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Novel Bifunctional Chiral Thiourea Catalyzed Highly Enantioselective aza-Henry Reaction†

Chungui Wang, Zhenghong Zhou,* and Chuchi Tang

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PRC

z.h.zhou@nankai.edu.cn

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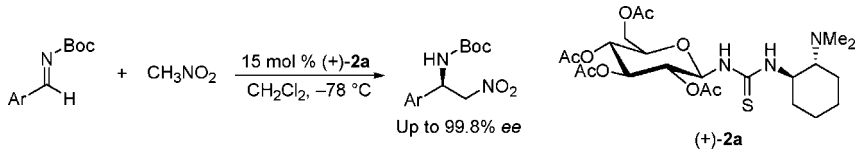
ABSTRACT



A novel bifunctional chiral thiourea organocatalyst bearing a glycosyl scaffold and a tertiary amino group was synthesized starting from readily available alpha-D-glucose. This thiourea was proven to be an effective organocatalyst for the asymmetric aza-Henry reaction between *N*-Boc imines and nitromethane. The corresponding adducts were obtained in good to excellent yields with excellent enantioselectivities (up to 99.8% ee). In addition, the reaction of nitroethane also proceeded smoothly with excellent enantioselectivity, albeit with low to good diastereoselectivities.

The nucleophilic addition of nitroalkanes to the C=N bond of imines, known as the aza-Henry (or nitro-Mannich) reaction, is a useful carbon−carbon bond-forming process in organic synthesis.[1] The resulting β-nitroamine derivatives can be readily transformed into valuable building blocks or biologically active compounds, such as vicinal diamines via reduction of the nitro group[2] and α-amino acids by means of the Nef reaction.[2,3] As a result, much attention has been paid to the aza-Henry reaction, especially for the catalytic asymmetric version of this reaction, during the past several years.[4,5] In 1999, Shibasaki reported the first example of a catalytic asymmetric aza-Henry reaction using a heterobimetallic catalyst [YbK_3(binaphthoxide)$_3$], in which up to 91% ee was obtained.[4a] Thereafter, significant progress has been

† Dedicated to professor Chuchi Tang on the occasion of his 70th birthday.

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witnessed for chiral metallic catalyst promoted enantioselective aza-Henry reaction.[4] However, besides these metal-catalyzed variants, the organocatalytic version remained unexplored until two reports of enantioselective organocatalytic aza-Henry reaction appeared in 2004. Takemoto has developed a bifunctional thiourea catalyst that results in moderate stereoselectivity in the addition of nitromethane to a variety of aromatic *N*-phosphinoyl imines,[5a] and Johnston has documented a chiral bisamidine triflate salt that provides up to 95% ee in the diastereo- and enantioselective addition of nitroethane to a range of *N*-Boc imines.[5f] Although only moderate ee values were observed for the thiourea **1a** catalyzed reaction between *N*-phosphinoyl imines and nitromethane,[5a] high stereoselectivity (up to 98% ee) was obtained when *N*-Boc imines were employed instead of *N*-phosphinoyl imines as the substrates.[5b] Using thiourea **1b**, Jacobsen developed another variation of the aza-Henry reaction of *N*-Boc imines, in which moderate de values and excellent ee values were attained.[5c] Most recently, Ricci[5d] and Schaus[5e] independently screened a variety of cinchona-based thiourea organocatalysts to catalyze the addition of nitromethane to acyl imines, in which satisfactory yields and enantiomeric excesses were provided. In addition, chiral proton catalysis,[5g] chiral urea catalysis,[5h] and chiral phase-transfer catalysis[5i,j] based on quinine or cinchonidine derived quaternary ammonium salts effecting the asymmetric aza-Henry reaction have also been described and gave rise to good diastereo- and enantioselectivities. As aforementioned, bifunctional thioureas have proven to be an efficient type of organocatalyst for the asymmetric aza-Henry reaction. Therefore, the development of new bifunctional thiourea catalysts is still in great demand. Carbohydrates are in general very attractive scaffolds because of their availabilty and well-defined stereocenters. Hence, a novel type of bifunctional thiourea **2** bearing a saccharide scaffold and a tertiary amino group was synthesized and employed as the catalyst in the asymmetric aza-Henry reaction. Herein, we report the discovery that thiourea **2a** efficiently promotes the aza-Henry reaction of nitromethane with *N*-Boc imines with excellent levels of enantioselectivity.

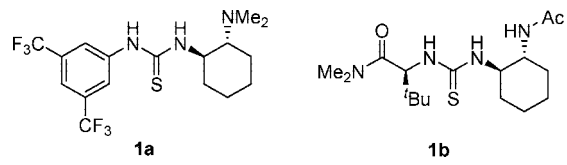
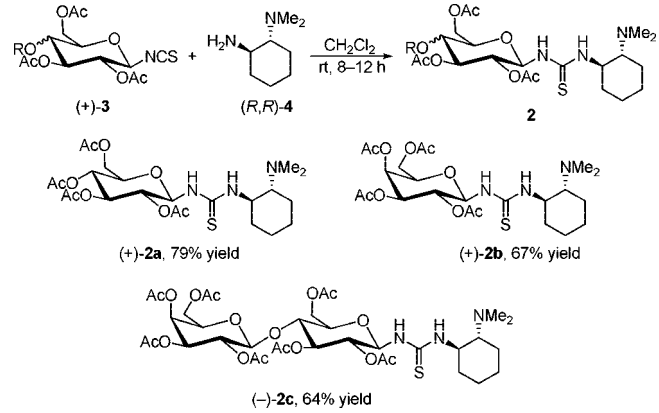


Figure 1. Thiourea organocatalysts.

