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Enantioselective synthesis of chiral 2,3-*cis*-disubstituted piperidines and C1-substituted tetrahydroisoquinolines by asymmetric Cu-catalyzed cyclizative aminoboration

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Chiral *N*-heterocycles such as piperidines and tetrahydroisoquinolines are privileged structural motifs in drug discovery and pharmaceutical industry. The development of efficient and practical asymmetric synthetic methods towards pharmaceutically important chiral *N*-heterocycles constitutes an important subject in synthetic chemistry. Asymmetric synthesis of 2,3-*cis*-disubstituted piperidines bearing two consecutive chiral centers is particularly challenging in terms of both diastereoselective and enantioselective control. In this work, a regiospecific and enantioselective cyclizative aminoboration is designed to tackle this problem by employing Cu/(*S*, *S*)-Ph-BPE as the chiral catalyst, leading to a series of 2,3-*cis*-disubstituted piperidines as well as C1-substituted tetrahydroisoquinolines in moderate to good yields and excellent enantioselectivities. The asymmetric six-membered ring-closing aminoboration features a broad substrate scope, mild reaction conditions, and excellent functional group compatibility. DFT calculation reveals the importance of noncovalent interactions between substrate and Cu catalyst in controlling the enantioselectivity. The synthetic utility and practicality of this cyclization protocol have been exemplified by the synthesis of the key chiral intermediates of avacopan and L-733,060.

Chiral substituted *N*-heterocycles such as piperidines, tetrahydroquinolines, and tetrahydroisoquinolines exist widely in the structures of biologically important natural products[1,2]. They also serve as privileged structural motifs in medicinal chemistry and drug discovery, as demonstrated by a number of chiral *N*-heterocyclic therapeutic agents (Fig. 1A)[3–5]. Among them, the 2,3-*cis*-disubstituted piperidines belong to a class of important *N*-heterocycles existed in the structures of C5a receptor inhibitor avacopan[6], NK_1 antagonist L-733,060[7] and vofopitant[8]. According to a recent search result from SciFinder, more than 6000 known natural products possess chiral 2,3-*cis*-disubstituted piperidine moieties, and over 300,000 therapeutic agents as well as intermediates contain such chiral motif, manifesting its privileged role in drug discovery and pharmaceutical industry. The prevalence and biological functions of such structures have rendered their syntheses an important research topic. However, most chiral 2,3-disubstituted piperidines and derivatives in pharmaceutical industry currently relied on chiral feedstock through multi-step synthesis[9–13] or inefficient chemical resolution(Fig. 1B)[14]. A two-step strategy of asymmetric organocatalytic bromoaminocyclization of linear olefins was developed by Yeung to initially generate chiral *trans*-2-aryl-3-

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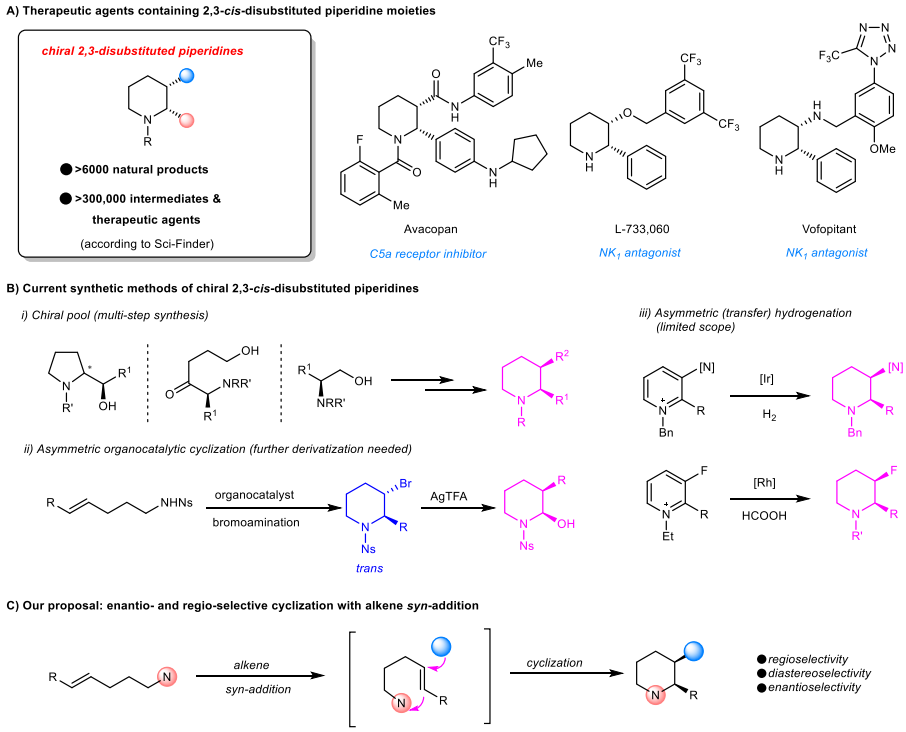

