Diastereoselective Henry Reaction Catalyzed by Guanidine–Thiourea Bifunctional Organocatalyst

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Abstract: A highly diastereoselective Henry reaction (diastereomer ratio of 84:16 to 99:1) of α-substituted aldehydes with nitromethane was developed using guanidine–thiourea bifunctional catalyst **1**. *N*,*N*-Dibenzyl-protected α-amino aldehydes (**2a**, **2d**–**h**) and α-hydroxy aldehydes protected as silyl ethers (**2i**–**j**) were suitable substrates. The matched combination of this catalytic system, i.e., *S*-aldehydes and (*R*,*R*)-**1** catalyst, can be understood in terms of the transition state of the asymmetric version of the Henry reaction catalyzed by **1**.

Key words: bifunctional organocatalyst, guanidine, thiourea, Henry reaction, diastereoselective reaction

The Henry (nitroaldol) reaction is an important carbon–carbon bond forming reaction that affords valuable synthetic intermediates,[1] and controlling the newly generating stereochemistry of the Henry adducts continues to be a challenging issue.[2] However, the selectivity of the diastereoselective version of this reaction utilizing chiral aldehydes is usually moderate to low when an achiral catalyst or no catalyst is used.[3] The first diastereoselective catalytic Henry reaction of optically active amino aldehydes with nitromethane was reported by Shibasaki's group, utilizing chiral LLB (lanthanide–Li–BINOL) catalyst.[4] Corey and Zhang subsequently employed cinchona alkaloid derivatives (quaternary ammonium salts) as chiral catalysts for this reaction, which was utilized in the synthesis of the HIV protease inhibitor amprenavir.[5] Besides these catalysts, a guanidine-type chiral organocatalyst[6] has also been reported for enantioselective[6a,b] and/or diastereoselective Henry reaction.[6i] Ma et al. reported diastereoselective Henry reactions with moderate to high selectivity utilizing chiral guanidine catalysts.[6i] We recently have developed the guanidine-containing bifunctional organocatalyst **1**, which efficiently catalyzes the enantioselective Henry reaction (Figure 1).[6f] Herein, we describe a highly diastereoselective Henry reaction utilizing the guanidine–thiourea bifunctional organocatalyst **1**.

Based upon our recent success with asymmetric Henry reaction catalyzed by **1**,[6f] we applied this catalyst to the diastereoselective Henry reaction of optically active α-substituted aldehydes with nitromethane. First, the reaction of the *N*,*N*-dibenzyl-α-amino aldehyde **2a**[7] derived from (*S*)-phenylalanine with nitromethane was carried out in toluene–H_2O (1:1) at 0 °C using KOH (8 mol%) and KI (50 mol%) in the presence of (*R*,*R*)-**1** (10 mol%) to give the nitro alcohols *anti*-**3a** and *syn*-**4a** in a ratio of 95:5 with 75% yield (Table 1, entry 1).[8] In this case, the enantiomeric excess of **3a** was found to be 99%. On the other hand, the diastereoselectivity of **3a** and **4a** was only 64:36 with 8% yield, when the reaction was performed using (*S*,*S*)-**1** (entry 2).

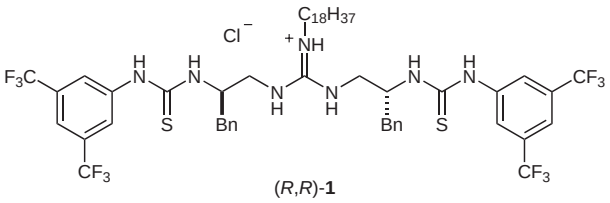
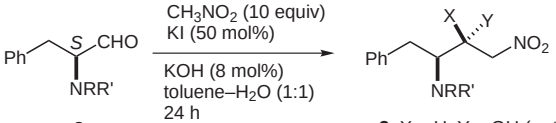


Figure 1 Structure of guanidine–thiourea bifunctional organocatalyst **1**

Table 1 Diastereoselective Henry Reaction of **2** and Nitromethane



2

3: X = H, Y = OH (*anti*)
4: X = OH, Y = H (*syn*)

Entry	Aldehyde	Catalyst **1**	Yield (%)	Ratio **3**:**4**[a]	ee of **3**, **4** (%)[b]
1	R = R′ = Bn (**2a**)	*R*,*R*	75	95:5	99, 85
2	**2a**	*S*,*S*	8	64:36	80, 62
3	R = H, R′ = Boc (**2b**)	*R*,*R*	70	50:50	20, 22
4	2b	*S*,*S*	67	50:50	20, 19
5	R = H, R′ = Cbz (**2c**)	*R*,*R*	70	50:50	25, 18
6	**2c**	*S*,*S*	68	50:50	28, 25

[a] The stereochemistry and diastereoselectivity of the products were determined by ^{1}H NMR.[5,]

[b] The ee values of the products were determined by HPLC using a chiral column.

