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Highly *anti*-Selective Asymmetric Nitro-Mannich Reactions Catalyzed by Bifunctional Amine-Thiourea-Bearing Multiple Hydrogen-Bonding Donors

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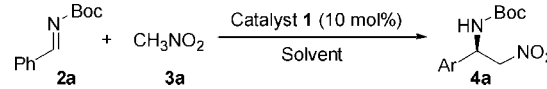
The addition of nitroalkanes to imines, known as the nitro-Mannich (or aza-Henry) reaction is a highly valuable carbon−carbon bond-forming process in organic synthesis.[1] Synthetically versatile β-nitro amines formed in this way can be readily converted to 1,2-diamines,[2] α-aminocarbonyl compounds.[3] Since the pioneering work of Shibasaki,[4] much attention has been paid to developing enantioselective catalytic protocols for this reaction over the past decade. Enantio- and diastereoselective nitro-Mannich reactions have been reported using chiral metal complexes[5] and organocatalysts, such as chiral thiourea,[6] chiral proton catalysts,[7] and chiral phase transfer catalysts.[8] Most recently, Shibasaki and co-workers reported a heterobimetallic Cu−Sm−Shiff base complexes catalyzed nitro-Mannich reactions with excellent *syn*-selectivity (>20:1) and enantioselectivity (83−98%).[9] For *anti*-selective nitro-Mannich reaction, however, such high diastereoselectivity and enantioselectivity have not been obtained so far. Among numerous literature examples, to our knowledge, there are only few organocatalytic asymmetric nitro-Mannich reactions reported which can afford both excellent enantioselectivity and high antiselectivity of greater than 10:1 for a broad scope of the reaction partners.[6b,f] Therefore, there is substantial room for improvement in terms of both selectivity and substrate scope for organocatalytic nitro-Mannich reaction.

Recently, we reported a new class of bifunctional amine−thiourea catalysts **1** bearing multiple hydrogen bonding donors, which showed excellent performance in catalytic asymmetric addition of acetylacetone to nitroolefins.[10] Extending the interest of these organocatalysts in asymmetric catalysis, herein we report that catalyst **1d** results in high *anti*-selectivities (93:7−99:1) and excellent enantioselectivities (96−99%) in the asymmetric nitro-Mannich reaction for a broad scope of substrates.[11]

Our initial study began with the reaction of *N*-Boc aldimine **2a** with nitromethane **3a** in which only one stereogenic center was formed, and the representative results are summarized in Table 1. Gratifyingly, the nitro-Mannich reaction proceeded readily at room temperature in the presence of 10 mol % of catalyst **1** under different conditions, and the desired product **4a** was obtained in high yields after 5 h. Among the catalysts tested, (1*R*,2*R*,1′*R*,2′*R*)-**1d** bearing two electron-withdrawing CF_3 groups on the aromatic ring of sulfonamide $NHSO_2Ar$ emerged as the most effective catalyst (Table 1, entry 4). A study of the reaction with **1d** at room temperature in various solvents identified dichloromethane and ether as suitable alternatives to acetonitrile (Table 1, entries 4, 7, and 8). The addition of 4A molecular sieves was taken to avoid the decomposing of the aldimine during the reactions (Table 1, entries 4 and 5). Reducing the temperature to −20 °C in acetonitrile or dichloromethane led to completed reaction with 99% ee in less than 10 h (Table 1, entry 10). Catalyst loading was successfully reduced to 5 mol % without any loss of enantioselectivity (Table 1, entry 11). Using methylated (1*R*,2*R*,1′*R*,2′*R*)-**1e** as the catalyst under the optimized reaction condition, the reaction became sluggish, and

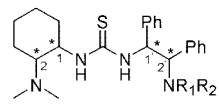
Table 1. Screening Studies of Oganocatalytic Asymmetric Nitro-Mannich Reaction of *N*-Boc Aldimine **2a** and Nitromethane **3a**[a]



entry	catalyst	solvent	MS (4Å)	temp (°C)	*t* (h)	yield[b] (%)	ee[c] (%)
1	**1a**	MeCN	+	rt	5	92	75
2	**1b**	MeCN	+	rt	5	95	80
3	**1c**	MeCN	+	rt	5	93	78
4	**1d**	MeCN	+	**rt**	**5**	**95**	96
5	**1d**	MeCN	−	rt	5	89	96
6	**1e**	MeCN	+	rt	48	20	11
7	**1d**	Et_2O	+	rt	5	94	94
8	**1d**	DCM	+	rt	5	95	95
9	**1d**	MeCN	+	0	8	95	98
10	**1d**	MeCN	+	−20	10	97	99
11[d]	**1d**	MeCN	+	−20	15	95	99

