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Enantioselective Electrophilic Amination of α-Cyanothioacetates with Azodicarboxylates Catalyzed by an Axially Chiral Guanidine Base

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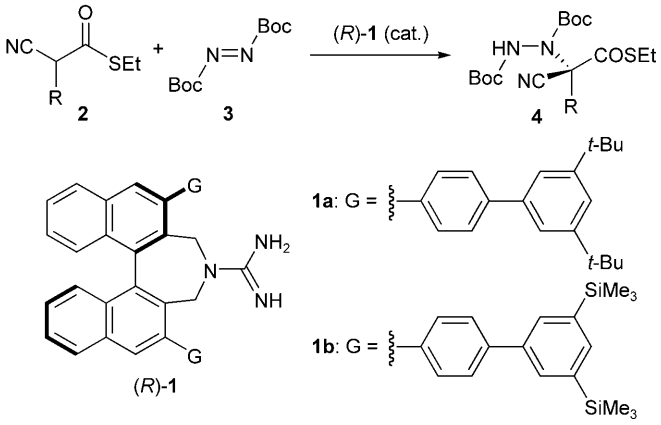
Abstract: An enantioselective electrophilic amination of α-substituted cyanothioacetates with azodicarboxylate is demonstrated using an axially chiral guanidine as a chiral Brønsted base catalyst. The corresponding product, having a quaternary stereogenic center at the α-carbon atom, is formed in excellent enantioselectivity.

Keywords: amination; amino acids; asymmetric catalysis; organocatalysis; quaternary stereocenters

α-Amino acids having a quaternary stereogenic center at the α-position are attractive compounds owing to their potent biological activities as non-proteinogenic analogues of natural α-amino acids and their increasing importance as constituents for preparing conformationally restricted peptides.[1] Catalysis of the enantioselective electrophilic amination of α,α-disubstituted carbonyl compounds using azodicarboxylates has emerged as an efficient strategy to address the challenging issue of constructing a nitrogen-substituted quaternary stereogenic center at the α-position of a carbonyl compound.[2–4] Recently, several excellent enantioselective catalytic reactions for electrophilic amination of α-substituted β-keto esters and their analogues have been developed using chiral metal-based catalysts[3] or organocatalysts.[2,4] Among these, the enantioselective amination of α-substituted α-cyanoacetates is a powerful method to construct a densely functionalized quaternary stereogenic center, and hence is a substantial step toward the enantioselective synthesis of α-amino acid derivatives having a quaternary α-carbon atom.[3d,4a,c,d,f,g,5] However, the methods are applicable to α-cyanoacetates with an aromatic group at the α-position. General approaches to the highly enantioselective amination of alkyl-substituted α-cyanoacetates have not been established to date,[4a,c,6] despite the potential for further elaboration of the corresponding amination products.

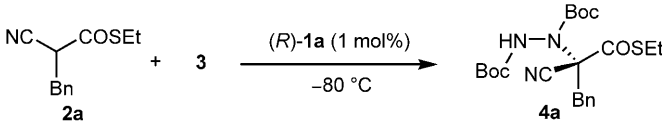
Recently, we successfully developed the novel axially chiral guanidines **1**[4e,7] as highly efficient Brønsted base catalysts for promotion of enantioselective transformations.[4e,7–9] Specifically, we reported on the enantioselective electrophilic amination of unsymmetrical 1,3-dicarbonyl compounds with di-*tert*-butyl azodicarboxylate catalyzed by a chiral guanidine catalyst (**1a**), which afforded excellent enantioselectivity and catalytic efficiency for cyclic β-keto esters; however, for the acyclic β-keto esters, the enantioselectivities were highly dependent on the alkyl substituent at the α-position of the keto ester.[4e] In this context, we aimed to develop the enantioselective electrophilic amination of α-alkyl-substituted α-cyanoacetate derivatives **2** with azodicarboxylate **3**. Herein, we report that the guanidine catalyst **1** exhibited excellent performance for the amination of α-cyanothioacetates **2** having a variety of primary alkyl substituents at the α-position, giving the products **4** in excellent enantioselectivity and chemical yield (Scheme 1).

