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Enantioselective Construction of Pyrroloindolines via Chiral Phosphoric Acid Catalyzed Cascade Michael Addition–Cyclization of Tryptamines

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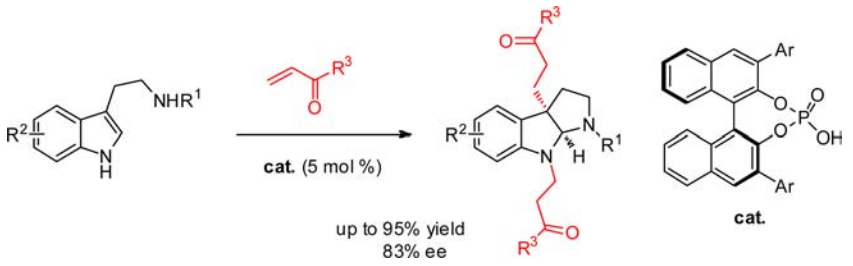
ABSTRACT



Enantioselective construction of pyrroloindolines *via* chiral phosphoric acid catalyzed cascade Michael addition–cyclization of tryptamines has been realized. With 5 mol % of chiral phosphoric acid, enantioenriched pyrroloindoline derivatives were obtained in good yields and enantioselectivity (up to 95% yield and 83% ee) from readily available tryptamines and enones.

Alkaloids containing a pyrroloindoline unit are a very attractive class of natural products for their structural complexity and significant biological properties.[1] The synthesis of these pyrroloindoline derived natural products and relevant pharmaceuticals has attracted enormous attention.[2] Biosynthetically, the pyrroloindoline units stem from the tryptophan and tryptophan-containing peptide.[2c] Due to the ready availability of the tryptamine derivatives, catalytically asymmetric synthesis of the pyrroloindoline compounds *via* a dearomatization reaction of tryptamines is highly desirable.[3]

Recently, we found that, in the presence of a catalytic amount of chiral phosphoric acid (**1a**, Ar = 9-phenanthryl),[4] the reaction of tetrahydrocarbazole with phenyl vinyl ketone (**2a**) provides the indolenine product **3** with a 17% yield and 68% ee (eq 1).[5] The low yield of this reaction is likely due to the fact that the basic imine

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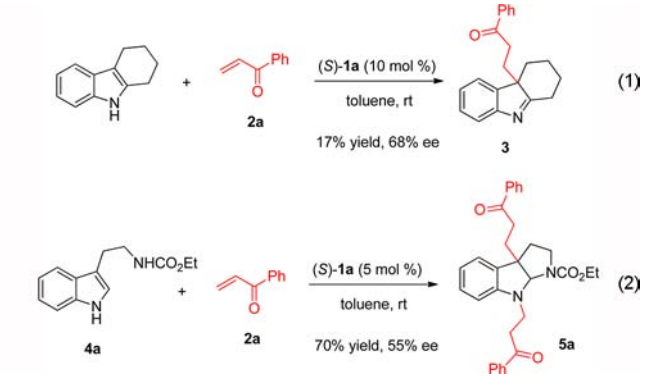
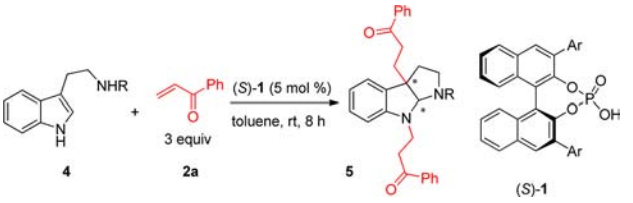
functional group in the product (**3**) interferes with an acidic catalyst to result in a low turnover number. We envisioned that a preinstalled nucleophile in the substrate would capture the imine group in the product to afford a less basic aniline derivative. Recently, we have developed asymmetric Michael−Mannich cacade reactions of indolyl derivatives catalyzed by a chiral primary amine and an acid cocatalyst.[6] Therefore, we envisaged that the employment of substrates with a pendant heteronuleophile tethered on the C3 position of indoles, such as tryptamine derivatives, in the chiral phosphoric acid catalyzed addition to vinyl ketones could provide the privileged pyrroloindoline products. Herein, we describe such an enantioselective cascade Michael addition−cyclization of tryptamines and vinyl ketone catalyzed by a chiral phosphoric acid.



