Development of bifunctional organocatalysts and application to asymmetric total synthesis of naucleofficine I and II

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The proline-type organocatalysts has been efficiently employed to catalyze a wide range of asymmetric transformations; however, there are still many synthetically useful and challenging transformations that remain unachievable in an asymmetric fashion. Herein, a chiral bifunctional organocatalyst with a spirocyclic pyrrolidine backbone-derived containing fluoroalkyl and aryl sulfonamide functionalities, are designed, prepared, and examined in the asymmetric Mannich/acylation/Wittig reaction sequence of 3,4-dihydro-β-carboline with acetaldehyde, acyl halides, and Wittig reagents. As a result, the spirocyclic pyrrolidine trifluoromethanesulfonamide catalyst can facilitate this versatile sequence as demonstrated by 18 examples displaying excellent enantioselectivity (up to 94% ee), as well as moderate to good yields (up to 54% over 3 steps). As a practical application, the asymmetric total synthesis of naucleofficine I (1a) and II (1b) in ten steps have been accomplished.
The metal-free organocatalysis based on the dual activation of amino acids and their analogs has been displaying versatile utilities in the synthesis of natural products and pharmaceuticals\textsuperscript{1–3}. The proline-type organocatalysts represent a large class of useful bifunctional catalytic systems, which have facilitated a wide range of asymmetric reactions of carboxyls, imines, and their variants, including aldol, Michael addition, Diels–Alder cycloaddition, Mannich reaction, and so on\textsuperscript{13–14}. Despite these advances, there are still many inspiring transformations that remain unachievable in asymmetric synthesis. Therefore, development of more and reliable bifunctional organocatalysts is of high demand for effecting these transformations. Aimed at the asymmetric synthesis of biologically important natural products and drug molecules, our current efforts have been focused on developing novel and effective catalysis systems to enable synthetically challenging transformations so as to explore the concise synthetic approaches. As indicated in Fig. 1, at least four kinds of different natural products, the naucleofinocin I (1a) and II (1b), yohimbine, and berbanes, contain the common complex N-fused bicyclic structures 6 with multi-substituents and stereocenters. Compounds 1a and 1b are isolated from \textit{Nauclea genus} and exhibit antibacterial and antiviral biological activities\textsuperscript{15,16}. They represent the characteristic structures of a number of monoterpenoid indole alkaloids and have not been synthesized so far, although some approaches to their analogs have been reported by employing free radical cyclization and the Pictet–Spengler reaction as key steps\textsuperscript{15–18}.

In previous reports, the spirocyclic pyrrolidine (SPD) backbone-derived organocatalysts have displayed high enantioselectivity in several reactions, possibly due to the rigid chiral environment of quaternary carbon stereocenter and spirocyclic scaffold, and the flexibility of the lone electron pair of the pyrrolidine moiety\textsuperscript{19–21}. In this regard, it is hypothesized that attachment of the strong acidic fluoroalkylsulphonamide motif to a sterically hindered SPD backbone would generate a new bifunctional catalyst, which would exhibit stronger acidity and superior enantio-induction ability compared with proline but still maintain the active pyrrolidine amine. Furthermore, the BINOL-phosphonyl \textit{Tin} (Table 1, Cat 8) exhibits much stronger acidity than BINOL-phosphoric acid alone, due to its stability of counter anion and strong electron-accepting property of Tf group\textsuperscript{22–23}. Herein, we present our research results on the asymmetric Mannich/acetylation/Wittig sequence to efficiently assemble the tetrahydro-β-carboline 5, which allows us to accomplish the total synthesis of naucleoficin I (1a) and naucleoficin II (1b) in a concise way.

