Total Synthesis Hot Paper

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Highly Enantioselective Bromocyclization of Tryptamines and Its Application in the Synthesis of (−)-Chimonanthine**

Weiqing Xie, Guangde Jiang, Huan Liu, Jiadong Hu, Xixian Pan, Hui Zhang, Xiaolong Wan, Yisheng Lai,* and Dawei Ma**

Cyclotryptamine alkaloids are a family of indole alkaloids encompassing the hexahydropyrrolo[2,3,-b]indole (HPI) ring framework (Figure 1).[1] These alkaloids have been isolated from diverse sources, including bacteria, fungi, higher plants, marine bryozoans, frogs, and human metabolism. It has been proposed that those alkaloids are biologically originated from tryptamine through an oxidative cyclization reaction. A class of cyclotryptamine alkaloids are dimer, trimer, and higher-ordered oligomers of HPI units connected by the C3′–C3 and C3–C7′ bonds (chimonanthine and hodgkinsine).[1] Most of the cyclotryptamine alkaloids contain one HPI unit by simple modification of the pyrroloindoline ring (psychotrimine)[2] or by forming additional rings (minfiensine[3] and hunteracine).[4] The formidable synthetic challenges posed by structural complexity, together with their interesting biological activities, have rendered them attractive synthetic targets.[1–6] During our studies on the total synthesis of indole alkaloids,[7] we envisioned that asymmetric bromocyclization of tryptamine **1** might give 3-bromohexahydropyrrolo[2,3,-*b*]indole **2**, which could serve as a versatile building block for assembling cyclotryptamine alkaloids (Figure 1).

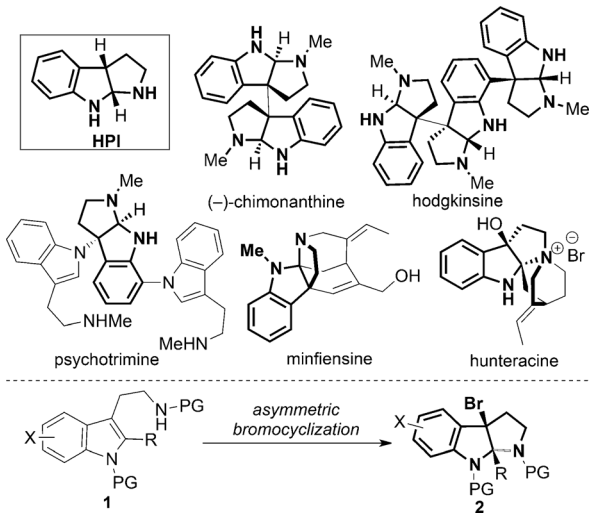

Figure 1. Representative indole alkaloids containing a hexahydropyrrolo-[2,3-*b*]indole (HPI) moiety and asymmetric bromocyclization of tryptamine to prepare chiral HPI. PG = protecting group.

In recent years, great advances have been made in halogenium-assisted organocatalytic enantioselective functionalization of alkenes.[8a,b] Highly enantioselective halocyclization reactions have been realized using cinchona-derived catalysts, chiral phosphoric acids, and other types of organocatalysts.[8,9] Very recently, Toste and co-workers reported a chiral anionic phase-transfer catalysis method for the halogenative functionalization of olefins.[9] Although halocyclization of tryptamine has been widely used in literature, the catalytic asymmetric halocyclization of tryptamine remains difficult, owing to a rapid uncatalyzed background reaction.[10] In 2011, the first enantioselective fluorocyclization of tryptamines catalyzed by $(DHQ)_2PHAL$ was disclosed by Gouverneur and co-workers.[11] However, the reaction gave only moderate to good enantioselectivities, and its application in natural product synthesis was questionable due to the inertness of the C–F bond. Herein, we wish to report the first highly enantioselective bromocyclization of tryptamine and its application in the enantioselective synthesis of the cyclotryptamine alkaloid (−)-chimonanthine.[11b]

Our study commenced with bromocyclization of tryptamine **1a** catalyzed by quinine derivatives with *N*-bromosuccinimide (NBS) as the bromine source (see the Supporting Information).[11] Disappointingly, only negligible enantioselectivity was obtained, presumably due to the uncatalyzed background bromocyclization reaction. To our delight, by employing DABCO-derived bromine salt **B1** (DABCO = 1,4-diazabicyclo[2.2.2]octane) as a brominating reagent and *R*-TRIP (TRIP = 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate) as a catalyst,[9d] pyrroloindoline **2a** could be obtained with 94% *ee* (Table 1, entry 1). Among chiral phosphoric acids tested, 8H-*R*-TRIP **L5** provided the best enantioselectivity (entries 3–6; see also the Supporting Information). When a different batch of bromine salt **B1** was used, it was found that the enantioselectivity decreased dramatically (entry 7). After careful examination of the ^1H NMR spectra of the different batches of bromine salt, we realized that a trace amount of bromine

