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Enantioselective Henry (nitroaldol) reaction catalyzed by axially chiral guanidines

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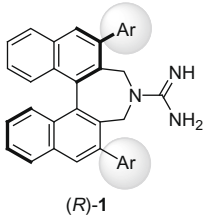
ABSTRACT

The enantioselective activation of nitroalkanes was attempted on the basis of the complexation between chiral guanidinium and nitronate through two hydrogen bonds. The proposed enantioselective activation was applied to the diastereo- and enantioselective Henry (nitroaldol) reaction of nitroalkanes with aldehydes using axially chiral guanidine bases as the catalyst. Optically active nitroaldol products were obtained in acceptable yields with fairly good enantio- and diastereoselectivities at low temperature.

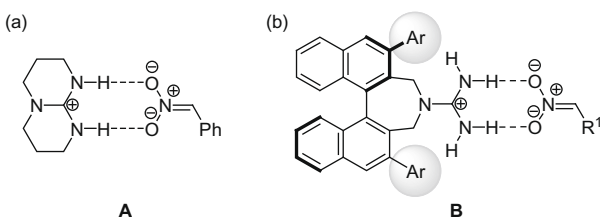
Organocatalysts have emerged as an efficient and powerful tool for accelerating organic transformations and tremendous effort has been devoted to the development of enantioselective transformations using these small organic molecules.[1] Enantioselective catalysis by chiral guanidines is one of the growing fields in organocatalytic approaches.[2] Several excellent studies on the development of chiral guanidine catalysts have been reported,[3,4] which take advantage of the strong basic character of guanidine derivatives coupled with their function as recognition moieties through hydrogen bonds.[5] In this context, we recently developed chiral guanidines **1** having a binaphthyl backbone as novel axially chiral Brønsted base catalysts for enantioselective transformations (Fig. 1).[4]

The guanidinium ion, the protonated form of guanidine, participates in numerous biological transformations and functions as an efficient recognition moiety of anionic substrates having carboxylate, phosphate, or nitrate functionalities through electrostatic interaction and the formation of two parallel hydrogen bonds.[6] Wynberg and co-workers reported that the bicyclic guanidine, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), deprotonates nitrotoluene to form tight ion pairs **A** with the nitronate anion through two hydrogen bonds (Fig. 2a).[7] Their structural elucidation of guanidinium nitronate **A** prompted us to investigate the activation of nitroalkanes **2** using axially chiral guanidines **1** (Fig. 2b). Deprotonation of nitroalkanes **2** by chiral guanidines **1** likely gives rise to ion pairs of chiral guanidinium nitronate **B** linked by two hydrogen bonds, where the nitronate anion generated is exposed to a chiral environment created by the substituents (Ar) introduced at the 3,3′-position of the axially chiral binaphthyl backbone. The resulting chiral guanidinium nitronate **B** would enable us to accomplish enantioselective transformations. For this purpose, we adopted the Henry (nitroaldol) reaction, which involves nitronates as the



(*R*)-**1**

Figure 1. Axially chiral guanidines **1** as enantioselective Brønsted base catalysts.



A **B**

Figure 2. Formation of guanidinium nitronate complex linked by two hydrogen bonds.

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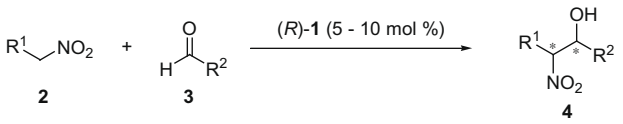
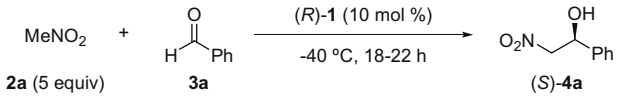
reactive intermediate. The Henry reaction is one of the most fundamental carbon–carbon bond forming reactions.[8] The development of enantioselective Henry reactions using chiral metal catalysts[9] or organocatalysts[10] has received considerable attention because the products can be transformed into a diverse array of optically active compounds via reduction to amines or Nef reaction to form carbonyl compounds. In the course of our continuing investigation aimed at developing enantioselective transformations using axially chiral guanidines **1**, we report herein the enantioselective Henry reaction of nitroalkanes **2** with aldehydes **3** catalyzed by **1** (Scheme 1).

