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One-Pot Asymmetric Synthesis of Seven-Membered Carbocycles Cyclohepta[*b*]indoles via a Sequential Organocatalytic Michael/Double Friedel–Crafts Alkylation Reaction

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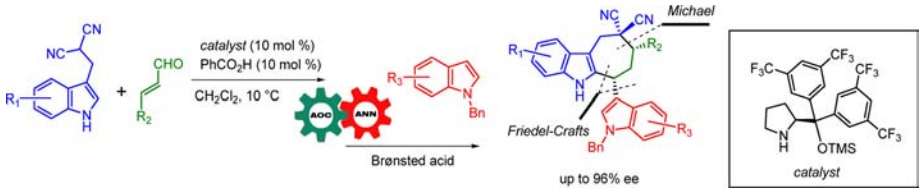
ABSTRACT



A new method has been developed for the enantioselective synthesis of highly functionalized cyclohepta[*b*]indoles with high enantioselectivity (up to 96% *ee*). The process combines an enantioselective organocatalytic Michael addition and a highly efficient double Friedel–Crafts reaction sequence in one pot with good yields and stereoselectivity. The structures and absolute configurations of the products were confirmed by X-ray analysis.

Seven-membered carbocycles constitute an important class of biologically active molecules that are prevalent in nature. Despite the substantial medicinal applications of these compounds and their prevalence in nature, methodologies for the synthesis of cycloheptane systems are scarce and challenging, as compared to their five- and six-membered carbocycle counterparts. The development of new methodologies for the construction of seven-membered carbocycles continues to attract the interest of chemists. The successful approaches to seven-membered carbocycles have included cycloaddition,[1] e.g., [6 + 1],[2] [3 + 2 + 2],[3] [5 + 2],[4] [4 + 3],[5] [4 + 2 + 1],[6] [3 + 3 + 1],[7] ring expansion,[8] and metal-mediated reactions.[9] In addition, owing to factors of distance and ring strain, the reaction rate of the ring closure cyclization to achieve seven-membered rings is much slower than the formation of five- and six-membered rings.[10] As a result, only a few examples of approaches involving

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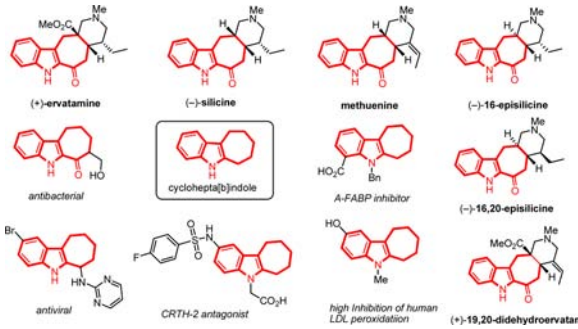
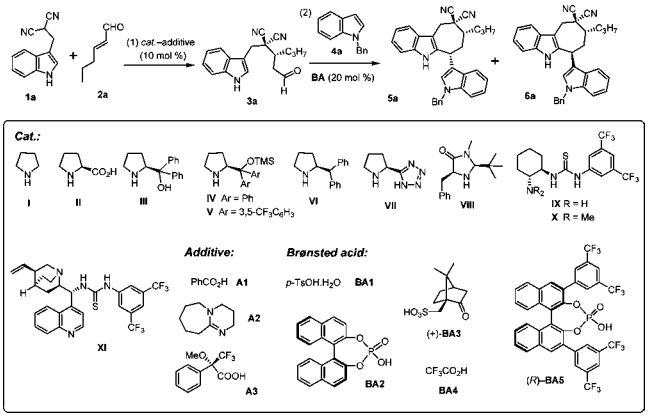


Figure 1. Natural products and medicinal drugs containing a cyclohepta[*b*]indole core.

intramolecular cyclization to afford seven-membered carbocycles have been realized.[11] Moreover, only a scant number of asymmetric organocatalytic syntheses[12] of chiral seven-membered carbocycles have been reported.[13] On the other hand, cyclohepta[*b*]indoles, a basic skeleton of many naturally occurring alkaloids with a broad spectrum of biological properties, e.g., antitumor, antibiotic, and anti-inflammatory activities, have received much attention in synthetic endeavors (Figure 1).[14] Nevertheless, no efficient asymmetric organocatalysis protocol for the synthesis of cyclohepta[*b*]indoles has been realized, and there is a definite need for such a synthetic procedure.

