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

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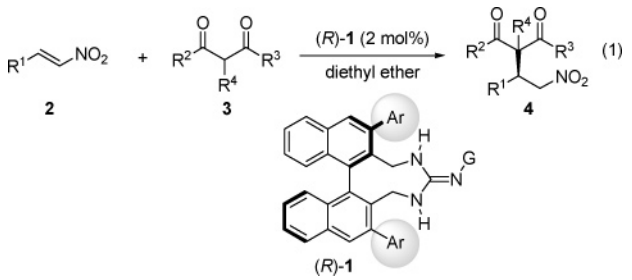
Guanidine is a ubiquitous element in natural products and plays a key role in many biological activities. In peptides, guanidine, a residue of arginine, exists in the protonated form as a guanidinium ion, which functions as an efficient recognition moiety of anionic functionalities, such as carboxylate, 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 targets[3] 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**; $R^1 = C_6H_5-$) 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 prominent effect on both catalytic activity and enantioselectivity. Whereas catalysts **1b** and **1c** with the electron-withdrawing group CF_3 proved to be poor in terms of turnover frequency, the introduction of the electron-donating group *tert*-butyl at the para-position, **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 para-substituted 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.

Table 1. 1,4-Addition Reaction of Conjugated Nitroalkene (**2**; $R^1 = C_6H_5-$) with Dialkyl Malonates Catalyzed by Various Axially Chiral Guanidines (**1**)[a]

entry	1	3[b]	4	time[c]	ee (%)[d]
1	**1a**: Ar = C_6H_5-, G = *n*-Pr	**3a**	**4a**	2 h	19
2	**1b**: Ar = 4-$CF_3C_6H_4-$, G = *n*-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-*t*-BuC_6H_4-, G = *n*-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** (R^1 = Ph), 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. [f] DBP = 3,5-di-*tert*-butylphenyl. [g] **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.

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,

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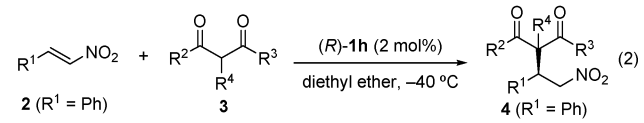
Table 2. 1,4-Addition Reaction of Various Conjugated Nitroalkenes (**2**) with Dimethyl Malonate (**3a**) Catalyzed by (*R*)-**1h** (eq 1)[a]

entry	R[1]of **2**	product	time (h)	yield (%)[b]	ee (%)[c]
1	2-MeOC$_6$H$_4$−	**4d**	2	98	97
2	2-BrC$_6$H$_4$−	**4e**	2	>99	98
3	2-NO$_2$C$_6$H$_4$−	**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$_6$H$_4$−	**4j**	2	>99	95
8	4-BrC$_6$H$_4$−	**4k**	4	>99	93
9	2-furyl−	**4l**	2	90	94
10	α-naphthyl−	**4m**	2	>99	96
11[d]	(CH$_3$)$_2$CHCH$_2$−	**4n**	10	>99	86
12[d]	(CH$_3$)$_2$CH−	**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.

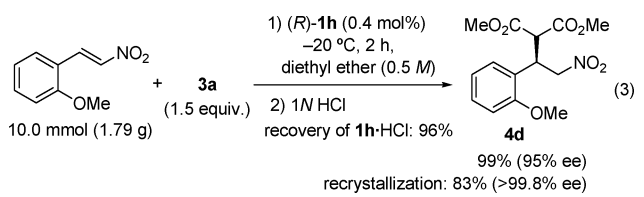
1h exhibited excellent performance for a broad range of nitroalkenes (**2**) in terms of catalytic activity and enantioselectivity. In the reactions of a variety of aromatic-substituted nitroalkenes (**2**) with **3a**, uniformly high chemical yields and enantioselectivities were obtained (entries 1−10). **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**).



	product	time (h)	yield (%)	ee (%)
3d: R^2 = R^3 = OMe, R^4 = Me	**4q**	12	82	98
3e: R^2 = R^3 = Me, 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 diisopropyl ether. [*3] Ee 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 enantioselectivity.



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.

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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.

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(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.

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