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Organocatalytic aldol reaction of indole-3-carbaldehydes with ketones: synthesis of chiral 3-substituted indoles

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ABSTRACT

An efficient aldol reaction of indole-3-carbaldehydes with ketones is described. O-TBS-protected L-threonine promoted the aldol addition of ketones to indole-3-carbaldehydes affording 3-indolylmethanols with good to excellent yields and diastereoselectivities, and excellent enantioselectivities.

Chiral indole units are common in many biologically active natural and unnatural compounds.[1] Recently, the preparation of optically active indole derivatives has attracted much attention,[2] and the development of asymmetric methodologies for constructing indole derivatives is currently a hot topic in organic synthesis.[3] Among the large number of biologically active compounds and natural indole products, the optically active 3-substituted indoles have been synthesized and investigated extensively.[3a] There are two main methods for preparing chiral 3-substituted indoles. One is the catalytic asymmetric addition of indoles to various electrophiles, such as α,β-unsaturated compounds,[4a] imines,[4b] and carbonyl compounds.[4c] The other is the catalytic asymmetric addition of various nucleophiles to 3-functionalized indoles, such as 3-indolylmethanols,[5,6] 3-vinylindoles,[7] and 3-indolylnitroalkenes.[8] Surprisingly, indole-3-carbaldehydes, which are simple 3-functionalized indoles, have not yet been used in the organocatalytic synthesis of chiral 3-substituted indoles.[9] This may be because the electron-rich indole ring decreases the electrophilicity of an indole-3-carbaldehyde, making activation by organocatalysts difficult.[4b] We believe that the electron-rich properties of indole-3-carbaldehydes can be changed by introducing suitable protecting groups. In this Letter, we report the first direct organocatalytic asymmetric aldol reaction[10] of *N*-benzenesulfonyl-protected indole-3-carbaldehydes with ketones, leading to good yields of chiral 3-indolylmethanols with excellent enantioselectivities and diastereoselectivities.

We investigated the reaction between indole-3-carbaldehyde **1a** and cyclohexanone **2a**, catalyzed by L-phenylalanine, in DMSO. The desired product **4a** was not obtained (Table 1, entry 1) because of the electron-rich properties of **1a**. However, when an electron-withdrawing group (benzenesulfonyl) was introduced on the nitrogen atom of **1a**, the reaction smoothly proceeded, and afforded the desired product **4b** in moderate yield, with excellent diastereoselectivity and good enantioselectivity (Table 1, entry 2). Encouraged by these experimental results, we evaluated various catalysts, including natural amino acids and modified amino acids **3a** and **3b** (Table 1, entries 2–8). The natural amino acids promoted this reaction and efficiently controlled the stereochemistry of **4b**, but the yields were moderate (Table 1, entries 2–6). O-protected L-threonines have been successfully used to catalyze aldol and Mannich reactions.[11] When the modified L-threonines **3a** and **3b** were used as catalysts, the yields of **4b** were greatly enhanced, and the stereochemical outcomes were maintained (Table 1, entries 7 and 8). The catalyst loading could be decreased to 15 mol%, which is lower than that using natural amino acids as catalysts. Further reduction of the catalyst load, greatly reduced the yields (Table 1, entry 9). The O-TBS-protected L-threonine **3a** was the best catalyst in terms of yield and stereochemical outcome, and was used to optimize the reaction conditions.

We investigated the yields in various solvents. A higher yield was obtained in DMSO than in other solvents (Table 1, entry 18).

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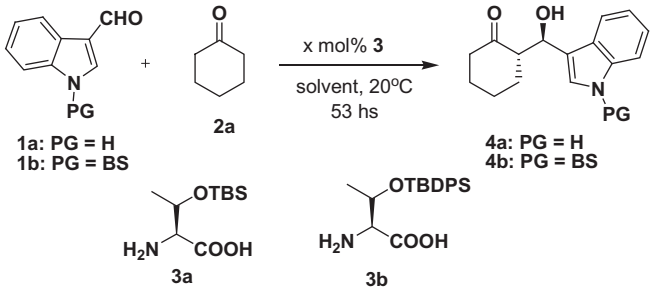
Table 1
Catalyst screening and optimization of reaction conditions[a]



