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Highly Asymmetric Bromocyclization of Tryptophol: Unexpected Accelerating Effect of DABCO-Derived Bromine Complex

Huan Liu,[†,∥] Guangde Jiang,[†,∥] Xixian Pan,[§] Xiaolong Wan,[‡] Yisheng Lai,*[,†] Dawei Ma,*[,‡] and Weiqing Xie*[,‡]

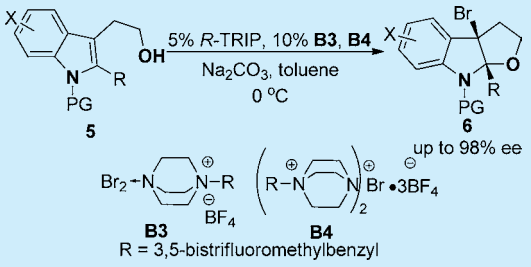
[†]State Key Laboratory of Natural Medicines, Center of Drug Discovery, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China

[‡]State Key Laboratory of Bioorganic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

[§]Department of Chemistry, School of Science, Shanghai University, No. 99, Shangda Road, Shanghai 200444, China

Supporting Information

ABSTRACT: Highly asymmetric bromocyclization of tryptophol by using chiral anionic phase-transfer catalyst and DABCO-derived brominating reagent is described. Optimization of the reaction conditions revealed that the reaction rate was accelerated together with improvement of enantioselectivity by addition of catalytic DABCO-derived brominating reagent. From tryptophol, 3-bromofuroindoline could be directly obtained in excellent enantioselectivities by employing this novel methodology.



As a naturally occurring scaffold in indole alkaloids such as (+)-madindoline (**2**),[1a] pseudoakuammigine (**3**),[1b] and aspidophylline A (**4**)[1c,d] (Figure 1), 3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (**1**) (furoindoline) is accessible directly from dearomatization cyclization of tryptophol.[2] For example, recently You and co-workers developed Cu-catalyzed cyclization of tryptophol with aryliodonium salt[2a] and Sc-catalyzed Michael addition and cyclization of tryptophol.[2b] Allylation[2c,e] and benzylation[2d] of tryptophol to deliver a furoindoline framework catalyzed by a Pd or Ru complex were also efficient protocols. Other methodologies for cyclization of tryptophol such as oxidative cyclization were also well documented.[3] Furthermore, furoindoline could also be constructed from other starting materials through different kinds of reactions (e.g., interrupted Fischer indolization, intramolecular oxidative coupling cyclization).[4] However, an asymmetric version of those kinds of transformations to build up a chiral furoindoline scaffold is still not well studied.[2e,3b,5a] In this regard, asymmetric halogenative cyclization of tryptophol affords an attractive protocol for synthesis of chiral 3-halofuroindoline, as halide is a versatile handle for further transformations. Although asymmetric fluorocyclization of tryptophol has been reported, the reaction suffered from high catalyst loading, moderate to good enantioselectivities, and high stability of the fluorine−carbon bond, which limited its synthetic application.[5]

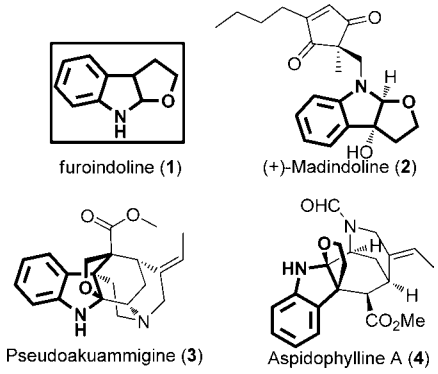


Figure 1. Selected indole alkaloids with furoindoline moiety.