**Results**

**Design plan.** The synthesis of natural products in Fig. 1 could be simplified to establishment of the single C3 stereocenter and installation of two unsaturated chains in 5. In this work, we focus on the synthesis of the alkaloids 1a and 1b, our retro-synthesis involves alternatively a late-stage O-hetero-Diels–Alder cycloaddition to construct the D/E rings with multi-functional groups and stereogenic centers in one step from the key intermediate 5 (Fig. 1). Therefore, we envision a versatile Mannich/acetylation/Wittig sequence would enable the construction of 5 from commercially available 3,4-dihydro-β-carboline 2, acetaldehyde, acyl halides, and corresponding Wittig reagents. To achieve this catalytic asymmetric sequence, however, some challenges exist, including the following: (1) the starting N-aliphatic imine is relatively inactive compared with generally used active Boc\textsuperscript{26,27}, Ts\textsuperscript{28,29}, aryl-imine species\textsuperscript{30,31}, and Cbz\textsuperscript{32}, which requires a stronger acidity to activate the C=\textit{N} bond via hydrogen bonding; (2) the active acetaldehyde\textsuperscript{33–39} could easily form byproducts via aldol condensation; and (3) asymmetric Mannich reaction of 3,4-dihydro-β-carboline and aldehydes is a challenging work, which has not been reported up to now, maybe due to the instability of the resulting amino aldehyde.

**Fig. 1** Design of asymmetric synthesis of monoterpenoid alkaloids. Retro-synthesis involves Diels–Alder reaction and Mannich/acetylation/Wittig sequent reaction.
Reaction condition optimization. Initially, four catalysts Cat 1–4 with substituents possessing different electronic properties were prepared from (S,S)-SPD-amine (for details, see Supplementary Note 2). Imine 2a was selected as a model substrate to screen the optimal condition of the Mannich sequence with acetaldehyde, acetyl bromide, and methyl(triphenylphosphoranylidene)-acetate. Fortunately, the expected Mannich sequence could take place in the presence of Cat 1 in DCE/H2O at 0 °C, affording mainly the desired product 5a albeit with the poor yield (21% over three steps) and moderate enantiomeric excesses (ee) (51%) (Table 1, entry 1). Encouraged by this result, the effect of additives was then investigated (for details, see Supplementary Table 1). The presence of a basic additive was found to be crucial to improve the reaction outcome, with Et3N giving the best result (entry 4), the main byproducts were the decomposition of the amino aldehyde in the second step of acylation and the byproducts of aldol condensation have not been detected. In contrast, the acid additives gave poor results and reversed the chirality of the resulting products (entries 2–3 vs. 4–6). Subsequently, decreasing the reaction temperature led to slightly lower yield and ee (entries 7–8). Further examination of the analogous Cat 2–4 revealed that the TfNH modified Cat 1 provided a much better result than Cat 2–4 with the weaker and stronger electron withdrawing property of tolylsulfonyl, p-(trifluoromethyl)-benzenesulfonyl, and methylsulfonyl, respectively (entries 9–11 vs. 4). In addition, other types of catalysts
with quite different levels of reactivity and/or stereo-effect from Cat 1 were subjected to the reaction and compared with Cat 1 under the same condition as entry 4. These include the following: (1) Cat 5, Cat 13, which does not have an acidic functional group; (2) Cat 6, which has a protecting group of pyrrolidine amine; (3) Cat 8, which has a single, stronger acidity and generally identified excellent enantio-induction of BINOL framework; and (4) Cat 9–12,40–44, which have similar reactivity but quite different stereo-effect of a linear derivative. Unfortunately, all of these catalysts gave poor results (entries 12–18). Particularly, Cat 7 failed to promote this sequence and only the starting material was recovered (entry 14). These results indicated that Cat 1 exhibited both excellent reactivity and high enantio-induction ability toward the studied transformation.