Fig. 1 | Asymmetric synthesis of chiral *N*-heterocycles. A Therapeutic agents containing chiral 2,3-*cis*-disubstituted piperidine moieties. **B** Current synthetic methods of chiral 2,3-*cis*-disubstituted piperidines. **C** Our proposal for synthesis of chiral 2,3-*cis*-disubstituted piperidines.

bromopiperidines and subsequently convert to 2,3-*cis*-subsituted piperidines[15]. The ideal asymmetric hydrogenation or transfer hydrogenation of substituted pyridinium salts with noble metal catalysts were recently accomplished by Zhang[16] and Xiao[17], respectively, to form directly chiral *cis*-2-aryl-3-aminopiperidines and *cis*-2-aryl-3-fluoropiperidines, albeit with limited substrate scope. Despite these advances, efficient asymmetric synthesis of chiral 2,3-*cis*-substituted piperidines with excellent diastereoselective and enantioselective control remains scarce but highly desirable. We envisioned that a ring-forming alkene *cis*-difunctionalization of a readily accessible unsaturated amine would form a 2,3-*cis*-disubsituted piperidines in a highly efficient fashion (Fig. 1C). The question is how to achieve high regioselectivity, diastereoselectivity, and enantioselectivity of such transformation.

Alkene difunctionalizations has become a straightforward approach to install two *syn*-functional groups across a carbon-carbon double bond[18–20]. The copper-catalyzed alkene aminoboration pioneered by Hirano and Miura utilizes *syn*-addition of a boron-copper(I) species over alkene followed by oxidative addition of acyloxyamine and reductive elimination, forming 2-borylated-1-amine product with perfectly *syn* relation[21–30](Fig. 2A). The copper-catalyzed intramolecular cyclizative alkene aminoboration has been explored, providing exclusively 5-membered *N*-heterocycles on terminal olefinic substrates[23]. The excellent regioselectivity observed on boron-copper(I) addition is presumably governed by steric reason, with boron adding on the terminal carbon (Fig. 2B)[31,32]. However, regioselective formation of 6-membered *N*-heterocycles by copper-catalyzed alkene aminoboration has never been reported. We envisioned that incorporation of an aryl coordination during boron-copper(I) addition would alter the regioselectivity during boron-copper(I) addition and such coordinatively controlled cyclizative aminoboration would form *cis*-2-aryl-3-borylated piperidines in one step from an easily accessible arylalkene with acyloxyamine moiety (Fig. 2C). Herein we report an enantioselective copper-catalyzed cyclizative aminoborylation, forming *cis*-2-aryl-3-substituted piperidines in high yields and excellent enantioselectivity. The cyclizative aminoboration method is also extended to *ortho*-substituted styrene substrates, leading to a series of chiral C1-substituted tetrahydroisoquinolines in highly enantioselective fashion.

Results and discussion

The development of cyclizative aminoborylation protocol

(*E*)-*O*-Benzoyl-*N*-benzyl-*N*-(5-phenylpent-4-en-1-yl)hydroxylamine (**1a**) was prepared as the substrate of study for copper-catalyzed intramolecular cyclizative alkene aminoboration. The reactions were carried out at rt in a designated solvent in the presence of a base (3 eq.) and B_2pin_2 (1.5 eq.) for 72 h with a copper precursor (10 mol %) and chiral ligand (10 mol %) (Table 1). The aminoboration products were directly treated with $NaBO_3$ to form the corresponding alcohols **2a** for ease of purification, whoses ee values were determined by chiral HPLC. The ligand effect for the asymmetric cyclizative aminoboration of **1a** was evaluated with different types of chiral bidentate ligands (See Supplementary Information for details) and (*S*, *S*)-Ph-BPE turned out to be the best ligand, providing **2a** in 47% yield and 87% ee (Table 1, entry 1) and no formation of 5-membered *N*-heterocycle side-product was observed. Subsequently, (*S*, *S*)-Ph-BPE was chose as the ligand to investigate the solvent effect of this reaction (Table 1, entries 2–4). When 1,4-dioxane was used as the solvent, **2a** was obtained with comparable enantioselectivity to that observed in THF, but with an improved yield (61%). The use of toluene or chlorobenzene was found to be beneficial to enantioselectivity. Notably, when chlorobenzene was used as the solvent, the product was obtained in 95% ee. However, the reaction yield dropped dramatically to 35% due to the low reactivity. To improve the reaction yield, we used chlorobenzene as the solvent to explore the base effect (Table 1, entries 5–7) and the protecting group of hydroxylamines (Details were included in Supplementary Information). When substrate **1a'** was used and the base was switched from KO*t*Bu to KOMe, the reaction yield increased to 50% (Table 1, entry 9) and the enantioselectivity was elevated to 96% ee. It should be noted that employment of 2 eq B_2pin_2 and 4 eq. KOMe led to