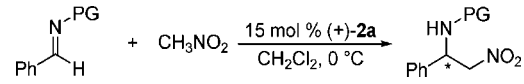
Starting from commercially available α-D-glucopyranose, glucosyl isothiocyanate **3** was prepared via acetylation, bromination, and nucleophilic substitution reactions.[6] (*R*,*R*)-*N*,*N*-Dimethyl cyclohexane-1,2-diamine **4** was synthesized through monoamino protection with phthalic anhydride, *N*,*N*-dimethylation, and subsequently deprotection starting from (*R*,*R*)-cyclohexane-1,2-diamine.[7] Consequently, coupling of **3** and **4** afforded the desired bifunctional thiourea catalyst **2a** in good yield. Following the same procedure, thiourea catalysts **2b** and **2c** were also synthesized from galactose and lactose, respectively (in a yield of 67% for **2b** and 73% for **2c**).

Scheme 1. Synthesis of Novel Thiourea **2**



With these novel catalysts in hand, we initially screened several imines with different N-protecting groups (PG) in the presence of **2a** (15 mol %) and nitromethane in methylene chloride at 0 °C (Table 1).

Table 1. Enantioselective aza-Henry Reaction of Different Imines with Nitromethane



entry	PG	time (h)	yield (%)[a]	ee (%)[b]
1	Ts	4.5	79	8
2	$Ph_2P(S)$	48	trace	
3	$Ph_2P(O)$	48	NR[c]	
4	Boc	16	85	90
5	CO_2Et	24	77	85
6	CO_2Bn	24	71	86

[a] Yield of the isolated product after chromatography on silica gel. [b] Determined chiral HPLC analysis. [c] NR means no reaction occurred.

Among the imines examined, *N*-alkoxycarbonylimines tended to provide the desired adducts with good enantioselectivities compared with other imines (Table 1, entries 1−6), and the best result was obtained for *N*-Boc imine in terms of chemical yield and enantiomeric excess (Table 1, entry 4, 95% yield, 90% ee). Although *N*-tosyl imine exhibited the best reactivity, an almost racemic product was attained

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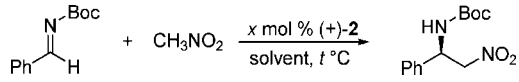
(Table 1, entry 1). In the case of *N*-(thio)phosphinoyl imines, the reactions were quite sluggish even after a prolonged reaction time (Table 1, entries 2 and 3).

In further experiments, other factors, such as solvent, catalyst loading, and reaction temperature, influencing the reaction were thoroughly investigated employing **2** as the catalyst and the reaction between *tert*-butyl benzylidenecarbamate and nitromethane as the model. The results are listed in Table 2.

Table 2. Optimization of the Reaction Conditions



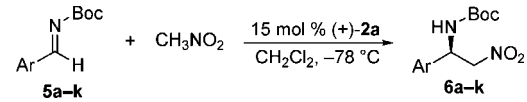
entry	**2** (mol %)	solvent	temp (°C)	yield (%)[a]	ee (%)[b]
1	**2a** (15)	CH_2Cl_2	0	85	90
2	**2a** (15)	MePh	0	87	85
3	**2a** (15)	THF	0	87	67
4	**2a** (15)	$CHCl_3$	0	90	80
5	**2a** (15)	MeOH	0	trace	
6	**2a** (15)	MeCN	0	88	91
7	**2a** (10)	CH_2Cl_2	0	77	85
8	**2a** (20)	CH_2Cl_2	0	78	87
9	**2b** (15)	CH_2Cl_2	0	89	85
10	**2c** (15)	CH_2Cl_2	0	89	78
11	**2a** (15)	CH_2Cl_2	−40	87	93
12	**2a** (15)	CH_2Cl_2	−60	86	96
13	**2a** (15)	CH_2Cl_2	−78	86	>99

[a] Yield of the isolated product after chromatography on silica gel. [b] Determined chiral HPLC analysis.