We started by investigating the effect of substituent (Ar) of catalyst (*R*)-**1**. An initial exploration was performed in the reaction of nitromethane **2a** with benzaldehyde **3a** using 10 mol % of **1** in THF. As shown in Table 1, both enantioselectivity and catalytic activity were strongly dependent on the Ar substituents introduced at the 3,3′-position of the binaphthyl backbone (entries 1–9). Catalyst **1a** having the parent binaphthyl backbone furnished corresponding product **4a** in low yield with a nearly racemic product (entry 1). Introduction of a simple phenyl moiety to the 3,3′-position was ineffective in terms of enantioselectivity, although the catalytic activity was improved markedly (entry 2). Further substitution at the *para*-position of the phenyl moiety showed no improvement in enantioselectivities (entries 3 and 4). However, detectable asymmetric induction, even at a low level, was observed



Scheme 1. Enantio- and diastereoselective Henry reaction catalyzed by axially chiral guanidines **1**.

Table 1
Optimization of conditions for enantioselective Henry reaction catalyzed by axially chiral guanidines (*R*)-**1**[a]



Entry	**1** (Ar)	Solvent	Yield[b] (%)	ee[c] (%)
1	**1a**:H	THF	20	6[d]
2	**1b**:phenyl	THF	63	<2
3	**1c**:4-PhC_6H_4–	THF	81	2
4	**1d**:4-$CF_3C_6H_4$–	THF	73	2[d]
5	**1e**:2-naphthyl	THF	90	19
6	**1f**:3,5-$Ph_2C_6H_4$–	THF	84	17
7	**1g**:3,5-*t*-$Bu_2C_6H_3$–	THF	76	30
8	**1h**:3,5-$(CF_3)_2C_6H_3$–	THF	81	48
9	**1i**:3,5-$(C_4F_9)_2C_6H_3$–	THF	93	34
10	**1h**	Toluene	56	10[d]
11	**1h**	CH_2Cl_2	57	16
12	**1h**	Ether	87	22
13	**1h**	DME[e]	81	22
14[f]	**1h**	THF	77	67

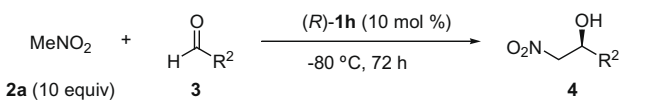
[a] Unless otherwise noted, all reactions were carried out using 0.02 mmol of **1** (10 mol %), 1.0 mmol of **2a** (5 equiv), and 0.2 mmol of **3a** at −40 °C for 18–22 h.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by chiral HPLC (DAICEL: Chiralcel OD–H) analysis. The absolute configuration was determined to be (*S*) by comparing with chiral HPLC data reported in the literature.[9b]
[d] The opposite enantiomer was obtained.
[e] DME: 1,2-dimethoxyethane.
[f] The reaction was carried out using 2.0 mmol of **2a** (10 equiv) at −80 °C for 72 h.

by introducing the bulkier 2-naphthyl substituent (entry 5). More sterically demanding phenyl groups having substituents at the 3,5-position had a beneficial effect on the enantioselectivity (entries 6–9). Among the substituents examined, the catalyst having 3,5-bis(trifluoromethyl)phenyl groups, that is, **1h**, was found to be the best in terms of both enantioselectivity and catalytic activity (entry 8).[11] Then, **1h** was employed as the catalyst of choice in the further screening for solvents (entries 10–13). Toluene and CH_2Cl_2 were not useful, giving **4a** in modest yields with low enantioselectivities (entries 10 and 11). In ethereal solvents, **1h** worked well to provide **4a** in good yields (entries 12 and 13), but the enantioselectivities did not surpass that observed in THF. Further optimization of the reaction conditions by lowering the reaction temperature increased enantioselectivity to 67% ee, although a prolonged reaction time was required (entry 14).[12]