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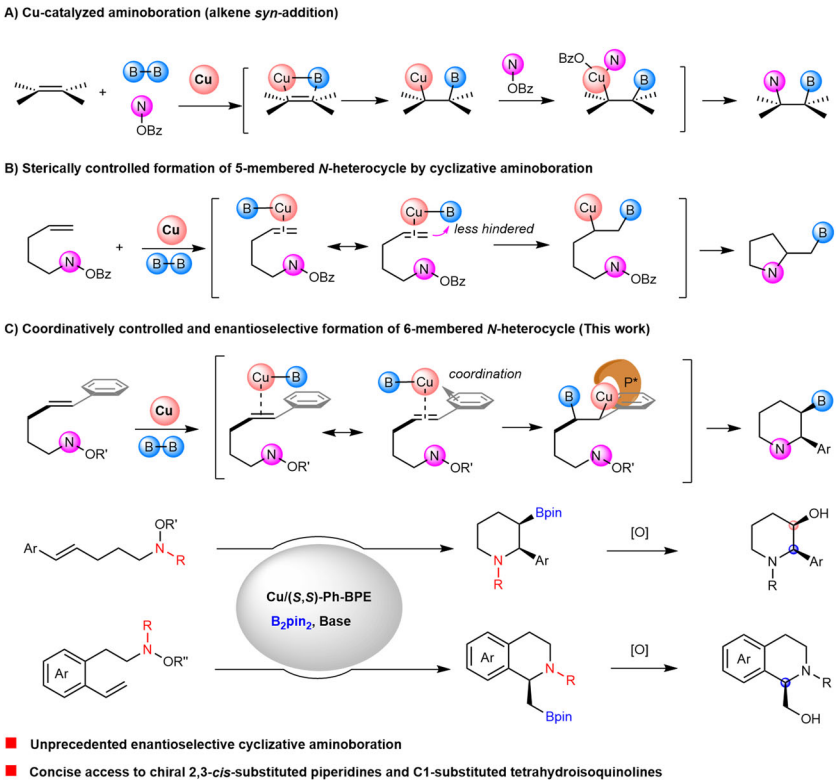
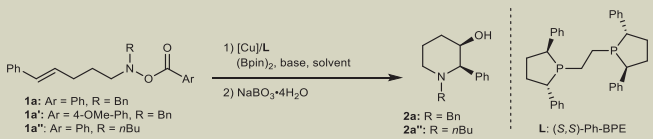


Fig. 2 | Regioselective and enantioselective cyclizative aminoboration. **A** Copper-catalyzed alkene *cis*-aminoboration. **B** Sterically controlled formation of 5-membered *N*-heterocycle by copper-catalyzed cyclizative aminoboration. **C** Coordinatively controlled formation of chiral 6-membered *N*-heterocycle by enantioselective copper-catalyzed cyclizative aminoboration.

Table 1 | Optimization studies



entry	[Cu]	base	solvent	yield	ee
'1	$Cu(CH_3CN)_4PF_6$	LiO*t*Bu	THF	47%	87%
2	$Cu(CH_3CN)_4PF_6$	LiO*t*Bu	Dioxane	61%	89%
3	$Cu(CH_3CN)_4PF_6$	LiO*t*Bu	Toluene	45%	91%
4	$Cu(CH_3CN)_4PF_6$	LiO*t*Bu	PhCl	35%	95%
5	$Cu(CH_3CN)_4PF_6$	NaOMe	PhCl	30%	95%
6	$Cu(CH_3CN)_4PF_6$	KO*t*Bu	PhCl	37%	95%
7	$Cu(CH_3CN)_4PF_6$	KOMe	PhCl	41%	96%
8[a]	$Cu(CH_3CN)_4PF_6$	KOMe	PhCl	23%	95%
9[b]	$Cu(CH_3CN)_4PF_6$	KOMe	PhCl	50%	96%
10[b]	CuI	KOMe	PhCl	45%	94%
11[b]	$[CuOTf]_2$·benzene	KOMe	PhCl	58%	96%
12[b]	**$[CuOTf]_2$·benzene**	**NaOMe**	**PhCl**	**75%(70%[c])**	**96%**
13[d]	$[CuOTf]_2$·benzene	NaOMe	PhCl	35%	98%

Reaction Conditions: (1) **1a** (0.11 mmol), B_2pin_2 (1.5 eq.), [Cu] (10 mol%), L (10 mol%), base (3 eq.), solvent (1 mL), 72 h; (2) $NaBO_3·4H_2O$ (5 eq.), THF/H_2O (v/v = 2/1); NMR yields; ee values were determined by chiral HPLC.
[a]B_2pin_2 (2 eq.), base (4 eq.).
[b]**1a'** as substrate.
[c]isolated yield.
[d]**1a''**as substrate.

