Modified guanidines as chiral superbases: application to asymmetric Michael reaction of glycine imine with acrylate or its related compounds

Tsutomu Ishikawa,*[a] Yukari Araki,[a] Takuya Kumamoto,[a] Hiroko Seki,[b] Keiko Fukuda[c] and Toshio Isobe[ac]

[a] *Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi, Inage, Chiba 263-8522, Japan*
[b] *Chemical Analysis Center, Chiba University, 1-33 Yayoi, Inage, Chiba 263-8522, Japan*
[c] *Central Research Laboratory, Shiratori Pharmaceutical Co. Ltd., 6-11-24 Tsudanuma, Narashino, Chiba 275-0016, Japan*

Received (in Cambridge, UK) 16th November 2000, Accepted 13th December 2000
First published as an Advance Article on the web 18th January 2001

Modified guanidines efficiently catalysed the asymmetric Michael reaction of a prochiral glycine derivative with acrylate or its related compounds either in solution or without a solvent under simple and mild conditions (> 95% ee).

Guanidines can be characterized as superbases[1] in organic synthesis due to their strong basicity.[2] We have explored the possibility of readily available modified guanidines[3] as re-useable chiral superbases in asymmetric synthesis.[4] Glycine imines are used as chiral templates for asymmetric synthesis of α-amino acids, in which enantioselective phase-transfer alkylation with alkyl halides has been established as a general method.[5] Ma and Cheng[6] attempted a conjugate addition of glycine imines with vinyl carbonyl compounds in the presence of C_2-symmetrical linear-type guanidines in place of phase-transfer catalysts;[7] however, the best ee observed by them was up to 30%. Re-examination of the Michael reaction using our modified guanidines under various conditions led to effective asymmetric induction (> 95% ee) when **4** (or **ent-4**, Fig. 1) was used as a catalyst either in solution or without a solvent. In this communication we present the utility of modified guanidines as clean chiral superbases in an asymmetric Michael reaction under simple and mild reaction conditions.

According to the reported conditions[6] we preliminarily examined the Michael reaction of *tert*-butyl diphenyliminoacetate (**1**) (1 equiv.) and ethyl acrylate (**2a**) (3.6 equiv.) in THF (0.26 mmol ml^{-1}) in the presence of 20 mol% of four different types of chiral guanidines **4**,[4] **5**,[3c] **6**,[3c] and **7**[3b] at 20 °C for about one week. Reasonable asymmetric induction (79% ee) was observed only in the case of **4** among the guanidines examined, albeit the chemical conversion was low (15%), in which an (*R*)-excess adduct **3a**[6] was yielded (see Table 1, run 1). In other cases, the reaction did not proceed. However, the guanidines used in these reactions were completely recovered in re-useable forms by chromatographic separation. These results led us to further examine the reaction using **4** under various conditions. Although a stoichiometric reaction in THF slightly increased the yield [34% yield (77% ee)], changing THF to other solvents in the catalytic reaction resulted in no improvement of the reaction rate although high enantioselectivities were maintained [9% yield (84% ee) in chloroform; 4% yield (73% ee) in toluene] except in ethanol [7% yield (42% ee)].

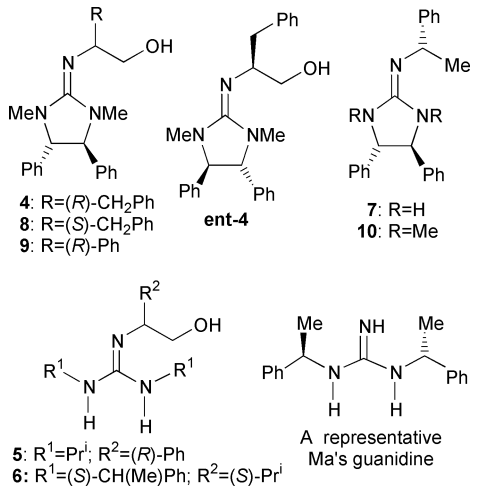
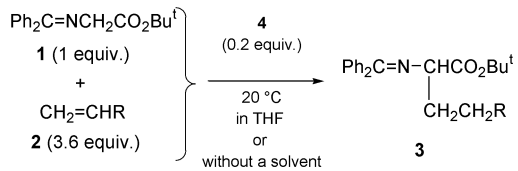


