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Discovery of Bifunctional Thiourea/Secondary-Amine Organocatalysts for the Highly Stereoselective Nitro-Mannich Reaction of α-Substituted Nitroacetates

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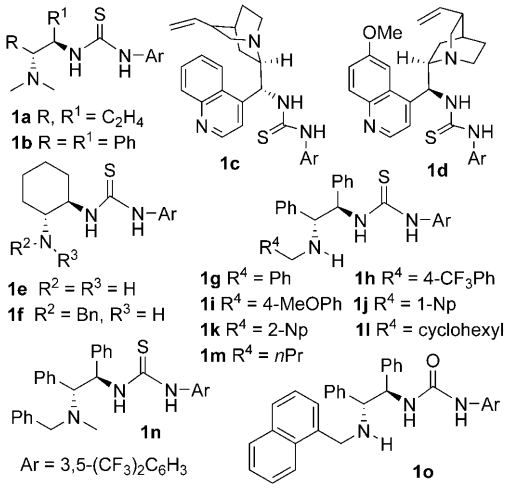
The nitro-Mannich reaction (or aza-Henry reaction) is a versatile C–C bond-forming process that can deliver valuable nitrogen-containing building blocks such as 1,2-diamines and α-amino carbonyl compounds.[1] Its asymmetric variant has provoked much interest in the last years. Good stereocontrol has been achieved in the reactions of simple nitroalkanes and nitroacetates with various imines, since the pioneering work of Shibasaki and Jørgensen, either utilizing metal-based[2] or organic catalysts.[3] However, despite these important advances, the applications of α-substituted nitroacetates[4] in this field, in which adjacent quaternary and tertiary chiral centers must be constructed concurrently,[5] are rarely explored,[6] and good results have been presented only very recently with bulky esters.[7] Here we would like to report the discovery of readily accessible thiourea/secondary-amine organocatalysts for the highly stereoselective nitro-Mannich reaction of simple esters of α-substituted nitroacids and *N*-Boc imines.

Bifunctional thiourea/tertiary-amines have been fruitfully utilized in a number of 1,2- or 1,4-addition reactions.[8,9] Unfortunately, our initial studies with the diversely structured catalysts **1a**–**1d** for the reation of ethyl 2-nitropropanoinate



2a with *N*-Boc imine **3a** catalyzed failed to give significant chiral induction (Table 1, entries 1–4), though excellent enantiomeric excess (*ee*) values have been achieved in the construction of a quaternary stereocenter with analogous α-substituted cyanoacetates.[10] Nevertheless, one apparently different feature of nitro group from cyano functionality is that the former possesses more preferable binding sites for hydrogen-bonding interactions. A low *ee* was also obtained by catalysis with a simple thiourea/primary-amine **1e** (entry 5). To our gratification, the enantioselectivity of the major isomer **4a** was dramatically increased with **1f**, with a secondary amine moiety, although the diastereoselectivity was still not satisfying (entry 6).[11] The N–H group of **1f** plays a crucial role in the catalytic transition state other

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Table 1. Screening studies of organocatalytic nitro-Mannich reaction of 2-nitropropanoinate **2a** and *N*-Boc benzaldimine **3a**.[a]

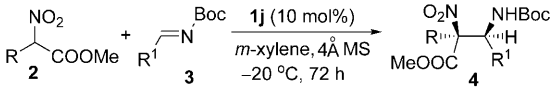
Entry	Cat.	Solvent	Yield [%][b]	dr[c]	*ee* [%][d]
1	**1a**	*m*-xylene	**4a**-50/**5a**-30	1.7:1	10
2	**1b**	*m*-xylene	**4a**-49/**5a**-31	1.6:1	25
3	**1c**	*m*-xylene	**4a**-51/**5a**-26	2.0:1	46
4	**1d**	*m*-xylene	**4a**-51/**5a**-23	2.2:1	23
5	**1e**	*m*-xylene	**4a**-52/**5a**-25	2.1:1	32
6	**1f**	*m*-xylene	**4a**-53/**5a**-30	1.8:1	85
7	**1g**	*m*-xylene	**4a**-70/**5a**-23	3.0:1	94
8	**1h**	*m*-xylene	**4a**-62/**5a**-17	3.6:1	93
9	**1i**	*m*-xylene	**4a**-72/**5a**-19	3.8:1	96
10	**1j**	*m*-xylene	**4a**-74/**5a**-23	3.2:1	96
11	**1k**	*m*-xylene	**4a**-72/**5a**-23	3.1:1	94
12	**1L**	*m*-xylene	**4a**-60/**5a**-26	2.3:1	80
13	**1m**	*m*-xylene	**4a**-57/**5a**-31	1.8:1	63
14	**1n**	*m*-xylene	**4a**-48/**5a**-28	1.7:1	10
15	**1o**	*m*-xylene	**4a**-68/**5a**-28	2.2:1	84
16	**1j**	toluene	**4a**-62/**5a**-26	2.4:1	92
17	**1j**	DCM	**4a**-57/**5a**-28	2.0:1	67
18	**1j**	THF	**4a**-54/**5a**-31	1.7:1	55
19[e]	**1j**	*m*-xylene	**4a**-60/**5a**-23	2.6:1	89
20[f]	**1j**	*m*-xylene	**4a**-84/**5a**-7	12.0:1	97
21[f,g]	**1j**	*m*-xylene	**4b**-86/**5b**-5	17.2:1	96