Substrate scope. Subsequently, the optimal condition of entry 4 (the bold values in table 1) was employed for substrate expansion. First, a variety of substituted 3,4-dihydro-β-carbolines 2b–2j with a variety of substituents on the indole rings were examined and all reacted smoothly to afford the desired products 5b–5j (Fig. 2a)45–49. In detail, the EWG (electron-withdrawing group) substitutions with F, Cl, and Br at C9–C11 of the indole ring generally gave high ee (90–92%) and good yields (51–54% over three steps) (5d–5h), whereas the EDG (electron-donating group) substitutions gave slightly lower ee (88% ee) and yields (45%) (5b and 5c). Interestingly, the C12 substitutions with either EWG (5i) or EDG (5j) both gave high ee (94% and 90% ee) but merely moderate yields (43% and 37%). Moreover, substitutions at the indole nitrogen atom with the EWG (5k) or EDG (5l) resulted in similarly lower ee (83% and 76%) and varied yields (52% and 32%). In addition, variation of acyl halides could also generate high ee (both 91% ee) and moderate yields (45% and 46%) (5m and 5n), respectively. Moreover, changing the Wittig reagents gave moderate yields (42% and 40%) and high ee (both 91% ee) (5o and 5p), which were the key intermediates for the synthesis of natural products 1a/1b. Notably, two 3,4-dihyrdroisoquinoline substrates were explored for the catalytic Mannich/Acylation/Wittig sequence, which also proved to be effective, generating the corresponding products 5q and 5r with good ee (81% and 87%) and moderate yields (41% and 36%), respectively (Fig. 2b). As a result, the explored Cat 1 could facilitate well the expected asymmetric Mannich sequence with a wide substrate tolerance in good to high efficiency in most cases.

Asymmetric total synthesis of naucleoficine I and II. To demonstrate the utility of this sequence, the asymmetric total synthesis of 1a/1b were carried out efficiently from intermediates 5o. First, 5p underwent an O-hetero-Diels–Alder cycloaddition under reflux in mesitylene to produce the advanced pentacyclic intermediate 7 with mainly cis-configuration of C3 and C15 (Fig. 3)50. Next, we turned to the asymmetric total synthesis of the natural alkaloids 1a and 1b from intermediate 5o, which was readily prepared on the gram-scale from 2a using 10 mol % (R,R)-Cat 1 in 42% yield and 91% ee (Fig. 4). After extensive screening of the reaction conditions (for details, see Supplementary Table 2), ZnBr2 was found to enable the expected O-hetero-Diels–Alder cyclization of 5o, efficiently affording the pentacyclic intermediate 8 with four desired stereocenters in 51% yield and >20:1 dr (Fig. 5), and there were amount of natural products that owned trans-configuration of C3 and C15 had not been synthesized. One-recrystallization of 8 in MeOH/Et2O enhanced the enantio-purity to >99% ee (85% yield) and its absolute configuration was confirmed by X-ray crystallographic analysis (for details, see Supplementary Table 6). However, a thermal cyclization of 5o in mesitylene under refluxing temperature resulted mainly in the formation of undesired C15-epimer. Hydroformylation of 8 with POC13/DMF afforded aldehyde 9 in 48% yield, which was treated with freshly prepared Me2CuLi to provide the separable products 10, 11, and 11′ (2.8: 2.5: 1) with 63% total yield. Fortunately, isomer 11′ could be readily converted to 11 with 85% yield when stirred in DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)/DCM. Subsequent reduction of 10 with NaBH4 furnished 12 with 86% yield. After extensive investigations51,52, protection of the hydroxyl group of 12 with hexamethyl disiloxane at refluxing temperature gave a silyl ether, which was subjected to elimination of methoxy group and removal of Boc with BF3·Et2O and TMSOTf in CH2CN to obtain acetol 14, and then the double bond isomerization to give 1a with 81% yield, so we developed an efficient method to construct the double bond of these natural products. In the same way, 1b was also synthesized separately from 11. The spectra data of synthetic (+)-1a and (−)-1b are consistent with literature13, and the ee of (+)-1a and (−)-1b are >99% determined by chiral high-performance liquid chromatography (HPLC).

