Asymmetric Catalysis

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Enantioselective Construction of Pyrroloindolines Catalyzed by Chiral Phosphoric Acids: Total Synthesis of (−)-Debromoflustramine B**

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Pyrroloindolines are an important class of alkaloids found in an array of natural products.[1] As shown in Figure 1, various substitutions on the indoline ring, especially at the C3 position, give rise to fascinating and biologically important

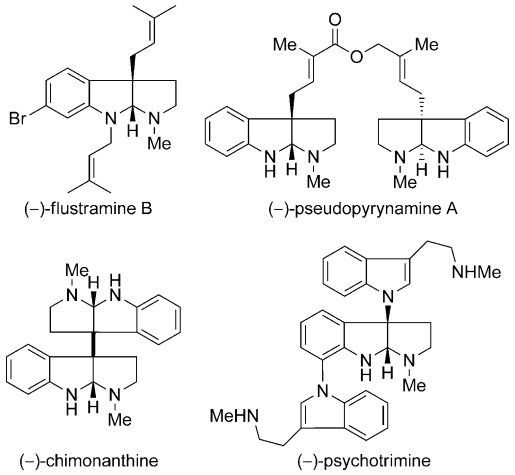

Figure 1. Representative pyrroloindoline natural products.

structures. The biological activities of these compounds have been well studied, the results of which have shown several promising applications, including muscle relaxants,[2] potassium channel-blockers,[3] and anti-cancer agents.[4] For this reason, the total synthesis of these natural products has received considerable attention, and has been accomplished by several research groups.[5–7] However, there are few examples employing catalytic asymmetric strategies to form the key pyrroloindoline substructure.[8]

Chirality at the C3 position of pyrroloindolines, bearing C–N bonds, though somewhat rare, is found in several natural products, such as the recently isolated alkaloid (−)-psychotrimine (Figure 1). The total synthesis of (±)-psychotrimine by an elegant indole–aniline coupling strategy was reported by Baran et al.[9] Also, Gouverneur et al. reported an organocatalyzed enantioselective fluorocyclization of indoles to form chiral 3-fluoropyrroloindolines, which is an interesting example of carbon–heteroatom bond formation with a pyrroloindoline substructure.[7c] However, to the best of our knowledge, the formation of a C–N bond in a catalytic asymmetric strategy with a pyrroloindoline motif is not known.[10,11] Development of a general catalytic method to install both carbon–carbon and carbon–nitrogen bonds in an enantioselective and controlled approach could be of interest for the preparation of chiral pyrroloindolines.

Chiral phosphoric acids have proven to be efficient catalysts for many important asymmetric transformations.[12] Despite these developments, the activation of a simple vinyl ketone as a synthetically useful electrophile is less well known, presumably owing to the expectation of poor activation.[13] Also, there is no example of an asymmetric electrophilic amination catalyzed by chiral phosphoric acids, which is a potentially useful method for the formation of chiral compounds with these types of C–N bonds.[14] Herein, we have circumvented these limitations, and report the first example of the asymmetric formation of pyrroloindolines catalyzed by chiral phosphoric acids, thus allowing access to both the carbon–carbon and carbon–nitrogen bonds of pyrroloindoline derivatives with good yields and high selectivities. This method was then employed in the total synthesis of (−)-debromoflustramine B.

The reaction of 10-carbomethoxytryptamine (**1a**) with methyl vinyl ketone (MVK) was selected as a model reaction to optimize the reaction conditions (Table 1).[15] To our surprise, **1a**, incorporates two MVK segments, forming **2a** as a single diastereoisomer in high yield, which is believed to be generated through a double Michael addition processes. As shown in Table 1, catalyst screening in toluene at −20 °C with 4 Å molecular sieves (MS), indicates that catalyst **PA3**, which bears a 2,4,6-triisopropylphenyl group in the 3,3′ position of BINOL, is the best catalyst in terms of enantioselectivity (Table 1, entries 1–3, and entries 8–10). An improved *ee* of 91 % was achieved by lowering the temperature to −50 °C (entry 4). With **PA4** or **PA5**, similar selectivities were observed along with slightly lower yields (entry 3 vs. entries 5 and 6).[16] Unsaturated **PA3** could be used to deliver the product with 86 % *ee* and 86 % yield (entry 7). Further optimization by variation of the solvent was conducted, with toluene proving to be more suitable than dichloromethane, trifluorotoluene, and ethyl acetate (entry 3 vs. entries 11–13). To our delight, a mixture of toluene and benzene furnished the product with 93 % *ee* (Table 1, entry 14) at −20 °C. However, no further improvement was observed when the reaction was conducted at −50 °C (entry 15). When the reaction scale was increased to 1.0 mmol, the same level of

