

Published on Web 01/11/2006

Axially Chiral Guanidine as Enantioselective Base Catalyst for 1,4-Addition Reaction of 1,3-Dicarbonyl Compounds with Conjugated Nitroalkenes

Masahiro Terada,* Hitoshi Ube, and Yusuke Yaguchi

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

Received November 18, 2005; E-mail: mterada@mail.tains.tohoku.ac.jp

Guanidine is a ubiquitous element in natural products and plays a key role in many biological activities. In peptides, guanidine, a residue of arginine, exists in the protonated form as a guanidinium ion, which functions as an efficient recognition moiety of anionic functionalities, such as carboxylate, phosphate, and nitronate, through double hydrogen bonds.¹ In addition to their biological roles, guanidine derivatives are widely utilized in synthetic organic chemistry as strong bases.² It is anticipated that the strong basic character of guanidine derivatives coupled with their ability to act as recognition elements will lend them to application as asymmetric base catalysts. Indeed, chiral guanidine catalysts are attractive targets³ in organocatalysis, a research topic of increasing interest.⁴ However, enantioselective catalysis using chiral guanidine bases has faced limited success.⁵ One major and intrinsic problem in the development of guanidine as an efficient chiral catalyst is its planar and hence highly symmetric structure. To overcome this structural drawback, a general approach to constructing chiral guanidine catalysts is to introduce a mono-to-polycyclic system composed of five- and/or six-membered rings with central chiralities.^{3,5,6} We present herein a new strategy for designing chiral guanidine molecules (1) as efficient organocatalysts, which features the introduction of an axially chiral binaphthyl backbone (eq 1).⁷ It is expected that the substituents (Ar) at the 3,3'-positions of the binaphthyl ring would unequivocally break the planar symmetry of the guanidine skeleton to create an efficient chiral environment for asymmetric organic transformations. To evaluate the catalytic efficiency of axially chiral guanidine (1) as an enantioselective base catalyst, we investigated the 1,4-addition of 1,3-dicarbonyl compounds (3) to conjugated nitroalkenes (2) (eq 1) because several enantioselective catalytic approaches were reported thus far,^{8,9} and hence this reaction seems to be appropriate to prove the potential of 1. Herein we report novel axially chiral guanidine (1) as a highly active and enantioselective organocatalyst for the 1,4-addition reactions.



We initially examined the effect of the Ar substituents introduced at the 3,3'-positions of the binaphthyl ring of **1**. The reaction of β -nitrostyrene (**2**; R¹ = C₆H₅-) with dimethyl malonate (**3a**) was performed using 2 mol % of (*R*)-**1** in diethyl ether at 0 °C. As shown in Table 1, it is noteworthy that not only the steric demand of the Ar substituents but also their electronic nature had a

Table 1.	1,4-Addition	Reaction o	f Conjugated	d Nitroalkene	(2; R
$= C_6 H_5 -)$) with Dialkyl	Malonates	Catalyzed b	y Various Ax	ially
Chiral Gu	anidines (1)	1	-		

entry	1	3 ^b	4	timec	ee (%) ^d
1	1a : Ar = C_6H_5- , G = <i>n</i> -Pr	3a	4a	2 h	19
2	1b : Ar = 4 -CF ₃ C ₆ H ₄ -, G = <i>n</i> -Pr	3a	4a	12 h	33
3	1c: $Ar = 3,5-(CF_3)_2C_6H_3-, G = n-Pr$	3a	4a	24 h ^e	47
4	1d : Ar = 4 - <i>t</i> -BuC ₆ H ₄ -, G = <i>n</i> -Pr	3a	4a	1.5 h	36
5	1e : $Ar = 4 - t - BuC_6H_4 - , G = Me$	3a	4a	1 h	61
6	1f : $Ar = 3,5-Ph_2C_6H_3-, G = Me$	3a	4a	50 min	80
7	1g : $Ar = 3,5-t-Bu_2C_6H_3-, G = Me$	3a	4a	15 min	81
8	$1h^{f} Ar = 3,5-(DBP)_2C_6H_3-, G = Me$	3a	4a	10 min	91
9	1h	3b	4b	20 min	85
10	1h	3c	4c	24 h ^g	57
11^{h}	1h	3a	4a	2 h	96
12^{h}	1h	3b	4b	2 h	92
13 ⁱ	1h	3a	4a	2 h	96