With the optimal reaction conditions in hand, we next investigated the scope and limitations of the present enantioselective Henry reaction using **1h**. As shown in Table 2, marked substituent effects of aldehydes **3** were observed with respect to chemical yields and enantioselectivities. In the reaction of aromatic aldehydes (entries 1–4), the enantioselectivities were dependent not only on the electronic effect but also on the position to which the substituent was introduced. When electron-donating methyl group was introduced to the phenyl ring (entries 1 and 2), similar enantioselectivity to parent benzaldehyde **3a** was observed (see: Table 1, entry 14). In contrast, the introduction of electron-withdrawing bromide to the phenyl ring compromised the enantioselectivities (entries 3 and 4). In particular, a considerable decrease in enantioselectivity was observed in *ortho*-substituted aldehyde **3e** even though **4e** was obtained in high yield (entry 4). The reaction of alkyl-substituted aldehyde **3f** was also examined; however, it gave **4f** with modest enantioselectivity (entry 5).

We further investigated the diastereo- and enantioselective Henry reaction using nitroethane **2b**. Substituent effects of the Ar group of catalyst (*R*)-**1** as well as solvent effects were examined again to determine their influence on not only enantio- but also diastereoselectivities (Table 3). An initial investigation of the reaction of **2b** with benzaldehyde **3a** using 5 mol % **1** in THF was performed (entries 1–4). The substituent effects of the Ar group on the enantioselectivities exhibited a similar tendency to that observed in the reaction of nitromethane **2a** (entries 1–4 vs Table 1). Whereas the catalyst having 3,5-di-*tert*-butylphenyl groups, that is, **1g**, displayed high *anti*-selectivity (entry 3), the same level of diastereoselectivity was observed in other catalysts **1,** including the unsubstituted catalyst **1a** (entry 1 vs 2 or 4). In terms of enantioselectivity, **1h** was reconfirmed to be a superior catalyst in the present diastereo- and enantioselective reaction (entry 4) and was employed for the further optimization of the reaction conditions.[11] In the present diastereose-

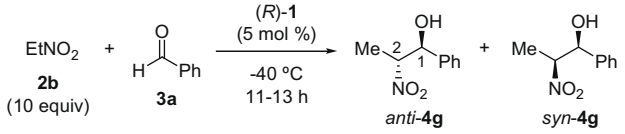
Table 2
Enantioselective Henry reaction of aldehydes **3** catalyzed by (*R*)-**1h**[a]



Entry	**3** (R^2)	**4**	Yield[b] (%)	ee[c] (%)
1	**3b**:4-MeC_6H_4–	**4b**	56	68
2	**3c**:2-MeC_6H_4–	**4c**	69	65
3	**3d**:4-BrC_6H_4–	**4d**	55	58
4	**3e**:2-BrC_6H_4–	**4e**	97	38
5	**3f**:PhCH_2CH_2–	**4f**	40	47

[a] All reactions were carried out using 0.02 mmol of **1** (10 mol %), 2.0 mmol of **2a** (10 equiv), and 0.2 mmol of **3** at −80 °C for 72 h.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis.