Fig. 1

We next examined the guanidine-catalysed Michael reaction of **1** with methyl vinyl ketone (MVK)[8] (**2b**) and acrylonitrile (**2c**) as a Michael acceptor in place of **2a** under the same conditions. The former reaction smoothly proceeded to afford an adduct **3b** in 90% yield, in which high enantioselectivity (96% ee) was observed (Table 1, run 2), whereas the starting **1** was completely recovered when **2c** was used (Table 1, run 3). These facts suggested that **4** could lead to effective asymmetric induction with the use of reactive Michael acceptors.

Solvent-free reactions,[9] in which rate acceleration is generally observed, have attracted much attention from the ecological point of view. Thus, **1** was treated with **2a** without a

Table 1 Guanidine-catalysed Michael reaction of **1** and **2** using **4** either in THF or without a solvent

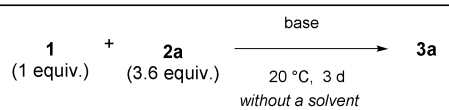


				3		
Run	Solvent	**2** (R)	Time	Yield[a] (%)	Ee (%)	Conf.[b]
1	THF	**a** (CO_2Et)	7 d	15	79[c]	*R*
2		**b** (COMe)	6 d[e]	90	96[f]	(*R*)
3		**c** (CN)	5 d	NR[g]	—	—
4	Without a solvent	**a** (CO_2Et)	3 d	85 (100)	97[c]	*R*
5		**b** (COMe)	15 h	90 (100)	80[f]	(*R*)
6		**c** (CN)	5 d	79 (100)	55[h]	(*R*)
7		**d** (CO_2Me)	3 d	98 (100)	93[i]	(*R*)

[a] Isolated, non-optimized yields. Parentheses show estimation of the product by ^{1}H NMR spectra. [b] Configuration of an excess enantiomer. Parentheses show the expected absolute configuration. [c] The (*R*)- and (*S*)-enantiomers were observed at retention times of 7.2 and 9.3 min, respectively, in HPLC using CHIRALCEL OD (Daicel Co. Ltd.,) under the following conditions; eluent: *n*-hexane–isopropanol = 100 : 1, flow rate: 1.0 ml min^{-1}, detection: 254 nm. [d] Reactions were carried out in 0.26 mmol ml^{-1} concentration of **1** in THF. [e] The adduct **3b** with the same ee was given in 40% yield after 15 h. [f] The (*R*)- and (*S*)-enantiomers were observed at retention times of 11.0 and 15.8 min, respectively, in the same HPLC as **3b**. [g] No reaction. [h] The (*R*)- and (*S*)-enantiomers were observed at retention times of 12.0 and 16.7 min, respectively, the same HPLC as **3b**. [i] The (*R*)- and (*S*)-enantiomers were observed at retention times of 6.5 and 7.3 min, respectively, in the same HPLC as **3b**.

DOI: 10.1039/b009193f

Table 2 Examination of solvent-free asymmetric Michael reaction of **1** with **2a** using various bases



		3a		
Run	Base (mol%)	Yield[a] (%)	Ee (%)[b]	Conf.[c]
1[d]	**4** (20)	85 (100)	97	*R*
2	**4** (5)	40	97	*R*
3	None	NR[e]	—	—
4	(−)-Quinine (20)	NR[e]	—	—
5	**ent-4** (20)	87 (100)	97	*S*
6	**8** (20)	8 (17)	53	*S*
7	**9** (20)	17 (35)	91	*R*
8	**10** (20)	NR[e]	—	—

[a] Isolated, non-optimized yields. Parentheses show estimation of the product by ^{1}H NMR spectra. [b] See footnote *d* in Table 1. [c] Configuration of an excess enantiomer. [d] The data in Table 1, entry 4. [e] No reaction.