We first studied the Michael addition−cyclization with ethyl carbamate protected tryptamine (**4a**) and phenyl vinyl ketone (**2a**) as the starting materials. To our delight, in the presence of 5 mol % (*S*)-**1a** in toluene, the dearomatization reaction of tryptamine derivative **4a** proceeded smoothly to afford pyrroloindoline product **5a** in 70% yield and 55% ee (eq 2). It should be noted that the *in situ* generated secondary amine proceeded in another Michael addition to afford the *N*-alkylated product.

To increase the enantioselectivity of this reaction, various chiral phosphoric acids were investigated (Table 1). It indicated that (*S*)-**1b** bearing 3,5-bis(trifluoromethyl)-phenyl groups gave the best enantioselectivity (72% ee, entry 1, Table 1). Further studies revealed that the protecting group on the amine side chain could influence the enantioselectivity (entries 10−14, Table 1). *tert*-Butyl carbamate protected tryptamine **4f** provided the corresponding dearomatized product **5f** with the highest ee (75% ee, entry 14, Table 1). When 4 Å molecular sieves (MS) were employed as an additive, the reaction proceeded with a higher yield and enantioselectivity (87% yield, 79% ee, entry 15, Table 1). Furthermore, decreasing the temperature resulted in a prolonged reaction time but with an increased ee value (81% yield, 83% ee, 72 h, entry 16, Table 1).

Table 1. Optimization of the Reaction Conditions for the Michael Addition−Cyclization of Tryptamine Derivatives



entry[a]	(*S*)-**1**, Ar	**5**, R	yield (%)[b]	ee (%)[c]
1[d]	**1b**, 3,5-$(CF_3)_2$-C_6H_3	**5a**, CO_2Et	95	72
2	**1c**, 4-NO_2-C_6H_4	**5a**, CO_2Et	95	62
3	**1d**, 1-naphthyl	**5a**, CO_2Et	93	3
4	**1e**, 2-naphthyl	**5a**, CO_2Et	95	50
5	**1f**, 9-anthryl	**5a**, CO_2Et	91	11
6	**1g**, 4-biphenyl	**5a**, CO_2Et	93	33
7	**1h**, $SiPh_3$	**5a**, CO_2Et	49	68
8	**1i**, 2,4,6-(^{i}Pr)$_3$-C_6H_2	**5a**, CO_2Et	93	51
9	**1j**, 4-^{t}Bu-2,6-(^{i}Pr)$_2$- C_6H_2	**5a**, CO_2Et	91	59
10[d]	**1b**, 3,5-$(CF_3)_2$-C_6H_3	**5b**, CO_2Me	95	67
11[d]	**1b**, 3,5-$(CF_3)_2$-C_6H_3	**5c**, $CO_2{}^n$Pr	96	71
12[d]	**1b**, 3,5-$(CF_3)_2$-C_6H_3	**5d**, $CO_2{}^n$Bu	97	72
13[d]	**1b**, 3,5-$(CF_3)_2$-C_6H_3	**5e**, CO_2Ph	93	67
14	**1b**, 3,5-$(CF_3)_2$-C_6H_3	**5f**, Boc	84	75
15[e]	**1b**, 3,5-$(CF_3)_2$-C_6H_3	**5f**, Boc	87	79
16[e,f]	**1b**, 3,5-$(CF_3)_2$-C_6H_3	**5f**, Boc	81	83

[a] Reaction conditions: 5 mol % (*S*)-**1**, 0.1 mol/L of **4** in toluene, 3 equiv of **2a**. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H). [d] 5 mol % (*R*)-**1b** was used as the catalyst. [e] 50 mg of 4 Å molecular sieves per 0.1 mmol of **4** were used. [f] The reaction was carried out at −20 °C.

To ascertain the generality of this cascade reaction, various tryptamine derivatives and enones were tested (Table 2). In most cases, the reaction went smoothly to provide the desired products in good yields and enantioselectivity (83−95% yield, 50−83% ee). Typtamine derivatives bearing electron-donating groups on indole were suitable substrates for this reaction to afford the pyrroloindoline products in 87−93% yield and 71−77% ee (entries 1−2, Table 2). However, introduction of an electron-withdrawing group such as 5-Cl on the indole resulted in a low yield due to the decreased nucleophilic ability (33% yield and 84% ee, entry 3, Table 2). Remarkably, raising the reaction temperature to 0 °C led to dramatically increased yields and good enantioselectivity (89−97% yield and 76−83% ee, entries 4-9, Table 2). Furthermore, various enones were also examined, and the desired products were obtained in 84−93% yields with 74−82% ee (entries 9−12, Table 2). But when methyl vinyl ketone (MVK) was used, the enantioselectivity was slightly decreased (95% yield and 50% ee, entry 13, Table 2). This methodology could also be used to synthesize a tetrahydrofuroindole derivative in an