Recently, the chiral anionic phase-transfer catalyst has been widely applied on asymmetric halogenation reactions since the pioneering work of Toste.[6] As the background reaction could be greatly suppressed, the chiral anionic phase-transfer catalyst is capable of realizing asymmetric halogenation transformations which are otherwise difficult to realize by other catalytic systems. For example, enantioselective halocyclization of tryptamine required high catalyst loading, and only moderate to good enantioselectivities were obtained by using quinine-derived catalysts due to the rapid unanalyzed background reaction.[5] By using DABCO-derived trihalide salt, we developed a highly enantioselective bromocyclization of tryptamine using chiral phosphoric acid as catalyst.[7] As part of our continuing work on the synthesis of indole alkaloids,[8] an enantioselective construction of chiral 3-bromofuroindoline scaffold is needed to furnish asymmetric synthesis of furoindoline-incorporated alkaloids. Herein, we disclosed a highly asymmetric bromocyclization of tryptophol by using chiral

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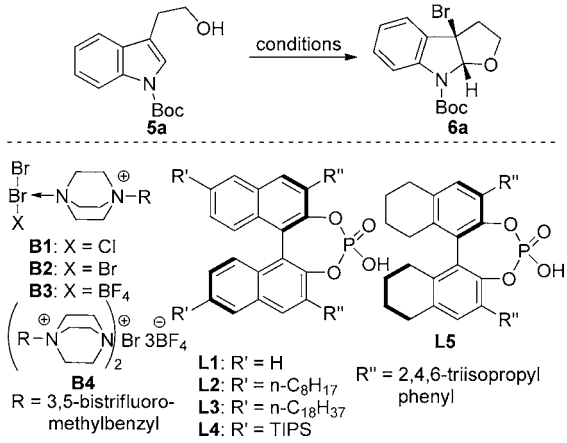
Table 1. Screening of Reaction Conditions[a]



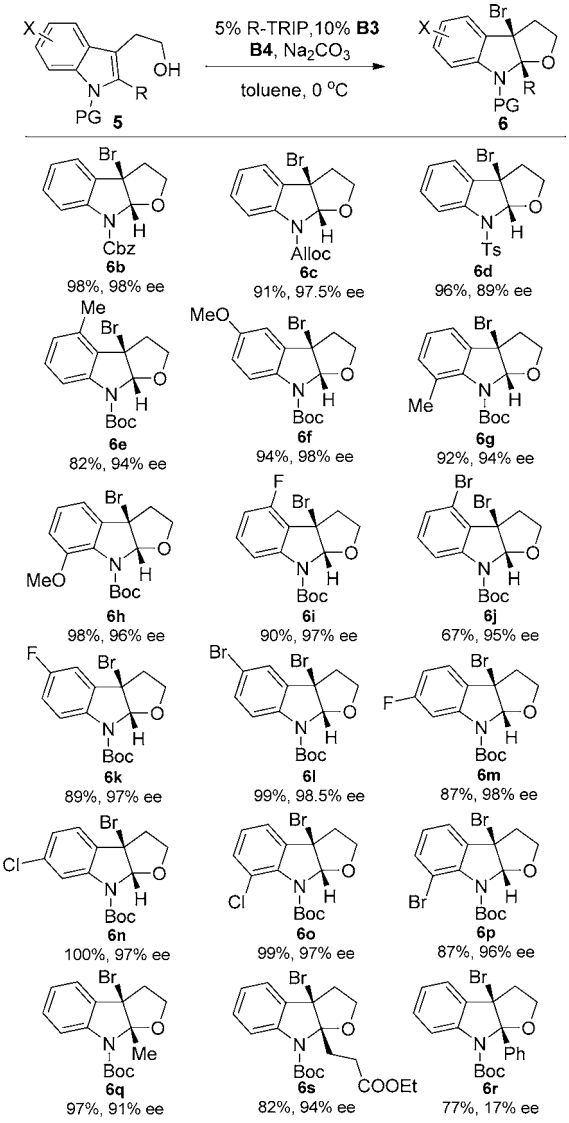
entry	catalyst	additive (0.1 equiv)	Br^+	time (h)	yield[b] (%)	ee[c] (%)
1	**L1**		**B1**	4.5	100	94
2	**L2**		**B1**	4	100	89
3	**L3**		**B1**	5.5	100	83
4	**L4**		**B1**	4	100	90
5	**L5**		**B1**	4	100	86
6	**L1**		**B2**	5.5	98	96
7	**L1**		**B3**	4.5	100	84
8	**L1**		**B4**	17	94	81
9	**L1**	**B1**	**B4**	5	94	95
10	**L1**	**B2**	**B4**	5	95	95
11	**L1**	**B3**	**B4**	3	97	98
12[d]	**L1**	**B3**	**B4**	5	62	90
13[e]	**L1**	**B3**	**B4**	5	66	95
14[f]	**L1**	**B3**	**B4**	5	52	94
15[g]	**L1**	**B3**	**B4**	4	77	65
16[h]	**L1**	**B3**	**B4**	4	95	97