Table 3
Diastereo- and enantioselective Henry reaction of nitroethane **2b** with **3a** catalyzed by axially chiral guanidines (*R*)-**1**[a]



Entry	1	Solvent	Yield[b] (%)	*Anti*/*syn*[c]	ee for *anti*[c,d] (%)	ee for *syn*[c,e] (%)
1	**1a**	THF	62	78:22	5	5
2	**1c**	THF	95	80:20	2	30
3	**1g**	THF	99	89:11	28	31
4	**1h**	THF	99	79:21	57	68
5	**1h**	ether	99	76:24	53	55
6	**1h**	*t*-BuOMe	92	88:12	58	59
7[f]	**1h**	THF	72	79:21	78	87
8[f]	**1h**	*t*-BuOMe	49	87:13	77	70

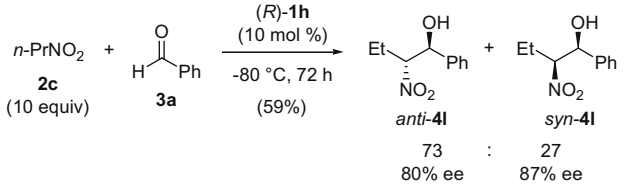
[a] Unless otherwise noted, all reactions were carried out using 0.01 mmol of **1** (5 mol %), 2.0 mmol of **2b** (10 equiv), and 0.2 mmol of **3a** at −40 °C for 11–13 h.
[b] Isolated yield.
[c] Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC (DAICEL: Chiralpak AD–H) analysis.
[d] The absolute configuration of *anti*-**4g** was determined to be (1*S*,2*R*) by comparing with analytical data reported in the literature.[10b]
[e] The absolute configuration of *syn*-**4g** was determined to be (1*S*,2*S*) by comparing with analytical data reported in the literature.[13]
[f] The reaction was carried out using 0.02 mmol of **1h** (10 mol %) at −80 °C for 65–70 h.

lective reaction, other ethereal solvents, diethyl ether and *t*-BuOMe, were also useful (entries 4–6). Similar enantioselectivity was observed in major *anti*-**4g**. Interestingly, the *anti*-selectivity increased when *t*-BuOMe was employed as solvent (entry 6). As expected, the enantioselectivities increased to 77–78% ee when the reaction temperature decreased to −80 °C, although the diastereoselectivity could not be improved at all (entries 4, 6 vs 7, 8).

Then, the scope and limitations of the diastereo- and enantioselective Henry reaction were investigated. A series of aromatic aldehydes **3** were employed in the reaction of nitroethane **2b** in THF. As shown in Table 4, electronic and positional effects of the substituents were observed similarly to the previous reactions of nitromethane **2a** (see Table 2). The introduction of electron-withdrawing bromide to aldehydes, that is, **3d** and **3e**, decreased the enantioselectivity (entries 3 and 4), while substitution with an electron-donating methyl group resulted in enantioselectivity that was comparable to that observed in parent benzaldehyde **3a** (entry 1 vs Table 3, entry 7). In contrast, diastereoselectivity was influenced by the position to which the substituent was introduced. Aldehydes having a substituent at the *ortho*-position exhibited higher *anti*-selectivities (entries 2 and 4). In particular, high *anti*-selectivity (94% *anti*) was achieved by the methyl substituent albeit its modest enantioselectivity (entry 2).

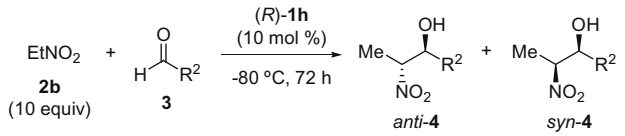
Finally, we investigated the catalytic reaction of nitropropane **2c** (Scheme 2). Corresponding product **4l** was obtained in acceptable yield with diastereo- and enantioselectivity similar to that observed in the reaction of nitroethane **2b**.

On the basis of experimental results coupled with the formation of chiral guanidinium nitronate complex **B** via two hydrogen bonds (see Fig. 2), a plausible transition state for the present catalytic reaction is depicted in Figure 3. By taking into account the *anti*-selectivity observed, the reaction would proceed via an acyclic extended transition state.[10b] Under the acyclic transition state mechanism, orientation of the substituent (R^2) of aldehyde would



Scheme 2. Enantio- and diastereoselective Henry reaction of nitropropane **2c** catalyzed by (*R*)-**1h**.

