*10** (15 mol%), and Cs_2CO_3 (3.0 equiv.) in cyclohexane (4.0 mL) at 30 °C for 5 d. THF tetrahydrofuran, Et ethyl, ^{n}Pr n-propyl, ^{n}Bu n-butyl, Phth phthaloyl.

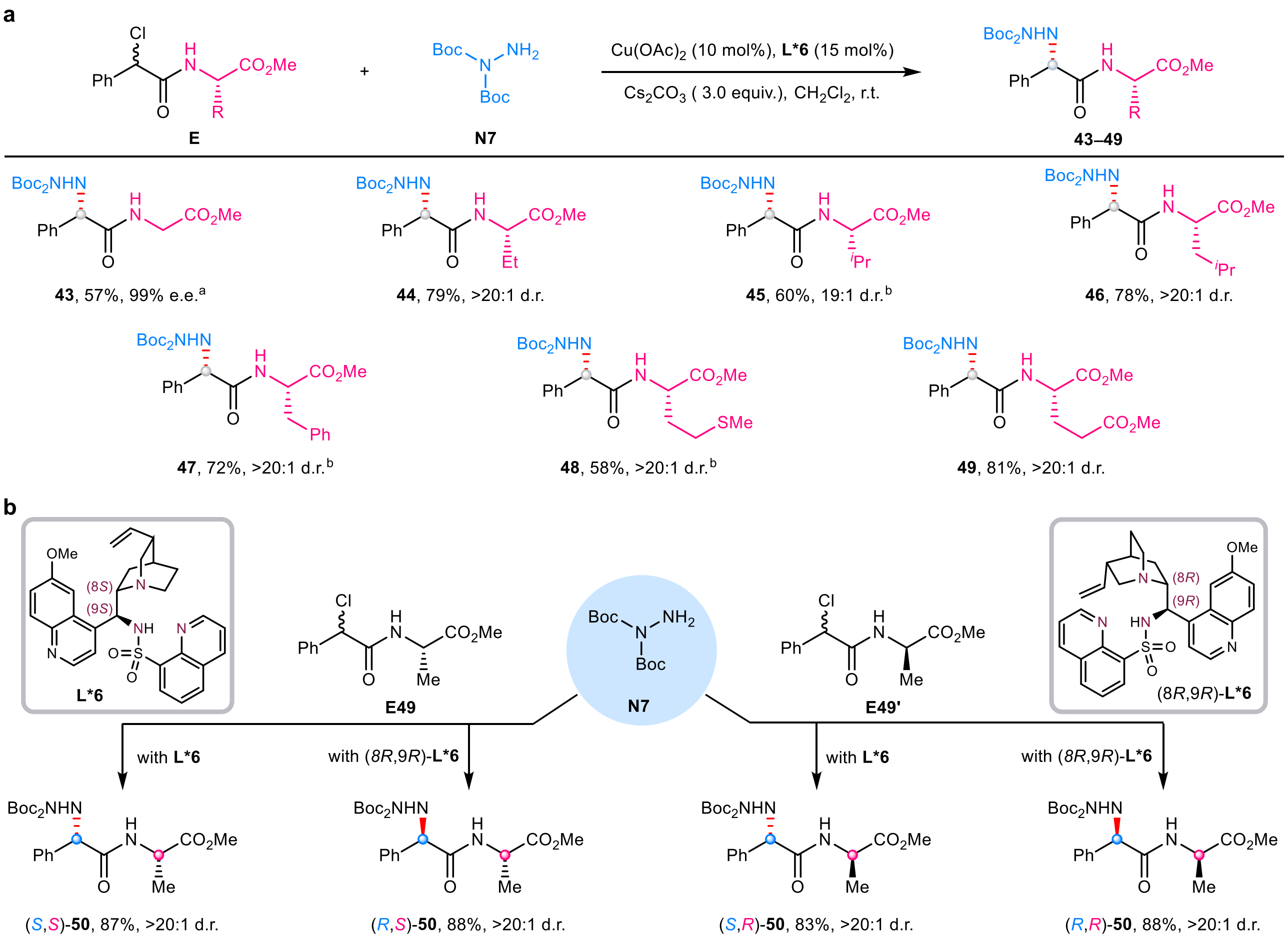

Fig. 5 | Synthesis of enantioenriched *N*-amino dipeptides and stereodivergent synthesis. a Synthesis of enantioenriched *N*-amino dipetides. **b** Stereodivergent synthesis of all four stereoisomers of **50**. [a]At 10 °C. [b]**L*5** was used.