^{*a*} Unless otherwise noted, all reactions were carried out with 0.002 mmol of (*R*)-1 (2 mol %), 0.1 mmol of 2 ($\mathbb{R}^1 = \mathbb{P}h$), and 0.5 mmol of 3 (5 equiv) in 1 mL of diethyl ether at 0 °C. ^{*b*} 3a, dimethyl malonate; 3b, diethyl malonate; 3c, diisopropyl malonate. ^{*c*} Time required for completion of the reaction. ^{*d*} Enantiomeric excess was determined by chiral HPLC analysis. Absolute configuration was determined to be *R* for 4a-c. See Supporting Information for details. ^{*e*} 4a was obtained in 34% yield after 24 h. ^{*i*} DBP = 3,5-di-*tert*-butylphenyl. ^{*s*} 4c was obtained in 68% yield after 24 h. ^{*h*} The reaction was performed at -40 °C. ^{*i*} The reaction was carried out with 0.15 mmol of 3a (1.5 equiv) at -40 °C.

prominent effect on both catalytic activity and enantioselectivity. Whereas catalysts 1b and 1c with the electron-withdrawing group CF₃ proved to be poor in terms of turnover frequency, the introduction of the electron-donating group tert-butyl at the paraposition, 1d, exhibited a positive effect (entries 1-4). The substituent G attached to the guanidine nitrogen atom also had a strong impact on the enantioselectivity (entry 4 vs 5); introduction of the less sterically hindered methyl substituent led to a marked improvement in enantioselectivity. Further modification of the phenyl ring at the 3,5-positions (1f,g,h) was the most effective, affording product (4a) in high enantioselectivities compared with that for the parasubstituted catalyst (1e) (entry 5 vs 6-8). In particular, 1h, which possesses the bulky substituent 3,5-bis(3,5-di-tert-butylphenyl)phenyl, exhibited the greatest catalytic efficiency (entry 8). The ester substituent of dialkyl malonates significantly affected both reactivity and selectivity (entries 8-10). The sterically less demanding dimethyl malonate (3a) is the best choice; the reaction was completed within only 10 min along with the high enantioselectivity (entry 8). The enantioselectivity was further increased by decreasing the reaction temperature from 0 to -40 °C (entries 11 and 12). Reducing the amount of 3a from 5.0 to 1.5 equiv compromised neither the turnover frequency nor the enantioselectivity (entry 13); β -nitrostyrene was quantitatively transformed into 4a within 2 h without any loss of enantioselectivity.

With a promising catalyst molecule and optimized reaction conditions in hand, we next examined the scope and the potential of the enantioselective 1,4-addition reaction. As shown in Table 2,

Table 2. 1,4-Addition Reaction of Various Conjugated Nitroalkenes (2) with Dimethyl Malonate (3a) Catalyzed by (*R*)-1h (eq 1)^a

•••					
entry	R1of 2	product	time (h)	yield (%) ^b	ee (%) ^c
1	2-MeOC ₆ H ₄ -	4d	2	98	97
2	$2-BrC_6H_4-$	4 e	2	>99	98
3	$2-NO_2C_6H_4-$	4f	4	86	91
5	3-MeOC ₆ H ₄ -	4g	2	94	94
4	3-BrC ₆ H ₄ -	4h	2	90	95
6	4-MeOC ₆ H ₄ -	4i	4	96	94
7	$4-ClC_6H_4-$	4j	2	>99	95
8	4-BrC ₆ H ₄ -	4 k	4	>99	93
9	2-furyl-	41	2	90	94
10	α-naphthyl-	4 m	2	>99	96
11^{d}	(CH ₃) ₂ CHCH ₂ -	4n	10	>99	86
12^{d}	$(CH_3)_2CH-$	4o	15	87	87
13^{d}	cyclohexyl-	4p	10	79	91

^{*a*} Unless otherwise noted, all reactions were carried out with 0.002 mmol of (*R*)-**1h** (2 mol %), 0.1 mmol of **2**, and 0.15 mmol of **3a** (1.5 equiv) in 1 mL of diethyl ether at -40 °C. ^{*b*} Isolated yield. ^{*c*} Enantiomeric excess was determined by chiral HPLC analysis. See Supporting Information for details. ^{*d*} A total of 0.005 mmol of (*R*)-**1h** (5 mol %) was employed in 1 mL of diisopropyl ether at -40 °C.

