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Enantioselective Aza-Henry Reaction with Acyclic Guanidine-Thiourea Bifunctional Organocatalyst

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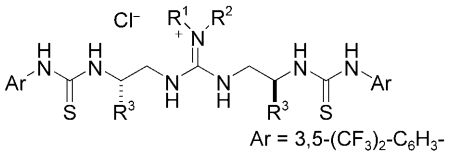
Abstract: A highly enantioselective aza-Henry reaction of imines with nitromethane was achieved with a reactive guanidine-thiourea bifunctional organocatalyst affording β-nitroamines with high enantioselectivity (up to 96% *ee*). The diastereo- and enantioselective version of this reaction with nitroalkanes also proceeded selectively (up to 99:1 *dr* with 99% *ee*).

Keywords: aza-Henry reaction; guanidines; organic catalysts; phase-transfer catalyst; thioureas

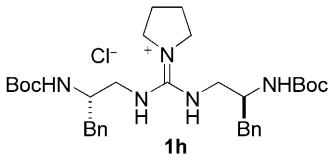
The aza-Henry reaction is a fundamental carbon-carbon bond-forming reaction in synthetic organic chemistry,[1] providing a synthetically useful chiral intermediate for β-nitro amines.[2] Since the pioneering catalytic asymmetric version of the reaction by Shibasaki's group, using a heterobimetallic catalyst,[3] many further developments have been reported.[4] Among them, an organocatalytic aza-Henry reaction was reported for the first time by Takemoto et al. using a chiral thiourea-*N*-dimethylamine group-conjugated catalyst.[5] Recently, various types of organocatalytic aza-Henry reactions have been reported, including the use of bisamidine,[6] *Cinchona* alkaloid derivatives[7] and (thio)urea as catalysts.[8] Although high enantio- and/or diastereoselectivities have been achieved, limited substrate generality and low catalytic activity are still issues. Herein, we describe the highly enantioselective aza-Henry reaction of both aromatic and aliphatic imines with nitromethane in the presence of an active bifunctional organocatalyst. A highly diastereo- and enantioselective version of the reaction with aromatic imines is also described.

Recently we have developed a guanidine-thiourea bifunctional acyclic catalyst, **1a**, for enantioselective, as well as diastereo- and enantioselective, Henry reactions under liquid-liquid biphasic conditions.[9] In this reaction, the catalyst **1a**, which has long alkyl chain on the guanidine moiety, forms a chiral surfactant. This surfactant and potassium iodide as an additive were effective for preventing the retro-reaction process, resulting in the observed high enantioselectivity. In contrast, the aza-Henry reaction does not involve a retro process, so here, we newly explored the solid-liquid biphasic aza-Henry reaction in the presence of a guanidine-thiourea bifunctional organocatalyst.

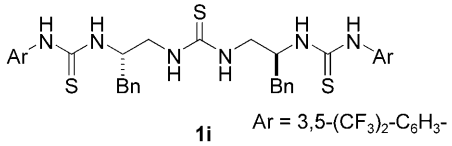
We investigated the catalytic activity and enantioselectivity in the reaction of imine **2a**[10] and nitromethane **3a** catalyzed by the guanidine-thiourea compounds **1** (Figure 1), focusing on the substituents of the guanidine group and the chiral spacer (Table 1). First, the effects of the R^1 and R^2 groups on guanidine were explored. The mono-substituted guanidines **1a** and **1b** (5 mol%) efficiently catalyzed the reaction within 30 min under Cs_2CO_3-THF biphasic conditions at 0 °C, but the enantioselectivity was poor (entries 1 and 2). In the case of bis-substituted guanidine **1c**, the enantioselectivity was increased to 74% *ee* (entry 3). Drastic improvements of both catalytic activity and enantioselectivity were seen with cyclic amine-substituted guanidines **1d** and **1e** (entries 4-7). In particular, **1d** having a pyrrolidine ring gave β-nitroamine **4a** in 92% yield with 93% *ee*. When the reaction temperature was lowered to −10 °C, the enantioselectivity increased to 96% without any decrease of the chemical yield. When the catalyst loading of **1d** was decreased to 3 mol%, the chemical yield and enantioselectivity were slightly decreased to 91% and 90% *ee* (entry 6). Next, the chiral spacer (R^3) was varied. The catalysts **1f** and **1g**, which have alanine- and valine-derived chiral spacers (R^3 = Me, *i*-Pr), respectively, gave **4a** with high yield, but the enantioselectivity was only moderate (entries 8 and 9). Since the catalysts **1h** and **1i**,[9d] lacking the thiourea or guanidine group, did not



1a: $R^1 = C_{18}H_{37}$, R^2 = H, R^3 = Bn
1b: $R^1 = C_4H_9$, R^2 = H, R^3 = Bn
1c: $R^1 = C_4H_9$, $R^2 = C_4H_9$, R^3 = Bn
1d: $R^1, R^2 = -CH_2(CH_2)_2CH_2-$, R^3 = Bn
1e: $R^1, R^2 = -CH_2(CH_2)_3CH_2-$, R^3 = Bn
1f: $R^1, R^2 = -CH_2(CH_2)_2CH_2-$, R^3 = Me
1g: $R^1, R^2 = -CH_2(CH_2)_2CH_2-$, R^3 = *i*-Pr



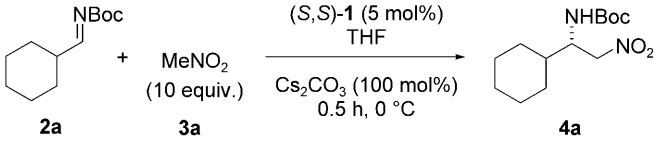
1h



1i

Figure 1. Structures of guanidine-thiourea bifunctional catalysts **1a–g** and monofunctional catalysts **1h** and **1i**.