[a] Unless noted otherwise, reactions were performed with **2a** (0.15 mmol), **3a** (0.23 mmol), **1** (10 mol%) and 4 Å MS (40 mg) in solvent (0.5 mL) at 5–10 °C for 48 h. [b] Isolated yield of pure **4a** and **5a**. [c] Calculated from the isolated isomers **4a** and **5a**. [d] Determined by HPLC analysis on chiral column; low *ee* (<20%) was observed for **5a** in all the tested reactions. [e] Without adding 4 Å MS. [f] At −20 °C for 72 h. [g] **2b** was used.

than merely acting as a Brønsted base, in contrast with that of tertiary-amine group. Moreover, superior stereocontrol could be attained with catalyst **1g** bearing chiral 1,2-diphenylethylenediamine (DPEN) scaffold (entry 7). Consequently, an array of thiourea/secondary-amines containing DPEN were devised. Similar data was obtained for catalysts **1h**–**1k** with arylmethyl substitutions (entries 8–11); however, much lower *ee* values were obtained for catalysts **1l** and **1m** bearing alkyl groups (entries 12 and 13). In contrast, a tertiary amine, *N*-benzyl-*N*-methyl catalyst **1n**, still provided poor enantioselectivity in the model reaction, which further proved that an N−H group was essential for the stereocontrol (entry 14 vs. 7). In addition, good enantioselectivity could be obtained catalyzed by urea-secondary amine **1o** (entry 15). Other solvents were also screened in the presence of **1j**, and reduced enantioselectivities were generally observed (entries 16–18). Moreover, the *ee* value was slightly decreased in the absence of 4 Å molecular sieves, probably a trace amount of water would affect the hydrogen-bonding interaction (entry 19). It was pleasing to find that the diastereomeric ratio (dr) ratio could be improved without affecting the high conversion by lowering the reaction temperature to −20 °C, while the time was extended to 72 h (entry 20). In addition, excellent *ee* and dr ratio were attained in the reaction of methyl 2-nitropropanoinate **2b** and imine **3a** (entry 21).

With the optimal catalytic conditions in hand, the reaction scope for α-substituted nitroacetates and *N*-Boc imines were investigated. The results were summarized in Table 2. In

Table 2. Stereoselective nitro-Mannich reaction of α-substituted nitroacetates **2** and *N*-Boc aldimines **3**.[a]



Entry	R	R^1	Yield [%][b]	dr[c]	*ee* [%][d]
1	Me	Ph	**4b**-86 (5)	17.2:1	96
2	Me	*p*-FC_6H_4	**4c**-78 (8)	9.8:1	96
3	Me	*m*-ClC_6H_4	**4d**-83 (8)	10.4:1	95
4	Me	*o*-ClC_6H_4	**4e**-79 (10)	7.9:1	91[e]
5	Me	*p*-MeC_6H_4	**4f**-86 (6)	14.3:1	96
6	Me	*m*-MeC_6H_4	**4g**-85 (5)	17.0:1	94
7	Me	2-furyl	**4h**-85 (10)	8.5:1	95
8	Me	2-thienyl	**4i**-75 (20)	3.8:1	91
9	$PhCH_2$	Ph	**4j**-68 (9)	7.6:1	93
10[f]	*i*Pr	Ph	**4k**-38 (7)	5.4:1	96
11	Ph	Ph	–	–	–