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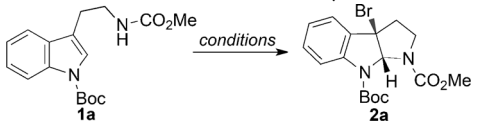
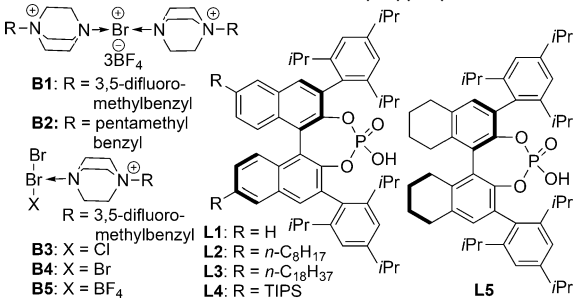
Table 1: Reaction condition screen for bromocyclization of **1a**.[a]



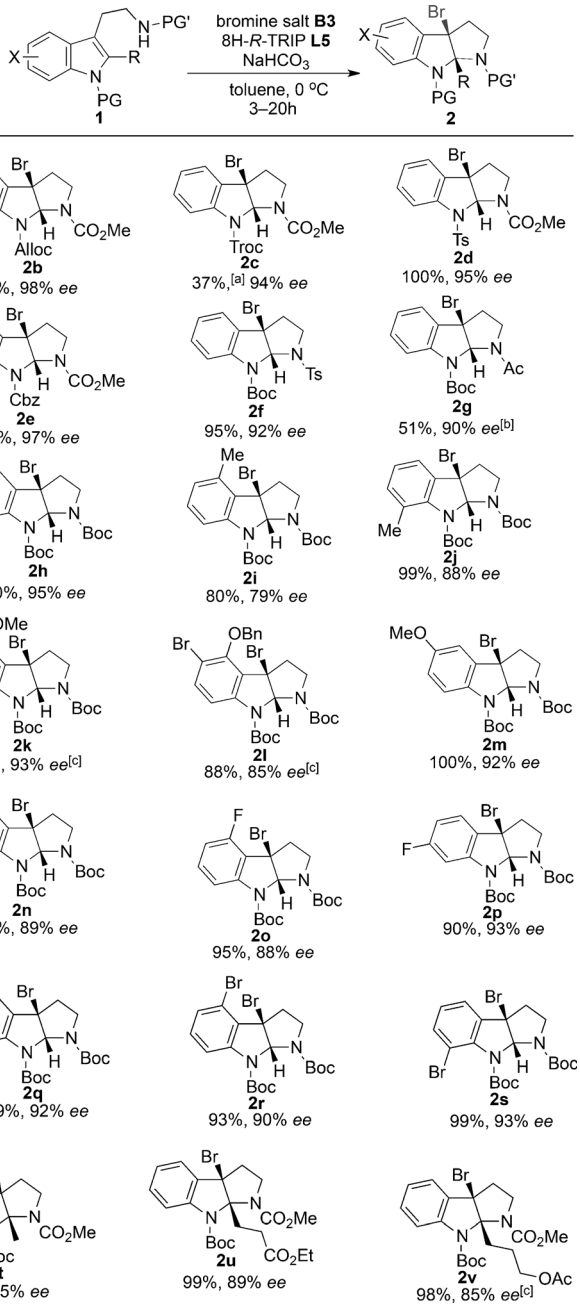
Entry	Br^+ salt	Cat.	Base	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**B1**	**L1**	Na_2CO_3	20	99	94
2	**B2**	**L1**	Na_2CO_3	20	40	82
3	**B1**	**L2**	Na_2CO_3	20	88	83
4	**B1**	**L3**	Na_2CO_3	20	97	91
5	**B1**	**L4**	Na_2CO_3	20	93	94
6	**B1**	**L5**	Na_2CO_3	16	98	96
7	**B1**[d]	**L5**	Na_2CO_3	20	98	88
8	**B1**[e]	**L5**	Na_2CO_3	11	100	96
9	**B3**	**L5**	Na_2CO_3	4	100	96
10	**B4**	**L5**	Na_2CO_3	18	100	96
11	**B5**	**L5**	Na_2CO_3	5	100	96
12	**B3**	**L5**	$NaHCO_3$	4	100	96
13	**B3**	**L5**	K_2CO_3	6	97	72
14	**B3**	**L5**	K_3PO_3	6	100	94
15	**B3**	**L5**	$NaHCO_3$	14	100	94[f]
16	**B3**	**L5**	$NaHCO_3$	20	99	88[e]
17	**B3**	**L5**	$NaHCO_3$	14	90	94[h]
18	**B3**	**L5**	$NaHCO_3$	20	85	89[i]

