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Introduction

Atropisomers, the most widely recognized class of compounds featuring axial chirality, consist of conformers with restricted rotation around a single bond that enable their isolation in a stable form. In recent decades, significant advancements have been made in the construction of atropisomeric scaffolds, particularly with respect to highly developed C_{sp},-C_{sp} axis biaryls1 and styrenes.2 In stark contrast, despite the widespread occurrence of C-N axis in bioactive compounds3 (Fig. 1A) and chiral ligands⁴ (Fig. 1B), the catalytic asymmetric synthesis of these atropisomeric scaffolds is seldom reported due to their inherently less stable configuration and lower rotational barrier.5 Traditional strategies for the construction of such enantioenriched frameworks rely on the functional group conversion of the existing C_{sp2}-N axis,⁶ such as N-functionalidesymmetrizations,8 zations,⁷ asymmetric cyclizations.⁹

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Organocatalytic enantioselective synthesis of C_{sp_2} -N atropisomers *via* formal C_{sp_2} -O bond amination[†]

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Compared with well-developed construction of $C_{sp_2}-C_{sp_2}$ atropisomers, the synthesis of $C_{sp_2}-N$ atropisomers remains in its infancy, which is recognized as both appealing and challenging. Herein, we achieved the first organocatalyzed asymmetric synthesis of $C_{sp_2}-N$ atropisomers by formal $C_{sp_2}-O$ amination. With the aid of a suitable acid, 3-alkynyl-3-hydroxyisoindolinones reacted smoothly with 1-methylnaphthalen-2-ols to afford a wide range of atropisomers by selective formation of the $C_{sp_2}-N$ axis. Particularly, both the kinetic (*Z*)-products and the thermodynamic (*E*)-products could be selectively formed. Furthermore, the rarely used combination of two chiral Brønsted acid catalysts achieved excellent enantiocontrol, which is intriguing and unusual in organocatalysis. Based on control experiments and DFT calculations, a cascade dehydration/addition/rearrangement process was proposed. More importantly, this work provided a new plat-form for direct atroposelective construction of the chiral $C_{sp_2}-N$ axis.

Although central-to-axial chirality conversion can induce chiral C–N axes, it is not a one-step synthesis.¹⁰ In this context, catalytic enantioselective construction of the C_{sp_2} –N axis is the most direct strategy, but this is also a highly challenging task that has been limitedly explored.

Currently, direct atroposelective construction of chiral C_{sp_2} -N axis mainly relies on two strategies: (i) organocatalytic asymmetric amination reactions, including electrophilic amination of electron-rich naphthalenes with azodicarboxylates/ quinone diimines¹¹ and nucleophilic amination of azonaphthalenes with electron-rich amines^{4c} (Scheme 1A); (ii) metalcatalyzed asymmetric coupling reactions of secondary amines with aryl halides¹² or diazo compounds¹³ (Scheme 1B). In both scenarios, limited substrate scope and harsh reaction conditions constitute the major issues. Particularly, Lin *et al.*



Fig. 1 Selected C-N atropisomeric compounds.



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gracefully disclosed a chiral phosphoric acid (CPA)-catalyzed atroposelective cascade reaction among 2,3-diketoesters, aromatic amines and 1,3-cyclohexanediones for the construction of axially chiral *N*-arylindoles (Scheme 1C).¹⁴ The reaction, however, still necessitated the utilization of dichloromethane at a temperature of 65 °C. Consequently, new efficient methods under mild conditions for the direct atroposelective construction of the $C_{sp,}$ –N bond remain in high demand.