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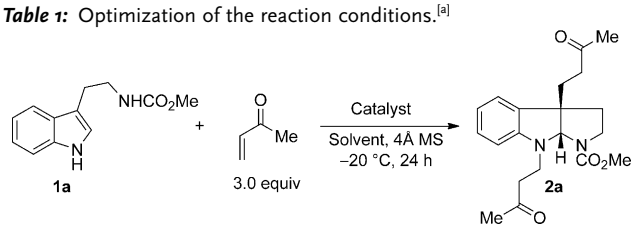
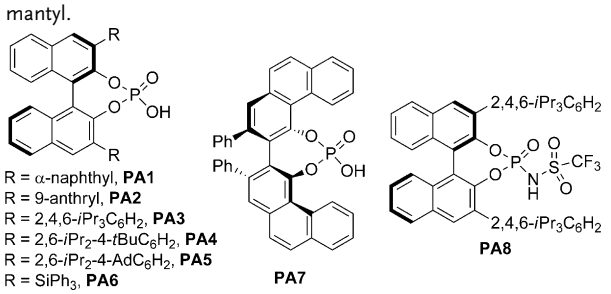
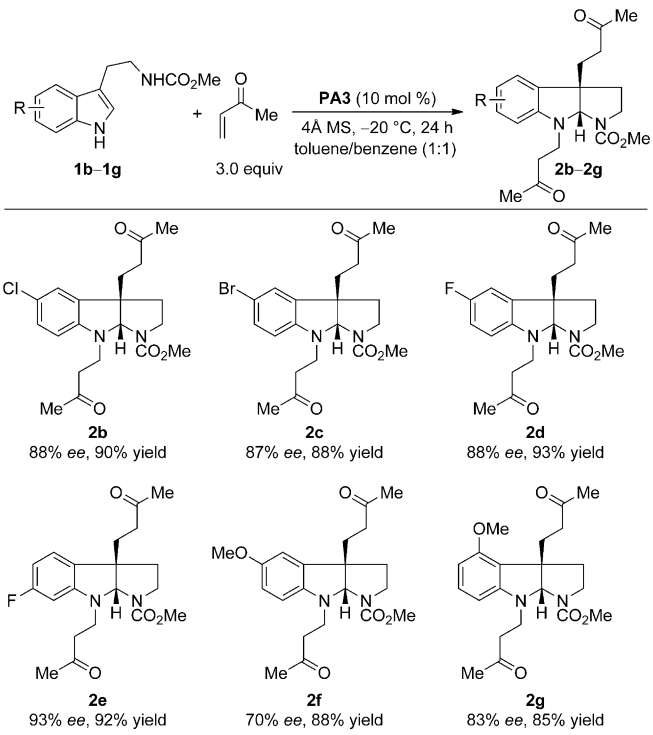
Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	**PA1**	toluene	93	40
2	**PA2**	toluene	90	50
3	**PA3**	toluene	90	85
4[d]	**PA3**	toluene	79	91
5	**PA4**	toluene	77	86
6	**PA5**	toluene	79	87
7	H_8-**PA3**	toluene	86	86
8	**PA6**	toluene	91	74
9	**PA7**	toluene	81	3
10	**PA8**	toluene	85	13
11	**PA3**	CH_2Cl_2	95	41
12	**PA3**	$PhCF_3$	89	36
13	**PA3**	EtOAc	93	40
14	**PA3**	toluene/benzene[d]	90	93
15[e]	**PA3**	toluene/benzene[d]	75	92
16[f]	**PA3**	toluene/benzene[d]	91	93
17[g]	**PA3**	toluene/benzene[d]	93	36