Bearing in mind the aforementioned background,[15] we have extended our general interest in organocatalytic asymmetric annulations[16,17] to encompass an approach to the cyclohepta[*b*]indole system via sequential organocatalytic Michael/double Friedel–Crafts alkylation reactions using a one-pot strategy.[18,19] Two key challenges needed to be addressed: cyclization of the seven-membered carbocycles and control of the stereochemistry of the substituents on the medium ring. Herein, we report the details of such an approach and the methodology that permitted efficient production of cyclohepta[*b*]indoles derivatives in excellent yields (up to 72%) and stereoselectivity with up to 96% *ee*.

Table 1. Screening of the Catalysts, Solvents, and Conditions for the Reaction[a]



entry	cat.-additive, BA	solvent	t_1/t_2 (h)	yield[b] (%)	dr[c] **5a/6a**	*ee*[d] **5a**
1	**I–A1, BA1**	CH_2Cl_2	36/3	20	68:32	0
2	**II–A1, BA1**	CH_2Cl_2	45/3	27	71:29	~0
3	**III–A1, BA1**	CH_2Cl_2	48/3	40	68:32	~0
4	**IV–A1**	CH_2Cl_2	24/0	0[e]	na	na
5	**V–A1, BA1**	CH_2Cl_2	60/3	63	75:25	76
6	**VI–A1, BA1**	CH_2Cl_2	120/3	23	50:50	~0
7	**VII–A1, BA1**	CH_2Cl_2	48/3	48	68:32	~0
8	**VIII–A1**	CH_2Cl_2	120/0	0[f]	na	na
9	**IX**	CH_2Cl_2	240/0	0[f]	na	na
10	**X, BA1**	CH_2Cl_2	90/6	14	nd	nd
11	**XI, BA1**	CH_2Cl_2	168/6	48	82/18	-15
12	**V–A1, BA1**	toluene	85/6	52	72:28	78
13	**V–A1, BA1**	$CHCl_3$	90/6	66	67:33	80
14	**V–A1,**	THF	120/0	0[f]	na	na
15	**V–A1, BA1**	CH_3CN	70/3	52	63:37	7
16	**V–A1, BA1**	EtOH	66/3	0[g]	na	na
17	**V–A2, BA1**	CH_2Cl_2	3/0	~0	na	na
18	**V–A3,**	CH_2Cl_2	240/0	0[f]	na	na
19[h]	**V–A1, BA1**	CH_2Cl_2	48[i]/12[i]	62	77:23	90
20[h]	**V–A1, BA1**	CH_2Cl_2	72[j]/30[j]	66	72:28	90
21[h]	**V–A1, BA1**	CH_2Cl_2	120[k]/48[k]	42	64:36	84
22[h]	**V–A1, BA2**	CH_2Cl_2	48[i]/30[j]	54	65:35	80
23[h]	**V–A1, (+)-BA3**	CH_2Cl_2	48[i]/24[i]	66	70:30	90
24[h]	**V–A1, BA4**	CH_2Cl_2	48[i]/48	5	nd	nd

[a] Unless otherwise noted, the reactions were performed on a 0.3 M of **1a** and with 2 equiv of **2a** at 30 °C, using 10 mol % of the catalyst and additive at 30 °C in a vial containing the appropriate solvent. [b] Isolated yields of **5a** and **6a**. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] *Ee* of **5a**, determined by HPLC with chiral column Chiralpak IB. [e] Self-condensation of **2a**. [f] No reaction; recovered **1a** and **2a**. [g] Decomposition of **3a** during the 2nd step reaction. [h] Reactions were performed on a 0.6 M of **1a** for 1st step reaction and diluted to 0.1 M in the 2nd step reaction. [i] Reaction at 10 °C. [j] Reaction at 5 °C. [k] Reaction at 0 °C. [l] Reaction at 30 °C. nd = not determined. na = not available. BA = Brønsted acid.