Table 4
Diastereo- and enantioselective Henry reaction of nitroethane **2b** with aldehydes **3** catalyzed by (*R*)-**1h**[a]



Entry	**3** (R^2)	**4**	Yield[b] (%)	*Anti*/*syn*[c]	ee for *anti*[c] (%)	ee for *syn*[c] (%)
1	**3b**:4-MeC_6H_4–	**4h**	56	76:24	81	89
2	**3c**:2-MeC_6H_4–	**4i**	75	94:6	69	74
3	**3d**:4-BrC_6H_4–	**4j**	81	80:20	58	57
4	**3e**:2-BrC_6H_4–	**4k**	66	87:13	56	10

[a] All reactions were carried out using 0.02 mmol of **1h** (10 mol %), 2.0 mmol of **2b** (10 equiv), and 0.2 mmol of **3a** at -80 °C for 72 h.
[b] Isolated yield.
[c] Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC analysis.

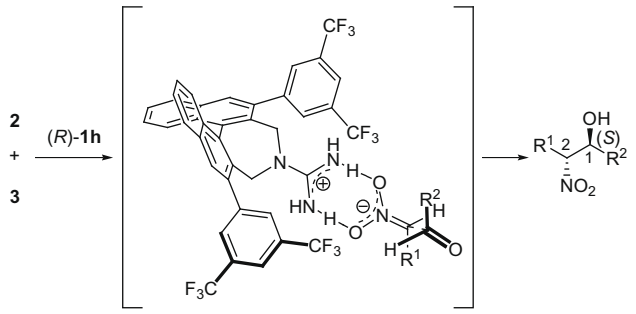


Figure 3. Plausible transition state model.

be regulated by the substituent (R^1) of nitronate to avoid steric repulsion between these two substituents. Judging from the absolute configuration of the product, the steric bulkiness of 3,5-bis(trifluoromethyl)phenyl substituents introduced at the 3,3′-position of the binaphthyl backbone would induce the direct attack of aldehyde onto *si*-face, establishing the (*S*)-configuration at C1 position, where the 3,5-bistrifluoromethylphenyl group and the substituent (R^2) of aldehyde occupy the position to eliminate unfavorable steric interaction.

In conclusion, we have demonstrated the diastereo- and enantioselective Henry reaction of nitroalkanes with aldehydes using axially chiral guanidine catalysts on the basis of the complexation between chiral guanidinium and nitronate through two hydrogen bonds. Optically active products were obtained in acceptable yields with fairly good enantio- and diastereoselectivities at low temperature. Further studies are in progress to develop efficient enantioselective transformations based on the enantioselective activation of nitroalkanes by axially chiral guanidines.

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11. During the course of the catalytic reaction, no epimerization occurred at the stereogenic center.
12. *Experimental procedure:* To a dry test tube was added 15.2 mg of catalyst (*R*)-**1h** (10 mol %, 0.02 mmol) and the atmosphere was replaced with nitrogen. The catalyst was dissolved in 1.0 mL of THF. 20.3 μL of benzaldehyde **3a** (0.2 mmol) and 108 μL of nitromethane **2a** (10 equiv, 2.0 mmol) were introduced at −80 °C. The resulting solution was stirred for 72 h. The reaction mixture was poured onto silica gel column and purified by column chromatography (Et_2O/*n*-hexane = 1:10–1:1) to give **4a**[9b] as a colorless oil in 77% yield. HPLC analysis Chiralcel OD–H (*n*-hexane/*i*-PrOH, 90:10, 1.0 mL/min, 230 nm, 10 °C) t_R = 15.9 min (minor), 20.2 min (major); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.82 (1H, br s), 4.54 (1H, dd, *J* = 13.4, 3.2 Hz), 4.62 (1H, dd, *J* = 13.4, 9.2 Hz), 5.48 (1H, dd, *J* = 9.2, 3.2 Hz), 7.33–7.45 (5H, m).
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