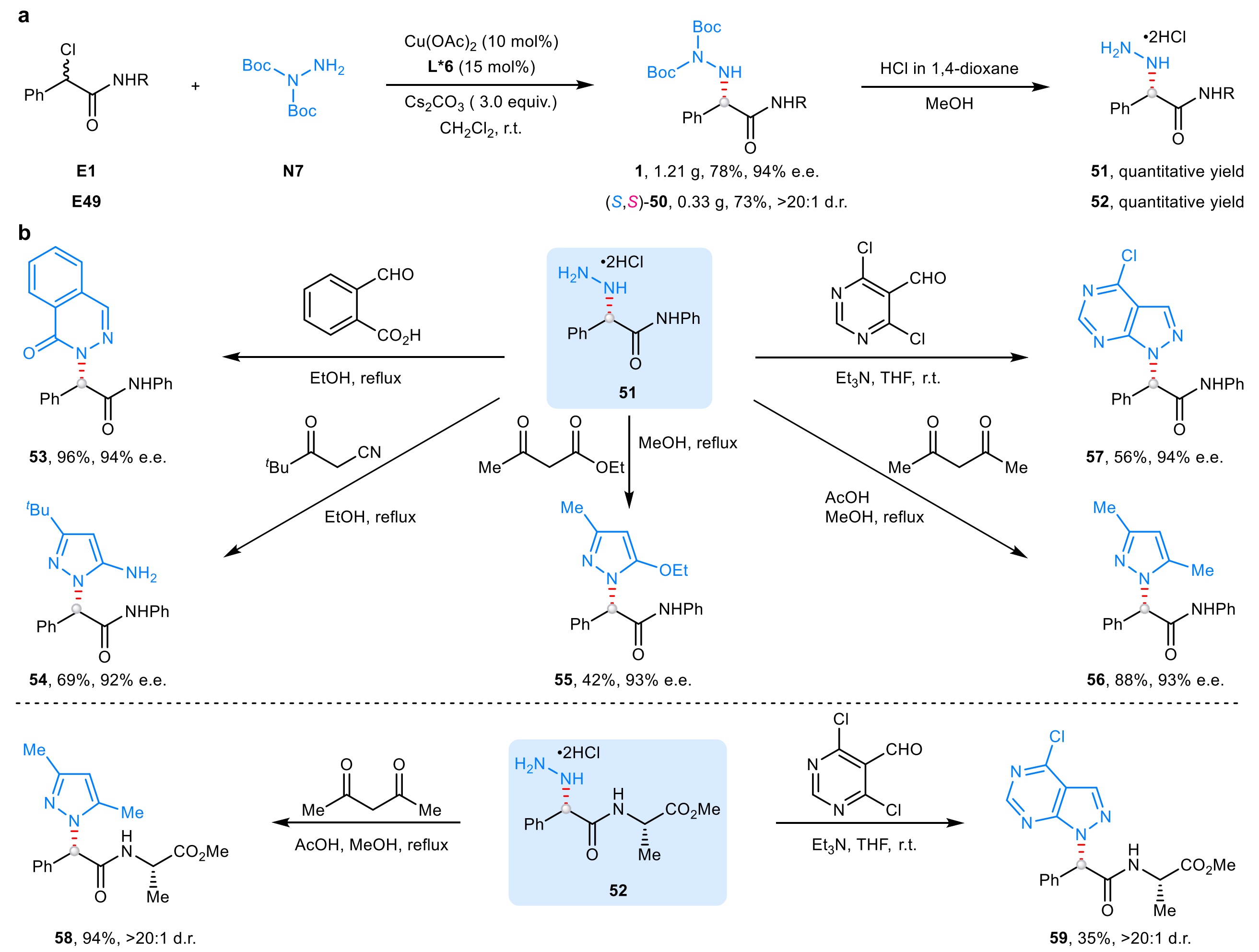

Fig. 6 | Synthetic utility. a Scale-up reactions and synthesis of unprotected enantioenriched hydrazines. **b** Synthesis of diverse enantioenriched aza-heterocycles.

moiety, which can be exploited to generate valuable enantioenriched aza-heterocycles (Fig. 6b). For instance, the unprotected hydrazine moiety in **51** undergoes condensation with various carbonyl compounds to form structurally diverse enantioenriched aza-heterocycles, including phthalazin-1(2*H*)-one (**53**), 1*H*-pyrazoles (**54**–**56**), and 1*H*-pyrazolo[3,4-*d*]pyrimidine (**57**). These transformations afford 42–96% yields without apparent erosion of enantiopurity. Furthermore, the hydrochloride salt of the enantioenriched hydrazine **52** enabled the synthesis of peptide-fused enantioenriched aza-heterocycles (**58** and **59**), further expanding the utility of this platform for constructing complex biologically relevant architectures. These results clearly demonstrate the broad application of this method for achieving structural diversity.

