Enantio- and Diastereoselective Nitro-Mannich Reactions with in situ Generated *N*-Boc-imines Catalyzed by a Bifunctional Thiourea–Guanidine Catalyst

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Abstract: The asymmetric nitro-Mannich reactions of nitroalkanes and in situ generated *N*-Boc-imines were achieved with a new type of thiourea–guanidine bifunctional organocatalyst. The novel transformations exhibited good diastereoselectivities, and the adducts bearing adjacent chiral centers were generally obtained in moderate to high enantioselectivities (up to 94% ee). This reaction provides a concise and alternative route converting readily accessible and stable *N*-carbamate amido sulfones into optically active 1,2-diamino compounds.

Key words: organocatalysis, nitro-Mannich reaction, thiourea–guanidine catalyst, in situ generated imines

Optically active 1,2-diamino compounds and their derivatives – acids, esters, and amides –, have attracted a great deal of attention among organic chemists and biochemists through the years due to the ubiquitous nature of 1,2-diamines as key structural fragments of biologically active compounds (Figure 1).[1] Additionally, the synthesis of these enantiopure materials has also represented a challenge for synthetic organic chemists due to the structural complexity of molecules with two vicinal chiral centers.

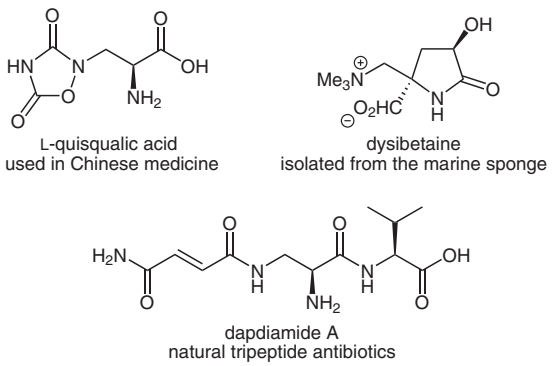

Figure 1

Among various synthetic approaches, catalytic asymmetric nitro-Mannich (or aza-Henry) reactions are elegant and efficient solutions for the stereocontrolled assembly of 1,2-diamino compounds and their derivatives.[2] As a result, great strides have been made over the last several years with both chiral metal[3] and organic catalysts[4] for the catalytic asymmetric version of this reaction. In the reported literature, *N*-carbamate-activated imines, derived from aryl, heteroaryl, and aliphatic aldehydes, are the commonly used electrophiles. However, the preparation of these imines requires harsh reaction conditions and their purification and storage are rather troublesome because of their inherent instability. It is noteworthy that α-amido sulfone is a useful and stable precursor for the in situ preparation of the imine acceptor.[5] Thus, practically and environment-friendly organocatalytic asymmetric Mannich-type reactions using α-amido sulfone have been investigated, for example, with chiral phase-transfer catalysts, cinchona alkaloids, and proline-type catalysts, though with limited success so far.[6]

Thiourea-based organic molecules have become the most prominent hydrogen-bond-donor catalysts in a wide variety of organic reactions.[7] Despite their tremendous utility, these bifunctional catalysts are derived from a very limited range of chiral structural scaffolds, including cyclohexane-1,2-diamine, 1,1′-binaphthyl-2,2′-diamine, and cinchona alkaloids. Very recently, Nagasawa and coworkers have developed the thiourea–guanidine catalyst[8] and applied it to aza-Henry reactions with easily hydrolyzable *N*-carbamate imines and unsubstituted linear nitroalkanes.[8e] This new type of bifunctional catalyst is expected to be applicable to a wide range of asymmetric reactions. To our knowledge, the direct and practical asymmetric nitro-Mannich reactions with in situ generation of carbamate-protected imines and functionalized nitroalkanes catalyzed by thiourea–guanidine catalysts have not yet been reported. Herein, we describe our contributions to the development of practical and efficient syntheses of the diversified chiral 1,2-diamino compounds.