[a]The reaction of tryptophol (0.1 mmol) with a bromine complex (0.13 mmol) was carried out in the presence of chiral phosphoric acid (0.005 mmol), Na_2CO_3 (0.4 mmol), and solvent (1 mL) at 0 °C. [b]Isolated yields. [c]The ee value of 3-bromofuroindoline was determined by HPLC by using a ChiralPak PA-2 column. [d]$NaHCO_3$ as base. [e]K_3PO_4 as base. [f]Cs_2CO_3 as base. [g]Hexane as solvent. [h]Xylene as solvent.

anionic phase-transfer catalyst, which would be applicable in the total syntheses of furoindoline alkaloids.

Encouraged by our initial work on asymmetric bromocyclization of tryptamine,[7] we attempted to apply the same reaction conditions to the asymmetric bromocyclization of tryptophol **5a**. To our disappointment, only moderate enantioselectivity was obtained under our previous optimal reaction conditions (Table 1, entry 5). Further catalyst screening showed that (*R*)-TRIP **L1** was the best catalyst, affording furoindoline **6a** in 100% yield and 94% ee (Table 1, entries 1−4). As for the brominating reagent, **B2** was the best bromine source than other bromium salts, affording 3-bromofuroindoline in 96% ee (Table 1, entry 6 and 8). As our previous observation showed that although **B4** was a less reactive brominating reagent, by addition of a catalytic amount of **B1**, **B2**, or **B3** the reaction rate could be greatly accelerated in the bromocyclization reaction of tryptamine, and the enantioselectivity was also improved.[7] Delightfully, by addition of a catalytic amount of **B3** to this reaction when **B4** was used as bromination reagent, furoindoline **6a** was produced in 98% ee in a shorter reaction time (Table 1, entries 9−11).[9] Although using **B1** and **B2** alone also

Scheme 1. Substrate Scope of Asymmetric Bromocyclization of Tryptophol[a]**−**[c]



[a]The reaction of tryptophol (0.1 mmol) with bromine complex **B4** (0.13 mmol) was carried out in the presence of *R*-TRIP **L1** (0.005 mmol), bromine complex **B3** (0.01 mmol), Na_2CO_3 (0.4 mmol) and toluene (1 mL) at 0 °C. [b]Isolated yields. [c]The ee value of 3-bromofuroindoline was determined by HPLC on chiral column.

furnished excellent outcomes (Table 1, entries 1 and 6), the **B1** and **B4** combination outperformed **B1** and **B2** with respect to reaction time and enantioselectivities when applied to different substrates under optimal reaction conditions (see the Supporting Information). Based this observation, **B1** and **B4** mixing reagents were chosen as the bromination reagent. Other bases such as $NaHCO_3$, K_3PO_4, and Cs_2CO_3 worked less efficiently than Na_2CO_3, resulting in low yields and reduced enantioselectivities (Table 1, entries 12−14, and the Supporting Information). Investigation the effect of solvent showed that toluene was the optimal solvent as other solvents gave inferior outcomes (Table 1, entries 5, 15, and 16, and the Supporting Information).