Mechanistic investigations

In order to gain insight into the reaction mechanism, a series of control experiments were performed. A radical trapping experiment with butylated hydroxytoluene (BHT) afforded product **1** in reduced yield alongside the formation of BHT-trapped product **60** under the standard conditions, indicating the generation of an alkyl radical from racemic α-haloamides via a halogen atom transfer (XAT) process (Fig. 7a). Furthermore, a linear relationship was observed between the enantiopurities of the products and the enantiopurities of the corresponding chiral ligands, suggesting that a mononuclear copper species coordinated with a chiral *N,N,N*-ligand is likely the active catalyst in this process (Fig. 7b). Additionally, Hammett analysis was conducted by employing *para*-substituted phenylhydrazines with varied electronic properties in conjunction with α-haloamide **E1** (Supplementary Fig. 5 for details), and a negative linear relationship was observed between the $\log(k_{Ar}/k_{Ph})$ and the substituent constants σ_p of the phenylhydrazines[71] (Fig. 7c). These findings are consistent with a transition state bearing partial positive charge in the rate-determining step, which presumably suggests the generation of the key electrophilic Cu^{III} intermediate. Based on these mechanistic results and our previous reports[59–61], we proposed a plausible mechanism as shown in Fig. 7d. First, Cu^{I} reacted with the chiral ligand **L*** and racemic α-haloamide in the presence of a base to generate a Cu^{I} intermediate **I**. Next, intermediate **I** undergoes an XAT process to form a Cu^{II}-bonded prochiral alkyl intermediate **II**, which undergoes an intramolecular radical rebound to form a Cu^{III} intermediate **III**. Subsequently, a polar outer-sphere nucleophilic attack of intermediate **III** by hydrazine derivative in the presence of a base delivers intermediate **IV**. Finally, ligand exchange with α-haloamide **E** regenerates intermediate **I** and releases the enantioenriched hydrazine, completing the catalytic cycle. For the key enantiodetermining C(sp^3)–N bond formation step, two transition states (*re*-**TS** and *si*-**TS**) are proposed, corresponding to the formation of the two product enantiomers[59] (Fig. 7e). The steric clash between the ligand sulfonyl group and the relatively bulky R^1 group in *si*-**TS** renders this transition state energetically disfavored. In contrast, the energetically favorable *re*-**TS** favors the formation of the desired products with the *S* absolute configuration, consistent with the experimental results.

