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Guanidine-Thiourea Bifunctional Organocatalyst for the Asymmetric Henry (Nitroaldol) Reaction

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Abstract: Novel bifunctional catalysts having guanidine and thiourea functional groups were developed for the asymmetric Henry (nitroaldol) reaction. Various structural developments of the catalyst revealed that the compound having an octadecyl-substituted guanidine and thiourea groups linked with a chiral spacer derived from phenylalanine, i.e., **1e**, efficiently promoted the Henry reaction. This bifunctional organocatalyst **1e** also gave high asymmetric inductions with aliphatic cyclic aldehydes and branched aliphatic aldehydes (82–90% ee).

Keywords: bifunctional organocatalyst; guanidines; nitroaldol; organic catalysis; thioureas

Introduction

The Henry reaction (nitroaldol reaction) is a fundamental carbon-carbon bond-forming reaction.[1] Transformations of the Henry reaction adducts, such as reduction to amines or oxidation (Nef reaction) to carbonyl compounds, give a variety of useful synthetic intermediates.[2] Thus, great efforts have been directed to the development of a catalytic asymmetric version of this reaction. Shibasaki et al. reported a series of bimetallic catalysts that proved to be effective for the asymmetric Henry reaction.[3] Trost et al. reported a dinuclear Zn catalyst that induces high enantioselectivity in the addition of nitromethane to a variety of cyclic, aliphatic and aromatic aldehydes.[4] Evans et al. developed a bis(oxazoline)-Cu catalyst for highly enantioselective Henry reactions.[5] As well as these metal-containing catalysts, environmentally friendly organocatalysts[6] have been introduced for the Henry reaction. [7–9] One class of organocatalysts, guanidine compounds, [7,10] interacts with nitro compounds through nitronate anion formation as a counter partner,[11] so chiral guanidine compounds are thought to be good candidates for asymmetric Henry reaction catalysts. Najera et al. have reported chiral aliphatic guanidine catalysts[7a] and recently Murphy et al. reported C_2-symmetrical cyclic guanidine compounds for the asymmetric Henry reaction.[7b] These guanidine compounds effectively catalyzed the Henry reaction, but afforded only low to moderate asymmetric inductions (20–50% ee). Recently, Ma et al. reported highly diastereoselective Henry reactions with nitromethane and aldehydes derived from amino acids, using a chiral aliphatic guanidine catalyst (92% de).[7c] However, the highly enantioselective, direct Henry reaction catalyzed by organocatalysts remains insufficiently developed. Herein, we report highly enantioselective Henry reactions catalyzed by a guanidine-thiouea bifunctional organocatalyst.

Results and Discussion

Bifunctional-type organocatalysts[12] are an attractive type of organocatalyst. Since the two functional groups in the bifunctional catalysts interact with different reaction components, various reactions are expected to be promoted efficiently. In the case of the Henry reaction, nitroalkanes and aldehydes are involved, and they are known to interact with and/or be activated by guanidines[11] and thioureas,[13] respectively. Thus, catalysts which contain guanidine and thiourea functional groups linked by a chiral spacer might promote the asymmetric Henry reaction. We therefore designed linear guanidine-thiourea linked bifunctional catalysts **1a–g** (Fig-

