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Organocatalytic Stereoselective Mannich Reaction of 3-Substituted Oxindoles

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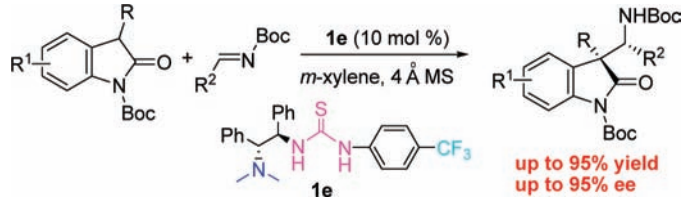
ABSTRACT



The asymmetric Mannich reaction of 3-substituted oxindoles and *N*-Boc imines was investigated for the first time, employing bifunctional thiourea-tertiary amine organocatalysts based on DPEN scaffold. The novel transformations exhibited high diastereoselectivities, and the Mannich adducts bearing adjacent quaternary and tertiary chiral centers were generally obtained in good to excellent enantioselectivities (up to 95% ee).

The construction of a chiral quaternary center represents one of the most challenging subjects in asymmetric synthesis and has provoked continuing interest over the past decades.[1] Among them, the application of prochiral 3-substititued oxindoles as nucleophiles provides a very straightforward approach to obtain a chiral quaternary center, and studies in this field receive special attention because oxindoles bearing C3-quaternary structures have been widely distributed in a number of natural products and pharmaceutical molecules.[2] A variety of catalytic asymmetric reactions of 3-substituted oxindoles, including fluorination,[3] hydroxylation,[4] acyl migration,[5] aldol reaction,[6] and AAA reaction,[7] have been well presented. However, to the best of our knowledge, the asymmetric Mannich reaction[8] of 3-substituted oxindoles and imines has not been investigated in the literature, as more challenging molecular complexity with adjacent quaternary and tertiary chiral centers must be created concurrently.[9] Here we would like to report the highly stereoselective Mannich

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reaction of 3-substituted oxindoles and *N*-Boc-imines catalyzed by environmentally benign organocatalysts.

Recently thiourea−tertiary amine compounds have demonstrated great success as bifunctional Brønsted acid−Brønsted base catalysts for an array of 1,2- and 1,4-addition reactions.[10,11] It could be envisaged that nucleophilic oxindoles and electrophilic *N*-Boc imines should be concertedly activated by such bifunctional catalysts, and the corresponding Mannich products with dense substitutions would be afforded stereoselectively. In addition, we proposed that the use of an *N*-Boc-protected oxindole bearing a bidentate motif would be more practicable since a double hydrogen bonding interaction could be generated with the protonated tertiary amine group.

Based on these considerations, bifunctional thiourea−tertiary amines **1a**−**d** (10 mol %, Figure 1) with diversely structured

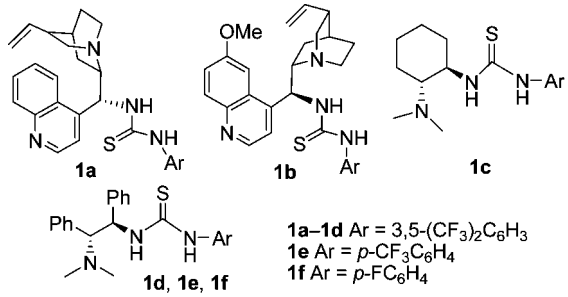
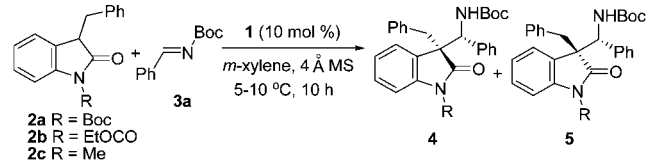


Figure 1. Structures of thiourea−tertiary amine catalysts.

scaffolds were screened in the Mannich reaction of 3-benzyloxindole **2a** and *N*-Boc-benzaldimine **3a** at 5−10 °C in *m*-xylene. Some 4 Å molecular sieves were added in order to remove the trace amount of water. Gratifyingly, this catalytic Mannich reaction generally exhibited high efficacy. The starting materials were smoothly consumed after 10 h, and the diastereomers **4a** and **5a** could be well separated (Table 1, entries 1−4). Catalyst **1d** possessing a chiral 1,2-

Table 1. Screening Studies of Organocatalytic Mannich Reaction of Oxindole **2a** and *N*-Boc-benzaldimine **3a**[a]



entry	cat. 1	yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	**4a**, 86/**5a**, 8	10.7:1	69
2	**1b**	**4a**, 87/**5a**, 10	8.7:1	82
3	**1c**	**4a**, 81/**5a**, 17	4.7:1	80
4	**1d**	**4a**, 92/**5a**, <5	>18.4:1	93
5	**1e**	**4a**, 94/**5a**, <5	>18.8:1	95
6	**1f**	**4a**, 92/**5a**, <5	>18.4:1	63
7[e]	**1e**	**4a**, 95/**5a**, <5	>18.6:1	91
8[f]	**1e**	**4b**, 90/**5b**, <5	>18.0:1	92
9[g]	**1e**	**4c**, 45/**5c**, 27	1.7:1	<5