[a] Unless otherwise noted, the reactions was carried out with 0.2 mmol of **2**, 1 mmol of **3**, and 50 mg powered 4Å molecular sieves in 0.5 mL of solvent; rt = room temperature. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] Run using 5 mol % catalyst.

the corresponding product was obtained in 20% yield with only 11% ee even in 48 h (Table 1, entry 6). This indicates that the third NH of sulfonamide on the 1,2-diphenylethenediamine moiety indeed plays a significant role in this nitro-Mannich reaction. The current system showed remarkable improvement over the previous organocatalyst nitro-Mannich reaction in terms of enantioselectivity and reactivity.[6b,d,f]



(1*R*,2*R*,1′*S*,2′*S*)-**1a:** R_1 = H, R_2 = Ts
(1*R*,2*R*,1′*R*,2′*R*)-**1b:** R_1 = H, R_2 = Ts
(1*R*,2*R*,1′*R*,2′*R*)-**1c:** R_1 = H, R_2 = Ms
(1*R*,2*R*,1′*R*,2′*R*)-**1d:** R_1 = H, R_2 = 3,5-$(CF_3)_2C_6H_3SO_2$
(1*R*,2*R*,1′*R*,2′*R*)-**1e:** R_1 = Me, R_2 = Ts

Encouraged by this result, we next investigated the nitro-Mannich reaction of various *N*-Boc aldimines with nitromethane under the optimized experimental conditions. Representative results are summarized in Table 2.[12] A variety of imines, which bear electron-rich, electron-neutral, or electron-deficient groups, reacted with nitromethane smoothly to afford the corresponding products (**4a-j**) in high yields (85−99%) and excellent enantioselectivities (96−99% ee) at −20 °C with 10−15 h (Table 2, entries 1−10). It appears that the position and the electronic property of the substituents on the aromatic rings have a very limited effect on the enantioselectivities. Noticeably, up to 99% ee was still obtained even for the challenging *ortho*-substituted substrates[6b,d] (**2d** and **2f**) and 1-naphthyl *N*-Boc aldimines[6f] (**2j**) (Table 2, entries 4, 6 and 10). The best literature report for **2f** is only 92% ee in 42 h using thiourea catalyst derived from α-D-glucose.[6d] Another attractive features of this methodology is the remarkable tolerance for heteroaryl and alkyl *N*-Boc aldimines (Table 2, entries 11−13).

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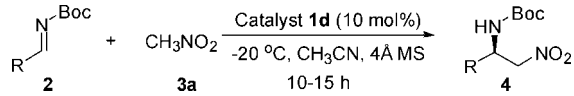
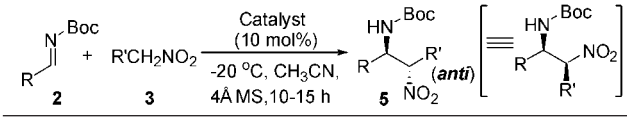
Table 2. Asymmetric Nitro-Mannich Reaction of *N*-Boc Aldimines **2** with Nitromethane **3a** Using Oganocatalyst **1d**[a]



entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph (**2a**)	**4a**	97	99
2	*p*-Me-Ph (**2b**)	**4b**	88	99
3	*p*-MeO-Ph (**2c**)	**4c**	85	99
4	*o*-MeO-Ph (**2d**)	**4d**	94	99
5	*p*-Cl-Ph (**2e**)	**4e**	93	99
6	*o*-Cl-Ph (**2f**)	**4f**	90	99
7[d]	*p*-F-Ph (**2g**)	**4g**	91	99
8	*p*-CF_3−Ph (**2h**)	**4h**	96	99
9	2-Naphthyl (**2i**)	**4i**	89	97
10	1-Naphthyl (**2j**)	**4j**	98	99
11	2-Furyl (**2k**)	**4k**	99	96
12	3-Pyridyl (**2l**)	**4l**	91	99
13	^{i}Bu (**2m**)	**4m**	99	98

[a] See Table 1. [b] See Table 1. [c] See Table 1. [d] Reaction was performed at −50 °C in 0.5 mL DCM in 12 h; 95% ee was achieved in acetonitrile at −20 °C.

