

Asymmetric Construction of Benzindoloquinolizidine: Application of An Organocatalytic Enantioselective Conjugate Addition-Cyclization Cascade Reaction

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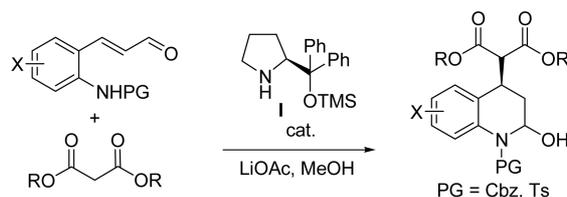
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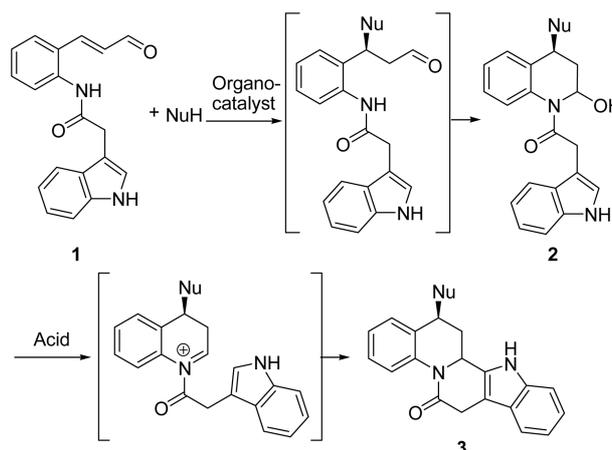
The synthesis of complex natural products and biologically active compounds has attracted the attention of organic chemists for a long time.¹ Many new types of chemical reactions have been developed to facilitate easier synthesis of complex compounds. Among the strategies, domino reactions, which have been utilized for the efficient and stereoselective construction of complex molecules from simple precursors in a single process, are widely used due to their high synthetic efficiency by reducing both the number of synthetic operation required and the quantities of chemicals and solvents used.² In recent years, organocatalysis has emerged as a powerful tool in asymmetric one-pot and domino reactions that provides efficient and environmentally benign access to enantiomerically pure complex molecules.^{3,4} In addition, the organocatalysts used in this process are generally non-toxic, readily available, and air-stable, which result in better reproducibility and greater operational simplicity than traditional metal catalysts. Herein we report an asymmetric synthetic strategy for the preparation of enantioenriched benzindoloquinolizidines, which involves an organocatalyst-mediated cascade reaction.

As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,⁵ we recently developed a novel catalytic asymmetric conjugate addition-cyclization domino reaction of *o*-*N*-protected aminocinnamaldehydes using an organocatalyst, which afforded chiral tetrahydroquinoline derivatives with high enantioselectivities (Scheme 1); Moreover, the most satisfactory results were obtained when Ts or Cbz group was used as the protecting group for the *o*-aminocinnamaldehydes.⁶

To further investigate these findings, we considered the use of another useful protecting group for *o*-aminocinnamaldehydes that could participate in the subsequent reaction, and so we examined the feasibility of using a 3-indoleacetyl moiety instead of Cbz or Ts as the protecting group. It was believed that the organocatalytic asymmetric conjugate addition-cyclization cascade reaction of 3-indoleacetyl protected *o*-aminocinnamaldehydes with dialkyl malonate could enable the direct synthesis of enantioenriched benzindoloquinolizidine derivatives asymmetric conjugate addition-cyclization cascade reaction of 3-indoleacetyl protected *o*-aminocinnamaldehydes with dialkyl malonate could enable



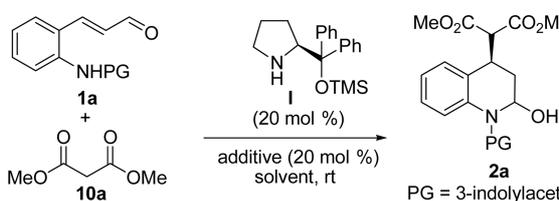
Scheme 1. Organocatalytic asymmetric conjugate addition-cyclization cascade reaction of *o*-*N*-protected aminocinnamaldehydes.