It is known to be challenging to break a C_{sp}-O bond attached to electron-rich aromatic rings, as a result of the high C-O bond dissociation energy. Generally, transition metal catalysts, including Ni- and Pd-catalysts, are required for such C-O bond activation.¹⁵ It is also known that aryl C-O bonds can be converted to C-N bonds with transition-metal-catalyzed catalysis, but no success has been achieved for direct construction of a chiral C_{sp2}-N axis by C_{sp2}-O bond activation.¹⁶ Moreover, transition-metal-free amination often necessitates harsh conditions, such as high temperature and strong alkali.17 Based on our previous research on indolinone derivatives18 and in continuation of our efforts on the organocatalytic reactions of functionalized alcohols,19 herein we discovered an intriguing dehydration/addition/rearrangement reaction between 1substituted naphthols and indolinone derivatives leading to the formation of unusual Csp2-N atropisomeric scaffolds (Scheme 1D). More importantly, the catalytic asymmetric variant of this process has also been achieved by the combination of two chiral Brønsted acid catalysts.20

Results and discussion

We employed 1-methylnaphthalen-2-ol **1a** (ref. 21) and 3alkynyl-3-hydroxyisoindolinone **2a** as the model substrates for this study. Initially, different Brønsted acids were chosen as catalysts in view of their proven performance (Table 1). In the presence of different sulfonic acids (A1–A3) and sufonimides (A4–A5) (Table 1, entries 1–5), two isomeric products (*Z*)-**3aa** and





 a Unless noted, under Ar atmosphere, a mixture of **1a** (0.05 mmol), **2a** (0.10 mmol) and **A** (10 mol%) in the solvent (0.5 mL) was stirred at room temperature (rt) for 24 h. b Determined by ¹H NMR with CH₂Br₂ as internal standard.

(*E*)-**3aa** were observed, which contained a newly formed C_{sp_2} -N axis. Furthermore, it was also found that compound (*Z*)-**3aa** was the kinetic product, and the thermodynamic product (*E*)-**3aa** could be obtained from (*Z*)-**3aa** under the stronger Brønsted acidic conditions (details in mechanism studies). After careful screening of Brønsted acids, **A1** was identified as the optimal catalyst to obtain the product (*Z*)-**3aa** with a yield of 63% (Table 1, entry 1). Alternatively, **A3** could enable the formation of (*E*)-**3aa** with an improved yield of 83% (Table 1, entry 3). The further solvent evaluation revealed that CH_2Cl_2 was the optimal choice (Table 1, entries 6–8). Importantly, by adjusting substrate concentration, an improved yield of product (*Z*)-**3aa** was achieved (Table 1, entries 9–11).

Under the optimized conditions, the scope of the cascade dehydration/addition/rearrangement reaction between 1methylnaphthalen-2-ols 1 and 3-alkynyl-3hydroxyisoindolinones 2 was examined at a relatively larger scale. Because the target products (Z)-3 could be converted to the thermodynamic products (E)-3, the time of each reaction was monitored by thin-layer chromatography (TLC). In some of these reactions, the amount of A1 was increased to 20 mol% to shorten the reaction time to reduce isomerization. As shown in Table 2A, a range of naphthols 1a-j reacted smoothly with 3alkynyl-3-hydroxyisoindolinone 2a to provide the corresponding (Z)-2-(naphthalen-2-yl)-isoindolin-1-ones (Z)-3aa-ja in moderate yields. These encouraging results indicated that the protocol could be applied to naphthols bearing different substituents, including trimethylsilyl (SiMe3, Table 2, (Z)-3ia) and terminal olefin (Table 2, (Z)-3ja). In addition, the A1-catalyzed reaction also showed excellent compatibility with 3-alkynyl-3hydroxyisoindolinones bearing different substituents in the

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Table 2Scope of reactions for (Z)-3 and (E)-3



^{*a*} A mixture of **1** (0.20 mmol), **2** (0.40 mmol) and **A1** (10 mol%) in CH₂Cl₂ (4.8 mL) was stirred at room temperature (rt) under Ar atmosphere for noted time. ^{*b*} A mixture of **1** (0.20 mmol), **2** (0.40 mmol) and **A1** (20 mol%) in CH₂Cl₂ (6.0 mL) was stirred at 30 °C under Ar atmosphere for the noted time. ^{*c*} A mixture of **1** (0.20 mmol), **2** (0.40 mmol) and **A3** (10 mol%) in CH₂Cl₂ (2.4 mL) was stirred at rt under Ar atmosphere for 24 h.

benzene ring, affording the desired products (*Z*)-**3ab–ah** in moderate to high yields (Table 2B). However, the methyl group in the 1-position of naphthol seemed to be essential. Replacing it by other substituents (H, Et) would lead to a complex mixture instead of desired product. The reaction of 1,3dimethylnaphthalen-2-ol also resulted in the complex mixture. The configuration of (*Z*)-**3aa** was unambiguously confirmed by X-ray crystallography (CCDC 2294518). The configurations of other products were assigned by analogy.