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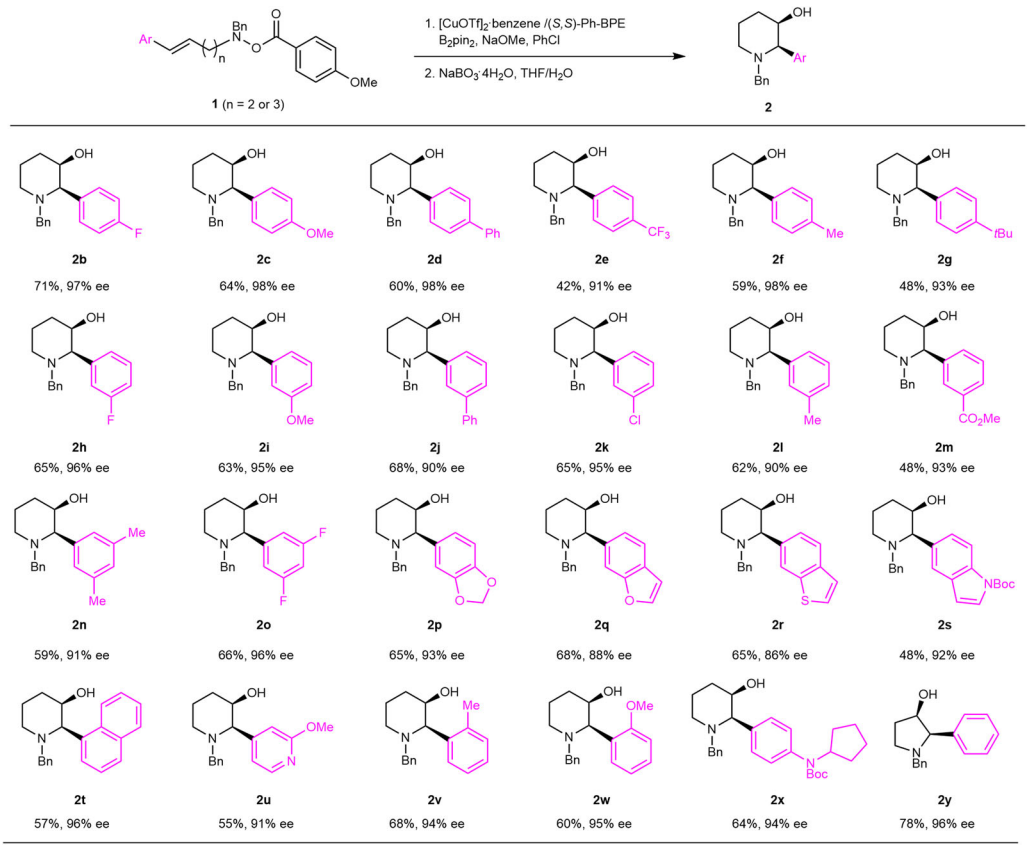

Fig. 3 | Enantioselective synthesis of 2,3-disubstituted piperidines. [a]Reaction conditions: 1) **1** (0.11 mmol), B_2pin_2 (1.5 eq.), $[CuOTf]_2$·benzene (5 mol%), (*S,S*)-Ph-BPE (10 mol%), NaOMe (3 eq.), 72 h; 2) $NaBO_3·4H_2O$ (5 eq.), THF/H_2O (v/v = 2/1); isolated yields; ee values were determined by chiral HPLC.

a decrease of the reaction yield (23%) (Fig. 3, entry 8), presumably due to substrate decomposition. Further optimization of reaction conditions indicated that $[CuOTf]_2$·benzene was a suitable copper source and product **2a** was obtained in 70% yield and 96% ee with NaOMe as the base (Table 1, entries 10-12). It was noted that styrene substrate possessing other *N*-alkyl groups, such as *n*-butyl group, was also tolerated and the reaction gave product **2a"** in 98% ee, albeit in decreased yield (35% yield) (entry 13).

With the optimized reaction conditions, we set out to investigate the scope of the cyclizative asymmetric aminoboration in the synthesis of chiral 2,3-disubstituted piperidines (Fig. 3). Firstly, substrates with various *para*-substituents on the aromatic ring, including methyl, *tert*-butyl, methoxy, phenyl, fluorine, and trifluoromethyl groups, were employed and all reactions yielded the corresponding cyclic products in moderate to good yields and with 91–98% ee (**2b**-**2g**). Substrates with different *meta*-substituents, including ester, phenyl, fluorine, chlorine, methyl, and methoxy groups, were all compatible to the aminoboration conditions (**2h**-**2m**). The reaction was also tolerable with substrates bearing two substituents on the benzene ring, producing the target products **2n**-**2p** in good yields and 91–96% ee. Substrates containing various heteroaryl rings were all suitable as chiral piperidine products (**2q**-**s, 2u**) possessing benzofuran, benzothiophene, indole, and pyridine rings were obtained in good yields and high enantioselectivities. In addition, the reaction proceeded smoothly with sterically hindered *ortho*-substituted aryl alkenes and products **2t, 2v** and **2w** were all isolated with good yields and 94–96% ee. Notably, the cyclizative aminoboration reaction enabled the synthesis of 4-cyclopentylamine-substituted product **2x** in 64% yield and 94% ee, which was the core scaffold of the anti-angiolipoma drug avacopan. Finally, 2,3-disubstituted pyrrolidine **2y** was successfully synthesized in 78% yield and 96% ee under the current conditions from the corresponding acyclic olefin substrate.