Scheme 2. Asymmetric synthesis of benzindoloquinolizidines.

the direct synthesis of enantioenriched benzindoloquinolizidine derivatives. The quinolizidine structural unit is common to many naturally occurring compounds that have a wide spectrum of biological activities.⁷ Therefore, natural alkaloids, together with non-natural derivatives containing quinolizidine scaffold, have long attracted extensive biological, chemical, and synthetic interest.⁸ The conceptual proposal of our synthetic strategy is shown in Scheme 2. In this process, the conjugate addition of 3-indoleacetyl protected *o*-aminocinnamaldehyde **1** with a nucleophile in the presence of chiral organocatalyst gives enantioenriched 4-substituted tetrahydroquinolin-2-ol **2** via hemiacetalization of the Michael adduct. Subsequent acid-catalyzed intramolecular Pictet-Spengler type cyclization would effectively provide benzindoloquinolizidine **3** enantioselectively.⁹

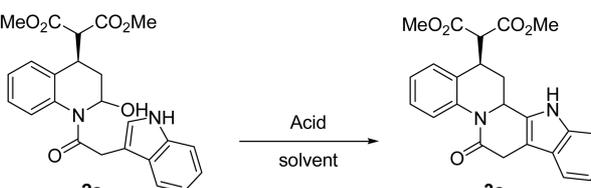
For the construction of enantioenriched benzindoloquinolizidine

Table 1. Screening studies for the organocatalytic conjugate addition-cyclization domino reaction of dimethyl malonate (**10a**) with *o*-*N*-(3-indolylacetyl)aminocinnamaldehyde **1a**^a


Entry	Additive	Solvent	Time (h)	Yield (%) ^b	ee (%) ^c
1	PhCO ₂ H	CH ₂ Cl ₂	48	26	nd ^d
2	PhCO ₂ H	MeOH	72	5	nd ^d
3	PhCO ₂ H	EtOH	48	9	nd ^d
4	PhCO ₂ H	CH ₃ CN	48	15	nd ^d
5	PhCO ₂ H	EtOAc	48	14	nd ^d
6	PhCO ₂ H	Toluene	72	40	80
7	PhCO ₂ H	THF	48	58	82
8	PhCO ₂ H	DMF	24	98	88
9	AcOH	DMF	48	84	90
10	2-NO ₂ C ₆ H ₄ CO ₂ H	DMF	48	68	91
11	4-NO ₂ C ₆ H ₄ CO ₂ H	DMF	48	86	93
12e	4-NO ₂ C ₆ H ₄ CO ₂ H	DMF	72	90	96
13	LiOAc	DMF	48	70	77
14	NaOAc	DMF	48	57	65

^aUnless otherwise specified, the reaction was carried out in solvent (0.3 M) with 1.5 equiv of dimethyl malonate **10a** relative to the *o*-*N*-(3-indolylacetyl)-aminocinnamaldehyde **1a** in the presence of 20 mol % catalyst and additive. ^bIsolated yield after chromatographic purification. ^cDetermined by chiral-phase HPLC analysis after oxidation. ^dNot determined. ^eReaction was performed at 0 °C.

lizidines, the asymmetric conjugate addition reaction of *o*-*N*-(3-indoleacetyl)aminocinnamaldehyde **1a** with dimethyl malonate **10a** was selected as a model reaction, in which the first step of our investigation was to evaluate optimal conditions by screening for appropriate solvents and additives. Based on results of our previous work, the α,α -diphenyl-L-prolinol TMS ether catalyst **I** was chosen as an organocatalyst in this conjugate reaction of **1a** with **10a**,^{10,11} and the results are shown in Table 1. The reaction was carried out at room temperature in CH₂Cl₂, using 20 mol % catalyst **I** with benzoic acid as an additive, and afforded the desired product **2a** in only 26% yield (entry 1). In contrast to the results of previous studies on the organocatalytic conjugate addition reaction of malonates with α,β -unsaturated aldehydes,^{5,6,12} the reaction medium had a relatively substantial effect on the conversion efficiency in this reaction. In particular, polar protic solvents such as MeOH and EtOH diminished reactivity, and the reactions produced only trace amounts of the desired products (entries 3 and 4). Subsequently, nonpolar and aprotic solvents such as CH₃CN, EtOAc, toluene, and THF were investigated in this reaction, and the reaction in THF showed reasonably good yield and enantioselectivity with 58% yield and 82% ee (entries 4–7). To our delight, when DMF, a polar aprotic solvent, was employed in this reaction, satisfactory results were obtained in terms of both

Table 2. Screening studies for the formation of benzindoloquinolizine **3a**^a


Entry	Acid	Equivalents	Solvent	Temperature (°C)	Time (h)	Yield (%) ^b
1	HCO ₂ H	5	CH ₂ Cl ₂	40	72	No rxn
2	AcOH	5	CH ₂ Cl ₂	40	72	No rxn
3	TFA	0.2	CH ₂ Cl ₂	0 → r.t.	3	20
4	HCl	0.2	CH ₂ Cl ₂	-78 → r.t.	3	32
5	HCl	1.2	CH ₂ Cl ₂	-78 → r.t.	3	41
6	HCl	8	CH ₂ Cl ₂	-78 → r.t.	2	47
7	HCl	8	Toluene	-78 → r.t.	2	39
8	HCl	8	CHCl ₃	-78 → r.t.	2	56