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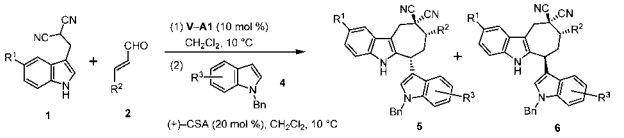
At the outset of our study for feasibility, Michael reaction of **1a** and **2a** was screened with a variety of organocatalysts in obtaining the conjugate addition adduct **3a** (Table 1).[20] Subsequently, treatment of **3a** in the presence of a Brønsted acid and indole **4a** afforded the cyclohepta-[*b*]indoles **5a** as a major product.[21] Eventually, we performed the two-step reaction sequence in one pot, and the results were promising. Notably, although **3a** contains enolizable α-protons for side reactions, the subsequent inter- and intramolecular Friedel–Crafts alkylation reactions catalyzed by the Brønsted acid proceeded with high efficiency and compatibility. Details of the optimization conditions are summarized in Table 1. Among the reactions performed with secondary amine steric shielding catalysts (**I**–**VIII**) and benzoic acid (Table 1, entries 1–8), the best result was obtained by the reaction with **V**–$PhCO_2H$ to give a 63% yield of **5a**/**6a** (75:25 dr) and 76% *ee* of **5a** (Table 1, entry 5). Other secondary amine catalysts afforded low yield and *ee* or with no observable Michael adduct **3a** (Table 1, entries 1–3 and 6–7). It is worth noting that with the subtle differences in the substituents on catalyst **IV** and **V**, the reaction with catalyst **IV**–$PhCO_2H$ gave no **3a** due to the self-condensation of **2a** (Table 1, entry 4).[22] The reaction of **1a** and **2a** with catalyst **VIII** did not proceed after 120 h, with recovery of starting materials (Table 1, entry 8). The reaction was also incomplete with the thiourea catalysts **IX** after 240 h of reaction (Table 1, entry 9). The reactions with thiourea **X** and **XI** provided much lower yields (Table 1, entries 10–11). We also applied various solvents in the reactions, and most of them afforded lower yields or gave no reaction with **V**–$PhCO_2H$ except for the reaction in $CHCl_3$ (Table 1, entries 12–16). The reaction in $CHCl_3$ gave as good a yield as the one in CH_2Cl_2 although with less dr (Table 1, entries 5 and 13). Changing the additive $PhCO_2H$ (**A1**) to DBU (**A2**) or Mosher's acid (**A3**) with catalyst **V** gave fruitless results (Table 1, entries 17–18).

In an effort to optimize the enantioselectivity, we performed the reaction at a lower temperature. We observed a sluggish reaction rate for the first step Michael reaction at a low temperature, an obstacle that we overcame by increasing the reaction concentration to 0.6 M. In addition, to prevent possible side reactions in the following double Friedel–Crafts reaction, we diluted the concentration of reagents for the second step reaction to 0.1 M. Under these conditions, the reaction at 10 °C gave a 62% yield of the product **5a**/**6a** (77:23) and 90% *ee* of **5a** (Table 1, entry 19). However, conducting the reaction at even lower temperatures (5 and 0 °C) retarded the reaction rate (Table 1, entries 20–21). We attempted to further optimize the reaction sequence by screening various Brønsted acid catalysts. The rate of inter- and intramolecular Friedel–Crafts alkylations with chiral phosphoric acid **BA2** at 10 °C was very slow, and the conditions at 30 °C provided a lower yield of products with lower enantioselectivity (Table 1, entry 22). Among other Brønsted acids tested, (+)-CSA gave the best results and gave slightly higher yields of the products **5a**/**6a** than the conditions with *p*-TsOH (**BA1**), although in slightly less dr (Table 1, entries 23 and 19). The reaction with a less acidic acid, e.g., TFA, yielded only a tiny amount of **5a**/**6a** along with the starting **4a** and **3a** after 48 h of reaction (Table 1, entry 24).

With the optimized conditions in hand, the one-pot Michael/double Friedel–Crafts alkylation reaction protocol was applied in the reaction with various malononitrile indoles **1**, α,β-unsaturated aldehydes **2**, and *N*-Bn-protected indole **4**, and the results were promising, generally with high yields and enantioselectivities (Table 2). Usually, the first step reaction was completed in 48 h, but a longer reaction