solvent (Table 1, run 4). A heterogeneous mixture of the two components containing **4** was simply stirred at 20 °C for 3 d.[10] Interestingly, both product formation and enantioselectivity were dramatically improved to give an (*R*)-excess **3a** with 97% ee in quantitative yield. Similarly, remarkable rate acceleration was observed on two other Michael acceptors **2b** and **2c**. In the former case (Table 1, run 5), reaction was completed after 15 h, in which relatively high enantioselctivity (80% ee) was kept. On the other hand, in the latter case (Table 1, run 6), **1** disappeared after 5 days to afford **3c** with 55% *ee* in spite of no reaction in solution (see Table 1, run 3). In addition, as expected, the use of methyl acrylate (**2d**) as a Michael acceptor led to the same satisfactory results obtained with **2a** (Table 1, run 7).

Thus, as a solvent-free reaction seems to be generally effective in the guanidine-catalysed Michael reaction of **1**, optimization was tried using **2a** as a Michael acceptor (Table 2). The same high *ee* was achieved even on reduction of the catalyst amount, albeit with lower chemical conversion (Table 2, run 2). No reaction was observed in the absence of a guanidine or in the presence of (−)-quinine (Table 2, runs 3 and 4). These facts indicated that **4** effectively catalysed the solvent-free reaction of **1** with **2a** in 20 mol% concentration.

The use of **ent-4**,[11] as expected, afforded an (*S*)-excess **3a** in quantitative yield with the same high enantioselectivity (Table 2, run 5). The (*S*)-excess **3a** was also obtained when **8**,[3a] a diastereomer of **4**, was used as a catalyst, but both chemical yield and asymmetric induction were lowered considerably (Table 2, run 6). Replacement of an (*R*)-phenylalaninol unit in **4** to an (*R*)-phenylglycinol one in **9**[3a] afforded an (*R*)-excess **3a** with relatively high selectivity. However, chemical conversion was not good (Table 2, run 7). On the other hand, the use of a guanidine **10**[4] lacking a hydroxyethyl function resulted in no reaction (Table 2, run 8).

Experimental evidence obtained in the above solvent-free reactions could be summarised as follows: (i) satisfactory chemical conversion with high enantioselectivity in the use of HOC_2H_4-substituted cyclic guanidines with (4*S*,5*S*,1′*R* or 4*R*,5*R*,1′*S*) configuration such as **4** indicates that the relative configurations of these three chiral centers are very important for effective asymmetric induction in addition to rate acceleration; (ii) predominant production of (*R*)-**3a** with **4** and **9** [or (*S*)-**3a** with **ent-4** and **8**] shows that a stereogenic center of the adduct should be strictly reflected by the chirality of a substituent at the external nitrogen; (iii) if the enolate of **1** could be formed by action of **4**, its *re*-face should be attacked by **2a** to yield an (*R*)-excess **3a**, for which the opposite *si*-face is severely blocked by the guanidine unit as shown in Fig. 2; (iv) although the absolute configuration of an excess enantiomer obtained in each reaction of **1** with **2b**, **2c** or **2d** has not been determined, an (*R*)-excess **3b**, **3c** or **3d** should be given in the reaction using **4**

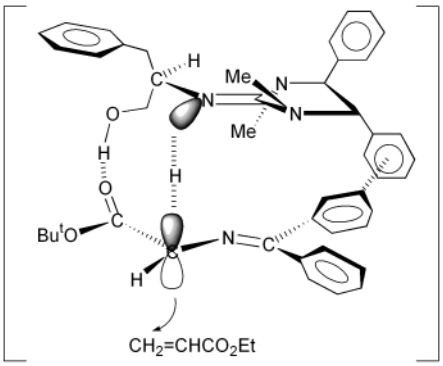


Fig. 2

due to the same face differentiation mentioned above, even in solution.