^aThe reaction was carried out in solvent (0.2 M) with the given acid at the given temperature. ^bIsolated yield after chromatographic purification.

yield and enantioselectivity, and the desired product **2a** was produced with 98% yield and 88% ee (entry 8). To further optimize the reaction conditions, various acid and base additives were examined for this reaction. An investigation of the effect of acid additives revealed excellent enantioselectivities (88–93% ee) in all cases where acid was used (entries 8–11), while the use of base additives resulted in inferior enantioselectivities (entries 13 and 14). Furthermore, it was found that a better enantioselectivity and a higher yield were obtained by using catalyst **I** (20 mol %) in DMF at 0 °C with 4-NO₂C₆H₄CO₂H (20 mol %) (90% yield, 96% ee, entry 12).

After establishing the best reaction conditions for the conjugate addition, the acid-catalyzed intramolecular Pictet-Spengler type cyclization was investigated.¹³ A careful screening of acids for the cyclization of the acyliminium ion of **2a** that was isolated from the previous conjugate addition reaction, revealed that HCl afforded the desired cyclic product in a moderate yield (Table 2, entry 4). A brief screening for the optimum amount of acid showed that a treatment of 8 equivalents of HCl in CHCl₃ was the best cyclization condition (entry 8). However, no product was observed when HCl was added to the mixture without isolation after full conversion of **1a** in the organocatalytic conjugate reaction using DMF as the solvent.

Having determined optimized reaction conditions for this system, a selection of malonates and *o*-*N*-(3-indoleacetyl)-aminocinnamaldehydes were reacted using this novel and short process for the synthesis of benzindoloquinolizine derivatives (Table 3). Various malonates including dimethyl, diethyl, diisopropyl, and dibenzyl esters showed high reactivities and excellent enantioselectivities in the conjugate addition reaction, and provided chiral benzindoloquinolizines with moderate yield under acid-catalyzed cyclization (entries 1–4). Moreover, variation of the substituent on the phenyl

Table 3. Organocatalytic enantioselective conjugate addition-cyclization domino reaction of malonates **10** with *o*-*N*-(3-indolylacetyl)aminocinnamaldehydes **1** followed by Pictet-Spengler type cyclization^a

Entry	R	X	Time (h)	Yield 2 (%) ^b	Yield 3 (%) ^b	dr ^c	ee (%) ^d
1	3a , Me	H	72	90	56	> 20:1	96
2	3b , Et	H	72	76	61	> 20:1	98
3	3c , <i>i</i> -Pr	H	120	62	48	> 20:1	96
4	3d , Bn	H	48	80	58	15:1	96
5	3e , Me	Cl	72	82	50	> 20:1	94
6	3f , Me	Br	72	87	64	> 20:1	93

^aGeneral conditions: (step 1) **1** (0.1 mmol), **10** (0.15 mmol), **I** (20 mol %) and 4-NO₂C₆H₄CO₂H (10 mol %) in DMF (0.3 M solution) at 0 °C; (step 2) HCl (8 equiv), CHCl₃ (0.2 M solution). ^bIsolated yield after chromatographic purification. ^cDetermined by ¹H NMR. ^dDetermined by chiral-phase HPLC analysis after oxidation of **2**.

group in *o*-*N*-(3-indoleacetyl)aminocinnamaldehyde facilitated similar results in these reactions, without a significant loss of enantioselectivity, which remained high (entries 5-6).

In conclusion, we have developed the synthetic methodology of enantioenriched benzindoloquinolizidines based on the organocatalytic enantioselective conjugate addition-cyclization cascade reaction of *o*-*N*-(3-indoleacetyl)aminocinnamaldehydes with malonates followed by an acid-catalyzed intramolecular Pictet-Spengler type cyclization. The asymmetric reaction using diphenylprolinol TMS ether as an organocatalyst produces the desired products with good to excellent yields and high enantioselectivities (up to 98% ee). The evaluation of the applications of this synthetic methodology for generating enantioenriched benzindoloquinolizidines and studies on the biological activity of these compounds against human prostate cancer in particular are now in progress. Results of these studies will be presented in due course.