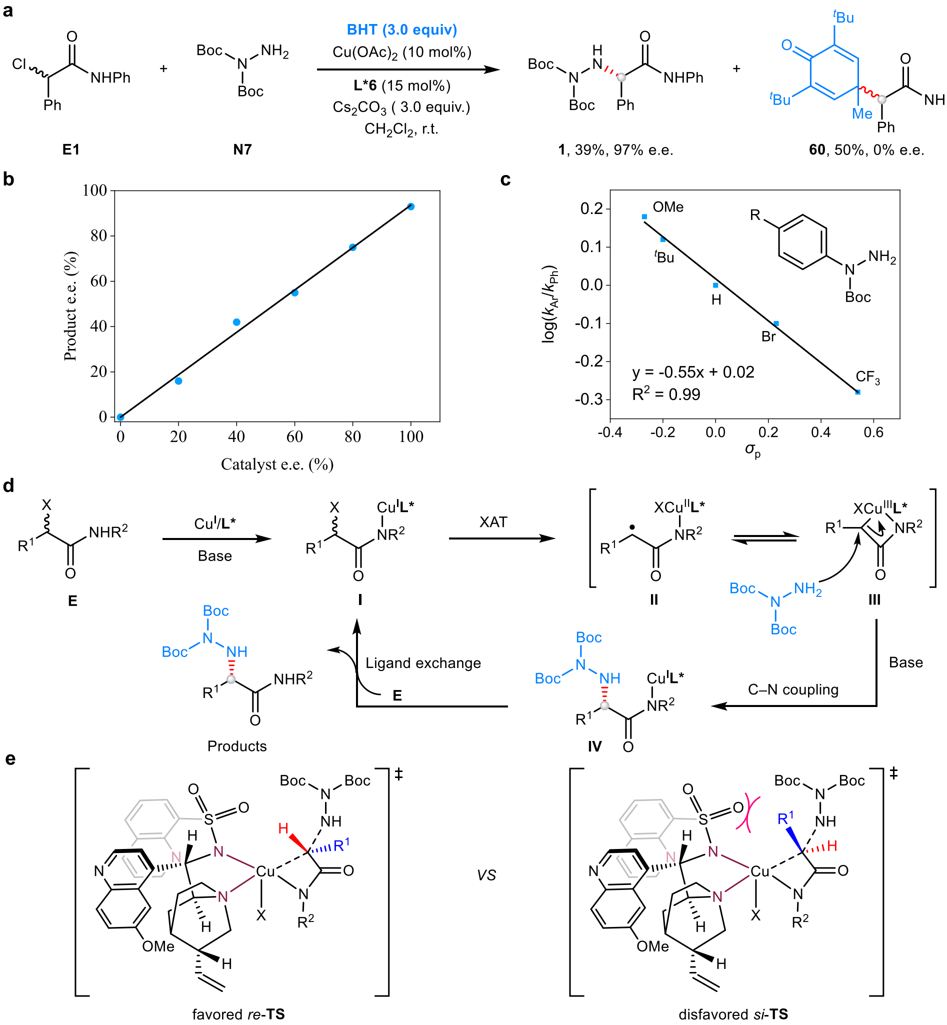

Fig. 7 | **Mechanistic experiments and proposal.** **a** Radical trapping experiment. **b** Non-linear effect study. **c** Hammett analysis with substituted phenylhydrazines. **d** Proposed mechanism. **e** Proposed enantiodiscrimination transition states. BHT butylated hydroxytoluene.

Discussion

In summary, we have developed a general copper-catalysed enantioconvergent *N*-alkylation of hydrazines with racemic α-haloamides, enabling the efficient synthesis of a wide array of useful enantioenriched hydrazines. The key to this success was the development of a radical-polar crossover nucleophilic substitution process as well as the employment of suitable hydrazine nucleophiles with readily removable protecting groups, thereby achieving remarkable regio- and enantioselectivity. The presence of readily removable protecting groups provides a highly flexible and practical platform for the construction of a series of enantioenriched *N*-amino dipeptides and azaheterocycles. More importantly, a catalytic stereodivergent process has been developed that can produce all four stereoisomers of enantioenriched hydrazines with two stereocenters, exhibiting high catalyst-controlled stereoselectivity. Further efforts will focus on developing the enantioconvergent cross-coupling of alkyl halides with more challenging nucleophiles, based on this radical-polar crossover nucleophilic substitution platform.

Methods

Representative procedure for the synthesis of 1–26, 42–50

Under an argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with $Cu(OAc)_2$ (3.6 mg, 0.02 mmol, 10 mol%), **L*6** (15.4 mg, 0.03 mmol, 15 mol%), Cs_2CO_3 (195.5 mg, 0.6 mmol, 3.0 equiv.) and anhydrous CH_2Cl_2 (2.0 mL). Then, the mixture was stirred at r.t. for 1 h. After that, racemic α-haloamides **E** (0.2 mmol, 1.0 equiv.), *N,N*-bis-Boc hydrazine **N7** (55.7 mg, 0.24 mmol, 1.2 equiv.) and anhydrous CH_2Cl_2 (2.0 mL) were sequentially added into the mixture and the reaction mixture was stirred at 10 °C for 48 h. Upon completion (monitored by thin-layer chromatography), the precipitate was filtered off and washed by EtOAc. The filtrate was evaporated and the residue was purified by preparative thin-layer chromatography on silica gel to afford the desired product.

Representative procedure for the synthesis of 27–41

Under an argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with $Cu(OAc)_2$ (3.6 mg, 0.02 mmol, 10 mol%), **L*9** (10.0 mg, 0.03 mmol, 15 mol%), Cs_2CO_3 (260.7 mg, 0.8 mmol, 4.0 equiv.) and anhydrous THF (2.0 mL). Then, the mixture was stirred at r.t. for 1 h. After that, racemic α-haloamides **E** (0.2 mmol, 1.0 equiv.), 1,1-diphenylhydrazine hydrochloride **N8** (54.0 mg, 0.24 mmol, 1.2 equiv.) and anhydrous THF (2.0 mL) were sequentially added into the mixture and the reaction mixture was stirred at r.t. for 72 h. Upon completion (monitored by thin-layer chromatography), the precipitate was filtered off and washed by EtOAc. The filtrate was evaporated and the residue was purified by preparative thin-layer chromatography on silica gel to afford the desired product.