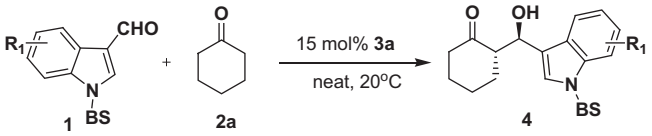
Entry	Catalyst (x)	Solvent	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%)
1	L-Phe (30)	DMSO	0[e]	–	–
2	L-Phe (30)	DMSO	54	93:7	82
3	L-Leu (30)	DMSO	57	98:2	92
4	L-Thr (30)	DMSO	28	96:4	93
5	L-Ser (30)	DMSO	56	97:3	95
6	L-Val (30)	DMSO	52	99:1	>99
7	**3a** (15)	DMSO	73	98:2	99
8	**3b** (15)	DMSO	67	96:4	98
9	**3a** (10)	DMSO	54	98:2	92
10	**3a** (15)	Toluene	43	95:5	>99
11	**3a** (15)	DMF	67	97:3	99
12	**3a** (15)	NMP	51	96:4	99
13	**3a** (15)	THF	40	96:4	99
14	**3a** (15)	CH_2Cl_2	58	95:5	99
15	**3a** (15)	CH_3OH	67	95:5	99
16	**3a** (15)	H_2O	62	98:2	>99
17	**3a** (15)	DMSO	42	95:5	98[f]
18	**3a** (15)	DMSO	77	96:4	98[g]
19	**3a** (15)	–	85	94:6	99[h]
20	**3a** (15)	–	77	90:10	99[g,h]

[a] Reaction conditions: **1b** (0.2 mmol), **2a** (4 mmol), solvent (0.5 mL), BS = $PhSO_2$–, TBS = ^{t}Bu(Me)$_2$Si–, TBDPS = ^{t}Bu(Ph)$_2$Si–.
[b] Isolated yield.
[c] Determined by HPLC.
[d] ee of *anti*-product determined by HPLC analysis on a chiral stationary phase.
[e] Using **1a** as reactant.
[f] Used 2 equiv of **2a**.
[g] Used 10 equiv of **2a**.
[h] Reaction for 72 h.

The yield was increased to 85% when no solvent was used (Table 1, entry 18). The number of equivalents of ketone used is important for the yield; for example, the yield decreased to 77% when 10 equiv of cyclohexanone **2a** was used in this reaction (Table 1, entry 20).

Under optimal reaction conditions, we examined the substrate scope.[12] We investigated various substituted indole-3-carbaldehydes. We found that catalyst **3a** efficiently promoted the reactions of cyclohexanone **2a** with various substituted indole-3-carbaldehydes **1**, and gave excellent stereochemical control. For example, indole-3-carbaldehydes bearing electron-donating groups participated in the reaction and afforded the desired products in good yields, with good to excellent diastereoselectivities and excellent enantioselectivities (Table 2, entries 2–6). Similar results were obtained using indole-3-carbaldehydes substituted with electron-withdrawing groups as acceptors (Table 2, entries 7–9). The yield increased to 96% when the strong electron-withdrawing group F was introduced into the indole ring (Table 2, entry 9). We found that indole-2-carbaldehyde **1k** could also undergo this transformation, leading to chiral 2-indolylmethanol in good yield, with good diastereoselectivity and excellent enantioselectivity (Table 2, entry 10). To the best of our knowledge, this is the first example of the synthesis of a chiral 2-indolylmethanol by organocatalysis.[13]

Table 2
Substrate scope of indole-3-carbaldehydes[a]

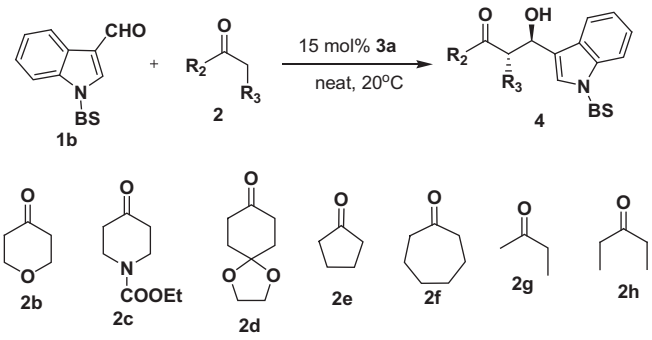


Entry	R_1, **1**	**4**	Time (h)	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%)
1	H, **1b**	**4b**	72	85	94:6	99
2	2-Me, **1c**	**4c**	91	66	97:3	99
3	5-Me, **1d**	**4d**	92	80	87:13	99
4	5-MeO, **1e**	**4e**	91	77	87:13	98
5	6-Me, **1f**	**4f**	91	85	88:12	>99
6	7-Me, **1g**	**4g**	91	76	96:4	>99
7	5-Cl, **1h**	**4h**	115	83	93:7	97[e]
8	5-Br, **1i**	**4i**	109	76	92:8	97[e]
9	6-F, **1j**	**4j**	71	96	88:12	98
10	**1k**[f]	**4k**	96	88	90:10	96[g]

[a] Reaction conditions: **1** (0.2 mmol), **2a** (4 mmol), **3a** (0.03 mmol), and 20 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] ee of *anti*-product determined by HPLC analysis on a chiral stationary phase.
[e] 0.5 mL DMSO and 10 equiv. **2a** were used.
[f] Compound **1k** = 1-(phenylsulfonyl)-1*H*-indole-2-carbaldehyde.
[g] At 0 °C.