Solvent evaluation revealed that all the tested solvents except for methanol, which probably inhibits hydrogen-bonding interaction between nitromethane and the thiourea moiety of **2**, afforded the desired product in good yield and ee values (Table 2, entries 1−6). The best results were observed when methylene chloride and acetonitrile were used (Table 2, entries 1 and 6, 90% and 91% ee, respectively). Since acetonitrile has a relatively higher freezing point (−48 °C), it is not applicable for low-temperature tests; therefore, we chose methylene chloride as the favorable solvent for this reaction. Although bifunctional thiourea catalysts **2b**,**c** can also promote this reaction, a moderate decrease in enantioselectivtiy was observed, which affords the desired adduct with 85% and 78% ee, respectively (Table 1, entries 9 and 10). Adjusting the catalyst loading (**2a**) demonstrated little influence on the ee value of the reaction. For example, the use of a larger or smaller amount of thiourea organocatalyst resulted in only a slight loss of stereocontrol (Table 2, entry 8, 87% ee and entry 7, 85% ee). Moreover, the reaction temperature was found to be an essential factor to the enantioselectivity of this reaction. Generally, lowering the temperature improved the enantiomeric excess of the reaction (Table 2, entries 1 and 11−13). It is worth noting that almost perfect enantiocontrol was realized with good chemical yield when the reaction was performed at −78 °C (Table 2, entry 11, >99% ee).

With the optimal reaction conditions in hand (15 mol % of **2a** as the catalyst, at −78 °C in methylene chloride), we investigated the scope and limitations of this asymmetric aza-Henry reaction. The results are summarized in Table 3.

Table 3. Chiral Thiourea **2** Catalyzed Asymmetric Addition of Nitromethane to *N*-Boc Imines[a]



entry	Ar group	**6**	time (h)	yield (%)[b,c]	ee (%)[d]
1	Ph (**5a**)	**a**	60	86	>99
2	4-$MeOC_6H_4$ (**5b**)	**b**	66	94	94
3	4-MeC_6H_4 (**5c**)	**c**	68	93(70)	83(>99)
4	4-ClC_6H_4 (**5d**)	**d**	60	93	>99
5	3-FC_6H_4 (**5e**)	**e**	39	87	>99
6	4-FC_6H_4 (**5f**)	**f**	65	91	>99
7	2-ClC_6H_4 (**5g**)	**g**	42	85	92
8	1-naphthyl (**5h**)	**h**	65	95	>99
9	2-furyl (**5i**)	**i**	62	86(69)	90(97)
10	4-$F_3CC_6H_4$ (**5j**)	**j**	64	85	94
11	2-$F_3CC_6H_4$ (**5k**)	**k**	61	84	96

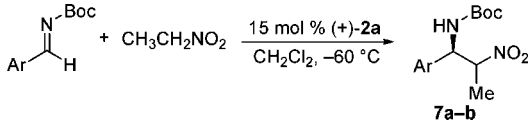
[a] The absolute configurations of the major isomer of the aza-Henry adducts **6** were assigned as *R* by comparison to the literature value of optical rotation in refs 5c, 5e, 5i, and 5j. [b] Yield of the isolated product after chromatography on silica gel. [c] Data in parentheses were obtained through a simple recrystallization from ethyl acetate/petroleum ether. [d] Determined by chiral HPLC analysis.

As shown in Table 3, in all cases, the corresponding aza-Henry adducts were obtained in satisfactory chemical yields within acceptable reaction times. Excellent enantioselectivities can be obtained for the substrates bearing electron-withdrawing substituents (**5d**−**g**, **5j**,**k**) and imine derived from 1-naphthyl aldehyde, and in most cases, almost perfect enantiocontrol was realized. The reaction of the electron-donating methoxy group substituted imine (**5b**) also proceeded smoothly to afford the desired product in excellent stereoselectivity. Although a slight decrease in ee value was observed for methyl-substituted imine (**5c**) and electron-rich heteroaromatic aldehyde-derived substrate (**5i**), the optical purity of the product can be significantly improved via a simple recrystallization (99.7% and 97.2% ee, respectively).

In addition, aza-Henry reactions with other nitro alkanes were preliminarily investigated. Nitroethane proved to be considerably less reactive under the standard conditions but underwent smooth reaction at an elevated temperature (−60 °C) to provide adducts **7** in excellent enantioselectivities with low to good diastereoselectivities. For example, benzadehyde-derived imine (**5a**) underwent reaction with excellent enantioselectivity (97.0% ee for *syn*-isomer) and provided products with synthetically useful levels of diastereoselectivity (*syn*/*anti* = 9.3/1). Although a low *syn*/*anti* ratio (1.2/1) was attained in the case of 3-fluorobenzaldehyde-based imine (**5e**), it was gratifying that high enantioselectivity was

obtained for the separable *anti*-isomer. Reaction with the more sterically challenging 2-nitropropane did not proceed at all.

Scheme 2. Chiral Thiourea **2a** Catalyzed Asymmetric Addition of Nitroethane to *N*-Boc Imines



In conclusion, we have developed a readily available novel bifunctional chiral thiourea organocatalyst bearing a glycosyl scaffold and a tertiary amino group. The high effectiveness of this novel organocatalyst was demonstrated by catalysis of the aza-Henry reaction of nitromethane with *N*-Boc imines with excellent enantioselectivity. In addition, the reaction of nitroethane was also effective to provide the corresponding adducts with high enantioselectivities, albeit with low to good diastereoselectivities. Further investigation on the diastereoselective aza-Henry reaction and application of this novel catalyst in other asymmetric reactions are ongoing in our laboratory.

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Supporting Information Available: Experimental procedures, characterization of the catalyst and copies of ^{1}H NMR spectra, and chiral HPLC spectra of the aza-Henry adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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