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Axially Chiral Guanidine as Highly Active and Enantioselective Catalyst for Electrophilic Amination of Unsymmetrically Substituted 1,3-Dicarbonyl Compounds

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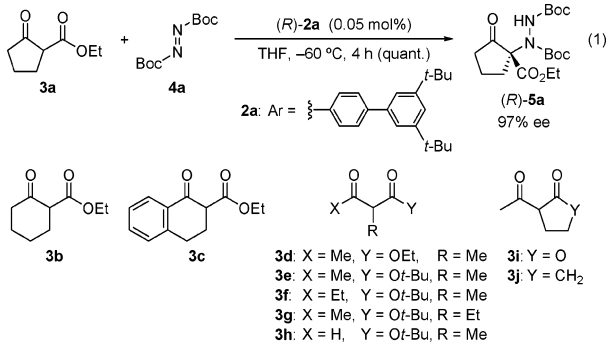
Arginine, one of the natural amino acids, is found in the active sites of numerous enzymes. The guanidinium moiety of the arginine residue is known to contribute to the stabilization of anionic reaction intermediates through electrostatic interactions and to substrate recognition at the active site through hydrogen bonding.[1] It is anticipated that these characteristics of the guanidinium ion coupled with the strong basic character of its conjugate base, guanidine, will make it suitable as an asymmetric base catalyst,[2,3] an attractive class of organocatalysts.[4] Recently we successfully developed novel chiral guanidine bases (**1**) as highly active and enantioselective catalysts for a 1,4-addition reaction of nitroalkenes with 1,3-dicarbonyl compounds.[5] The characteristic feature of **1** is the introduction of the axially chiral binaphthyl backbone with a nine-membered-ring structure (Figure 1a). In our continued efforts to develop efficient chiral guanidine catalysts, we designed a new type of axially chiral guanidine (**2**) with a seven-membered-ring structure (Figure 1b). The corresponding protonated forms, guanidinium ion **1′** and **2′**, both allow for the formation of multi-hydrogen bonds through the N−H protons; however, the guanidinium ion **2′** is particularly interesting as it has C_2 symmetry. We hence envisioned using the newly designed catalyst (**2**) to facilitate asymmetric induction at the α-carbon of unsymmetrically substituted 1,3-dicarbonyl compounds (**3**) (X ≠ Y). As illustrated in Figure 1c, two binding modes of the ion pairs would be generated from **2′** along with an enolate form of **3** through multi-hydrogen-bonding interactions between oxygen atoms and the N−H protons of **2′**. It is anticipated that differences in the stereoelectronic nature of unsymmetrical substituents (X, Y) of **3**, as well as the aromatic substituents (Ar) introduced at the 3,3′-positions of the binaphthyl backbone of **2**, would affect the preferred binding modes. Moreover the aromatic substituents (Ar), arranged with C_2 symmetry, would create an efficient chiral environment to discriminate between the enantiotopic faces of the enolate form of **3**. Taking advantage of the uniqueness of **2** as a platform for asymmetric induction at the α-carbon of **3**, we designed to study the enantioselective α-hydrazination of α-monosubstituted 1,3-dicarbonyl compounds (**3**) (R ≠ H) with azodicarboxylates (**4**) as the electrophilic nitrogen sources.[6−8] The method provides efficient access to the construction of a nitrogen-substituted quaternary stereocenter in an optically active form.[9] Herein we describe highly efficient and enantioselective electrophilic aminations catalyzed by a novel axially chiral guanidine (**2**), as represented by eq 1.