Ih exhibited excellent performance for a broad range of nitroalkenes (2) in terms of catalytic activity and enantioselectivity. In the reactions of a variety of aromatic-substituted nitroalkenes (2) with **3a**, uniformly high chemical yields and enantioselectivities were obtained (entries 1–10). **1h** also displayed high catalytic efficiency for aliphatic nitroalkenes, which are challenging substrates in terms of reactivity and selectivity (entries 11-13).^{8,9} Although slightly lower enantioselectivities than that of their aromatic counterparts were observed, the reactions proceeded within a reasonable period by increasing the catalyst loading to 5 mol %.¹⁰ Various types of 1,3-dicarbonyl compounds (**3**) were also applicable to the present catalytic system (eq 2). Excellent yields and high enantioselectivities at the β -position to the nitro group were obtained for α -substituted malonate (**3d**), 1,3-diketone (**3e**), and β -ketoester (**3f**).

R ¹ NO ₂ + 2 (R ¹ = Ph)	$R^2 \xrightarrow{O}_{R^4} R^3$	(<i>R</i>)- diethy	1h (2 mol%	$\stackrel{(b)}{\longrightarrow} \mathbb{R}^2$	$R^{1} = Ph$	2 (2)
	F	product	time (h)	yield (%)	ee (%)	
3d: R ² = R ³ = ON	/le, R ⁴ = Me	4q	12	82	98	
3e : R ² = R ³ = Me	e, R ⁴ = H	4r	4	88	91	
3f: R ² = Me, R ³ :	= OMe, R ⁴ = H	4s *¹	2* ²	98	91, 91* ³	
* ¹ 1:1 diastereomeric	mixture. * ² In dii	sopropyl	ether. *3Ee	e of each	diastereomer	·.

The high catalytic efficiency of **1h** was further evaluated by a gram-scale experiment with low catalyst loading. As highlighted in eq 3, 0.4 mol % of **1h** was sufficient for the completion of the reaction within 2 h, and a single recrystallization gave the optically pure product (**4d**) in 83% yield. Furthermore, **1h** was recovered in a nearly quantitative manner (96%) as an HCl salt by acidic workup following column purification. The HCl salt of **1h** was readily neutralized by a basic resin and reusable for subsequent runs without any detrimental effects on the catalytic activity and the enantiose-lectivity.



In conclusion, we have developed axially chiral guanidine **1** as a remarkably active organocatalyst that facilitates the highly enantioselective 1,4-addition reaction of 1,3-dicarbonyl compounds with a broad range of conjugated nitroalkenes to provide various types of optically active nitroalkane derivatives of synthetic and biological importance. We also found a significant effect of Ar substitution at the 3,3'-positions of the binaphthyl ring. Further studies are in progress to elucidate the substituent effect and the origin of the enantioselectivity.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and The Sumitomo Foundation.

Supporting Information Available: Representative experimental procedure including the results of **1h** reused and moisture tolerance of the catalysis, spectroscopic data for axially chiral guanidine catalyst (**1**) and the 1,4-addition products (**4**) (PDF), and stereochemical proof. This material is available free of charge via the Internet at http:// pubs.acs.org.

