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Diastereoselective Henry reactions of *N*,*N*-dibenzyl α-amino aldehydes with nitromethane catalyzed by enantiopure guanidines

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Abstract—Several enantiopure guanidines are studied as the catalysts of Henry reactions of *N*,*N*-dibenzyl α-amino aldehydes with nitromethane. Good diastereoselectivity is observed in the reactions of L-valine or L-isoleucine derived aldehydes catalyzed by a (*R*)-1-(1-naphthyl)ethylamine derived guanidine. © 2002 Elsevier Science Ltd. All rights reserved.

The Henry reaction[1] of enantiopure *N*-protected α-amino aldehydes with nitromethane provides 3-amino-2-hydroxy-1-nitro derivatives. They are readily converted into pharmacologically important molecules such as the anti-HIV drug amprenavir[2] as well as α-hydroxyl β-aminoacids, a valuable backbone of peptide mimetics.[3] It was reported that the diastereoselectivity of this reaction was poor when achiral catalysts were used.[2a,4] In order to overcome this drawback, two chiral catalysts including a rare earth–Li-(*R*)–BINOL complex[2b] and a rigid chiral quaternary ammonium salt[2a] were explored and improved diastereoselectivity was observed. However, the former catalyst system suffered from inconvenient operation whilst the latter still gave unsatisfactory diastereoselectivity. Thus, other catalyst systems are still needed.

As a class of asymmetric catalysts, enantiopure guanidines have advantages in convenient reaction operation and efficient catalyst recycling. The potential of this type of catalyst has received considerable attention recently.[5] In connection with our efforts on the development of chiral guanidine catalyzed reactions,[5c] we have synthesized a group of enantiopure guanidines with diversity as shown in Fig. 1. The compounds, except for **1g** and **1h**, were assembled from the corresponding enantiopure monoamines or diamines via direct reaction with BrCN.[6] The guanidine **1g** was obtained from the reaction of the corresponding primary amine with *N*,*N*-di-Boc-triflylguanidine[7] followed by deprotection, whilst **1h** was prepared according to a known procedure.[2b] After screening these guanidines for Henry reactions of enantiopure *N*,*N*-dibenzyl α-amino aldehydes[8] with nitromethane, we found that some of them induced these reactions in a highly diastereoselective manner. Herein we wish to report our results.

As shown in Table 1, the reaction of the α-amino aldehyde **2a** derived from (*S*)-phenylalanine with nitromethane was carried out in toluene at −20°C using 10 mol% of the guanidine **1a** as catalyst to provide **3a** and its 2-epimer **4a** in 96% yield. The ratio of **3a**:**4a** was about 4.8:1 (entry 1). The stereochemistry of **3a** and **4a** was assigned by comparison of their ^{1}H NMR data with those reported.[2a] Using the guanidine **1b** gave a slightly improved result (entry 2). The absolute configurations of the guanidines obviously influenced the diastereoselectivity because the (*R*,*R*)-guanidine **1i** showed a higher preference towards **3a** than (*S*,*S*)-guanidine **1j** (compare entries 9 and 10). This result also implied that the chiralities of both catalyst and substrate influenced the asymmetric induction. Further attempts to increase the diastereoselectivity by utilizing guanidines **1c**–**f** derived from different primary monoamines were found to give similar results (entries 3–6). The best selectivity was obtained when the bicyclic guanidine **1h** was used. However, a different diastereoselectivity pattern was observed when the substrate was switched to the amino aldehyde **2b**. In this case the best result (92% de) was obtained when the (*R*)-1-(1-naphthyl)ethylamine derived guanidine **1d** was employed as the catalyst (entry 14). The other similar catalysts (**1c**, **1e** and **1f**) gave considerably lower