[a] Reaction conditions: **1a** (0.1 mmol), bromine salt (0.13 mmol), catalyst (0.01 mmol), base (0.4 mmol), solvent (2 mL), 0 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a Chiralpak AD-H column. [d] A different batch of bromine salt **B1** was used. [e] Bromine salt **B5** (0.05 equiv) was added. [f] **L5** (0.05 equiv) was used. [g] **L5** (0.025 equiv) was used. [h] The reaction was run at −20 °C. [i] The reaction was run at −40 °C. TIPS = triisopropylsilyl.



salt **B5** in **B1** played an important role. In the presence of a catalytic amount of **B5**, the reaction was accelerated and gave improved enantioselectivity (entry 8; see also the Supporting Information). Further experiments revealed that the more readily available bromine salt **B3** gave better results than other brominating reagents (entries 9 and 12–18);[12] among the reagents tested, $NaHCO_3$ was found to be the optimal base and toluene was the best solvent (entries 12–14; see also the Supporting Information). Reducing the amount of catalyst resulted in a diminished enantioselectivity and required a longer reaction time (entries 15 and 16). Additionally, reaction at low temperatures did not improve the enantioselectivity (entries 17 and 18).

With the optimized reaction conditions in hand, we next tested the reaction scope by varying substituted tryptamines. As summarized in Scheme 1, all substrates bearing carbamate, acyl, or sulfonate protecting groups on both nitrogen

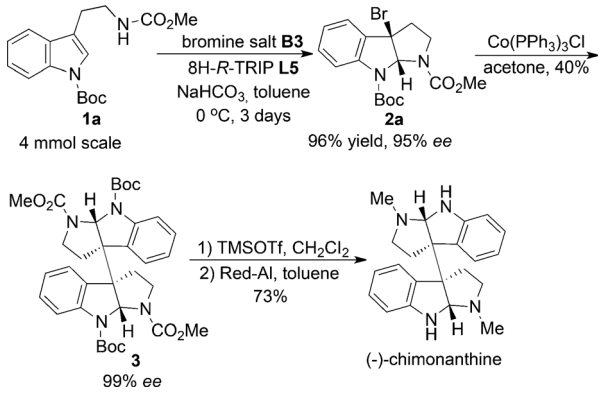


Scheme 1. Substrate scope for the asymmetric bromocyclization of **1**. Reaction conditions: **1a** (0.1 mmol), bromine salt (0.13 mmol), **L5** (0.01 mmol), base (0.4 mmol), toluene (2 mL), 0 °C. [a] Starting material (60%) was recovered. [b] The reaction was run at −20 °C, only 80% *ee* was obtained at 0 °C. [c] **B1** as the brominating reagent. Ac = acetyl, Alloc = allyloxycarbonyl, Boc = *tert*-butoxycarbonyl, Cbz = carbobenzyloxy, Troc = 2,2,2-trichloroethoxycarbonyl, Ts = *para*-toluenesulfonyl.

atoms worked well under these conditions,[13] leading to the formation of the cyclization products in 90–98% *ee*. The electronic nature of the substrate has little influence on the reactivity, as products **2i–s** were obtained in 80–99% yield. When 4-alkoxy-substituted tryptamines were used, bromination of the indole ring also occurred to afford **2k** and **2l** as the major products. Relatively low enantioselectivities were observed in the case of 4-substituted tryptamines (**2i**, **2k**, **2l**,

2o and **2r**), which indicates that steric interaction had some influence on asymmetric induction. Furthermore, 2-substituted tryptamines were also applicable, producing **2t–v** with 85–95% *ee*. We could assign the absolute configuration of the products as (3a*R*, 8a*R*) by X-ray analysis of the bromopyrroloindoline **2d**.[14,15]

To synthesize (−)-chimonanthine, we conducted the bromocyclization of **1a** on a gram scale. The reaction afforded **2a** in 96% yield with 95% *ee*, although a prolonged reaction time was needed for complete conversion (Scheme 2). Next,

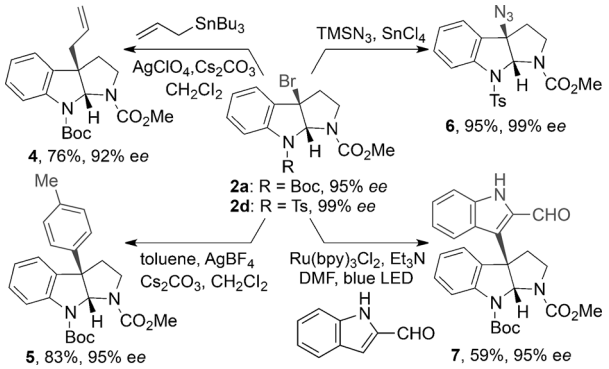


Scheme 2. Synthesis of (−)-chimonanthine.