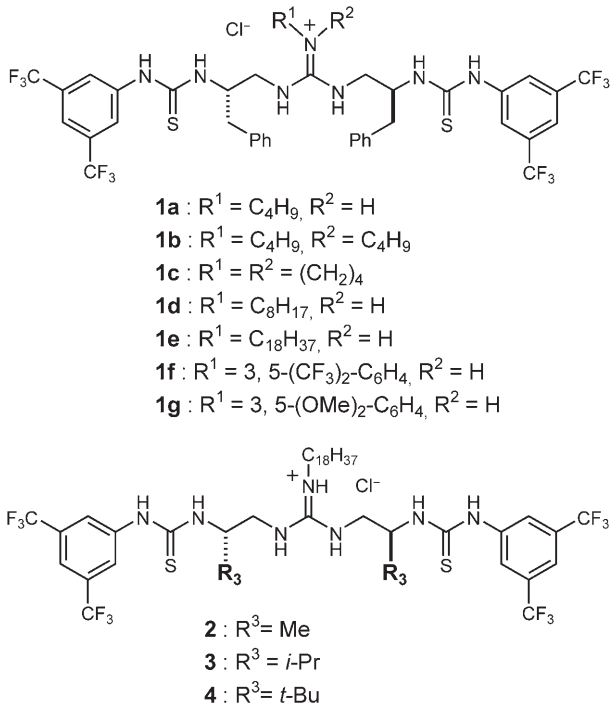
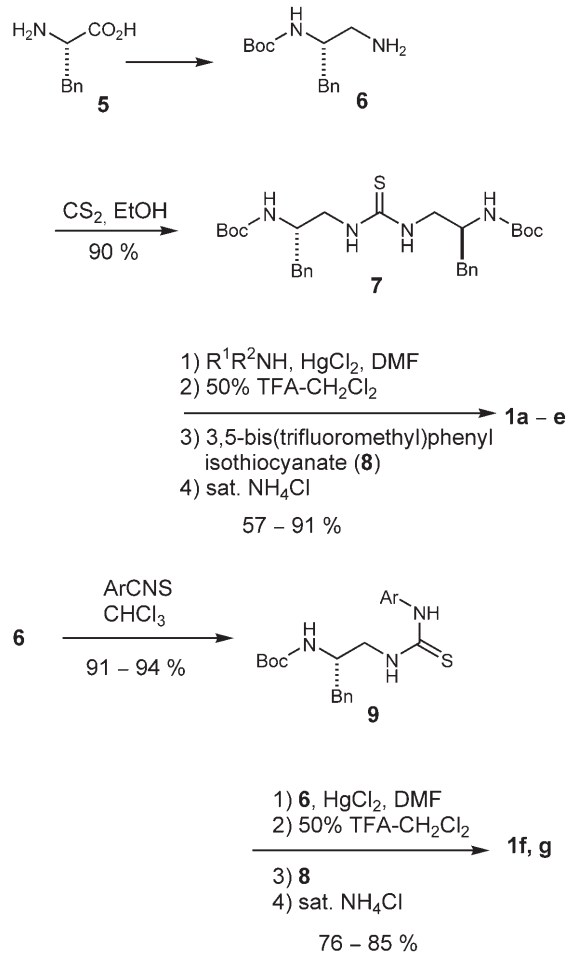


Figure 1. Structures of guanidine-thiourea type bifunctional compounds



Scheme 1. Synthesis of catalysts **1a**–**g**.

ure 1). In the thiourea moiety of **1**, aromatic rings having electron-withdrawing groups were introduced for the efficient activation of carbonyl compounds. Various substituents were also introduced onto the guanidine group.

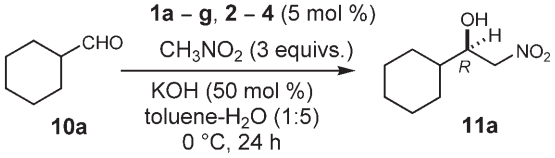
The thiourea-guanidine bifunctional compounds **1a**–**g** were prepared as depicted in Scheme 1. The amine **6**, which was derived from L-phenylalanine (**5**), was converted into the thiourea **7** with carbon disulfide in 90% yield. Various amines, such as butylamine, dibutylamine, pyrrolidine, octylamine and octadecylamine were reacted with the thiourea **7** using mercury(II) chloride. The Boc groups were removed with TFA, and subsequent thiourea formation with thioisocyanate **8** followed by treatment with ammonium chloride gave **1a**–**e** in 57%–91% yields. The aromatic group-substituted **1f** and **1g** were synthesized from **6** *via* the dissymmetrical thiourea **9** in 77% and 75% yield, respectively.

With the guanidine-thiourea bifunctional catalysts **1** in hand, the Henry reaction between nitromethane and cyclohexanecarboxaldehyde (**10a**) was explored. The reaction was performed in the presence of 5 mol % of catalysts under biphasic conditions in toluene-aqueous potassium hydroxide at 0 °C, and the results are summarized in Table 1. The catalysts **1a**, **1b**, **1c**, **1f** and **1g** did not give good results (entries 1–3, 6 and 7). Since increasing the solubility of the catalyst in the organic solvent is known to be effective for promoting the reaction, especially under phase-transfer conditions, octyl- and octadecyl-substituted catalysts **1d** and **1e** were examined. Compound **1e** efficiently promoted the Henry reaction, giving **11a** in 91% yield and 43% ee (entry 5).