Discussion

In summary, a chiral bifunctional organocatalyst has been successfully developed, which is a good assembly of strong acid and sterically hindered SPD framework, and thus exhibits high reactivity as well as excellent stereo-induction ability toward the asymmetric Mannich reaction of 3,4-dihydro-β-carboline with a broad substrate toleration. Furthermore, synthetic utility of this Mannich sequence has been exemplified through the asymmetric total synthesis of naucleoficine I (1a) and II (1b) in a concise way. Further expanded studies on asymmetric catalysis with our bifunctional organocatalysts toward other transformations and synthesis of other natural products are underway.

Methods

General information. All reactions requiring anhydrous conditions were carried out under argon atmosphere using oven-dried glassware (130 °C), which was cooled under argon. All solvents were purified and dried by standard techniques, and distilled prior to use. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. The products were purified by flash column chromatography on silica gel (200–300 mesh) or neutral alumina (200–300 mesh). 1H NMR, 13C NMR, and 19F NMR spectra were obtained on Bruker AM-400, JEOL JNM-ECS-400, or Varian Mercury-600. Chemical shifts (δ) were reported in p.p.m. relative to residual solvent signals (CDCl3: 7.26 p.p.m. for 1H NMR, 77.0 p.p.m. for 13C NMR; DMSO-d6: 2.50 p.p.m. for 1H NMR, 39.5 p.p.m. for 13C NMR; CD3OD: 3.31 p.p.m. for 1H NMR, 49.0 p.p.m. for 13C NMR). The following abbreviations were used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; m, multiplet. High-resolution mass spectral analysis data were measured on the Bruker ApexII with ESI resource. Infrared spectra were recorded on Nicolet FT-1700X spectrometer. Melting points were measured on a melting point apparatus and were uncorrected. The ee of the products were determined by HPLC analysis. X-ray diffraction data were collected on Agilent SuperNova Eos diffractometer. Optical rotations were detected on RUDOLPH A21202 J-APTV/GW.

General procedure for the Mannich sequent reaction. To a solution of substituted 3,4-dihydro-β-carboline 2 (0.1 mmol), Cat 1 (5.4 mg, 0.02 mmol) in DCE/H2O (1 mL, v/v 1: 1) were added Et3N (7 µL, 0.05 mmol) and aldehyde (16 µL, 0.3 mmol) at 0 °C. The mixture was stirred at this temperature until the substrate disappeared via TLC detection. Then the resulting solution was concentrated in vacuo. Then 1 mL DCM, K2CO3 (27.6 mg, 0.2 mmol), and acetyl bromide 3a (10 µL, 0.12 mmol) were added at 0 °C sequentially. About 30 min later, 4a (66.8 mg, 0.2 mmol) was added to the reaction at room temperature and reacted at the same temperature for 12 h. The mixture was then quenched with water and the mixture was extracted with DCM. Then the combined organic phase was washed with saturated brine, dried over anhydrous Na2SO4, and concentrated in vacuo. The residue was purified through column chromatography on neutral alumina to give substrates 5.
Fig. 2 The substrate scope of the Mannich/Acylation/Wittig reaction. Reaction condition: 2a (0.1 mmol), acetaldehyde (0.3 mmol), (S,S)-Cat 1 (0.02 mmol), and Et3N (0.05 mmol), in 0.5 mL DCE and 0.5 mL H2O, then acyl halide 3 (0.15 mmol) and Wittig reagent 4 (0.2 mmol). Isolated yield over three steps. Enantiomeric excess determined by HPLC analysis. a The scope of 3,4-dihydro-β-carboline substrates. b The scope of 3,4-dihydro-isoquinoline substrates.

Fig. 3 Further transformation. Thermocatalytic hetero-Diels-Alder reaction mainly obtained the cis-product of C3 and C15.
Fig. 4 Gram-scale synthesis of 5o. Reactions were performed with 10% mol (R,R)-Cat 1

Fig. 5 Asymmetric total synthesis of naucleofficine I and II. The key steps include O-hetero-Diels-Alder cycloaddition, hydroformylation, and double bond isomerization

Data availability
The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (Cat 1: CCDC 1875257; Cat 2: CCDC 1875256). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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