The substrate scope with ketones was also investigated. Various ketones, including cyclic ketones and acyclic ketones, were tested (Table 3). Ketones with six-membered rings afforded the aldol adducts in high yields and with excellent diastereoselectivities and enantioselectivities (Table 3, entries 1–4). The diastereoselective ratio significantly decreased when cyclopentanone **2e** was used

Table 3
Substrate scope of ketones[a]



Entry	2	**4**	Time (h)	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%)
1	**2a**	**4b**	72	85	94:6	99
2	**2b**	**4l**	96	85	98:2	98[e]
3	**2c**	**4m**	72	94	98:2	99
4	**2d**	**4n**	94	86	97:3	98[e]
5	**2e**	**4o**	30	92	54:46	96
6	**2e**	**4o**	80	88	77:23	99[f]
7	**2f**	**4p**	72	28	87:13	92
8	**2g**	**4q**	88	36	40:60	94[g]
9	**2h**	**4r**	90	Trace	ND[h]	ND
10	Acetone	**4s**	97	Trace	ND	ND

[a] Reaction conditions: **1a** (0.2 mmol), **2** (4 mmol), and **3a** (0.03 mmol).
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] ee of *anti*-product determined by HPLC analysis on a chiral stationary phase.
[e] 0.5 mL DMSO and 10 equiv. **2a** were used.
[f] At 0 °C.
[g] ee of *syn*-product, R_2 = R_3 = Me.
[h] ND = not determined.

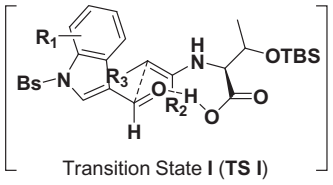


Figure 1. The plausible transition state.

as the donor (Table 3, entry 5). When this reaction was carried out at a lower temperature, the diastereoselectivity ratio increased to 77:23 (Table 3, entry 6). The cycloheptanone **2f** yield was only 28% (Table 3, entry 7). Acyclic ketones were not good reaction partners; for example, butanone reacted with **1a** to give the aldol product in 36% yield with poor diastereoselectivity (Table 3, entry 8), but 3-pentanone and acetone did not react with **1a** efficiently (Table 3, entries 9 and 10).

The relative and absolute configurations of **4b** (*S*, *R*) were determined by X-ray crystallography (see the Supplementary data).[14] The stereochemistries of the other aldol products were assigned by comparison with **4b**.

The actually mechanism of this reaction is still unclear. We thought the selectivity of this reaction was realized through a similar transition state (TS **I**) to that reported by Córdova and co-workers (Fig. 1).[15]

In conclusion, we present an efficient aldol reaction of ketones with indole-3-carbaldehydes, catalyzed by O-TBS-protected L-threonine **3a**. Our method is a good choice for synthesizing chiral 3-indolylmethanols and 2-indolylmethanols. All the products have excellent enantioselectivities, and good to excellent diastereoselectivities and yields.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.056.

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12. *Typical procedure:* A 10 mL dried tube was charged with indole-3-carbaldehyde **1b** (0.2 mmol), **2a** (4 mmol), and catalyst **3a** (0.03 mmol) at 20 °C. The mixture was vigorously stirred and the reaction progress was monitored via TLC. After the completion of the reaction, two drops of saturated NH_4Cl solution were added to quench the reaction. The organic layer was separated and the water phase was extracted by EtOAc. The organic phase was combined and dried by Na_2SO_4. The product **4b** (85%) was obtained by flash chromatography (petroleum:AcOEt = 4:1) as a white solid: $[\alpha]_D^{20}$ = +3.8 (*c* 0.052, CH_3CH_2OH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.99 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.4 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.35–7.30 (m, 1H), 7.22 (d, *J* = 7.1 Hz, 1H), 5.05 (d, *J* = 8.5 Hz, 1H), 4.05 (s, 1H), 2.84 (dd, *J* = 15.0, 10.1 Hz, 1H), 2.50 (d, *J* = 13.3 Hz, 1H), 2.43–2.32 (m, 1H), 2.08 (s, 1H), 1.79–1.47 (m, 4H), 1.37–1.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 215.4, 138.0, 135.5, 133.9, 129.3, 129.1, 126.8, 125.0, 124.0, 123.4, 122.4, 121.0, 113.7, 68.6, 55.8, 42.7, 31.0, 27.7, 24.7; HRMS(ESI): calcd for $C_{21}H_{21}NNaO_4S$ (M^++Na): 406.1083, found: 406.1067.
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14. CCDC 926458 (**4b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
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