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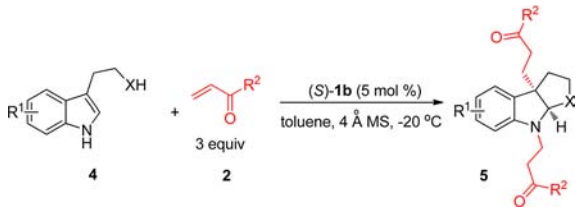
(7) For details, see the Supporting Information.

Table 2. Substrate Scope for the Michael Addition–Cyclization of Tryptamine Derivatives



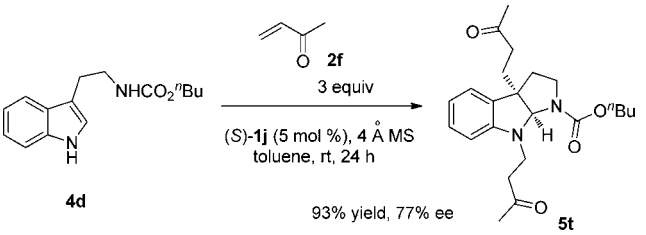
entry[a]	**4**, R^1, X	**2**, R^2	**5**, yield (%)[b]	ee (%)[c]
1	**4g**, 5-Me, NBoc	**2a**, C_6H_5	**5g**, 93	77
2	**4h**, 5-MeO, NBoc	**2a**, C_6H_5	**5h**, 87	71
3	**4i**, 5-Cl, NBoc	**2a**, C_6H_5	**5i**, 33	84
4[d]	**4i**, 5-Cl, NBoc	**2a**, C_6H_5	**5i**, 89	79
5[d]	**4j**, 5-F, NBoc	**2a**, C_6H_5	**5j**, 97	76
6[d]	**4k**, 6-Cl, NBoc	**2a**, C_6H_5	**5k**, 92	83
7[d]	**4l**, 6-F, NBoc	**2a**, C_6H_5	**5l**, 90	81
8[e]	**4m**, 6-Br, NBoc	**2a**, C_6H_5	**5m**, 94	83
9	**4f**, H, NBoc	**2b**, 4–Cl-C_6H_4	**5n**, 93	79
10	**4f**, H, NBoc	**2c**, 4–Br-C_6H_4	**5o**, 95	80
11	**4f**, H, NBoc	**2d**, 2-naphthyl	**5p**, 85	82
12	**4f**, H, NBoc	**2e**, 4-NO_2–C_6H_4	**5q**, 84	74
13[d]	**4f**, H, NBoc	**2f**, Me	**5r**, 95	50
14[d]	**4n**, H, O	**2a**, C_6H_5	**5s**, 94	55

[a] Reaction conditions: 5 mol % (*S*)-1, 0.1 mol/L of **4** in toluene, 3 equiv of **2**, 50 mg of 4 Å molecular sieves per 0.1 mmol of **4** were added, −20 °C. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The reaction was carried out at 0 °C. [e] The absolute configuration of the products was determined by an X-ray analysis of enantiopure derivative of **5m**.[7]

excellent yield but with a moderate enantioselectivity (94% yield and 55% ee, entry 14, Table 2).

To extend the substrate scope, further optimization of the reaction conditions using MVK as the Michael acceptor was conducted.[7] Fortunately, we found that, in the presence of 5 mol % (*S*)-**1j**, the reaction of **4d** with MVK (3 equiv) furnished the desired product in 93% yield and 77% ee (Scheme 1).

Scheme 1. Reaction of **4d** with MVK



In conclusion, we have developed an efficient synthesis of pyrroloindoline derivatives in excellent yields with good enantioselectivity. This chiral phosphoric acid catalyzed Michael addition–cyclization cascade reaction allows a facile access to enantioenriched pyrroloindoline derivatives from readily available tryptamine derivatives and enones. Further application of this methodology to the synthesis of natural products containing the pyrroloindoline core is currently underway in our laboratory.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.