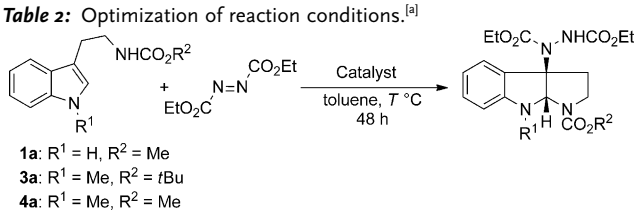
[a] Reaction conditions: **1a** (0.10 mmol, 1.0 equiv), MVK (0.3 mmol, 3.0 equiv), catalyst (10 mol%), 4 Å MS (50 mg), solvent (1 mL, 0.10 M) under argon. [b] Yield of isolated product. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] In a 1:1 ratio. [e] $T = -50$ °C. [f] Reaction scale: 1.0 mmol of **1a**. [g] 10-carbomethoxy-1-methyltryptamine (**4a**) was used instead of **1a**. Ad = adamantyl.





Scheme 1. Substrate scope. Reaction conditions: **1b–1g** (0.10 mmol, 1.0 equiv), MVK (0.3 mmol, 3.0 equiv), **PA3** (10 mol%), 4 Å MS (50 mg), toluene (0.50 mL) and benzene (0.50 mL, 0.10 M) under argon. Yields shown are of isolated products. Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Table 2: Optimization of reaction conditions.[a]



Entry	Substrate	Catalyst	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	**PA1**	RT	85	16
2	**1a**	**PA2**	RT	74	6
3	**1a**	**PA3**	RT	66	52
4	**1a**	**PA6**	RT	60	68
5	**3a**	**PA1**	RT	84	79
6	**3a**	**PA2**	RT	77	81
7	**3a**	**PA3**	RT	46	88
8	**3a**	**PA6**	RT	trace	n/d
9	**4a**	**PA3**	RT	49	92
10	**4a**	**PA3**	50	76	89
11	**4a**	**PA3**	70	trace	n/d
12[d]	**4a**	**PA3**	RT	53	92

[a] Reaction conditions: **1a**, **3a** or **4a** (0.10 mmol, 1.0 equiv), DEAD (0.15 mmol, 1.5 equiv), catalyst (10 mol%), toluene (1.0 mL, 0.10 M) under argon. [b] Yield of isolated product. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] Reaction scale: 1.0 mmol of **1a**. n/d = not determined.

enantioselectivity was observed (entry 16). When **1a** was replaced with 10-carbomethoxy-1-methyl-tryptamine, only 36% *ee* was obtained (entry 17).

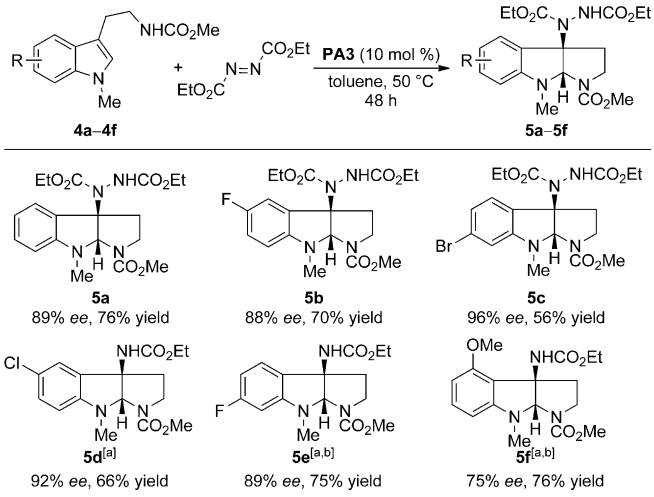
With the optimized reaction conditions in hand, the reaction scope was then studied. As shown in Scheme 1, the introduction of either electron-withdrawing or electron-donating groups to the phenyl ring of tryptamine provided the desired pyrroloindolines with good enantioselectivity and in high yield (Scheme 1, **2b**–**2g**). The enantioselectivity of products bearing electron-donating groups was found to be slightly lower than that of products with electron-withdrawing groups (Scheme 1, **2f** and **2g** vs. **2b**–**2e**).