The generality for the formation of the thermodynamic products (E)-3 was also examined (Table 2C). Notably, the presented products were obtained in high yields after further optimizations. Exceptionally, some thermodynamic products

were either formed in low efficiency or hard to isolated from the reaction mixture. The configuration of (*E*)-**3aa** was confirmed by X-ray crystallography (CCDC 2294530). Taken together, a divergent cascade reaction between 1-methylnaphthalen-2-ols and 3-alkynyl-3-hydroxyisoindolinones was achieved for the direct construction of C_{sp_2} -N bond from C_{sp_2} -O bond to furnish the kinetic products (*Z*)-3 and the thermodynamic products (*E*)-3, respectively.

The successful construction of the C_{sp_2} -N axis inspired us to further develop an enantioselective variant of this process. Thus, the reaction between **1a** and **2a** was studied for the initial evaluation of some chiral phosphoric acids (Table 3, entries 1– 2) and chiral phosphoramides (Table 3, entries 3–7) as potential

Table 3 Conditions optimization of the enantioselective reaction

CPA (10 mol%) Solvent, 24 h, RT (R, Z)-3aa 2a Ρh R، **C1**. R = $2.4.6 - (i - Pr)_3 C_6 H_2$ 0 .0 C2, R = 2,4,6-Ph₃C₆H₂ .0 NHTf C3, R = 2,4,6-(cyclopentyl)₃C₆H₂ юн B1, R = 2,4,6-(*i*-Pr)₃C₆H₂ C4, R = 9-phenanthreny **B2**, R = 2,4,6-Ph₃C₆H₂ C5, R = 3,5-(CF₃)₂C₆H₃ Entry^a CPA Solvent Temp [°C] Yield $[\%]^b$ ee [%]^c **B1** 1 CH₂Cl₂ Trace rt 2 **B2** CH₂Cl₂ Trace rt 3 **C1** CH₂Cl₂ 64 65 rt 4 C2CH₂Cl₂ 2046 rt 5 **C3** CH_2Cl_2 4453 rt 6 C4 CH_2Cl_2 rt Trace 7 7 C5 CH_2Cl_2 rt 18 8^d C1/B1 CH_2Cl_2 rt 40 61 9^e C2/B2 CH_2Cl_2 rt 34 90 10 C1/B2 CH₂Cl₂ rt 44 90 11^{f} C1/B2 MeCN rt Trace 12^{f} C1/B2 EtOAc rt Trace 13^{f} C1/B2 THF rt Trace 14^g CH₂Cl₂ 90 C1/B2 rt 44 15^h C1/B2 CH_2Cl_2 32 88 rt 16^g C1/B2 CH_2Cl_2 0 Trace $17^{g,i}$ C1/B2 CH_2Cl_2 rt to 0 56 93

^{*a*} Unless noted, under Ar atmosphere, a mixture of **1a** (0.05 mmol), **2a** (0.10 mmol) and **CPA** (10 mol%) in the solvent (2.0 mL) was stirred at room temperature (rt) for 24 h. ^{*b*} Determined by ¹H NMR with CH_2Br_2 as internal standard. ^{*c*} Determined by chiral-HPLC analysis. ^{*d*} C1 (10 mol%), **B1** (10 mol%). ^{*e*} C2 (10 mol%), **B2** (10 mol%). ^{*f*} C1 (10 mol%), **B2** (10 mol%). ^{*s*} C1 (8 mol%), **B2** (8 mol%). ^{*h*} C1 (5 mol%), **B2** (5 mol%). ^{*i*} The mixture was stirred at rt under Ar atmosphere for 5 min (2a was totally dissolved), then it was cooled to 0 °C for 6 days.