homodimerization of **2a** catalyzed by $Co(PPh_3)_3Cl$ provided bispyrroloindoline **3** in 40% yield and 99% *ee*.[16,17] Removal of the *tert*-butoxycarbonyl (Boc) protecting group with trimethylsilyltrifluoromethylsulfonate (TMSOTf), and reduction of the methylcarbamate moiety with Red-Al furnished (−)-chimonanthine in 73% yield; the analytical data were in agreement with those reported for natural (−)-chimonanthine.

To further demonstrate the synthetic utility of the present reaction, we attempted the conversion of the bromides **2** into other functionalized hexahydropyrrolo[2,3,-*b*]indoles. As depicted in Scheme 3, allylation of **2a** with a tin reagent under the assistance of $AgClO_4/Cs_2CO_3$ produced **4** in 76% yield with slightly decreased enantiopurity.[18] Friedel–Crafts reaction of **2a** with toluene provided **5**. The azidopyrroloindoline **6**, a key intermediate for assembling psychotrimine,[2e] could be obtained by treatment of **2d** with $TMSN_3/SnCl_4$.[13c] Furthermore, the coupling of **2a** with indole-2-carbaldehyde to produce bisindole **7** could be achieved with a photoredox catalyst, according to the procedure of Stephenson et al. (Scheme 3).[19]

In summary, a highly enantioselective bromocyclization of tryptamine has been developed using chiral anionic phase-transfer catalysts and easily accessible brominating reagents. A number of 3-bromopyrroloindoles could be assembled in good yields with excellent enantioselectivities. The method allowed a short enantioselective synthesis of (−)-chimonanthine, and facile access to some functionalized hexahydropyrrolo[2,3,-*b*]indoles. Applications of this reaction for synthesizing other cyclotryptamine alkaloids are being investigated in our laboratory, and the results will be disclosed in due course.



Scheme 3. Derivatization of 3-bromohexahydropyrrolo[2,3,-*b*]indole. bpy = bipyridine, Ts = *para*-toluenesulfonyl.

Experimental Section

General reaction procedure: Toluene (1 mL) was added at 0 °C to a mixture of substituted tryptamine **1** (32 mg, 0.01 mmol), *R*-8H-TRIP **L7** (7.6 mg, 0.01 mmol), bromine salt **B3** (35 mg, 0.13 mmol), and $NaHCO_3$ (34 mg, 0.4 mmol). The mixture was stirred at this temperature until thin layer chromatography (TLC) analysis showed the complete conversion of **1**. The reaction mixture was then filtered through a pad of celite, washed with ethyl acetate, and concentrated in vacuo. The residue was purified by preparative TLC to afford bromide **2**.

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[17] The improvement of the enantiopurity of dimer **3** could be ascribed to the difference in the reaction rate for homodimerization coupling and heterodimerization coupling of **2a**. The enantiomer of **2a** reacted preferentially with **2a** to form *meso*-**3**, which was removed by chromatography. Thus, the enantiopurity of the homodimerization product **3** was improved to 99% by a resolution process.

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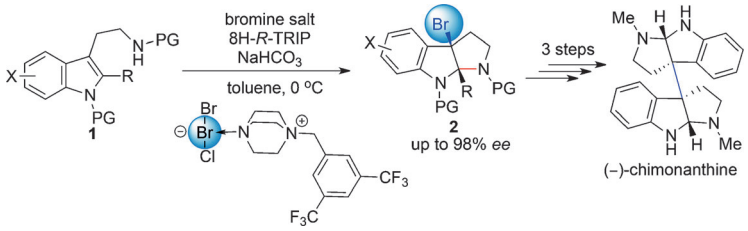
Communications

Total Synthesis

W. Xie,* G. Jiang, H. Liu, J. Hu, X. Pan, H. Zhang, X. Wan, Y. Lai,* D. Ma* ——— ■■■■–■■■■

Highly Enantioselective Bromocyclization of Tryptamines and Its Application in the Synthesis of (−)-Chimonanthine



A shorter path: A highly enantioselective bromocyclization of tryptamine has been developed using an anionic chiral phase-transfer catalyst. This method provides a direct approach for preparing chiral 3-bromopyrroloindoline from tryptamine, which enables a four-step enantioselective synthesis of (−)-chimonanthine. PG = protecting group.