We began by investigating the effects of substituent (Ar) of catalyst (**2**). Electrophilic amination of cyclic β-keto ester (**3a**) employing di-*tert*-butyl azodicarboxylate (**4a**) was conducted at −60 °C using 2 mol % of **2**. The representative results are summarized in Table 1. We first employed 3,5-diphenylphenyl, which served as the efficient substituent in the nine-membered-ring guanidine catalyst (**1**),[5,10] but poor asymmetric induction was observed in the catalysis by **2b** (entry 1). We speculated that the reach of the steric demand exerted by the aromatic substituents is important in providing an efficient chiral environment around the substrate recognition site at the guanidine moiety. We thus extended the reach of the aromatic substituents by introducing an additional group at the para position of the aromatic ring; for this purpose a series of *p*-biphenyl derivatives (**2a**, **2c**−**e**) was examined (entries 2−5). As expected, the less sterically hindered but further reaching *p*-biphenyl **2c** led to a slight increase in enantioselectivity compared to the 3,5-diphenylphenyl **2b** (entry 1 vs 2). A dramatic increase in enantioselectivity was achieved by employing **2d**, which possesses a 3,5-diphenyl on the terminal ring of the *p*-biphenyl substituent (entry 3). Further modifications at the 3,5-positions of the terminal phenyl group exhibited marked effects on both catalytic efficiency and asymmetric induction (entries 4 and 5); the use of **2a** resulted in a quantitative formation of **5a** in 5 min along with excellent enantioselectivity, at 97% ee (entry 5). We also found that the steric

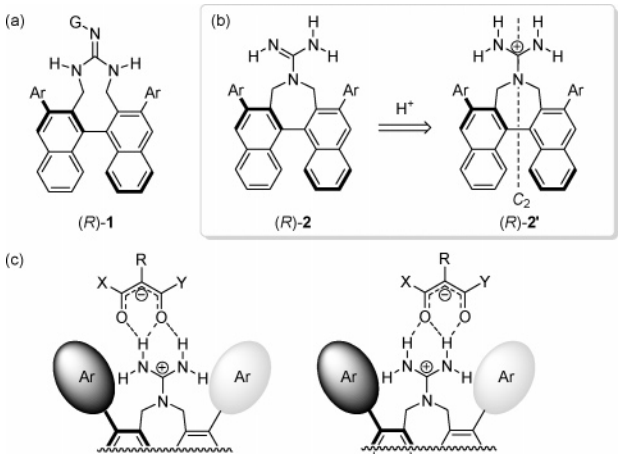


Figure 1. (a) Axially chiral guanidine with nine-membered ring (**1**); (b) axially chiral guanidine with seven-membered ring (**2**) and its protonated form, a C_2 symmetric guanidinium ion (**2′**); (c) two binding modes of the ion pairs derived from **2′** with enolate form of XC═OCHRC═OY (**3**) (X ≠ Y).

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Table 1. Enantioselective Amination of Ethyl 2-Oxocyclopentanecarboxylate (**3a**) with Azodicarboxylates (**4**) Catalyzed by Various Axially Chiral Guanidines (**2**)[a]

entry	2	4	5	time[b]	ee (%)[c]
1	**2b**: Ar = 3,5-$Ph_2C_6H_3$−	**4a**	**5a**	8 h	18
2	**2c**: Ar = 4-PhC_6H_4−	**4a**	**5a**	1 h	24
3	**2d**: Ar = 4-(3,5-$Ph_2C_6H_3$)C_6H_4−	**4a**	**5a**	1 h	86
4	**2e**: Ar = 4-{3,5-$(CF_3)_2C_6H_3$}C_6H_4−	**4a**	**5a**	5 min	93
5	**2a**: Ar = 4-(3,5-*t*-$Bu_2C_6H_3$)C_6H_4−	**4a**	**5a**	5 min	97
6	**2a**	**4b**[d]	**5ab**	5 min	89
7	**2a**	**4c**[e]	**5ac**	30 min	50

[a] Unless otherwise noted, all reactions were carried out with 0.002 mmol of (*R*)-**2** (2 mol %), 0.11 mmol of **3a**, and 0.10 mmol of **4** in 1 mL of THF at −60 °C. [b] Time required for completion of the reaction. [c] Enantiomeric excess was determined by chiral HPLC analysis. Absolute configuration was determined to be *R* for **5a** and **5ac**. See Supporting Information for details. [d] **4b**: Diisopropyl azodicarboxylate. [e] **4c**: Dibenzyl azodicarboxylate.

demand of azodicarboxylates (**4**) is crucial to attain high asymmetric induction (entries 6 and 7). As highlighted in eq 1, **2a** is clearly superior to reported organocatalysts[6] for the enantioselective amination with respect to the catalyst loading, catalytic activity, and asymmetric induction. The enantioselectivities and the yields were entirely maintained even when we lowered the loading of **2a** from 2 to 0.05 mol % (entry 5 vs eq 1).