Data availability

All data are available in the main text and Supplementary Information and also available from the corresponding author upon request. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2450611 (for **8**), 2517400 (for **27**), and 2450615 (for **42**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

References

1. Morgan, K. D., Andersen, R. J. & Ryan, K. S. Piperazic acid-containing natural products: structures and biosynthesis. *Nat. Prod. Rep.* **36**, 1628–1653 (2019).
2. Le Goff, G. & Ouazzani, J. Natural hydrazine-containing compounds: biosynthesis, isolation, biological activities and synthesis. *Bioorg. Med. Chem.* **22**, 6529–6544 (2014).
3. Zhu, H. et al. Carbidopa, a drug in use for management of Parkinson disease inhibits T cell activation and autoimmunity. *PLoS ONE* **12**, e0183484 (2017).
4. Tran, K., Lombardi, P. J. & Leighton, J. L. An efficient asymmetric synthesis of manzacidin C. *Org. Lett.* **10**, 3165–3167 (2008).
5. Wei, Z.-W. et al. Free piperazic acid as a precursor to nonribosomal peptides. *J. Am. Chem. Soc.* **144**, 13556–13564 (2022).
6. Gould, E. et al. The development of highly active acyclic chiral hydrazides for asymmetric iminium ion organocatalysis. *Org. Biomol. Chem.* **11**, 7877–7892 (2013).
7. Sarnowski, M. P., Kang, C. W., Elbatrawi, Y. M., Wojtas, L. & Del Valle, J. R. Peptide *N*-amination supports β-sheet conformations. *Angew. Chem. Int. Ed.* **56**, 2083–2086 (2017).
8. Angera, I. J., Wright, M. M. & Del Valle, J. R. Beyond *N*-alkylation: synthesis, structure, and function of *N*-amino peptides. *Acc. Chem. Res.* **57**, 1287–1297 (2024).
9. Suzuki, T. et al. Discovery of novel spiro-piperidine derivatives as highly potent and selective melanin-concentrating hormone 1 receptor antagonists. *Bioorg. Med. Chem. Lett.* **19**, 3072–3077 (2009).
10. Hughes, D. L. Patent review of manufacturing routes to recently approved oncology drugs: ibrutinib, cobimetinib, and alectinib. *Org. Process Res. Dev.* **20**, 1855–1869 (2016).
11. Sugiura, M. & Kobayashi, S. *N*-Acylhydrazones as versatile electrophiles for the synthesis of nitrogen-containing compounds. *Angew. Chem. Int. Ed.* **44**, 5176–5186 (2005).
12. He, H.-Y., Niikura, H., Du, Y.-L. & Ryan, K. S. Synthetic and biosynthetic routes to nitrogen–nitrogen bonds. *Chem. Soc. Rev.* **51**, 2991–3046 (2022).
13. Yang, P., Lim, L. H., Chuanprasit, P., Hirao, H. & Zhou, J. Nickel-catalysed enantioselective reductive amination of ketones with both arylamines and benzhydrazide. *Angew. Chem. Int. Ed.* **55**, 12083–12087 (2016).
14. Yang, P. et al. Nickel-catalysed *N*-alkylation of acylhydrazines and arylamines using alcohols and enantioselective examples. *Angew. Chem. Int. Ed.* **56**, 14702–14706 (2017).
15. Chen, T. et al. Cobalt-catalysed enantioselective reductive amination of ketones with hydrazides. *Org. Lett.* **26**, 769–774 (2024).
16. Cabré, A., Verdaguer, X. & Riera, A. Recent advances in the enantioselective synthesis of chiral amines via transition metal-catalysed asymmetric hydrogenation. *Chem. Rev.* **122**, 269–339 (2022).
17. Xu, H., Yang, P., Chuanprasit, P., Hirao, H. & Zhou, J. Nickel-catalysed asymmetric transfer hydrogenation of hydrazones and other ketimines. *Angew. Chem. Int. Ed.* **54**, 5112–5116 (2015).
18. Chen, Z.-P., Hu, S.-B., Chen, M.-W. & Zhou, Y.-G. Synthesis of chiral fluorinated hydrazines via Pd-catalysed asymmetric hydrogenation. *Org. Lett.* **18**, 2676–2679 (2016).
19. Hu, Q. et al. Rh-catalysed chemo- and enantioselective hydrogenation of allylic hydrazones. *Chem. Eur. J.* **23**, 1040–1043 (2017).
20. Hu, Y. et al. Cobalt-catalysed asymmetric hydrogenation of C=N bonds enabled by assisted coordination and nonbonding interactions. *Angew. Chem. Int. Ed.* **58**, 15767–15771 (2019).