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These results indicate that the combination of catalyst (*R*,*R*)-**1** and (*S*)-α-amino aldehyde is required to obtain a nitro alcohol with high diastereoselectivity. This is well explained by our previously proposed transition state for the asymmetric Henry reaction catalyzed by **1** (Figure 2). In our proposed transition state, the guanidine group of **1** coordinates nitromethane through ionic interactions,[9] and the thiourea group interacts with aldehyde, lowering the LUMO energy of the carbonyl group, which acts as a Brønsted acid.[10] In this case, the aldehyde R group favors the *anti* conformer rather than a gauche position (Figure 2, transition state **I**), and affords a nitro alcohol with high enantioselectivity.[6f] This transition state can be applied to the diastereoselective version of the Henry reaction, and the possible transition states of the combinations of *S*-aldehyde catalyst (*S*,*S*)-**1** and (*R*,*R*)-**1** are depicted in Figure 2, **II** and **III**, respectively. In the former combination (corresponding to the transition state **II**), there is steric interference between the phenyl group and the guanidine–nitromethane complex moiety. In contrast, no serious steric hindrance arises in the latter combination, i.e., *S*-aldehyde and catalyst (*R*,*R*)-**1**, which corresponds to the transition state **III**. Thus, the nitro alcohol **3a** is obtained with high selectivity and good yield. Moreover, no epimerization of the aldehyde **2a** occurred under these reaction conditions, and the enantiomeric excess of **3a** was 99% (Table 1, entry 1). Interestingly, no diastereoselectivity was observed when the protective group of the amine in α-amino aldehyde was changed to Boc or Cbz (Table 1, entries 3 and 5). The carbonyl group of the carbamate is thought to disrupt the coordination of the carbonyl group of the aldehyde to the catalyst **1**. Furthermore, aldehydes **2b** and **2c** are not stable under the reaction conditions, and epimerizations were observed in all cases (Table 1, entries 3–6).

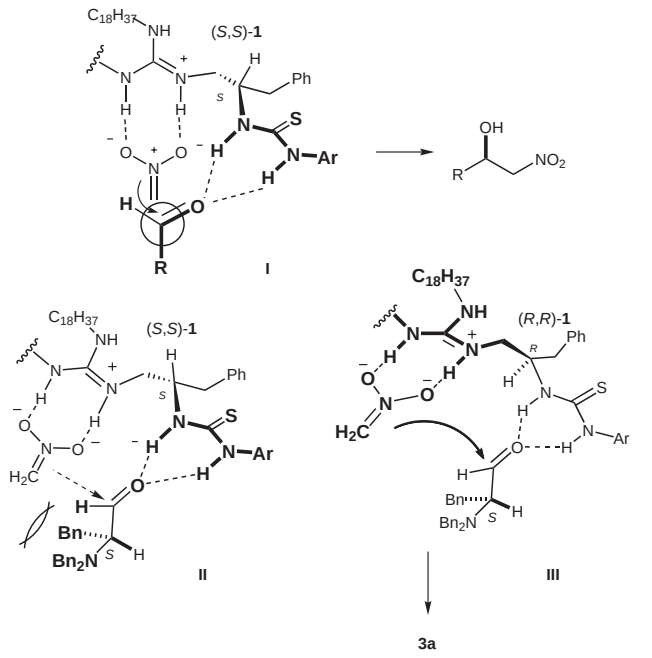
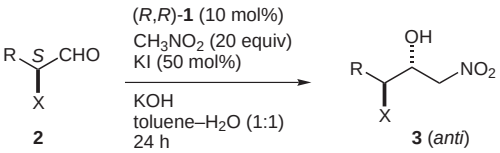
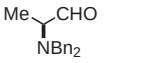
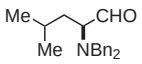
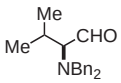
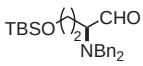
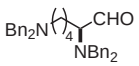
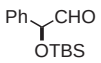
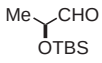