References

- (a) Hannon, C. L.; Anslyn, E. V. *Bioorganic Chemistry Frontiers*; Springer-Verlag: Berlin, 1993; Vol. 3, pp 193–255. (b) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* 1997, 97, 1609–1646.
- (2) Yamamoto, Y.; Kojima, S. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons Inc.: New York, 1991; Vol. 2, pp 485–526.
- (3) For reviews, see: (a) Ishikawa, T.; Isobe, T. Chem.-Eur. J. 2002, 8, 552–557. (b) Ishikawa, T.; Isobe, T. J. Synth. Org. Chem. Jpn. 2003, 61, 58–66.
- (4) (a) Dalko, P. I.; Moisan, L. Angew. Chem., Int. Ed. 2004, 43, 5138– 5175. (b) Berkessel, A.; Gröger, H. Asymmetric Organocatalysis: From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis; Wiley-VCH: Weinheim, Germany, 2005. (c) Seayad, J.; List, B. Org. Biomol. Chem. 2005, 3, 719–724. (d) Hayashi, Y. J. Synth. Org. Chem. Jpn. 2005, 63, 464–477.
- Jpn. 2005, 63, 464-477.
 (5) For some excellent studies describing enantioselective catalysis by chiral guanidine bases, see: (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. J. Am. Chem. Soc. 1996, 118, 4910-4911. (b) Corey, E. J.; Grogan, M. J. Org. Lett. 1999, 1, 157-160. (c) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. Chem. Commun. 2001, 245-246. (d) Kita, T.; Georgieva, A.; Hasahimoto, Y.; Nakata, T.; Nagasawa, K. Angew. Chem., Int. Ed. 2002, 41, 2832-2834. (e) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. Tetrahedron Lett. 2003, 44, 8677-8680.
- (6) (a) Chinchilla, R.; Najera, C.; Sanchez-Agullo, P. *Tetrahedron: Asymmetry* 1994, 5, 1393-1402. (b) Isobe, T.; Fukuda, K.; Ishikawa, T. *Tetrahedron: Asymmetry* 1998, 9, 1729-1735. (c) Ma, D.; Cheng, K. *Tetrahedron: Asymmetry* 1999, 10, 713-719. (d) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* 2001, 243-244. (e) McManus, J. C.; Carey, J. S.; Taylor, R. J. K. *Synlett* 2003, 365-368. (f) McManus, J. C.; Genski, T.; Carey, J. S.; Taylor, R. J. K. *Synlett* 2003, 369-371.
- (7) For axially chiral guanidines as recognition elements, see: Clews, J.; Curtis, A. D. M.; Malkin, H. *Tetrahedron* 2000, 56, 8735–8746.
- (8) For organocatalytic 1,4-addition reactions of nitroalkenes with malonates, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. J. Am. Chem. Soc. 2003, 125, 12672-12673. (b) Li, H.; Wang, Y.; Tang, L.; Deng, L. J. Am. Chem. Soc. 2004, 126, 9906-9907. (c) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. J. Am. Chem. Soc. 2005, 127, 119-125. (d) Hoashi, Y.; Yabuta, T.; Takemoto, Y. J. Am. Chem. Soc. 2005, 127, 119-125. (d) Hoashi, Y.; Yabuta, T.; Takemoto, Y. J. Am. Chem. Soc. 2005, 127, 119-125. (d) Hoashi, Y.; Yabuta, T.; Takemoto, Y. Tetrahedron Lett. 2004, 45, 9185-9188. (e) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. Angew. Chem., Int. Ed. 2005, 44, 105-108. (f) McCooey, S. H.; Connon, S. J. Angew. Chem., Int. Ed. 2005, 448, 105-6370. (g) Ye, J.; Dixon, D. J.; Hynes, P. S. Chem. Commun. 2005, 4481-4483.
- (9) For metal-based catalytic 1,4-addition reactions of nitroalkenes with malonates, see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. J. Am. Chem. Soc. 1999, 121, 10215– 10216. (b) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. J. Am. Chem. Soc. 2002, 124, 13097–13105. (c) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. J. Am. Chem. Soc. 2004, 126, 11148–11149. (d) Evans, D. A.; Seidel, D. J. Am. Chem. Soc. 2005, 127, 9958–9959.
- (10) During the preparation of this paper, Connon et al. (ref 8f) reported the enantioselective 1,4-addition reactions catalyzed by (thio)urea derivatives of cinchona alkaloids as a highly active organocatalyst. Even by using 5 mol % of this (thio)urea catalyst, more than 6 days are required for conversion of the hindered cyclohexyl-substituted nitroalkene to 4p in an acceptable yield.

JA057848D