Next, we attempted to improve the asymmetric induction. While retaining the R^1 and R^2 groups of **1e**, the starting amino acid, L-phenylalanine (**5**) was changed to L-alanine, L-valine and L-*tert*-leucine (R^3 = methyl, isopropyl and *tert*-butyl, respectively) to give **2**–**4** (Figure 1). Compounds **2**–**4** effectively promoted the Henry reaction in 55–89% yield (Table 1, entries 8–10), but the ee value of **11a** was greatest when the R^3 group was the original benzyl group, i.e., **1e**.

To explore the optimal reaction conditions of **10a** with nitromethane in the presence of **1e**, firstly, various inorganic salts were examined as additives, since the effects of the counter anion of not only ammonium salts,[14] but also guanidinium salts[7b] have been reported to influence both catalytic activity and asymmetric induction. Table 2 summarizes the effects of the inorganic salts. The tetrafluoroborates KBF_4 and $NaBF_4$ did not give high ee values (entries 1 and 2).[15] With KBr and NaBr, the ee values were increased to 57% and 60%, respectively (entries 3 and 4). The softer anionic species, LiI and NaI, were effective in terms of ee value (entries

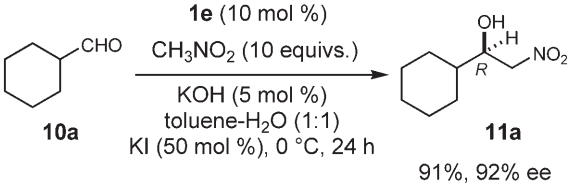
Table 1. Henry reaction with bifunctional catalysts **1a**–**g** and **2**–**4**.



Entry	Cat.	Yield [%]	ee [%]
1	**1a**	37	33
2	**1b**	24	18[a]
3	**1c**	22	6
4	**1d**	34	8
5	**1e**	91	43
6	**1f**	trace	nd
7	**1g**	39	17
8	**2**	80	14
9	**3**	89	36
10	**4**	55	9[a]

[a] (*S*)-**11a** was obtained as the major product.

5 and 6). The best result was obtained with KI: **11a** was obtained in 88% yield and 74% ee (entry 7).[16] We next examined the optimum ratio of the solvents. Finally, a 1 to 1 ratio of toluene-H_2O in the presence of nitromethane (10 equivs.), **1e** (10 mol %), KI (50 mol %) and KOH (5 mol %) at 0 °C, gave the Henry product **11a** in 91% yield and up to 92% ee [Eq. (1)].[17]

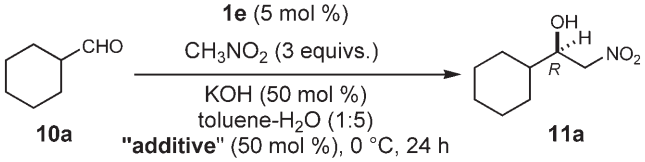


(1)

Using these optimized reaction conditions, the reactions of various aldehydes were examined, and the results are summarized in Table 3. In the case of aliphatic cyclic and α-branched-chain aldehydes, the corresponding Henry adducts **11b**–**e** were generated in high yield and high ee of 82–88% (entries 1–4). However the unbranched aliphatic aldehyde **10f** gave the adduct **11f** with only a moderate enantiomeric excess of 55% (entry 6). The reaction rate of this Henry reaction can be controlled by changing the amount of KOH. In the case of reactive aldehydes **10c**–**f**, a lower amount of KOH (5–10 mol %) probably contributed to the high asymmetric inductions by reducing the reaction rate (entries 2–5).

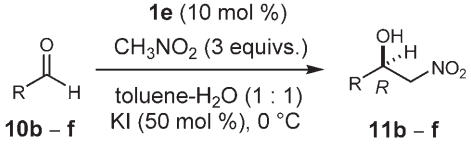
Since the stereochemistry of the newly generated alcohol in **11** is *R*, the transition state of this Henry reaction can be considered to be as shown in Figure 2. Nitromethane and the aldehyde **10** coordinate to the guanidinine and thiourea groups, respectively, through hydrogen-bonding interactions. In this case, the substituent

Table 2. Effects of additives on Henry reaction catalyzed by **1e**.