Table 2. Scope of Organocatalytic Sequential Michael/Double Friedel–Crafts Alkylation Reactions[a]



entry	R_1, R_2, R_3	yield[b] (%)	dr[c] 5/6	*ee*[d] 5/6 (%)
1	**a** R^1 = H; R^2 = *n*-C_3H_7; R^3 = H	66	70:30	90/95
2	**b** R^1 = H; R^2 = *n*-C_4H_9; R^3 = H	68	74:26	90/90
3	**c** R^1 = H; R^2 = (*Z*)-hex-3-enyl; R^3 = H	62	75:25	90/93
4	**d** R^1 = H; R^2 = *n*-C_5H_{11}; R^3 = H	65	72:28	90/92
5[e]	**e** R^1 = OMe; R^2 = *n*-C_3H_7; R^3 = H	60	80:20	87/nd
6[f]	**f** R^1 =Br; R^2 = *n*-C_3H_7; R^3 = H	60	70:30	90/96
7	**g** R^1 = H; R^2 = *n*-C_3H_7; R^3 = 5-Cl	62	85:15	91/nd
8	**h** R^1 = H; R^2 = *n*-C_3H_7; R^3 = 5-Br	68	88:12[i]	90/nd
9	**i** R^1 = H; R^2 = *n*-C_3H_7; R^3 = 5-CN	50	86:14	94/nd
10	**j** R^1 = H; R^2 = *n*-C_3H_7; R^3 = 6-Cl	65	85:15	91/nd
11	**k** R^1 = H; R^2 = *n*-C_3H_7; R^3 = 7-Br	70	89:11	89/nd
12	**l** R^1 = H; R^2 = *n*-C_3H_7; R^3 = 4-Br	72	85:15	93/nd
13[g]	**m** R^1 = H; R^2 = *n*-C_3H_7; R^3 = 5-OMe	63	70:30	90/96
14[h]	**n** R^1 = H; R^2 = *n*-C_3H_7; R^3 = 5-Me	60	70:30	89/95

[a] Unless otherwise noted, the reactions were performed on a 0.2-mmol scale of **1**, in a ratio of 1:2 for **1**/**2**, using 10 mol % of the catalyst **V**–$PhCO_2H$ at 10 °C for 48 h, followed by addition of (+)-CSA (20 mol %) and reacted at 10 °C for 24 h. [b] Isolated yields of **5** and **6**. [c] Determined by ^1H NMR of the crude reaction mixture. [d] *Ee* of **5** and **6**, respectively. *Ee* of **5** was determined by HPLC with chiral column Chiralpak IB. *Ee* of **6** determined by HPLC with chiral column Chiralpak IC, except for **6a** which was done by Chiralpak IB. [e] 80 h for 1st step and 48 h for 2nd step reactions. [f] TsOH (20 mol %) was used for the 2nd step reaction. [g] 96 h for the 2nd step reaction. [h] 48 h for the 2nd step reaction. [i] (*R*)-**BA5** (20 mol %) was used for the 2nd step reaction, and **5h** was the only isomer obtained (95% *ee*, dr > 20:1). nd = not determined.

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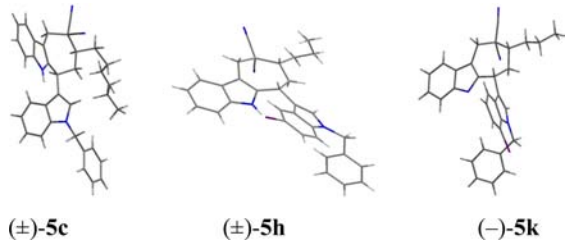


Figure 2. Stereoplots of the X-ray crystal structures of (±)-**5c**, (±)-**5h**, and (−)-**5k**: C, gray; N, blue; Br, purple.

time was required in the case with 2-((5-methoxy-1*H*-indol-3-yl)methyl)malononitrile, the 5-methoxy indole derivative **5e** (Table 2, entry 5). In addition, the second step reactions in examples with (+)-CSA were usually completed in 24 h. However, a longer time was needed for the example with **5e** (Table 2, entry 5), and for the examples of the electron-donating substituents on **4** (Table 2, entries 13 and 14). For **3f**, the 5-bromo indole derivative, the second-step reaction was treated with TsOH (20 mol %) since the reaction with (+)-CSA required a much longer reaction time (> 160 h).