[a] Unless noted otherwise, reactions were performed with **2a** (0.15 mmol), **3a** (0.23 mmol), **1** (10 mol%) and 4 Å MS (40 mg) in *m*-xylene (0.5 mL) at −20 °C for 72 h. [b] Isolated yield; data in parenthesis is related to the isolated minor isomer **5**. [c] Calculated from the isolated **4** and **5**. [d] Based on HPLC analysis on chiral column. [e] The absolute configuration of **4e** was determined by X-ray analysis (Figure 1),[13] and other products were assigned by analogy. [f] Ethyl ester of α-isopropylnitroacid was used.

general the major chiral isomers **4** could be directly isolated in pure form in good to high yields. The solid-state structure of **4e**, as derived from X-ray crystallography, is shown in Figure 1. For methyl 2-nitropropanoinate **2b**, excellent diastereo- and enantioselectivities were observed for aryl imines bearing diverse electron-withdrawing or -donating substitutions (Table 2, entries 1–6). Good results were also obtained for heteroaryl imines (entries 7 and 8).[12] Other α-substituted nitroacetates were also studied; the α-benzyl derivative gave rise to high stereoselectivity in the reaction with *N*-Boc benzaldimine (entry 9). Even the bulky sub-

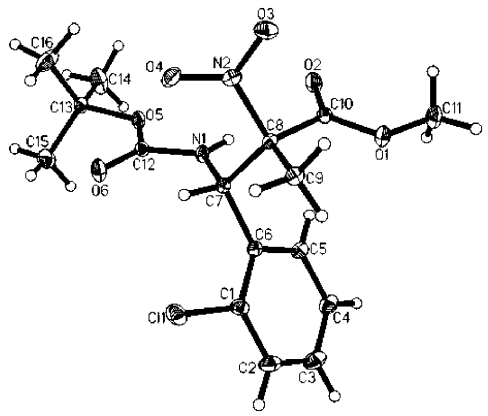
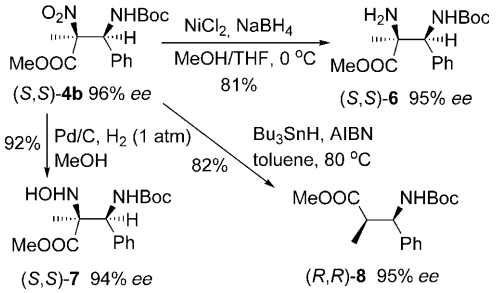


Figure 1. X-ray structure of enantiopure **4e**.

strate with an α-isopropyl group could be successfully applied, while a modest isolated yield with excellent enantioselectivity was attained for the major isomer **4k** (entry 10). Nevertheless, the nitro-Mannich products resulting from α-phenyl nitroacetate and *N*-Boc benzaldimine were found to be labile at ambient temperature, probably owing to the crowded structure (entry 11).

As illustrated in Scheme 1, the nitro-Mannich adducts could be smoothly converted to some versatile building blocks for organic syntheses. The monoprotected chiral 2,3-



Scheme 1. Synthesis of various chiral amino acid derivatives.

diamino acid ester **6** was obtained without racemization by the reduction with $NaBH_4/NiCl_2$.[7,14] Interestingly, the hydroxylamino derivative **7** could be chemoselectively obtained by the mild hydrogenation with $Pd/C/H_2$ (1 atm). Moreover, the α-nitro group of **4b** could be stereoselectively removed under a radical reduction conditions to give compound **8**; thus this method might supply an alternative approach to the synthesis of chiral $\beta^{2,3}$-amino acid.[15]

In conclusion, we have presented the highly stereoselective nitro-Mannich reaction of simple esters of α-substituted nitro-acetic acids and *N*-Boc aldimines by employing novel bifunctional thiourea/secondary-amine catalysts. Some biologically important chiral amino acid derivatives with dense functionalizations could be readily attained. Currently an investigation into the catalytic mechanism[16] and expansion of the new bifunctional organocatalysts in other asymmetric transformations are in progress.

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[13] CCDC-693595 (**4e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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[16] For preliminary catalytic mechanism exploration by a DFT computational study, see Supporting Information.

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