The newly developed method for the enantioselective construction of pyrroloindolines was further applied to the more challenging amination of tryptamine (Table 2). The reaction of 10-carbomethoxytryptamine (**1a**) with diethyl diazene-1,2-dicarboxylate (DEAD) was optimized under different catalysts in toluene (Table 2, entries 1–4). **PA6** was shown to be the best catalyst, affording the desired amination product with 68% *ee* (entry 4). In an attempt to further

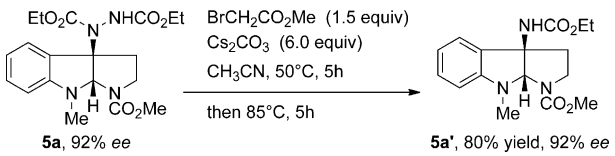
improve the enantioselectivity, different substrates were employed. To our delight, up to 88% *ee* was obtained upon amination of 10-Boc-1-methyltryptamine (**3a**; Boc = *tert*-butoxycarbonyl) catalyzed by **PA3** (entry 7). With **3a**, **PA6** only provided low reactivity, owing to the bukly triphenyl silane group (entry 8). When 10-carbomethoxy-1-methyltryptamine (**4a**) was used as the substrate, a slightly higher enantioselectivity and moderate yield were obtained (92% *ee*, 49% yield; entry 9). The yield can be improved to 76% with almost the same selectivity by increasing the temperature to 50 °C (entry 10). Several by-products were formed by further increasing the temperature to 70 °C (entry 11).[17] Conducting the reaction on a 1.0 mmol scale provided the same enantioselectivity (entry 12).

To demonstrate the synthetic utility of the products, we investigated product transformations (Scheme 3). The N–N bond in **5a** was successfully cleaved with methyl bromoacetate/cesium carbonate in acetonitrile to afford **5a′**, with good yield and complete retention of selectivity.[18]

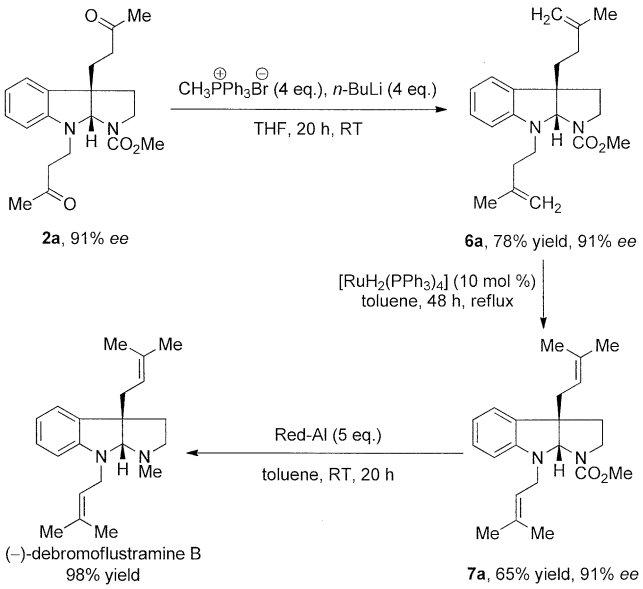
It was also found that, when fluorine, chlorine, or bromine was present on the tryptamine substrate, the amination product was isolated with good yield and highly enantioselectivity (Scheme 2, **5b**–**5e**).



Scheme 2. Asymmetric amination of tryptamines. Reaction conditions: **4a**–**4f** (0.10 mmol, 1.0 equiv), DEAD (0.15 mmol, 1.5 equiv), **PA3** (10 mol%), toluene (1.0 mL, 0.10 M) at 50 °C under argon. [a] The products **5d**–**5f** were obtained under the reaction conditions given in Scheme 3 from the corresponding direct amination products, which could not be separated by chiral HPLC; yields shown are overall yields from two steps. [b] The catalytic amination reactions were carried out in the presence of **PA2** at room temperature, as shown in Table 2, entry 6; **PA3** catalyzed amination reaction provide low reactivity in these examples. Yields refer to isolated products. Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.



Scheme 3. N–N bond cleavage.



Scheme 4. Total synthesis of (–)-debromoflustramine B.