[a] Unless noted otherwise, **2a** was used as the nucleophile in *m*-xylene. [b] Isolated yields of pure diastereomer **4** and **5**. [c] Calculated from the isolated yields of **4** and **5**. [d] Determined by chiral HPLC analysis. [e] Toluene was used. [f] **2b** was used. [g] **2c** was used.

diphenylethylene−diamine (DPEN) skeleton demonstrated to be the superior one in regard to both diastereo- and enantioselectivity.[12] The major isomer **4a** was directly isolated in 92% yield with 93% ee (entry 4). Subsequently, other thiourea catalysts derived from DPEN were investigated. Even slightly better results were attained by employing catalyst **1e** with a *p*-trifluoromethylphenyl substitution (entry 5), but considerably reduced enantioselectivity was observed in the presence of catalyst **1f** with a *p*-fluorophenyl group (entry 6). A little lower ee value was gained when toluene was used (entry 7). On the other hand, we further explored the effects of *N*-protection group of oxindole catalyzed by **1e**. Similar results could be achieved for **2b** with an *N*-ethoxycarbonyl group (entry 8, for **4b**, 90% yield, 92% ee). In contrast, *N*-methyloxindole **2c** showed much lower reactivity, and very poor stereoselectivity was obtained for the corresponding Mannich adducts **4c** and **5c** (entry 9). This indicates that the bidentate nature of *N*-protected oxindoles is crucial for the stereocontrol.[3a]

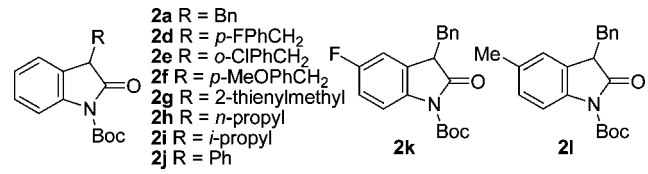


Figure 2. Structures of 3-substituted oxindoles.

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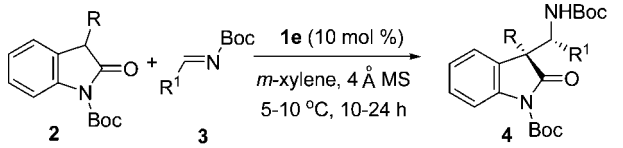
With the optimal reaction conditions in hand, we then examined a variety of oxindoles **2** (Figure 2) and imines **3** to establish the general utility of this novel asymmetric transformation. The reaction scopes generally proved to be broad with respect to both reactants. The major diastereomer **4** could be directly isolated, and the minor products **5** were obtained in less than 10% yield for all the reactions tested. As revealed in Table 2, in the reactions of *N*-Boc-benzaldimine, excellent enantioselectivities were gained for variously substituted 3-benzyloxindoles **2d**−**f** (Table 2, entries 2−4). Oxindole **2g** bearing a 2-thienylmethyl group also afforded a high ee value (entry 5). 3-*n*-Propyloxindole **2h** showed slower reactivity, while good yield could be obtained after 24 h in 91% ee (entry 6). Nevertheless, the Mannich reaction of oxindole **2i** bearing a bulky 3-isopropyl group was quite sluggish. Moderate yield was isolated with 20 mol % of **1e** after 72 h (entry 7), while better yield with similar enantioselectivity could be provided when less hindered *N*-Cbz-benzaldimine was used (entry 8). Unfortunately, 3-phenyloxindole **2j** gave rise to racemic product, *and later it was found that this reaction could proceed rapidly without any catalyst* (entry 9). Poor enantioselectivity was obtained even at −40 °C (entry 9, data in parentheses). Good ee values were attained for oxindoles **2k** and **2l** with electron-withdrawing or -donating substituents on aryl ring (entries 10 and 11). On the other hand, some aryl and heteroaryl imines were explored with oxindole **2a**. The electronic nature of the substituents has limited influences on the stereo outcome, and satisfactory data were generally attained (entries 12−16). However, alkyl imines exhibited quite low reactivity toward **2a**. Good yield could be delivered in the reaction of more active 3-phenyloxindole **2j**, but the enantioselectivity could not be enforced (entry 17).