Figure 2 Proposed transition state of the Henry reaction catalyzed by **1**

Table 2 Diastereoselective Henry Reaction with Various Aldehydes



Entry	Aldehyde	KOH (mol%)	Product, yield (%)	Ratio *anti*:*syn*[a]	ee of **3** (%)[b]
1	 **2d**	20	**3d** (70)	99:1	99
2[c]	 **2e**	6	**3e** (70)	99:1	95
3[d]	 **2f**	10	**3f** (33)	99:1	99
4	 **2g**	10	**3g** (70)	99:1	95
5[c]	 **2h**	10	**3h** (62)	99:1	99
6	 **2i**	5	**3i** (82)	86:14	99
7	 **2j**	2	**3j** (80)	84:16	99

[a] The ratios (*anti*:*syn*) were determined by HPLC.
[b] The ee values were determined by HPLC using a chiral column.
[c] 10 equiv of nitromethane were used.
[d] 30 equiv of nitromethane were used.

The diastereoselective Henry reaction of various aldehydes **2d–j** catalyzed by (*R*,*R*)-**1** was explored, and the results are summarized in Table 2. In the case of *N*,*N*-dibenzyl α-amino aldehydes derived from the corresponding amino acids, *anti*-nitro alcohols **3d**–**h** were obtained with high diastereoselectivity (entries 1–5).[6i] However, the bulky β-branched aldehyde **2f** gave the alcohol **3f** in only 33% yield, although the selectivity was still high (entry 3). Reaction with α-substituted aldehydes **2i** and **2j** derived from (*S*)-mandelic acid and (*S*)-lactic acid also proceeded and gave the nitro alcohols **3i** and **3j** with good selectivity (84:16 to 86:14) and high yield (entries 6, 7).[11] In all cases, no epimerization of the aldehydes occurred under the reaction conditions.

In conclusion, a highly diastereoselective Henry reaction of α-substituted aldehydes and nitromethane was demonstrated utilizing the guanidine–thiourea bifunctional organocatalyst **1**. The differences of diastereoselectivity of α-substituted aldehydes **2** with (*R*,*R*)- and (*S*,*S*)-**1** can be consistently explained in terms of the previously proposed transition state for the asymmetric Henry reaction. Further applications of the guanidine–thiourea bifunctional catalyst **1** to a variety of reactions are in progress.

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(8) **Diastereoselective Henry Reaction of 2a with Nitromethane in the Presence of (*R*,*R*)-1.** To a mixture of (*R*,*R*)-**1** (8.4 mg, 0.0073 mmol), KI (6.0 mg, 0.037 mmol), **2a** (24.0 mg, 0.073 mmol) and nitromethane (392 μL, 0.73 mmol) in toluene (0.7 mL) was added 8 mM aq KOH (0.7 mL) at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 24 h. Then, sat. aq NH_4Cl was added, and the organic layer was extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane–EtOAc = 20:1, 10:1, 5:1, 1:0) to give **3a** (21.1 mg, 75%) and (*R*,*R*)-**1** (8.3 mg, 99% recovery). The relative stereochemistry and diastereoselectivity of **3a** (95:5) were determined based on the ^{1}H NMR spectra reported by Corey et al.[5] The enantiomeric excess of **3a** (99% ee) was determined by means of chiral HPLC analysis. [CHIRALCEL OJ-H, 0.46 cm (∅) × 25 cm (L), *n*-hexane–ethanol = 90:10, 1.0 mL/min, minor: 28.8 min, major: 31.3 min].
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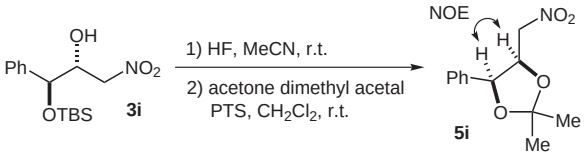
(11) The stereochemistry of **3i** was determined from the NOE of **5i**. The stereochemistry of **3j** was determined by comparison of the ^{1}H NMR spectrum with that of **3i** (Scheme 1).



Scheme 1