Table 3. High anti-Selective Catalytic Asymmetric Nitro-Mannich Reactions of *N*-Boc Aldimines with Nitroalkanes[a]



entry	R	R′	catalyst	product	yield[b] (%)	dr[c] (anti:syn)	ee[d] (%)
1	Ph (**2a**)	Me (**3b**)	**1a**	**5ab**	88	80:20	76
2	Ph (**2a**)	Me (**3b**)	**1b**	**5ab**	90	93:7	87
3	Ph (**2a**)	Me (**3b**)	**1d**	**5ab**	92	97:3	99
4	*p*-Me-Ph (**2b**)	Me (**3b**)	**1d**	**5bb**	90	96:4	98
5	*p*-MeO-Ph (**2c**)	Me (**3b**)	**1d**	**5cb**	95	98:2	98
6	*p*-Cl-Ph (**2e**)	Me (**3b**)	**1d**	**5eb**	88	97:3	99
7	*o*-Cl-Ph (**2f**)	Me (**3b**)	**1d**	**5fb**	93	96:4	96
8	*p*-CF_3−Ph (**2g**)	Me (**3b**)	**1d**	**5gb**	97	97:3	99
9	2-naphthyl (**2i**)	Me (**3b**)	**1d**	**5ib**	91	97:3	97
10	2-furyl (**2k**)	Me (**3b**)	**1d**	**5kb**	93	94:6	96
11	3-pyridyl (**2l**)	Me (**3b**)	**1d**	**5lb**	88	96:4	99
12	Ph (**2a**)	Et (**3c**)	**1d**	**5ac**	94	99:1	99
13	*p*-Me-Ph (**2b**)	Et (**3c**)	**1d**	**5bc**	99	97:3	99
14	*p*-MeO-Ph (**2c**)	Et (**3c**)	**1d**	**5cc**	93	99:1	98
15	Ph (**2a**)	Bn (**3d**)	**1d**	**5ad**	95	99:1	99
16	^{i}Bu (**2m**)	Me (**3b**)	**1d**	**5mb**	93	93:7	97

[a] See Table 1. [b] See Table 1. [c] Diastereomeric ratio was determined by HPLC analysis. Minor syn-isomer was not detected on the crude ^{1}H NMR. [d] Enantiomeric excesses were determined by chiral HPLC analysis.

Having succeeded in the enantioselective nitro-Mannich reaction of *N*-Boc aldimine with nitromethane, we then investigate the nitro-Mannich reaction of *N*-Boc aldimine with other nitroalkanes that can result in the generation of two contiguous nitrogen-bearing stereogenic centers. The scope of the reaction of nitroalkanes **3** with *N*-Boc aldimines **2** is summarized in Table 3.[11,12] Indeed, all tested nitroalkanes and various *N*-Boc aldimines have proven to be excellent substrates with respect to diastereo-/enantioselectivity and reactivity using **1d** as the catalyst. Nitroethane **3b** and nitroalkanes **3c** and **3d** showed the same reactivity as nitromethane **3a**, and the corresponding products were obtained in high yields and excellent diastereo-/enantioselectivities (93:7−99:1 dr; 96−99% ee). The consistently excellent diastereo-/enantioselectivity obtained with the sterically hindered *ortho*-substituted *N*-Boc aldimine (**2f**), 2-naphthyl *N*-Boc aldimine (**2i**), and heteroaryl aldimines (**2k** and **2l**) is noteworthy (Table 3, entries 7, 9, 10, and 11), as such *N*-Boc aldimines were shown to be relatively challenging substrates in previous studies involving chiral metal complexes[9] and organocatalysts[6b,f] Alkyl *N*-Boc aldimine also works well in this reaction leading to 93:7 dr and 97% ee (Table 3, entry 16).

In conclusion, we have developed highly *anti*-selective (93:7−99:1) and excellent enantioselective (96−99% ee) nitro-Mannich reactions catalyzed by chiral bifunctional thiourea catalyst bearing multiple hydrogen-bonding donors that perform well over a broad scope of substrates. This methodology presented herein is the best result for organocatalytic asymmetric nitro-Mannich reactions reported so far, and nicely complements the highly *syn*-selective version using a herterobimetallic Cu−Sm−Shiff base complex. Further investigations into the mechanism and applications of the present bifunctional thiourea catalysts in other catalytic asymmetric reactions are underway in our laboratory.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The absolute configurations of the known products were assigned by HPLC and optical rotation comparisons with the reported data (see refs 6b, 6d, and Supporting Information), and those of other adducts were deduced on the basis of these results.

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