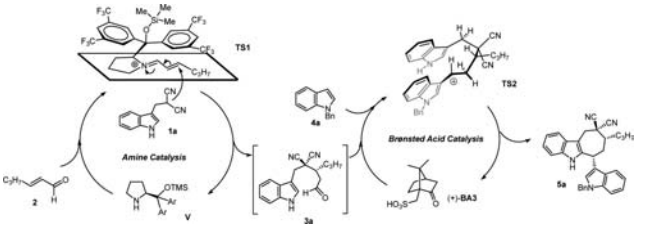
It is noteworthy that the second-step reactions with halo- or cyanoindole **4** gave a higher diastereomeric ratio than the reactions with **4a** (Table 2, entries 7−12). The reason for the discrepancy is unclear and may be related to the substitution effect on the enhancement of the $\pi-\pi$ stacking conformation of **3a** that favors the transition state toward **5** (vide infra). Owing to the great development of modern Brønsted acid catalysis, a second-step cyclization was tested with the more acidic chiral Brønsted acid. Interestingly, a reaction with the chiral binaphthyl-2,2′-diylhydrogenphosphate derivative, (*R*)-**BA5**, exclusively afforded **5h** (95% *ee*, dr > 20:1), Table 2, entry 8, footnote i. The structure and relative stereochemistry of the products were assigned based on the X-ray analysis of (±)-**5c**, (±)-**5h**,[23] and the absolute configuration was established by X-ray single-crystal analysis of (−)-**5k** (Figure 2).

To explain the stereochemical outcome of this transformation, we have proposed a plausible mechanism (Scheme 1). Initial nucleophilic attack of indole malononitrile **1a** on the iminium-activated α,β-unsaturated aldehyde **2** via **TS1** from the *Re* face under the catalyst control by efficient shielding of the *Si*-face gives the Michael addition adduct **3**. Subsequently, treatment of **3a** with 1-benzyl-1*H*-indole (**4a**) and (+)-CSA provided the iminium-activated cation intermediate which underwent cyclization via **TS2**,[24] preferring the stabilized $\pi-\pi$ stacking and half-chair cycloheptane conformer, to afford cyclohepta[*b*]indoles **5a** as the major isomer. Notably, the reaction demonstrates a proof-of-principle of the control of stereoselectivity in an intramolecular cyclization toward the cycloheptane skeleton by an asymmetric organocatalytic cascade.

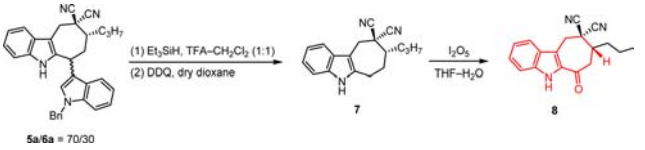
(23) Prepared from the reaction with pyrrolidine (**I**)−$PHCO_2H$, as a standard for HPLC analysis.

(24) Conformer distribution search on the cation intermediate was conducted by SPARTAN'10 using Molecular Mechanics MMFF, and the most energetically favorable conformer is depicted as **TS2** in Scheme 1.

Scheme 1. Proposed Mechanism for the One-Pot Transformation



Scheme 2. Synthetic Extension to the Ervatamine Tricyclic System



Finally, we explored the possibility of extending the protocol to the cyclohepta[*b*]indol-6-one, the basic tricyclic skeleton of naturally occurring ervatamine, and its family (Scheme 2). Reduction of the mixture of **5a**/**6a** with triethylsilane in TFA−CH_2Cl_2, followed by oxidation of the indoline intermediate with DDQ, gave hexahydrocyclohepta[*b*]indole **7** in 60% yield. Oxidation of **7** with iodine pentaoxide in THF−H_2O afforded a 40% yield of the cyclohepta[*b*]indolone **8**, the tricyclic framework presented in many naturally occurring cyclohepta[*b*]indole, e.g., ervatamine and silicine.

In summary, we have described a concise synthesis of optically active cyclohepta[*b*]indoles, the multifunctionalized seven-membered carbocycles, with high enantioselectivities by sequential organocatalytic Michael/double Friedel−Crafts alkylation reactions. Particularly noteworthy is the synergistic use of secondary amine organocatalysis (with the fluorine-substituted amine catalyst) and the chiral Brønsted acid catalysis for an efficient one-pot reaction strategy with highly stereoselective cyclization, under mild reaction conditions.

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Supporting Information Available. Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for (±)-**5c**, (±)-**5h**, and (−)-**5k** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.