We envisaged that the imine acceptor could be easily generated from the corresponding α-amido sulfone under proper alkaline conditions. Meanwhile, nucleophilic carbanion from nitroalkane might be produced under the same conditions as well. Then the guanidinium group and

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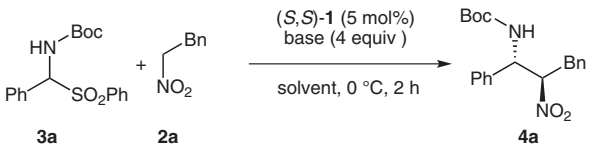
thiourea group selectively coordinated to the nucleophile (nitroalkane) and the electrophile (imine) through ionic and hydrogen-bonding interaction, respectively, and the chiral induction was controlled by the chiral skeleton.

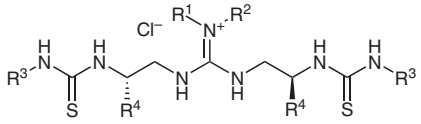
As a model reaction we chose to study the reaction of nitroethane **2a** bearing an aromatic group with the stable α-amido sulfone derived from benzaldehyde **3a** (Table 1). We focused our catalyst-screening efforts on thiourea–guanidine catalyst **1a–i** and performed the reaction in the presence of four equivalents K_2CO_3 in dichloromethane at 0 °C (Table 1, entries 1–6). Catalysts **1a** and **1b** with monosubstituted guanidines failed to afford significant chiral induction, though good yields could be achieved in two hours (Table 1, entries 1 and 2). Gratifyingly, systematic variation of the catalyst structure revealed that bis-substituted guanidine **1c** provided promising enantio- and diastereoselectivity (Table 1, entry 3). Moreover, superior stereocontrol (86% ee and dr = 4.0:1) could be attained with catalyst **1d** bearing a cyclic amine-substituted guanidine (Table 1, entry 4). The absolute configuration of **4a** was determined by comparison of the ^{1}H NMR data and the HPLC retention time with that of literature data.[4c,i] Consequently, replacing the 3,5-bis(trifluoromethyl)phenyl group with other aryl groups decreased the enantioselectivities as a result of weak hydrogen-bonding abilities (Table 1, entries 5 and 6). Attempts to optimize R^4 on the chiral skeleton through the preparation of derivatives **1g–h** failed. Neither linear nor branch alkyl groups could afford good stereoselectivity (Table 1, entries 7 and 8). The catalysts **1i** and **1j** with only one thiourea unit were capable of promoting the reaction efficiently, but unfortunately, providing inferior chiral induction (Table 1, entries 9 and 10). Other solvents and inorganic bases were also screened in the presence of **1d** (Table 1, entries 11–15). Among the solvents tested, toluene was proven to be the best one in terms of both chemical yield and stereocontrol (Table 1, entry 12). Adjusting the inorganic base demonstrated little influence on the ee value of the reaction (Table 1, entries 14 and 15). When the reaction was initiated at lower temperature, a small decrease in conversion was noted compared to the reaction at 0 °C, without improving the ee values dramatically (Table 1, entry 16).

Then we examined the scope of the reaction under the optimized conditions. Results obtained in the addition of diversified nitroalkanes **2** to a variety of α-amido sulfones **3** are summarized in Table 2. All of the reactions were conducted in toluene at 0 °C in the presence of **1d** as a catalyst. In all cases, the major chiral isomers **4** could be directly isolated in pure form in good to high yields. Introduction of electron-donating or electron-withdrawing groups on the aromatic ring of imines had limited influences on the stereo outcome, and satisfactory data were generally attained (Table 2, entries 1–3). When α-amido sulfone **3d** possessing a heteroaromatic ring was used as substrate, the ee value and dr of the adduct **4d** slightly decreased (Table 2, entries 4). Next, we examined other functionalized nitroalkanes as reaction partners (Table 2, entries 5–8). These types of nucleophiles would be more

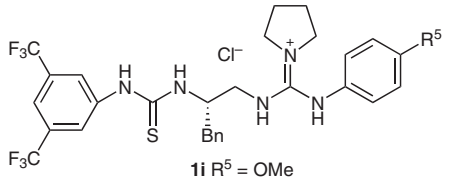
Table 1 Screening Studies of Organocatalytic Nitro-Mannich Reaction of Nitroacetate **2a** and α-Amido Sulfone **3a**[a]