With a promising catalyst molecule in hand, we next examined the scope and the limitation of the enantioselective amination catalyzed by **2a**. As shown in Table 2, cyclic β-keto esters with a six-membered ring displayed excellent enantioselectivity (entries 1 and 2). While the ethyl substituent at the α-position (**3g**) resulted in a considerable loss of enantioselectivity (entry 6), acyclic systems (**3d**−**f**) with a methyl substituent at the α-position were effective in the present enantioselective catalysis (entries 3−5); the corresponding products (**5d**−**f**) were obtained in good enantiomeric excess. 2-Formyl ester (**3h**) was also a useful substrate for this reaction giving the desired product (**5h**) in nearly quantitative yield with an acceptable level of ee (entry 7). Unfortunately **2a** was not effective for β-keto lactone (**3i**) (entry 8); the enantioselectivity was seriously diminished. In the reaction of 1,3-diketone (**3j**) (entry 9), where problems in discrimination of the similar ketone functionalities might be expected, **2a** exhibited excellent performance, providing amination product (**5j**) in high enantioselectivity. The absolute stereochemistry of **5a** and **5d** was determined to be *R* and *S*, respectively, after transformation to stereochemically known compounds. It should be noted that the stereochemical outcome of the cyclic derivative (**5a**) was opposite to that of the acyclic one (**5d**). Although the precise mechanism for the asymmetric induction is not yet clear, the dramatic change in stereochemical outcome between cyclic **5a** and acyclic **5d** could be ascribed to the differences in the preferred mode of binding (Figure 1c). Following this assumption, the low enantioselectivity observed for **3i** is presumably due to comparable formation of the two modes of binding.

Table 2. Enantioselective Amination of Various 1,3-Dicarbonyl Compounds (**3**) with Azodicarboxylate (**4a**) Catalyzed by (*R*)-**2a**[a]

entry	3	5	time (h)	yield (%)[b]	ee (%)[c]
1	**3b**	**5b**	24	>99	98
2	**3c**	**5c**	1	>99	97
3	**3d**	**5d**	0.5	99	85
4	**3e**	**5e**	3	>99	88
5	**3f**	**5f**	24	90	86
6	**3g**	**5g**	24	54	62
7	**3h**	**5h**	0.5	99	83
8	**3i**	**5i**	24	>99	15
9	**3j**	**5j**	5	99	91

[a] Unless otherwise noted, all reactions were carried out with 0.002 mmol of (*R*)-**2a** (2 mol %), 0.11 mmol of **3**, and 0.10 mmol of **4a** in 1 mL of THF at −60 °C. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis. Absolute configuration was determined to be *S* for **5d**. See Supporting Information for details.

In conclusion, we have developed an efficient organocatalyst **2** as a new family of axially chiral guanidine bases that facilitates the highly enantioselective electrophilic amination of unsymmetrically substituted 1,3-dicarbonyl compounds with high catalytic activity. Further studies are in progress to elucidate the dramatic changes in stereochemical outcome observed between cyclic and acyclic systems.

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Supporting Information Available: Representative experimental procedure, spectroscopic data for axially chiral guanidine catalysts (**2**) and electrophilic amination products (**5**), and determination of absolute stereochemistry of **5a** and **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The reaction of **3a** with **4a** catalyzed by nine-membered-ring guanidine (*R*)-**1** (Ar = 3,5-$Ph_2C_6H_3$−, G = Me, 2 mol %) gave (*R*)-**5a** in 69% ee (−60 °C, 30 min, >99% yield).

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