21. Schuster, C. H., Dropinski, J. F., Shevlin, M., Li, H. & Chen, S. Ruthenium-catalysed enantioselective hydrogenation of hydrazones. *Org. Lett.* **22**, 7562–7566 (2020).
22. Hutton, A. E. et al. Engineered biocatalyst for enantioselective hydrazone reduction. *Angew. Chem. Int. Ed.* **64**, e202424350 (2025).
23. Kobayashi, S., Mori, Y., Fossey, J. S. & Salter, M. M. Catalytic enantioselective formation of C–C bonds by addition to imines and hydrazones: a ten-year update. *Chem. Rev.* **111**, 2626–2704 (2011).
24. Tan, K. L. & Jacobsen, E. N. Indium-mediated asymmetric allylation of acylhydrazones using a chiral urea catalyst. *Angew. Chem. Int. Ed.* **46**, 1315–1317 (2007).
25. Fujita, M. et al. Zn-catalysed asymmetric allylation for the synthesis of optically active allylglycine derivatives. regio- and stereoselective formal α-addition of allylboronates to hydrazono esters. *J. Am. Chem. Soc.* **130**, 2914–2915 (2008).
26. Yalalov, D. A., Tsogoeva, S. B., Shubina, T. E., Martynova, I. M. & Clark, T. Evidence for an enol mechanism in a highly enantioselective Mannich-type reaction catalysed by primary amine–thiourea. *Angew. Chem. Int. Ed.* **47**, 6624–6628 (2008).
27. Zamfir, A. & Tsogoeva, S. B. Asymmetric hydrocyanation of hydrazones catalysed by in situ formed *O*-silylated BINOL-phosphate: a convenient access to versatile α-hydrazino acids. *Org. Lett.* **12**, 188–191 (2010).
28. Jonker, S. J. T. et al. Catalytic asymmetric propargyl- and allylboration of hydrazonoesters: a metal-free approach to sterically encumbered chiral α-amino acid derivatives. *Chem. Commun.* **54**, 12852–12855 (2018).
29. Alberca, S. et al. Enantioselective synthesis of α-aryl α-hydrazino phosphonates. *Chem. Sci.* **15**, 7725–7731 (2024).
30. Nair, V., Biju, A. T., Mathew, S. C. & Babu, B. P. Carbon-nitrogen bond-forming reactions of dialkyl azodicarboxylate: a promising synthetic strategy. *Chem. Asian J.* **3**, 810–820 (2008).
31. Scarpi, D., Visi, S. & Occhiato, E. G. Recent advances in the α-hydrazination (α-amination) of carbonyl compounds. *Eur. J. Org. Chem.* **28**, e202500049 (2025).
32. Kumaragurubaran, N., Juhl, K., Zhuang, W., Bøgevig, A. & Jørgensen, K. A. Direct L-proline-catalysed asymmetric α-amination of ketones. *J. Am. Chem. Soc.* **124**, 6254–6255 (2002).
33. Poulsen, T. B., Alemparte, C. & Jørgensen, K. A. Enantioselective organocatalytic allylic amination. *J. Am. Chem. Soc.* **127**, 11614–11615 (2005).
34. Yang, Z. et al. Asymmetric α-amination of 4-substituted pyrazolones catalysed by a chiral $Gd(OTf)_3$/*N,N′*-dioxide complex: highly enantioselective synthesis of 4-amino-5-pyrazolone derivatives. *Org. Lett.* **13**, 596–599 (2011).
35. Ji, C.-B. et al. Direct amination of α-substituted nitroacetates using di-*tert*-butyl azodicarboxylate catalysed by hatakeyama's catalyst β-ICD. *Org. Biomol. Chem.* **10**, 1158–1161 (2012).
36. Paria, S., Kang, Q.-K., Hatanaka, M. & Maruoka, K. Design of efficient chiral bifunctional phase-transfer catalysts possessing an amino functionality for asymmetric aminations. *ACS Catal* **9**, 78–82 (2019).
37. Nishimura, K., Ogura, Y., Takeda, K., Guo, W. & Ishihara, K. Chiral *π*–Cu(II) catalysts for the enantioselective α-amination of *N*-acyl-3,5-dimethylpyrazoles. *Org. Lett.* **24**, 7685–7689 (2022).
38. Yang, W.-J., Zhang, J.-H., Li, N., Xie, M.-S. & Guo, H.-M. Ni(II)-catalysed enantioselective α-hydrazination of α-fluoroesters: access to chiral quaternary α-fluorinated α-amino acid derivatives. *Org. Chem. Front.* **12**, 2746–2751 (2025).
39. Sandmeier, T., Goetzke, F. W., Krautwald, S. & Carreira, E. M. Iridium-catalysed enantioselective allylic substitution with aqueous solution of nucleophiles. *J. Am. Chem. Soc.* **141**, 12212–12218 (2019).