Experimental

General Procedure. An amber 2-dram vial equipped with a magnetic stir bar, containing catalyst **I** (98 mg, 0.30 mmol), *o*-*N*-(3-indoleacetyl)aminocinnamaldehyde **1a** (457 mg, 1.5 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) was charged with DMF (8 mL) at 0 °C. The solution was stirred for 5 min before the addition of dimethyl malonate **10a** (257 L, 2.3 mmol). The resulting mixture was stirred at constant temperature until complete consumption of *o*-*N*-(3-indoleacetyl)aminocinnamaldehyde **1a** was observed as determined by TLC. The resulting mixture was directly purified by silica gel chromatography (50% EtOAc/hexanes) to afford the desired compound **2a** as a colorless gum (584 mg, 90% yield, 96% ee). To a solution of tetrahydroquinolin-2-ol **2a** (96 mg, 0.22 mmol) in CHCl₃ (1.2 mL) at -78 °C was added HCl (0.44 mL, 1.8 mmol, 4 M solution in 1,4-dioxane). After 20 minutes, the mixture was allowed to warm up to room temperature and stirred for 2 h. The reaction was quenched with sat. NaHCO₃ solution and extracted with

CH₂Cl₂. The combined extract was washed with brine, dried over sodium sulfate, concentrated, and purified by flash column chromatography (40% EtOAc/Hexane) to afford the benzindoloquinolizidine **3a** as a colorless gum (52 mg, 56% yield). The enantioselectivity was determined by HPLC analysis of the tetrahydroquinolinone product, which was prepared by oxidation (PCC, CH₂Cl₂) of **2a**, using a Chiralcel AD-H column and AD-H guard column (20% EtOH:hexanes, 1.0 mL/min flow, λ = 220 nm); *minor*- isomer *t*_r = 25.0 min and *major*- isomer *t*_r = 37.6 min.

Dimethyl 2-((14*R*)-6,7,12,12*b*,13,14-Hexahydro-6-oxo-indolo[2,3-*a*]quinolizine-14-yl)malonate (3a**):** [α]_D²² -33.4 (*c* 0.24, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.41 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.15 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.01-7.44 (m, 6H), 4.74 (dd, *J* = 2.8, 12.8 Hz, 1H), 3.75 (s, 3H), 3.60-3.72 (m, 2H), 3.57 (s, 3H), 3.43 (d, *J* = 19.6 Hz, 1H), 2.54 (d, *J* = 16.4 Hz, 1H), 1.51 (td, *J* = 4.4, 12.8 Hz, 1H), 1.17 (dt, *J* = 2.8, 14.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 172.1, 171.2, 168.0, 167.6, 155.2, 138.0, 136.2, 129.6, 129.3, 128.8, 127.0, 124.4, 123.7, 122.6, 122.1, 118.5, 57.7, 55.3, 52.9, 52.6, 38.6, 36.1, 25.6; HRMS (ESI): Calcd for C₂₄H₂₂N₂O₅Na (M+Na)⁺: 441.1426. Found: 441.1428.

Diethyl 2-((14*R*)-6,7,12,12*b*,13,14-Hexahydro-6-oxo-indolo[2,3-*a*]quinolizine-14-yl)malonate (3b**):** [α]_D²¹ -55.3 (*c* 0.26, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.01 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.02-7.44 (m, 6H), 4.77 (dd, *J* = 2.8, 12.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.05 (q, *J* = 6.8 Hz, 2H), 3.65-3.72 (m, 1H), 3.59 (d, *J* = 10.0 Hz, 1H), 3.43 (d, *J* = 16.4 Hz, 1H), 2.54 (d, *J* = 16.4 Hz, 1H), 1.50 (td, *J* = 4.4, 14.0 Hz, 1H), 1.22-1.30 (m, 4H), 1.11 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.2, 171.2, 167.6, 167.3, 155.2, 138.0, 136.2, 129.8, 129.2, 128.7, 127.0, 124.5, 123.6, 122.6, 122.1, 118.4, 62.0, 61.7, 58.0, 55.4, 38.6, 36.0, 25.7, 14.1, 13.8; HRMS (ESI): Calcd for C₂₆H₂₆N₂O₅Na (M+Na)⁺: 469.1739. Found: 469.1738.