Table 2. Asymmetric Mannich Reaction of 3-Substituted Oxindoles **2** and *N*-Boc-imines **3**



entry	**2**	R^1	yield[a] (%)	dr[b]	ee[c] (%)
1	**2a**	Ph	**4a**, 94	>18.8:1	95
2	**2d**	Ph	**4d**, 95	>19.0:1	95
3	**2e**	Ph	**4e**, 85	>17.0:1	90
4	**2f**	Ph	**4f**, 90	>18.0:1	89
5	**2g**	Ph	**4g**, 83	17.0:1	91
6	**2h**	Ph	**4h**, 76	>15.0:1	92
7[d]	**2i**	Ph	**4i**, 40	>8.0:1	83
8[d,e]	**2i**	Ph	**4j**, 60	12.0:1	82
9	**2j**	Ph	**4k**, 87 (80)[f]	12.4:1	3(11)[f]
10	**2k**	Ph	**4l**, 93	>18.6:1	88
11	**2l**	Ph	**4m**, 88	11.0:1	84
12	**2a**	*p*-F-Ph	**4n**, 95	>19.0:1	91
13	**2a**	*m*-Cl-Ph	**4o**, 90	11.3:1	93
14	**2a**	*o*-Cl-Ph	**4p**, 94	>18.8:1	88
15	**2a**	*p*-Me-Ph	**4q**, 89	11.0:1	85
16	**2a**	2-thienyl	**4r**, 90	12.8:1	94[g]
17	**2j**	*i*-propyl	**4s**, 75	15.0:1	<5

[a] Isolated yield of pure **4**. [b] Calculated from the isolated yield of **4** and **5**. [c] Determined by chiral HPLC analysis. [d] With 20 mol % of **1e** for 72 h. [e] *N*-Cbz-benzaldimine was used. [f] Data in parentheses were obtained at −40 °C. [g] The absolute configuration of **4r** was determined by X-ray analysis (see Figure 3). The other products were assigned by analogy.

To determine the absolute configuration of the asymmetric Mannich products, single crystals suitable for X-ray crystallographic analysis were fortunately obtained from enantiopure **4r** that bears a sulfur atom. As shown in Figure 3, it contains a (*C2S*,*C16S*) configuration.

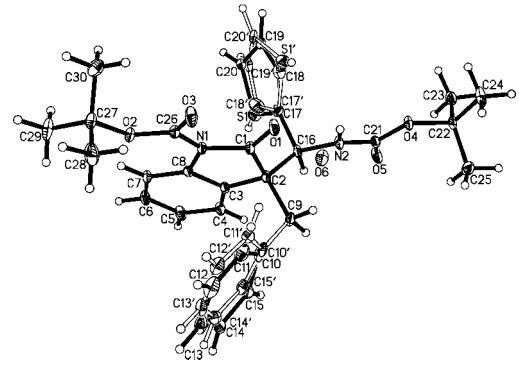
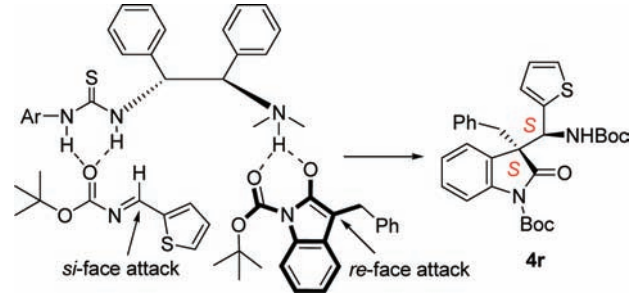


Figure 3. X-ray crystallographic structure of enantiopure **4r**.

On the basis of the observed absolute configuration of enantiopure **4r**, a plausible catalytic mechanism by concerted activation was proposed. As illustrated in Scheme 1, a double hydrogen bonding interaction might be formed between two N−H of thiourea and the carbonyl of protected imine. On the other hand, another double hydrogen bonding interaction would be generated between the protonated tertiary amine group and two carbonyls of the protected oxindole. Subsequently, *si*-face attack of the electrophilic imine through *re*-face of the enolate would afford the desired Mannich adduct **4r** with (*S*,*S*)-configuration.

Scheme 1. Plausible Catalytic Mechanism for the Formation of Chiral Mannich Adducts **4r** by Concerted Activation



(12) For the limited application of bifunctional thiourea−tertiary amine from DPEN, see: Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097.

In conclusion, we have successfully presented the first stereoselective Mannich reaction of 3-substituted oxindoles and *N*-Boc-imines by employing bifunctional thiourea−tertiary amine catalysts derived from chiral DPEN. In general, excellent diastereo- and enantioselectivities could be obtained for a spectrum of substrates. This novel methodology provides facile access to densely substituted oxindole derivatives with adjacent quaternary and tertiary chiral centers. Current studies are underway to expand the synthetic utility of this reaction.

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Supporting Information Available: Experimental procedures, structural proofs including CIF file of enantiopure **4r**, and NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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