40. Gong, Y. et al. Trifluoroethanol-assisted asymmetric propargylic hydrazination to α-tertiary ethynylhydrazines enabled by sterically confined pyridinebisoxazolines. *Nat. Commun.* **16**, 4571 (2025).
41. Zhang, D.-Y., Shao, L., Xu, J. & Hu, X.-P. Copper-catalysed asymmetric formal [3 + 2] cycloaddition of propargylic acetates with hydrazines: enantioselective synthesis of optically active 2-pyrazolines. *ACS Catal* **5**, 5026–5030 (2015).
42. Kainz, Q. M. et al. Asymmetric copper-catalysed C–N cross-couplings induced by visible light. *Science* **351**, 681–684 (2016).
43. Chen, C., Peters, J. C. & Fu, G. C. Photoinduced copper-catalysed asymmetric amidation via ligand cooperativity. *Nature* **596**, 250–256 (2021).
44. Cho, H., Suematsu, H., Oyala, P. H., Peters, J. C. & Fu, G. C. Photoinduced, copper-catalysed enantioconvergent alkylations of anilines by racemic tertiary electrophiles: synthesis and mechanism. *J. Am. Chem. Soc.* **144**, 4550–4558 (2022).
45. Chen, C. & Fu, G. C. Copper-catalysed enantioconvergent alkylation of oxygen nucleophiles. *Nature* **618**, 301–307 (2023).
46. Mondal, A. & Fu, G. C. Photoinduced, copper-catalysed enantioconvergent synthesis of β-aminoalcohol derivatives. *J. Am. Chem. Soc.* **147**, 10859–10863 (2025).
47. Zhang, Y.-F. et al. Enantioconvergent Cu-catalysed radical C–N coupling of racemic secondary alkyl halides to access α-chiral primary amines. *J. Am. Chem. Soc.* **143**, 15413–15419 (2021).
48. Zhang, Y.-F. et al. Copper-catalysed enantioconvergent radical C(sp^3)–N cross-coupling: access to α,α-disubstituted amino acids. *Angew. Chem. Int. Ed.* **62**, e202302983 (2023).
49. Chen, J.-J. et al. Copper-catalysed enantioconvergent radical C(sp^3)–N cross-coupling of activated racemic alkyl halides with (hetero)aromatic amines under ambient conditions. *J. Am. Chem. Soc.* **145**, 14686–14696 (2023).
50. Zheng, J.-J. et al. Copper-catalysed enantioconvergent radical C(sp^3)–N cross-coupling to access chiral α-amino-β-lactams. *Precis. Chem.* **1**, 576–582 (2023).
51. Zhang, Y.-F. et al. Asymmetric amination of alkyl radicals with two minimally different alkyl substituents. *Science* **388**, 283–291 (2025).
52. Hinman, R. Base strengths of some alkylhydrazines. *J. Org. Chem.* **23**, 1587–1588 (1958).
53. Gu, Q.-S., Li, Z.-L. & Liu, X.-Y. Copper(I)-catalysed asymmetric reactions involving radicals. *Acc. Chem. Res.* **53**, 170–181 (2020).
54. Dong, X.-Y., Li, Z.-L., Gu, Q.-S. & Liu, X.-Y. Ligand development for copper-catalysed enantioconvergent radical cross-coupling of racemic alkyl halides. *J. Am. Chem. Soc.* **144**, 17319–17329 (2022).
55. Dong, X.-Y. et al. A general asymmetric copper-catalysed Sonogashira C(sp^3)–C(sp) coupling. *Nat. Chem.* **11**, 1158–1166 (2019).
56. Wang, F.-L. et al. Mechanism-based ligand design for copper-catalysed enantioconvergent C(sp^3)–C(sp) cross-coupling of tertiary electrophiles with alkynes. *Nat. Chem.* **14**, 949–957 (2022).
57. Wang, L.-L. et al. A general copper-catalysed enantioconvergent radical Michaelis–Becker-type C(sp^3)–P cross-coupling. *Nat. Synth.* **2**, 430–438 (2023).
58. Tian, Y. et al. A general copper-catalysed enantioconvergent C(sp^3)–S cross-coupling via biomimetic radical homolytic substitution. *Nat. Chem.* **16**, 466–475 (2024).
59. Chen, J.-J. et al. Enantioconvergent Cu-catalysed *N*-alkylation of aliphatic amines. *Nature* **618**, 294–300 (2023).
60. Du, X.-Y. et al. Copper-catalysed enantioconvergent radical *N*-alkylation of diverse (hetero)aromatic amines. *J. Am. Chem. Soc.* **146**, 9444–9454 (2024).
61. Zhang, J.-Y. et al. Copper-catalysed enantioconvergent *O*-alkylation of alcohols with racemic α-tertiary haloamides to access enantioenriched hindered dialkyl ethers. *Nat. Catal.* **8**, 919–930 (2025).
62. Hirata, G. et al. Chemistry of tertiary carbon center in the formation of congested C–O ether bonds. *Angew. Chem. Int. Ed.* **60**, 4329–4334 (2021).
63. Nigst, T. A., Ammer, J. & Mayr, H. Ambident reactivities of methylhydrazines. *Angew. Chem. Int. Ed.* **51**, 1353–1356 (2012).
64. Tshepelevitsh, S. et al. On the basicity of organic bases in different media. *Eur. J. Org. Chem.* **2019**, 6735–6748 (2019).
65. Bredihhin, A., Groth, U. M. & Mäeorg, U. Efficient methodology for selective alkylation of hydrazine derivatives. *Org. Lett.* **9**, 1097–1099 (2007).
66. Sibi, M. P. & Soeta, T. Enantioselective conjugate addition of hydrazines to α, β-unsaturated imides. synthesis of chiral pyrazolidinones. *J. Am. Chem. Soc.* **129**, 4522–4523 (2007).
67. Tšupova, S. & Mäeorg, U. Pd-catalysed regioselective allylation of mono- and disubstituted hydrazines. *Org. Lett.* **15**, 3381–3383 (2013).
68. Xu, K., Gilles, T. & Breit, B. Asymmetric synthesis of *N*-allylic indoles via regio- and enantioselective allylation of aryl hydrazines. *Nat. Commun.* **6**, 7616 (2015).
69. Wang, Y., Xu, J.-K., Gu, Y. & Tian, S.-K. Catalytic stereospecific allylation of protected hydrazines with enantioenriched primary allylic amines. *Org. Chem. Front.* **1**, 812–816 (2014).
70. Beletskaya, I. P., Nájera, C. & Yus, M. Stereodivergent catalysis. *Chem. Rev.* **118**, 5080–5200 (2018).
71. Hansch, C., Leo, A. & Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **91**, 165–195 (1991).