catalysts. Indeed, chiral phosphoramide C1 was found to be a promising catalyst, affording the desired (R, Z)-3aa in 64% yield with 65% ee (Table 3, entry 3). While a single catalyst could not eventually improve the enantioselectivity to an excellent level, we were curious about the use of combined Brønstred acid systems. The combination of a chiral phosphoric acid and a chiral phosphoramide was then surveyed (Table 3, entries 8-10). Pleasingly, when phosphoramide C1 was used together with chiral phosphoric acid B2, the desired (R, Z)-3aa was formed with 90% ee (Table 3, entry 10). Notably, control experiments indicated that the use of any other combination or any single acid could not reach such a high level of enantiocontrol. Other solvents could not improve the reaction outcome (Table 3, entries 11-13). Notably, the loading of B2 and C1 could be further reduced to 8.0 mol% without compromising the efficiency (Table 3, entry 14). No product was obtained when the reaction was carried out at 0 °C (Table 3, entry 16). It is worth noting that substrate 2a has a low solubility at 0 °C. Therefore, a programmed cooling protocol was used to smoothly afford the target product (R, Z)-3aa with 93% ee (Table 3, entry 17).

Under the established conditions, the scope of this combined catalytic system was examined for this intriguing process for the direct formation of atroposelective C_{spa}-N axis (Table 4). The kinetic products (R, Z)-3 were exclusively obtained under the optimized conditions. More specifically, a range of naphthols 1a-j reacted smoothly with 3-alkynyl-3hydroxyisoindolinone 2a to provide the corresponding enantioenriched products (R, Z)-3aa-ja in moderate yields. The halogen (Br, Cl) could be introduced into the aromatic ring of naphthol, affording (R, Z)-3ba-fa in 32-68% yields with 79-92% ee. The reaction of naphthol with bulky substituents (3,5-(t-Bu)₂C₆H₃, 2-naphthyl) could also proceed smoothy, furnishing the corresponding products (R, Z)-3ga in 32% yield with 76% ee and (R, Z)-3ha in 64% yield with 94% ee, respectively. Particularly, trimethylsilyl and the terminal olefin unit were also compatible, and (R, Z)-3ia was obtained in 45% yield with 85% ee and (R, Z)-3ja in 40% yield with 94% ee. Moreover, a series of 3-alkynyl-3-hydroxyisoindolinones with different substituents $(3-MeC_6H_4, 3-ClC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4)$ were also reactive to afford the desired products in generally moderate yields with high enantioselectivities. The reactions could be run at a relatively large scale (0.5 mmol), which afforded the desired products with comparable results as the small-scale reactions. The configuration of (R, Z)-3aa was confirmed by X-ray crystallography (CCDC 2294540).

To gain more information about the reaction mechanism, we have performed a series of control experiments. First of all, product (Z)-**3aa** could be converted to (E)-**3aa** in the presence of catalyst **A3**, which confirmed that the former is the kinetic product and the latter is the thermodynamic product (Scheme 2A).

Furthermore, no reaction took place between naphthalen-2ol 1a and enone 4 from 3-alkynyl-3-hydroxyisoindolinone 2a under the standard conditions, suggesting that enone 4 was not a viable intermediate (Scheme 2B, eqn (1)). When $H_2^{18}O$ was added to the A1-mediated reaction, the ¹⁸O atom was incorporated into the product (Z)-3aa-18O (Scheme 2B, eqn (2)). Importantly, with 4 Å molecular sieves as additive, this process provided an allene as product, which was a mixture of diastereomers IM-up (weak polarity) and IM-down (strong polarity). The structure of this allene product was confirmed unambiguously by X-ray crystallography (CCDC 2294537, Scheme 2B, eqn (3)). Interestingly, the diastereomeric ratio (IM-up and IM-down) changed over time, likely via reverse reaction. Furthermore, with B2 as catalyst, the allene diastereomers could be isolated as enantioenriched form (59% ee for IM-up, 39% ee for IM-down), both of which could lead to enantioenriched product (R, Z)-3aa in the presence of the racemic catalyst C1 (Scheme 2B, eqn (4)), suggesting that the conversion from allene to product could be stereospecific. Moreover, the racemic allene diastereomers were also generated in the presence of catalyst A1 combined with 4 Å molecular sieves. Notably, treated with the combined catalysts, chiral C1 and B2, enantioenriched (R, Z)-3aa could be still obtained (Scheme 2B, eqn (5)). We reasoned that, even though racemic, the allene intermediate could reverse to their precursors in the presence of the chiral acid to generate enantioenriched allene, which resulted in the