Entry	Additive	Yield [%]	ee [%]
1	KBF_4	77	47
2	$NaBF_4$	64	38
3	KBr	76	57
4	NaBr	65	60
5	LiI	65	66
6	NaI	64	67
7	KI	88	74

Table 3. Henry reaction with various aldehydes.



Entry	R	KOH [mol %]	Time [h]	Yield [%]	ee [%]
1	**10b**	40	5	76	82 (*R*)
2[a]	**10c**	5	45	85	88 (*R*)
3	**10d**	10	19	88	83 (*R*)
4[a]	**10e**	10	36	70	88 (*R*)
5	**10f**	5	18	79	55 (*R*)

[a] 10 equivs. of nitromethane was used.

in the aldehyde (R group) favors an *anti* conformer rather than a *gauche* position, and nitromethane and the aldehyde **10** react to form the new carbon-carbon bond. Thus, (*R*)-**11** should be generated as the major coupling product.

Conclusion

In summary, we have developed the new bifunctional organocatalyst **1e** for the asymmetric Henry reaction. This

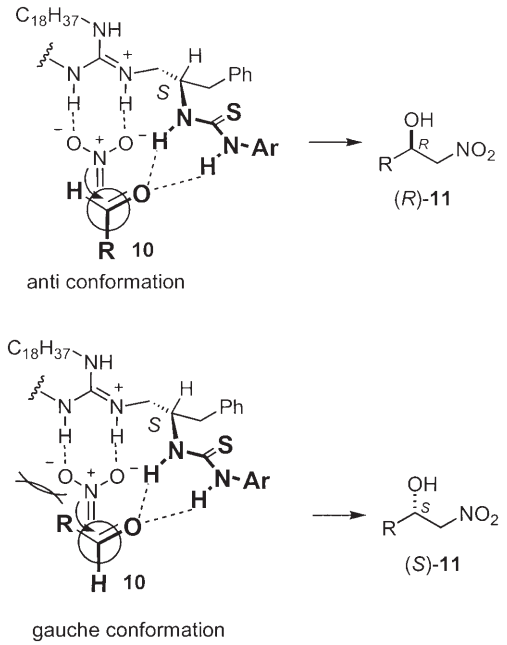


Figure 2. Proposed transition state of the guanidine-thiourea bifunctional compound-catalyzed Henry reaction.

catalyst utilizes guanidine and thiourea groups for the nitromethane and aldehyde interaction and/or activation, respectively. The long alkyl chain (octadecyl group) of the guanidine substituent of **1e** was also mandatory to promote the reaction effectively. In the presence of KI as an additive, **1e** catalyzed the Henry reaction in 70–91% yield and 82–92% ee with α-branched aldehydes. Although an asymmetric induction is still insufficient in the case of unbranched aldehydes, the catalyst could be easily modified by changing the chiral spacer, which might improve the asymmetric induction for a variety of substrates. Further works along this line is in progress.

Experimental Section

General Remarks

Flash chromatography was performed using silica gel 60 (spherical, particle size 0.040–0.100 mm; Kanto Co., Inc., Japan). Optical rotations were measured with a JASCO DIP polarimeter 370. IR spectra were measured with JASCO VALOR-III FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL ALPHA500 instrument. Mass spectra were recorded on JEOL JMA-HX110 spectrometer. Characterization data for compounds **1a–g** and **2–4** can be found in the Supporting Information.

Typical Procedure for the Asymmetric Henry Reaction

To a mixture of **1e** (12.9 mg, 0.0112 mmol), KI (9.3 mg, 0.0558 mmol) and nitromethane (65.2 μL, 1.12 mmol) in toluene (1.12 mL)/5 mM aqueous KOH (1.12 mL) was added cyclohexanecarboxaldehyde (**10a**; 13.4 μL, 0.112 mmol) at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 24 h. Then saturated aqueous NH_4Cl was added, and the organic layer was extracted with ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated under vacuum, and the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 20/1 → 5/1 → chloroform/methanol = 9/1) to give **11a** (yield: 17.4 mg, 91%) and **1e** (12.8 mg, 99% recovery). The enantiomeric excess of **11a** (92% ee) was determined by means of chiral HPLC analysis [Chiralcel OD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 97/3, 1.0 mL/min, (*R*) major; 19.3 min, (*S*) minor; 21.2 min]. The absolute stereochemistry of **11a** was determined based on the retention time reported by Trost et al.[4a,5]