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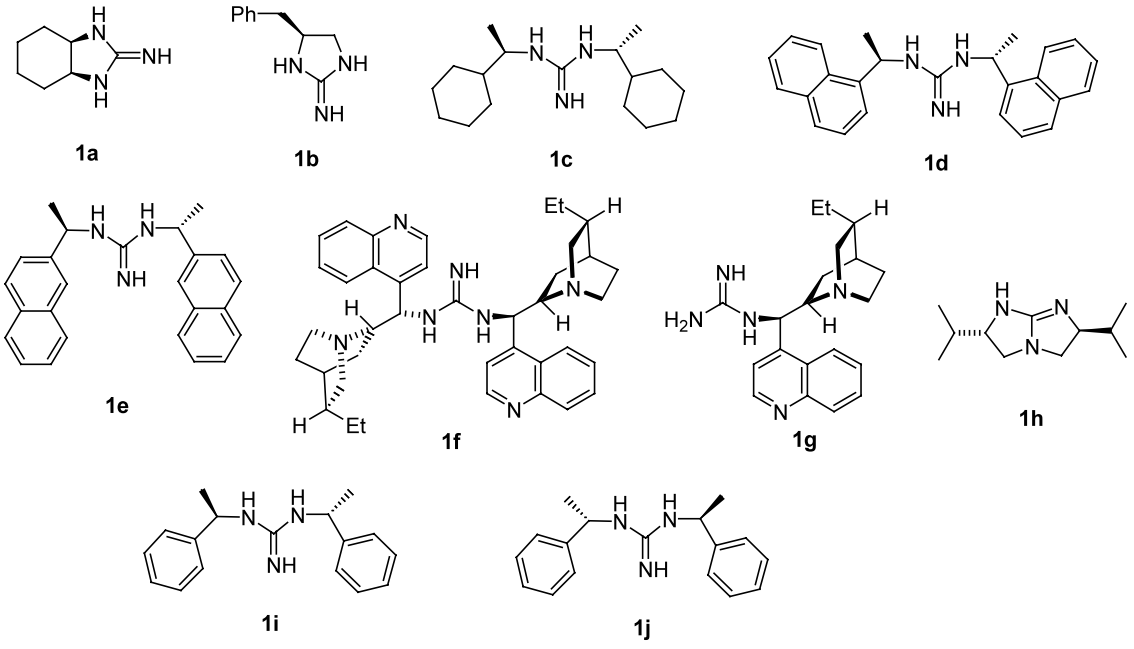
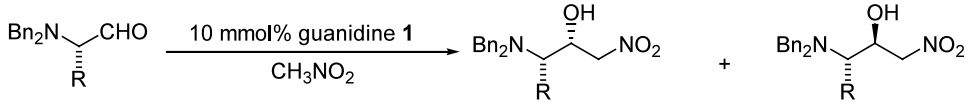


Figure 1.

Table 1. Henry reactions of aldehydes **2** with nitromethane catalyzed by various enantiopure guanidines[a]



Guanidine	2a				2b			
	Entry	Time (h)	Yield (%)[b]	**3a**:**4a**[c]	Entry	Time (h)	Yield (%)[b]	**3b**:**4b**[c]
1a	1	10	96	4.8:1	11	48	96	8.7:1
1b	2	20	75	6:1	12	48	72	17:1
1c	3	10	95	6.2:1	13	48	85	13.7:1
1d	4	15	95	6.7:1	14	48	92	24.1:1
1e	5	20	92	6.4:1	15	48	85	15:1
1f	6	20	92	6.6:1	16	48	70	13.6:1
1g	7	10	95	5.9:1	17	48	90	13.9:1
1h	8	20	92	8.8:1	18	48	87	17.2:1
1i	9	15	92	6.1:1				
1j	10	15	93	3.9:1				
TMG	19	4	97	2.9:1				

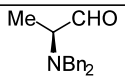
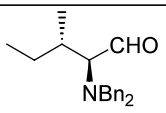
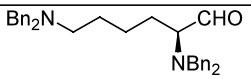
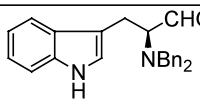
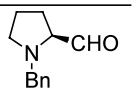
[a] Reaction conditions: α-amino aldehyde (1 mmol), nitromethane (10 mmol), guanidine (0.1 mmol) in 2 mL of toluene, −20°C.
[b] Isolated yield.
[c] Determined by HPLC.

diastereoselectivity (compare entries 14 with 13, 15, and 16). Enantiopure guanidines were essential for improvement of the diastereoselectivity of the present reaction because tetramethylguanidine (TMG) provided a poor result (entry 19).

Considering the fact that guanidine **1d** showed better asymmetric inducing ability in the above two reactions, we chose it as a catalyst to investigate other reactions of α-amino aldehydes. As summarized in Table 2, the diastereoselectivity was still highly dependent on the substrates. When the L-isoleucine derived aldehyde was used as the substrate, good diastereoselectivity (91%) was observed. Other substrates provided moderate or poor (for the L-proline derived aldehyde) diastereoselectivity.

In conclusion, we have demonstrated that some enantiopure guanidines are effective catalysts for the diastereoselective Henry reaction of α-amino aldehydes

Table 2. Guanidine **1d** catalyzed Henry reactions[a]

Substrate					
time (h)	8	48	48	48	10
yield (%)[b]	93	85	93	85	95
de[c]	75.4	90.9	78.0	76.0	32.4

[a] Reaction conditions: α-amino aldehyde (1 mmol), nitromethane (10 mmol), guanidine (0.1 mmol) in 2 mL of toluene, –20°C.
[b] Isolated yield.
[c] Determined by HPLC.

and nitromethane. Although in many cases these catalysts only gave moderate diastereoselectivity, the good results observed in some cases indicated that the present catalysts provide an efficient, alternative catalyst system for this important reaction.[9] Further improvement utilizing other guanidine catalysts is in progress.

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