Synthetic applications

To demonstrate the synthetic utilities of the asymmetric cyclizative aminoboration protocol, a scale-up experiment of substrate **1a'** was conducted at 2 mmol scale (Fig. 4A). The reaction proceeded smoothly and yielded chiral piperidine **2a**, the key chiral intermediate of NK1 antagonist L-733,060[11], in 62% yield and 96% ee. Furthermore, chiral piperidine derivatives **3** and **4** were successfully synthesized in good yields and high enantioselectivities by reacting the in situ formed **2a'** with furan-2-yl-lithium and thiophene-2-yl-lithium, respectively (Fig. 4B). A one-carbon elongation was accomplished from **2a'** under Matteson conditions and subsequent oxidation afforded primary alcohol **5** in 48% overall yield and 96% ee. Additionally, Zweifel-type olefination of **2a'** delivered the vinylation product **6** in 93% yield with 94% ee. Finally, compound **1x** proceeded the cyclizative aminoboration under similar reaction conditions at 1.2 mmol scale, forming chiral alcohol **7** in 52% yield and 95% ee (Fig. 4C). Subsequent swap of the benzyl protecting group with Boc group successfully afforded compound **8**, a key chiral intermediate for asymmetric synthesis of *ent*-avacopan[33]. The successful formation of key chiral intermediates of several therapeutic agents demonstrated the practicality and usefulness of this methodology.

Enantioselective synthesis of tetrahydroisoquinolines

Chiral C1-substituted tetrahydroisoquinolines exist widely in the structures of numerous biologically active natural products[34–36]. The enantioselective Cu-catalyzed cyclizative aminoboration could also extend to *ortho*-substituted styrene substrates **9**. Asymmetric

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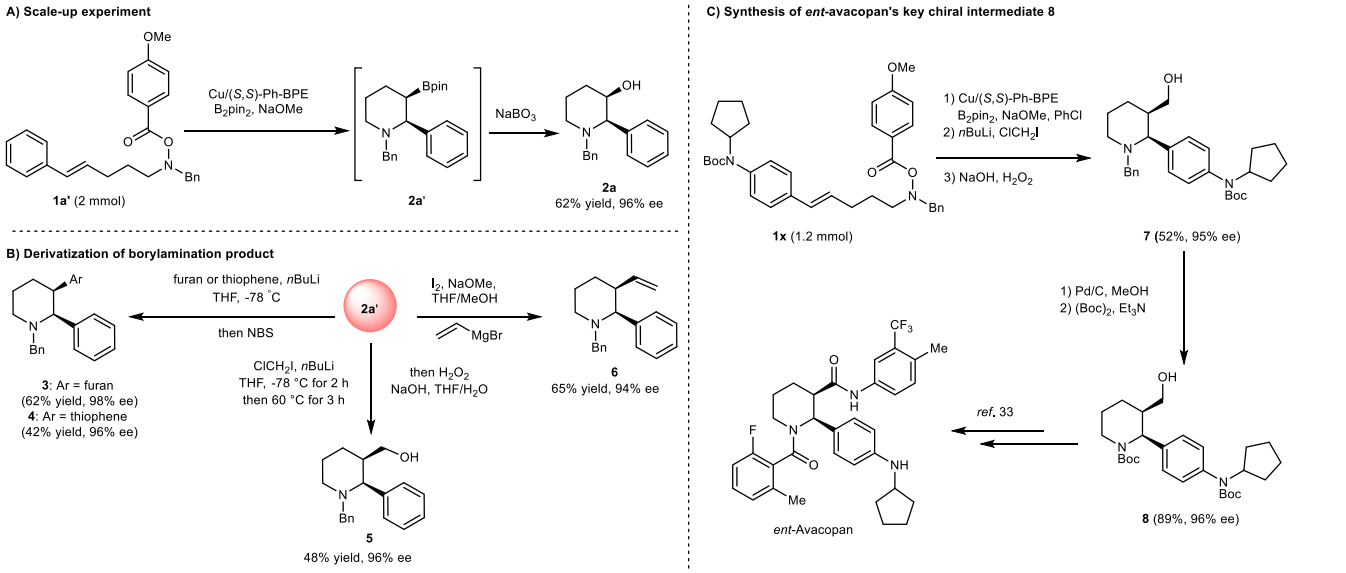

Fig. 4 | Synthetic applications. A Scale-up experiment. **B** Derivatization of borylamination product. **C** Synthesis of ent-avacopan's key chiral intermediate **8**.