Table 1. Substituent effects on yield and enantioselectivity in the reaction **2a** and **3a** with catalysts **1**.[a]



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

Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**1a**	89	9
2	**1b**	90	17
3	**1c**	61	74
4	**1d**	92	93
5[d]	**1d**	92	96
6[e]	**1d**	91	90
7	**1e**	80	85
8	**1f**	90	71
9	**1g**	91	71
10	**1h**	76	0
11	**1i**	88	12

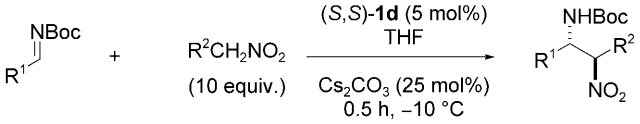
[a] Reactions were carried out on a 0.1 mmol scale in 1.0 mL of THF.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis.[7a]
[d] Reaction was run at −10 °C.
[e] 3 mol% catalyst was used at −10 °C.

show any asymmetric induction, the guanidine and thiourea groups in **1d** were considered to act cooperatively in the asymmetric induction (entries 10 and 11).

The scope of imine substrates was examined under the optimized conditions (Table 1, entry 5). Every reaction was completed within 30 min (Table 2, entries 1–6). Aliphatic and aromatic imines gave the corresponding aza-Henry products **4** in good yield (82–96%) with high enantioselectivity (90–96% *ee*). The diastereo- and enantioselective version of the aza-Henry reaction was also explored with imines **2e–g** and nitroalkanes **3b–d** (Table 2, entries 7–13). In all cases, the *anti*-β-nitro amines **4** were obtained in good yield (81–94%) and with high diastereo- and enantioselectivities (90:10–99:1 *dr*, 96–99% *ee*).

In summary, we have developed a highly enantioselective aza-Henry reaction by using the newly developed guanidine-thiourea bifunctional organocatalyst **1d**. This reaction is applicable to various aliphatic and aromatic imines. The diastereo- and enantioselective version of this reaction with nitroalkanes and aromat-

Table 2. Catalytic asymmetric aza-Henry reaction of imines **2** with nitroalkanes **3**.[a]



2b: R^1 = *c*-C_5H_9
2c: R^1 = *i*-Pr
2d: R^1 = *n*-C_6H_{13}
2e: R^1 = C_6H_5
2f: R^1 = 4-Me-C_6H_4
2g: R^1 = 4-Cl-C_6H_4

3a: R^2 = H
3b: R^2 = Me
3c: R^2 = Et
3d: R^2 = $TBSOCH_2$

4b – n

Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	**2b**	**3a**	84 (**4b**)	95	–
2	**2c**	**3a**	92 (**4c**)	96	–
3[e]	**2d**	**3a**	82 (**4d**)	90	–
4	**2e**	**3a**	96 (**4e**)	96	–
5	**2f**	**3a**	85 (**4f**)	90	–
6	**2g**	**3a**	88 (**4g**)	96	–
7[f]	**2e**	**3b**	94 (**4h**)	99	99:1
8[g]	**2e**	**3c**	90 (**4i**)	99	99:1
9[g]	**2e**	**3d**	85 (**4j**)	98	94:6
10[h]	**2f**	**3b**	89 (**4k**)	99	92:8
11[h]	**2f**	**3c**	89 (**4l**)	97	90:10
12	**2g**	**3b**	81 (**4m**)	97	96:4
13	**2g**	**3c**	94 (**4n**)	96	95:5

[a] Reactions were carried out on a 0.1 mmol scale in 1.0 mL of THF.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by chiral HPLC analysis.[5b,7a,8a]
[d] Diastereomer ratios were determined by HPLC analysis.[5b,8a]
[e] Reaction was run at 0 °C.
[f] Reaction was run at −10 °C with Cs_2CO_3 (50 mol%).
[g] Reaction was run at −20 °C with Cs_2CO_3 (50 mol%).
[h] Reaction was run at −25 °C with Cs_2CO_3 (50 mol%) for 2 h.

ic imines also proceeded with extremely high selectivities.

Experimental Section

Typical Procedure for Enantioselective Aza-Henry Reaction

To a mixture of (*S*,*S*)-**1d** (4.8 mg, 5 μmol), Cs_2CO_3 (32.6 mg, 0.1 mmol) and imine (**2a**) (21.2 mg, 0.1 mmol) in THF (1 mL) was added nitromethane (**3a**) (54 μL, 1.0 mmol) at −10 °C. The resulting mixture was stirred vigorously at −10 °C for 30 min. To the reaction mixture was added saturated aqueous NH_4Cl, and the organic layer was extracted with ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 50:1 to 25:1) to give nitroamine **4a**; yield: 25.3 mg (92%). The enantiomeric excess of **4a** (96% *ee*) was determined by means of chiral HPLC analysis [Chiral AD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 90:10, 0.8 mL min^{-1}, major; 12.3 min, minor; 9.4 min].[7a]

Acknowledgements

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