Diisopropyl 2-((14*R*)-6,7,12,12*b*,13,14-Hexahydro-6-oxo-indolo[2,3-*a*]quinolizine-14-yl)malonate (3c**):** [α]_D²⁴ -43.8 (*c* 0.58, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.00 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.01-7.43 (m, 6H), 5.04 (septet, *J* = 6.4 Hz, 1H), 4.92 (septet, *J* = 6.4 Hz, 1H), 4.80 (dd, *J* = 2.8, 12.8 Hz, 1H), 3.64-3.71 (m, 1H), 3.53 (d, *J* = 10.0 Hz, 1H), 3.42 (d, *J* = 16.4 Hz, 1H), 2.52 (d, *J* = 16.4 Hz, 1H), 1.48 (td, *J* = 4.8, 14.0 Hz, 1H), 1.22-1.28 (m, 7H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.03 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 171.4, 167.3, 167.0, 142.2, 138.2, 136.3, 130.1, 129.3, 128.7, 127.1, 124.8, 123.8, 122.7, 118.5, 69.9, 69.6, 61.0, 58.5, 55.6, 38.8, 35.8, 21.8, 21.7, 21.6, 21.5; HRMS (ESI): Calcd for C₂₈H₃₀N₂O₅Na (M+Na)⁺: 497.2052. Found: 497.2053.

Dibenzyl 2-((14*R*)-6,7,12,12*b*,13,14-Hexahydro-6-oxo-indolo[2,3-*a*]quinolizine-14-yl)malonate (3d**):** [α]_D²⁴ -21.7 (*c* 0.26, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.97 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 6.85-7.40 (m, 16H), 5.11 (s, 2H), 4.95 (dd, *J* = 12.4, 23.6 Hz, 2H), 4.57 (dd, *J* = 2.8, 12.8 Hz, 1H), 3.67-3.74 (m, 2H), 3.23 (d, *J* = 16.4 Hz, 1H), 2.43 (d, *J* = 16.4 Hz, 1H), 1.44 (td, *J* = 4.4, 14.4 Hz, 1H), 1.16 (ddd, *J* = 2.0, 3.2, 14.4 Hz, 1H); ¹³C

NMR (100 MHz, CDCl₃) δ 172.6, 172.2, 171.4, 167.5, 148.6, 147.2, 138.2, 128.9, 128.8, 128.7, 128.6, 128.5, 124.3, 122.6, 121.7, 118.5, 116.4, 67.8, 67.7, 60.8, 58.0, 38.7, 36.1, 25.7; HRMS (ESI): Calcd for C₃₆H₃₀N₂O₅Na (M+Na)⁺: 593.2052. Found: 593.2055.

Dimethyl 2-((14R)-2-Chloro-6,7,12,12b,13,14-hexahydro-6-oxo-indolo[2,3-a]quinolizine-14-yl)malonate (3e): [α]_D²⁸ 13.1 (c 0.23, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.97 (d, J = 8.8 Hz, 1H), 8.12 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.17-7.43 (m, 5H), 4.70 (dd, J = 2.8, 12.8 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.54-3.64 (m, 2H), 3.32 (d, J = 16.8 Hz, 1H), 2.53 (d, J = 16.8 Hz, 1H), 1.45 (td, J = 4.4, 13.6 Hz, 1H), 1.15 (dt, J = 2.4, 14.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 167.9, 167.5, 154.7, 142.2, 142.1, 141.9, 141.6, 141.4, 140.0, 139.0, 134.8, 129.4, 128.9, 127.2, 126.2, 119.9, 57.6, 55.3, 52.9, 37.1, 29.8, 25.5; HRMS (ESI): Calcd for C₂₄H₂₁ClN₂O₅Na (M+Na)⁺: 475.1037. Found: 475.1038.

Dimethyl 2-((14R)-2-Bromo-6,7,12,12b,13,14-hexahydro-6-oxo-indolo[2,3-a]quinolizine-14-yl)malonate (3f): [α]_D²⁸ 44.3 (c 0.60, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.91 (d, J = 8.8 Hz, 1H), 8.11 (s, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.20-7.45 (m, 5H), 4.69 (dd, J = 2.8, 12.8 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.56-3.62 (m, 2H), 3.41 (d, J = 16.4 Hz, 1H), 2.52 (d, J = 16.8 Hz, 1H), 1.43 (td, J = 4.0, 14.0 Hz, 1H), 1.15 (dt, J = 2.4, 14.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 167.9, 167.45, 148.6, 135.8, 135.3, 132.4, 131.8, 129.5, 127.2, 126.6, 122.5, 122.4, 120.2, 116.5, 57.6, 55.3, 52.9, 38.6, 35.9, 25.5; HRMS (ESI): Calcd for C₂₄H₂₁BrN₂O₅Na (M+Na)⁺: 519.0532. Found: 519.0530.

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