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 22025103, 92256301, 22331006, to X.-Y.L.; 22401136, to J.-J.C.; 22201125, to P.-F.W.), the National Key R&D Program of China (No. 2021YFF0701604, to X.-Y.L.), Guangdong Major Project of Basic and Applied Basic Research (No. 2023B0303000020, to X.-Y.L.), Guangdong Basic and Applied Basic Research Foundation (No. 2024A1515010325, to J.-J.C.), New Cornerstone Science Foundation (to X.-Y.L.), Shenzhen Science and Technology Program (Nos. KQTD20210811090112004, to X.-Y.L. and Q.-S.G.; JCYJ20220818100600001, to X.-Y.L. JCYJ20240813094223031, to J.-J.C.), High-Level of Special Funds (No. G03050K003, to X.-Y.L.), and High-Level Key Discipline Construction Project (No. G030210001, to X.-Y.L. and Q.-S.G.) is gratefully acknowledged. The authors acknowledge the assistance of SUSTech Core Research Facilities.

Author contributions

N.L. and J.-J.C. designed the experiments and analyzed the data. N.L., S.-Y.H., P.-F.W. and J.-J.C. performed the experiments. Q.-S.G., Z.-L.L., J.-J.C. and X.-Y.L. discussed the results and wrote the manuscript. J.-J.C. and X.-Y.L. conceived and supervised the project.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-026-68961-9.

Correspondence and requests for materials should be addressed to Ji-Jun Chen or Xin-Yuan Liu.

Peer review information *Nature Communications* thanks Jian Zhou and the other anonymous reviewer(s) for their contribution to the peer review of this work. A peer review file is available.