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Table 4 Scope of reactions for (R, Z)-**3**^{*a*}



^{*a*} Under Ar atmosphere, a mixture of **1** (0.20 mmol), **2** (0.40 mmol), **C1** (8 mol%) and **B2** (8 mol%) in CH₂Cl₂ (8.0 mL) was stirred at room temperature (rt) for 5 min, then it was cooled to 0 °C for 6 h. Products (*R*, *Z*)-3 were obtained in isolated yields. The ee was determined by chiral-HPLC analysis.



Scheme 2 Further investigations.

enantioenrichment in the final product. In this case, the ratedetermining step is likely at a later stage (after allene formation), which would allow reversible steps before the addition of water to allene.

Interestingly, enantiopurity of product (R, Z)-**3aa** has a linear correlation to both the enantiopurity of **C1** (Scheme 3A) and **B2** (Scheme 3B), suggesting that both of them are contributing to

the key enantiodetermining transition state. It is worth noting that such a scenario with two different chiral Brønsted acids contributing to enantiocontrol is extremely uncommon, to the best of our knowledge.

To understand the mechanism, density functional theory (DFT) calculations were performed on the racemic reaction. The results indicated that this intriguing process comprises of



Scheme 3 Non-linear effect.



Fig. 2 DFT study. Energetic profiles of the reaction at the M06-2X-D3/6-311G(d,p)-SMD(DCM)//M06-2X-D3/6-31G(d) level of theory and the energy values are in given kcal mol⁻¹.

dehydration, allene formation, water addition, cyclization, and ring-opening (Fig. 2). It starts substrate coordination to naphthalene-2-sulfonic acid (A1) by hydrogen bonding followed by elimination of water to form intermediate INT3 with an energy barrier of 16.7 kcal mol⁻¹. Next, a nucleophilic attack from the naphthol to the resulting imine INT4 occurs together with synergistic proton transfer, leading to the allene intermediate INT5, with an energy barrier 12.4 kcal mol⁻¹. In the presence of water, the electron-rich allene motif can be further activated by acid and trigger a water addition to form INT9. Next, an intramolecular cyclization takes place by the nucleophilic attack of the N-atom to the carbonyl group to form a C–N bond. Further dehydration forms iminium INT13. Finally, a facile ring-opening process driven by the aromatization furnishes the final product. It is worth noting that the water

elimination from **INT11** is the rate-determining step, which is consistent with the control experiments showing that the allene formation might be likely reversible.

Conclusions

In summary, we have successfully developed the first organocatalyzed asymmetric synthesis of C_{sp_2} –N atropisomers by formal C_{sp_2} –O amination. Different from known methods for the access to C_{sp_2} –N atropisomers by functionalization of existing C–N bonds, our process involved construction of the key C–N bond with concomitant asymmetric control. By adjusting the strength of the acid catalyst and reaction time, both the kinetic product (*Z*)-isomers and the thermodynamic product (*E*)-isomers could be selectively formed. More importantly, the rarely used combination of two chiral Brønsted acid catalysts proved critical to the excellent enantiocontrol. Control experiments confirmed that both of them are required for the high enantioselectivity and both are involved in the enantiodetermining transition state. However, more accurate information about the enantiodetermining transition state is unknown at this point. DFT calculations also provided important information to the general reaction pathway, which involves allene as the key intermediate. Additional studies on this intriguing process are under-way in our laboratories.

Data availability

Experimental procedures, spectral data and DFT data can be found in the ESI.†

Author contributions

Pengfei Li, Jianwei Sun and Chenxiao Qian wrote the manuscript. Pengfei Li and Jianwei Sun supervised the project. Pengfei Li conceived the project. Chenxiao Qian and Tingting Huang performed condition optimization, scope study and control experiments. Jing Huang and Lijuan Song performed DFT studies. All the authors proofread and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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