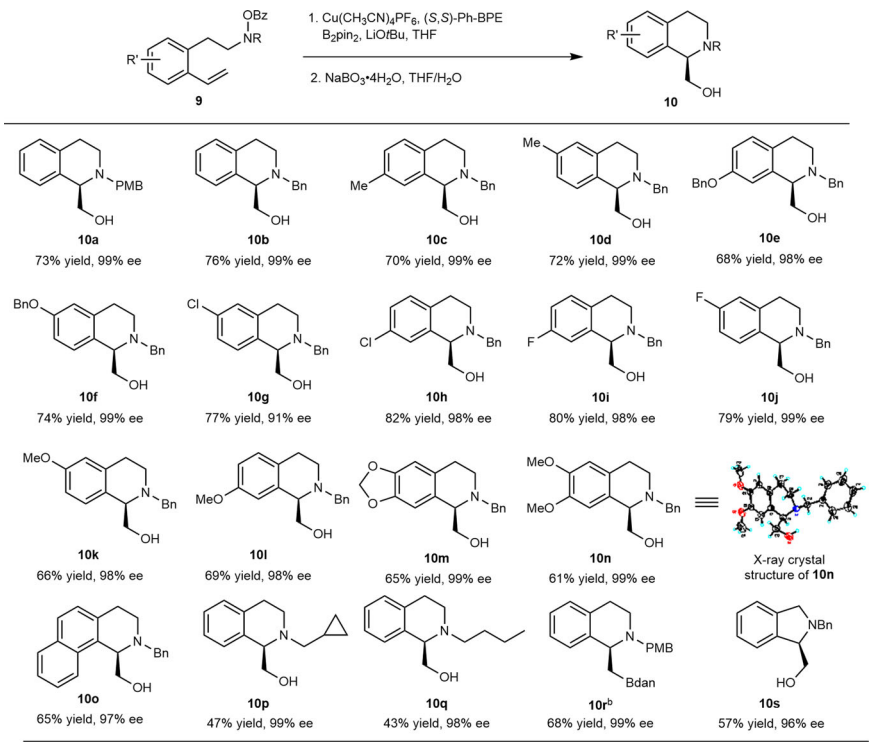

Fig. 5 | Enantioselective synthesis of tetrahydroisoquinolines. [a]Reaction conditions: 1) **9** (0.25 mmol), B_2pin_2 (1.5 eq.), $Cu(CH_3CN)_4PF_6$ (10 mol%), (*S,S*)-Ph-BPE (10 mol%), LiO*t*Bu (3 eq.), THF (2 mL), 24 h; 2) $NaBO_3{\cdot}4H_2O$ (5 eq.), THF/H_2O (v/v = 2/1). Isolated yields; ee values were determined by chiral HPLC. [b]using Bpin-Bdan as B source.

cyclizative aminoboration of **9** proceeded at rt in THF in the presence of LiO*t*Bu (3 eq.) and B_2pin_2 (1.5 eq.) with $Cu(CH_3CN)_4PF_6$ (10 mol %) and (*S, S*)-Ph-BPE (10 mol%) as the catalyst system, leading to a series of chiral C1-hydroxymethyl substituted tetrahydroisoquinolines in moderate to good yields and almost perfect enantioselectivities after $NaBO_3$ oxidation (Fig. 5). The reaction was compatible with various substituents on the benzene ring including methyl, methoxy, fluorine, chlorine, and benzyloxy groups, affording products **10a**–**l** in good yields (66-82%) and excellent enantioselectivities (91-99% ee's). Substrates bearing anthracenyl, piperonyl, and 3,4-dimethoxy groups were all tolerable, providing **10m**-**10o** in acceptable yields (61-65%) and high ee values (97-99%). Furthermore, styrenes with *N*-butyl and *N*-cyclopropylmethyl amine moieties were fine substrates, giving rise to **10p** and **10q**, respectively, in high ee's (96-98%). The relatively low yields of **10p** and **10q** were presumably due to the instability of trialkyl tertiary amine products during $NaBO_3$ oxidation. Moreover, when the boron source was changed to Bpin-Bdan, the reaction afforded the Bdan-substituted product **10r** in 68% isolated yield without interfering the high enantioselectivity (99% ee). Additionally, isoindoline product **10s** was successfully obtained in 57% yield and 96% ee, demonstrating the generality of this cyclization for the synthesis of chiral *N*-heterocyclic compounds.