3a **2a** **4a**



1a R^1 = *n*-Bu, R^2 = H, R^3 = 3,5-$(CF_3)_2C_6H_3$, R^4 = Bn
1b R^1 = *i*-Pr, R^2 = H, R^3 = 3,5-$(CF_3)_2C_6H_3$, R^4 = Bn
1c R^1 = *n*-Bu, R^2 = *n*-Bu, R^3 = 3,5-$(CF_3)_2C_6H_3$, R^4 = Bn
1d R^1–R^2 = $CH_2Me)_2CH_2$, R^3 = 3,5-$(CF_3)_2C_6H_3$, R^4 = Bn
1e R^1–R^2 = $CH_2(Me)_2CH_2$, R^3 = 4-ClC_6H_4, R^4 = Bn
1f R^1–R^2 = $CH_2(Me)_2CH_2$, R^3 = 4-MeC_6H_4, R^4 = Bn
1g R^1–R^2 = $CH_2(Me)_2CH_2$, R^3 = 3,5-$(CF_3)_2C_6H_3$, R^4 = Me
1h R^1–R^2 = $CH_2(Me)_2CH_2$, R^3 = 3,5-$(CF_3)_2C_6H_3$, R^4 = *i*-Pr



1i R^5 = OMe
1j R^5 = CF_3

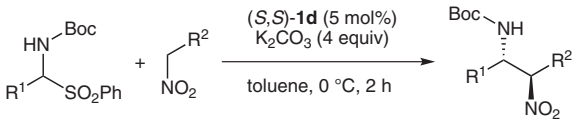
Entry	Cat.	Solvent	Base	Yield (%)[b]	dr[c]	ee (%)[d,e]
1	**1a**	CH_2Cl_2	K_2CO_3	43 (41)	1:1	<10
2	**1b**	CH_2Cl_2	K_2CO_3	38 (39)	1:1	<10
3	**1c**	CH_2Cl_2	K_2CO_3	62 (20)	3.1:1	56
4	**1d**	CH_2Cl_2	K_2CO_3	68 (17)	4.0:1	86
5	**1e**	CH_2Cl_2	K_2CO_3	52 (30)	1.7:1	62
6	**1f**	CH_2Cl_2	K_2CO_3	49 (36)	1.3:1	46
7	**1g**	CH_2Cl_2	K_2CO_3	50 (33)	1.5:1	35
8	**1h**	CH_2Cl_2	K_2CO_3	55 (26)	2.1:1	40
9	**1i**	CH_2Cl_2	K_2CO_3	50 (28)	1.8:1	61
10	**1j**	CH_2Cl_2	K_2CO_3	52 (32)	1.6:1	65
11	**1d**	MeCN	K_2CO_3	64 (20)	3.2:1	64
12	**1d**	toluene	K_2CO_3	76 (14)	5.4:1	90
13	**1d**	THF	K_2CO_3	43 (17)	2.5:1	75
14	**1d**	toluene	Na_2CO_3	56 (13)	4.3:1	88
15	**1d**	toluene	CsOH	65 (19)	3.4:1	85
16[f]	**1d**	toluene	K_2CO_3	56 (14)	4.0:1	89

[a] Reaction conditions: **2a** (0.2 mmol), **3a** (0.1 mmol), **1** (5 mol%), solvent (1 mL), 0 °C, 2 h.
[b] Isolated yield of pure diastereomer. Data in parentheses are related to the isolated minor isomer.
[c] Calculated from the isolated yield of **4a** and its isomer.
[d] Determined by chiral HPLC analysis.
[e] The absolute configuration was determined by comparison of the HPLC retention time with that of literature data.
[f] At –20 °C for 12 h.

promising from the viewpoint of utility of the corresponding products as synthetic intermediates. To synthesize the 2,3-diamino alcohol, benzyl-protected 2-nitroethanol was treated with α-amido sulfone **3a**, and this provided the desired product with good enantioselectivity and diastereoselectivity (Table 2, entry 5). Similarly, high stereoselectivities were consistently obtained in the reaction with several nitroalkanol derivatives bearing longer carbon chains (Table 2, entries 6–8). Finally, we investigated the reaction of commonly employed linear alkyl nitroalkanes with α-amido sulfones. Under the same reaction conditions, the reactions proceeded smoothly to afford the products **4i** in 90% ee and **4j** in 92% ee, respectively (Table 2, entries 9 and 10). These results demonstrated that there was no observable effect of the substituted groups of nitroalkanes on the efficiency of the nitro-Mannich reactions. It was also noteworthy that alkyl α-amido sulfone also worked well in this reaction with nitroethane, while the diastereoselectivity somewhat decreased (Table 2, entry 11).