Spectral data for 11a:[4a,5] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.48 (dd, *J* = 13.1 Hz, 2.7 Hz, 1H), 4.42 (dd, *J* = 13.1 Hz, 8.9 Hz, 1H), 4.10 (m, 1H), 2.42 (br s, 1H), 1.82 (m, 2H), 1.68 (m, 2H), 1.47 (m, 1H), 1.30–1.06 (m, 6H).

Spectral data for 11b: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.48 (dd, *J* = 13.2 Hz, 2.7 Hz, 1H), 4.39 (dd, *J* = 13.2 Hz, 9.0 Hz, 1H), 4.14 (m, 1H), 2.56 (br s, 1H), 1.93 (m, 1H), 1.84 (m, 1H), 1.76–1.57 (m, 5H), 1.47 (m, 1H), 1.28 (m, 1H). The enantiomeric excess of **11b** was determined by the use of chiral HPLC analysis [Chiralcel OD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 98/2, 1.0 mL/min, (*R*) major; 22.5 min, (*S*) minor; 25.0 min].

Spectral data for 11c:[4a,5] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.53 (dd, *J* = 12.9 Hz, 2.0 Hz, 1H), 4.37 (dd, *J* = 12.9 Hz, 10.1 Hz, 1H), 4.04 (dd, *J* = 10.1 Hz, 2.0 Hz, 1H), 2.42 (br s, 1H), 0.99 (s, 9H). The enantiomeric excess of 11c was determined by the use of chiral HPLC analysis [Chiralcel OD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 97/3, 1.0 mL/min, (*R*) major; 15.1 min, (*S*) minor; 18.8 min].

Spectral data for 11d:[4a,5] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.48 (dd, *J* = 13.2 Hz, 3.2 Hz, 1H), 4.40 (dd, *J* = 13.2 Hz, 8.5 Hz, 1H), 4.11 (m, 1H), 1.81 (m, 1H), 1.01 (d, *J* = 4.1 Hz, 3H), 0.97 (d, *J* = 4.4 Hz, 3 H). The enantiomeric excess of **11d** was determined by the use of chiral HPLC analysis [Chiralcel OD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 97/3, 1.0 mL/min, (*R*) major; 18.3 min, (*S*) minor; 21.7 min].

Spectral data for 11e:[4a] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.46 (d, *J* = 2.2 Hz, 1H), 4.43 (s, 1H), 4.42–4.31 (m, 1H), 2.38 (d, *J* = 4.6 Hz, 1H), 1.56–1.21 (m, 5H), 0.94 (t, *J* = 7.2 Hz, 6 H). The enantiomeric excess of **11e** was determined by the use of chiral HPLC analysis [Chiralcel OD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 98/2, 1.0 mL/min, (*R*) major; 21.0 min, (*S*) minor; 25.2 min].

Spectral data for 11f:[4a,5] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.18 (m, 5H), 4.41 (s, 1H), 4.39 (d, *J* = 2.0 Hz, 1H), 4.35–4.26 (m, 1H), 2.92–2.20 (m, 2H), 2.64 (br s, 1H), 1.94–1.72 (m, 2H). The enantiomeric excess of **11f** was determined by the use of chiral HPLC analysis [Chiralcel AD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 95/5, 1.0 mL/min, (*R*) major; 23.2 min, (*S*) minor; 29.5 min].

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[15] Additions of a hard-type counter anion, tetrafluoroborate, were reported to be effective for the alkylation reaction of glycinate Schiff bases with good reactivity and ee values in the case of TadiAs and Cinchona alkaloid derivative catalysts.[7b,14]

[16] The effects of iodide as a counter anion of guanidine on the ee values are not clear at this stage.
[17] When the reaction was performed in the presence of triethylamine instead of KOH in toluene (homogeneous conditions), the yield of **11a** was decreased to 13% (58% ee). In the case of the reaction under the base form of **1e** in toluene (homogeneous conditions), the reaction did not proceed.