With the optimal reaction conditions established, the substrate scope of this reaction was subsequently examined to synthesize various chiral 3-bromofuroindoline. For the

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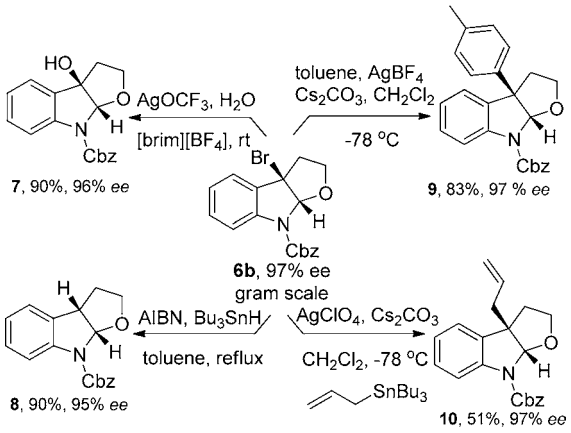
Scheme 2. Derivatization of 3-Bromofuranoindole 6b



protecting groups on indole, carbamate (Cbz and Alloc) was found to be tolerated in this reaction, affording the furoindoline in excellent enantioselectivity (Scheme 1, **6b** and **6c**). While employing strong electron-withdrawing substituents such as Ts, the corresponding furoindoline was obtained only in moderate enantioselectivity (89% ee, Scheme 1, **6d**). The substituent on the indole ring was evaluated next, and either electron-rich or electron-deficient substituents were perfectly compatible with the reaction conditions, delivering the cyclization product in excellent enantioselectivities (94−98.5% ee, Scheme 1, **6g** and **6l**). In particular, 2-substituted tryptophols were also found to be suitable substrates, providing furoindoline with two continuous quaternary carbon centers in excellent diastereoselectivity and enantioselectivity (Scheme 1, **6q** and **6s**). However, only low enantioselectivity (17% ee) was obtained due to steric hindrance when a phenyl group was put on C-2 of the indole ring (Scheme 1, **6r**). The absolute configuration of 3-bromofuroindoline **5** was determined to be (3*R*,8*S*) by X-ray crystallographic analysis of **6g** and **6q**.[10]

Gram-scale asymmetric synthesis of 3-bromofuroindoline **6b** was also implemented to show the practical application of this reaction (Scheme 2), which afforded **6b** in excellent enantioselectivity. The bromide of 3-bromofuroindoline **6b** provided a versatile handle for further transformations to deliver important intermediates for synthesizing furoindoline alkaloids. Hydration in the presence of CF_3CO_2Ag[11] in ionic liquid solvent produced 3-hydroxylfuroindole **7** in quantitative yield, which is the core structure of (+)-madindoline. Removal of bromide mediated by AIBN/Bu_3SnH smoothly gave furoindoline **8** with a slight loss of chiral purity. Friedel−Craft reactions of bromofuroindoline **6b** using toluene or allylstannane resulted in 3-arylfuroindoline **9** and 3-allylfuroindoline **10**, respectively, with retention of chiral purities.[12]

In summary, a highly asymmetric bromocyclization of tryptophol was described by using chiral anionic phase-transfer catalyst and DABCO-derived brominating reagent salt. Enhancement of reaction rate and enantioselectivity was observed by addition of a catalytic amount of DABCO-derived bromine complex. This reaction provided a direct synthesis of chiral 3-bromofuroindoline from tryptophol in excellent enantioselectivities, and currently, application of this methodology in the synthesis of indole alkaloids is under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and copies of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yslai@cpu.edu.cn.
*E-mail: madw@sioc.ac.cn.
*E-mail: xiewq@sioc.ac.cn.

Author Contributions

‖These authors contributed equally.

Notes

The authors declare no competing financial interest.

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(9) Currently, what caused the acceleration of the reaction is still unknown, since mixing bromium **B3** and **B4** did not produce any new bromine species as indicated by ^{1}HNMR spectra (see the Supporting Information). Based on the data in Table 1, we can only deduce that some reactive bromium species was gradually produced as the reaction proceeded, and thus the uncatalyzed background reaction was greatly inhibited.

(10) CCDC 982332 (**6g**) and CCDC 982331 (**6q**) contain the supplementary crystallographic data for this paper. 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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