In summary, we have successfully presented the stereoselective nitro-Mannich reaction of diversified nitroalkanes and readily accessible and stable *N*-carbamate amido sulfones by employing bifunctional thiourea–guanidine catalyst.[9] In general, good diastereo- and enantioselectivities could be obtained with a spectrum of substrates. This novel methodology provides facile access to 1,2-diamino compounds and their derivatives with two adjacent chiral centers. Further investigations on the application of this novel bifunctional organocatalyst in other asymmetric transformations are under way in our laboratory.

Table 2 Asymmetric Nitro-Mannich Reaction of Functionalized Nitroalkanes **2** and α-Amido Sulfones **3**[a]



Entry	R^1	R^2	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	Bn	**4a** 76 (14)	5.4:1	90
2	4-MeC_6H_4	Bn	**4b** 78 (15)	5.2:1	94
3	4-$F_3CC_6H_4$	Bn	**4c** 71 (11)	6.5:1	89
4	3-pyridyl	Bn	**4d** 52 (16)	3.3:1	78
5	Ph	CH_2OBn	**4e** 80 (12)	6.7:1	92
6	Ph	$(CH_2)_2OBn$	**4f** 78 (15)	5.2:1	90
7	Ph	$(CH_2)_3OBn$	**4g** 72 (14)	5.1:1	87
8	Ph	$(CH_2)_3OTf$	**4h** 75 (13)	5.8:1	88
9	Ph	Me	**4i** 77 (18)	4.2:1	90
10	Ph	C_5H_{11}	**4j** 69 (14)	4.9:1	92
11	*i*-Bu	Me	**4k** 55 (24)	2.3:1	84

[a] Reaction conditions: **2** (0.2 mmol), **3** (0.1 mmol), **1d** (5 mol%), toluene (1 mL), 0 °C, 2 h.
[b] Isolated yield of pure diastereomer. Data in parentheses are related to the isolated minor isomer.
[c] Calculated from the isolated yield of **4** and its isomer.
[d] Determined by chiral HPLC analysis.

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(9) **Typical Procedure for the Asymmetric Nitro-Mannich Reaction for the Synthesis of Compound 4a**
To a mixture of α-amido sulfone **3a** (0.1 mmol), chiral catalyst (*S*,*S*)-**1d** (0.005 mmol, 5 mol%), and K_2CO_3 (0.4 mmol) in toluene (1.0 mL) at 0 °C was added nitroalkane **2a** (0.2 mmol) in one portion. The resulting mixture was stirred at 0 °C for 2 h. Then, a sat. aq NH_4Cl solution was added, and the organic layer was extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Compound **4a** was obtained as a white solid in 76% yield after flash column chromatography (PE–EtOAc = 50:1), and the ee was determined to be 86% by HPLC on Chiralpak AD-H column (15% 2-PrOH–*n*-hexane, 1 mL/min), λ = 220 nm, t_R (major) = 15.9 min, t_R minor) = 17.8 min; mp 189–190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.41 (m, 3 H), 7.26–7.31 (m, 4 H), 7.12–7.25 (m, 3 H), 5.19–5.30 (m, 2 H), 4.99–5.10 (br s, 1 H), 3.25–3.35 (m, 1 H), 3.13–3.20 (dd, *J* = 3.5, 14.8 Hz, 1 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.0, 136.4, 135.5, 129.2, 129.0, 128.9, 128.8, 127.5, 127.0, 92.7, 80.8, 57.3, 36.2, 28.2 ppm. ESI-HRMS: *m/z* calcd for $C_{20}H_{24}N_2O_4$ + Na: 379.1634; found: 379.1636.