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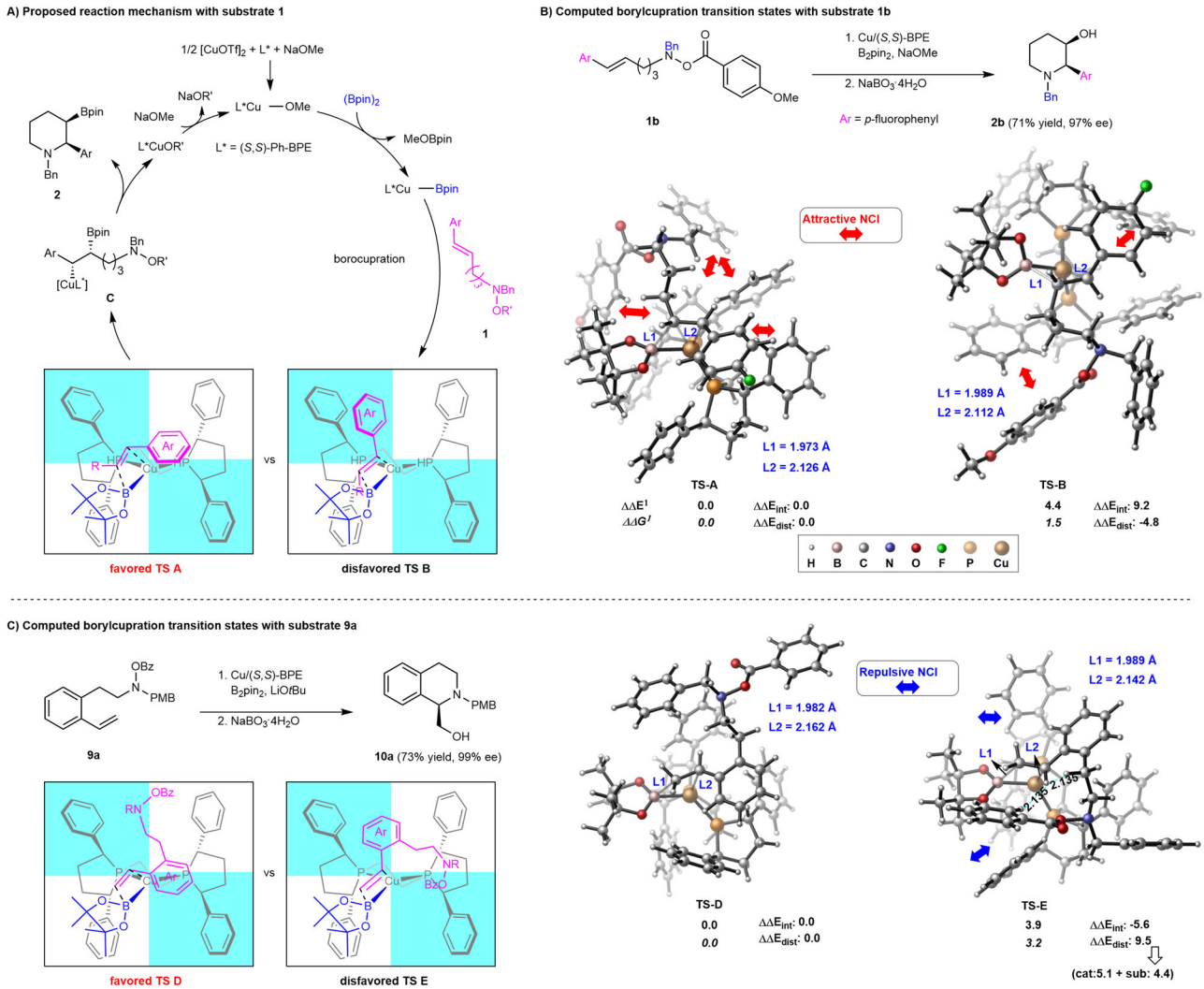

Fig. 6 | Proposed catalytic cycle and DFT calculation results on enantio-determining steps in the synthesis of 2b (TS-A vs. TS-B) and 10a (TS-D vs. TS-E). **A** Proposed catalytic cycle. **B** Computed borylcupration transition states with substrate 1b and proposed stereochemical models. **C** Computed borylcupration transition states with substrate 9a and proposed stereochemical models. Relative electronic energies (ΔE, bold decimals), Gibbs free energies (ΔG, bold italic decimals), interaction energy (ΔEint) and distortion energy (ΔEdist) in kcal/mol are presented. Calculated at M06/6-311 + G(d,p)/SDD//B3LYP/6-31 G(d)-D3/SDD level, with SMD solvation model (solvent = chlorobenzene).