The synthetic application of this method was demonstrated by the total synthesis of (–)-debromoflustramine B (Scheme 4). Flustramine B was isolated from bryozoa *Flusta foliacea* in 1979[19] and was subsequently found to have promising bioactivity.[2,3] A remarkably concise synthesis of (±)-debromoflustramine B was first achieved by Ganesan in 2003.[20] The only catalytic asymmetric total synthesis of (–)-flustramine B was reported in 2004 by MacMillan et al.[8b] Very recently, the Trost group described the total synthesis of (–)-debromoflustramine B, with a key catalytic asymmetric allylation step.[8a] We envisioned that the double Michael product, **2a**, would provide a suitable framework for the synthesis of (–)-debromoflustramine B. As shown in Scheme 4, Wittig olefination of chiral **2a** provides terminal alkene **6a** in high yield and without loss of enantiopurity. Isomerization of the terminal olefin to the internal alkene proved to be challenging owing to the equilibrium between two isomers within a prenyl group.[17,21] Eventually, a 65% yield of the desired internal alkene **7a** was achieved after optimization[22] with excellent enantioselectivity, and 30% recovered starting material. Straightforward reduction of **7a** with sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) furnished highly enantiopure (–)-debromoflustramine B in quantative yield.[9a,b] The synthesis required a total of five steps from commercially available tryptamine, with a 45% overall yield (71% based on recovered starting material) was achieved. This total synthesis is one of the most concise and efficient approaches to this framework.

Although the detailed mechanism for these novel transformations is unknown, we propose transition states based on the following experimental results and knowledge: 1) The reaction of 10-carbomethoxy-1-methyltryptamine with MVK under the optimized reaction conditions provided the product with 36% *ee* (93% *ee* for 10-carbomethoxytryptamine, Table 1, entry 14 vs. entry 17), which indicates a hydrogen bond between the catalyst and the N–H of the indole ring.

Similar interaction has also been proposed by You[23a] for the indole Friedel–Crafts reaction and Akiyama[23b] in the indole Michael addition. 2) NMR studies were carried out to further examine the mechanism. Adding an equal amount of 10-carbomethoxytryptamine (**1a**) to **PA3** in [D_6]benzene resulted in the resonance (^{1}H NMR analysis) of the chiral proton on **PA3** shifting upfield from 6.9 ppm to 6.5 ppm, while the ^{13}C NMR spectrum of **1a** showed two peaks for C9, C11, and C12. The hydrogen bond between the chiral proton on **P3** and the carbonyl group on **1a** was proposed to address the shift.[24] Moreover, ^{1}H NMR studies of a mixture of MVK and **1a** showed the downfield shift of N1–H and N10–H, which indicates a hydrogen bond between MVK and **1a**. Also, NMR studies showed no shift for a mixture of MVK and **PA3**. For the amination reaction, the same experiment was studied and similar changes were observed.[24] 3) The reaction of tryptophol with MVK under the optimized reaction conditions provided the product with 12% *ee*, which might be due to the lack of a hydrogen bond between the catalyst and the carbomethoxy group. Based on the above preliminary results, the transition states in Figure 2, were proposed to account for the high enantioselectivities observed in both reactions. However, an in-depth investigation is required to better understand the mechanism.

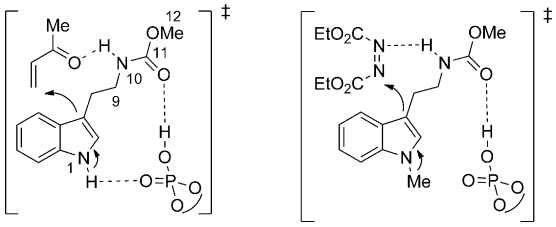


Figure 2. Proposed transition states.

In conclusion, we have developed a novel method for the highly enantioselective formation of pyrroloindolines, a common structure in alkaloid natural products, which is catalyzed by a chiral phosphoric acid. Two important kinds of pyrroloindolines, with either carbon–carbon or carbon–nitrogen linkages, were accessed by Michael addition and the animation of tryptamine, respectively. The synthetic utility of this approach has been highlighted in the concise asymmetric total synthesis of (−)-debromoflustramine B.

Experimental Section

10-carbomethoxytryptamine (**1a**; 0.10 mmol, 1.0 equiv), **PA3** (0.010 mmol, 7.5 mg) and activated 4 Å MS (50 mg) were added to a flame-dried test tube. The vessel was placed under vacuum and the atmosphere exchanged with argon three times before adding toluene (0.50 mL) and benzene (0.50 mL). The mixture was allowed to stir for 10 min at −20 °C before adding methyl vinyl ketone (0.30 mmol, 24 μL, 3.0 equiv). After 24 h at −20 °C, the reaction mixture was purified by silica gel column chromatography (hexane/ethyl acetate 1:1.5) to yield product **2**.

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[24] For details and original spectra, see the Supporting Information.