In summary, it was found that modified guanidines efficiently catalysed the asymmetric Michael reaction of a prochiral glycine derivative with vinyl compounds either in solution or without a solvent under simple and mild conditions. These guanidine-catalysed asymmetric Michael reactions[12] could contribute to development of green chemistry,[13] because modified guanidines are considered to be re-useable (economically favored) and easily functionalizable (widely applicable) artificial organic bases.

Notes and references

1 M. Costa, G. P. Chiusoli, D. Taffurelli and G. Dalmonego, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1541.

2 Y. Yamamoto and S. Kojima, in *The Chemistry of Amidines and Imidates*, Vol. 2, eds, S. Patai and Z. Rappoport, John Wiley and Sons Inc., New York, 1991, pp. 485.

3 (*a*) T. Isobe, K. Fukuda and T. Ishikawa, *J. Org. Chem.*, 2000, **65**, 7770; (*b*) T. Isobe, K. Fukuda, T. Tokunaga, H. Seki, K. Yamaguchi and T. Ishikawa, *J. Org. Chem.*, 2000, **65**, 7774; (*c*) T. Isobe, K. Fukuda, K. Yamaguchi, H. Seki, T. Tokunaga and T. Ishikawa, *J. Org. Chem.*, 2000, **65**, 7779.

4 T. Isobe, K. Fukuda and T. Ishikawa, *Tetrahedron: Asymmetry*, 1998, **9**, 1729.

5 For the early work, see: M. J. O'Donnell, W. D. Bennett and S. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 2353; M. J. O'Donnell, I. A. Esikova, A. Mi, D. F. Shullenberger and S. Wu in *Phase-Transfer Catalysis* (ACS Symposium Series 659), ed. M. E. Halpern, ACS, Washington D. C., 1997, Chapter 10; B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1997, **38**, 8595. For recent work, see: A. Nelson, *Angew. Chem., Int. Ed.*, 1999, **38**, 1583; J. Ezquerra, C. Pedregal, I. Merino, J. Florez, J. Barluenga, S. G.-Granda and M.-A. Llorea, *J. Org. Chem.*, 1999, **64**, 6554; T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 1999, **121**, 6519; T. Abellan, R. Chinchilla, N. Galindo, G. Guillena, C. Najera and J. M. Sansano, *Eur. J. Org. Chem.*, 2000, 2689.

6 D. Ma and K. Cheng, *Tetrahedron: Asymmetry*, 1999, **10**, 713.

7 Corey *et al*. reported the quaternary ammonium salt-catalysed asymmetric Michael reaction: E. J. Corey, M. C. Noe and F. Xu, *Tetrahedron Lett.*, 1998, **39**, 5347; F.-Y. Zhang and E. J. Corey, *Org. Lett.*, 2000, **2**, 1097.

8 Although Ma and Cheng[6] had also tried the Michael reaction of **1** with **2b**, the enantioselectivity was quite low (16.5% ee).

9 For examples, see: K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025; V. K. Aggarwal and A. Mereu, *Chem. Commun.*, 2000, 2310; J. O. Metzger, *Angew. Chem., Int. Ed.*, 1998, **37**, 2975.

10 A heterogeneous mixture turned into a homogeneous one after completion of the reaction.

11 The guanidine was prepared from (*R*,*R*)-1,2-diphenylethylenediamine according to the reported method.[4]

12 Some guanidines have been applied to asymmetric Michael reactions as chiral bases, however low or no enantioselectivity had been observed in the guanidine-catalysed reactions, see: V. Alcazar, J. R. Moran and J. deMendoza, *Tetrahedron Lett.*, 1995, **36**, 3941; A. Howard-Jones, P. J. Murphy, D. A. Thomas and P. W. R. Caulkett, *J. Org. Chem.*, 1999, **64**, 1039. During our research works an effective Strecker reaction catalysed by a C_2-symmetrical bicyclic guanidine was reported in spite of the reaction in solution: E. J. Corey and M. J. Grogan, *Org. Lett.*, 1999, **1**, 157.

13 P. T. Anastas and J. C. Warner in *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998.