Mechanistic studies

A plausible reaction mechanism was proposed for the current cyclizative aminoboration reaction based on related reports on Cu-catalyzed borylative reactions (Fig. 6A)[21,29,37–40]. An active copper-boron species is initially formed in the presence of base and B_2pin_2. This species then engages in the migratory insertion with the carbon-carbon double bond of substrate (borocupration process), generating an alkyl-copper intermediate **C**. The intermediate subsequently undergoes a cyclizative C-N bond formation to afford product **2** and regenerates the active copper catalyst. The borocupration process is conceived to be the enantio-determining step and DFT calculations were performed in order to illuminate the origin of enantioselectivity. As shown in Fig. 6B, the optimized structure of favored TS **A**, in which the two substituents of the *trans* olefin substrate would orientate towards the two vacant quadrants of the Cu/(*S*, *S*)-Ph-BPE catalyst (Fig. 6A), is stabilized by numerous C-H···H-C and C-H···π non-covalent interactions (NCIs) between the substrate and Cu species. On the contrary, notably fewer NCIs are observed for disfavored TS **B** (See supplementary Figs S3–S6 for detailed NCI analysis). The calculated difference in Gibbs free energy barrier between favored TS **A** which leads to piperidine product with observed configuration and disfavored TS **B** providing the opposite configuration is 1.5 kcal/mol, which is in line with the obtained enantioselectivity. In the synthesis of tetrahydroisoquinoline **10a** from **9a**, the bulky aryl moiety of olefin **8a** would reside at one of the unshielded quadrants upon approaching the catalytic active site of Cu catalyst, while the Bpin unit would be accommodated at the other unhindered quadrant, giving TS **D** and TS **E** (Fig. 6C). The calculated difference in Gibbs free energy barrier between the two transition states is 3.2 kcal/mol. TS **D** is the favored transition state leading to **10a** in 99% ee, while TS **E** is found to be higher in energy due to several repulsive NCIs between olefin substrate and ligand backbone, as well as within Cu-Bpin species (See supplementary Figs S3–S6 for detailed NCI analysis).

In conclusion, we have developed a Cu-catalyzed asymmetric cyclizative aminoboration taking advantage of a coordinately controlled regioselective borocupration, providing a general and practical way for the synthesis of pharmaceutically important chiral 2,3-*cis*-disubstituted piperidines in moderate to good yields and excellent enantioselectivities. The method features mild reaction conditions, good functional group tolerance, excellent regioselectivity, diastereoselectivity and enantioselectivity with Cu/(*S*, *S*)-Ph-BPE as the catalyst system. Its broad substrate scope has also extended to the expeditious

synthesis of C1-substituted tetrahydroisoquinolines and isoindolines in excellent enantioselectivities. DFT calculation reveals the importance of noncovalent interactions between substrate and Cu catalyst in controlling the enantioselectivity. The facile synthesis of key chiral piperidine intermediates of avacopan and L-733,060 has demonstrated the synthetic utilities and practicality of asymmetric cyclizative aminoboration for drug discovery and pharmaceutical development.

Methods

General procedure for the synthesis of chiral 2,3-disubstituted piperidines

To a sealed tube was added $[CuOTf]_2$·PhH (5 mol%), (*S, S*)-Ph-BPE (10 mol%), NaOMe (3.0 eq.) and anhydrous PhCl (1.0 mL) in the glove box. The tube was stirred for 5 min before the addition of a solution of B_2pin_2 (1.5 eq.) in anhydrous PhCl (0.5 mL). After 15 min, the hydroxylamine ester **1**(1 eq.) in anhydrous PhCl (0.5 mL) was added. Then the tube was sealed, taken out of the glove box and stirred at rt for 72 h before quenching with water (20 mL). The mixture was extracted with EtOAc (20 mL×3) and the organic phases were combined and concentrated. The residue was dissolved in THF/water (4 mL/2 mL), followed by addition of $NaBO_3$·$4H_2O$ (5 eq.). After 16 h, the reaction was quenched with saturated $Na_2S_2O_3$ (aq) (5 mL). The mixture was extracted with EtOAc (20 mL×3). The organic phases were combined and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by silica gel column chromatography (A mixture of PE/EA with the appropriate ratio as the eluent).

General procedure for the synthesis of chiral tetrahydroisoquinolines

To a sealed tube was added $Cu(CH_3CN)_4PF_6$ (10 mol%), (*S, S*)-Ph-BPE (10 mol%), Li*O*t*B*u (3.0 eq.) and anhydrous THF (1.0 mL). The tube was evacuated and refilled with argon and stirred for 5 min before the addition of a solution of B_2pin_2 (1.5 eq.) in anhydrous THF (0.5 mL). After 15 min, the hydroxylamine ester **9** (1 eq.) in anhydrous THF (0.5 mL) was added to the tube and the mixture was stirred at rt for 24 h before quenching with water (20 mL). The mixture was extracted with EtOAc (20 mL×3) and concentrated. The residue was dissolved in THF/water (4 mL/2 mL), followed by addition of $NaBO_3$·$4H_2O$ (5 eq.). After 16 h, the reaction was quenched with saturated $Na_2S_2O_3$ (aq) (5 mL). The mixture was extracted with EtOAc (20 mL×3). The organic phases were combined and dried over Na_2SO_4. After filtration and concentration, the product was purified by silica gel column chromatography (A mixture of PE/acetone with the appropriate ratio as the eluent).

Data availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. X-ray crystallographic data for **10n** are found in Fig. S1.

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Author contributions

D. Z. performed experiments. Q. Z. performed DFT calculations. W. T. and H. Y. conceived and directed the project and wrote the paper. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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