Our investigation began by using thioacetate **2** as a substrate in the present electrophilic amination because of the potential for further derivatization of the thioester moiety in the obtained products (**4**). An initial attempt at electrophilic amination was performed using benzyl-substituted cyanothioacetates **2a**, di-*tert*-butyl azodicarboxylate (**3**), and 1 mol% of guanidine catalyst **1a** in THF at −80 °C. To our delight, **1a** worked efficiently and afforded the desired **4a** quantitatively in good enantioselectivity, as shown in Table 1 (entry 1). Screening of ethereal solvents showed a significant rate enhancement and completion of the reaction within 20 min when either diethyl ether or 1,2-dimethoxyethane (DME) was employed (entries 2 and 3). More importantly, an increase in enantioselectivity was achieved in these reaction media. Interest-



Scheme 1. Electrophilic amination of α-alkyl-substituted α-cyanothioacetates **2** catalyzed by axially chiral guanidines **1**.

Table 1. Enantioselective electrophilic amination of α-cyanothioacetate **2a** with azodicarboxylate **3** catalyzed by by (*R*)-**1a**.[a]

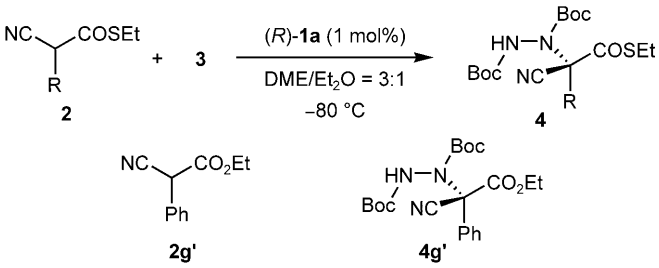


Entry	Solvent	Time	Yield [%]	% *ee*[b]
1	THF	4 h	>98	88
2	Et_2O	20 min	>98	96
3[c]	DME[d]	15 min	98	95
4	acetone	3.5 h	98	88
5	DME/Et_2O = 3:1	2.5 h	>98	98
6	DME/acetone = 3:1	2.5 h	97	98

[a] Unless otherwise noted, all reactions were carried out with 0.22 mmol of **2a**, 0.2 mmol of **3**, and 0.002 mmol of (*R*)-**1a** (1 mol%), in 2 mL of the indicated solvent at −80 °C.
[b] Enantiomeric excess was determined by chiral stationary phases HPLC analysis.
[c] Reaction run at −50 °C.
[d] DME: 1,2-dimethoxyethane.

ingly, acetone was also applicable to the present catalytic reaction, affording **4a** in nearly quantitative yield with good enantioselectivity (entry 4). Among the solvents examined, DME is particularly effective, giving an enantioselectivity that was as high as that obtained in diethyl ether even at an elevated reaction temperature of −50 °C. We therefore attempted to employ a mixed solvent system to avoid freezing of DME (mp −58 °C). As expected, mixing of DME with other solvents, not only diethyl ether but also acetone, resulted in an increase in enantioselectivity (entries 5 and 6), reaching 98% *ee* at −80 °C in both cases. The DME/diethyl ether mixed solvent system was employed for

Table 2. Enantioselective electrophilic amination of various α-cyanothioacetates **2** with azodicarboxylate **3** catalyzed by (*R*)-**1a**.[a]



Entry	**2** (R)	*t* [h]	**4**	Yield [%]	% *ee*[b]
1	**2b**: Me	1	**4b**	98	85
2[c]	**2b**	1	**4b**	98	89
3[c,d]	**2b**	3.5	**4b**	>98	91
4[c,d]	**2a**: Bn	8	**4a**	>98	87
5	**2c**: Et	0.5	**4c**	96	97
6	**2d**: *i*Bu	4.5	**4d**	>98	94
7	**2e**: allyl	1	**4e**	91	97
8[e]	**2f**: *i*Pr	3.5	**4f**	>98	54
9	**2g**: Ph	48	**4g**	65	41
10	**2g′**: Ph	6	**4g′**	>98	88
11[f]	**2a**: Bn	48	**4a**	92	98

[a] Unless otherwise noted, all reactions were carried out with 0.22 mmol of **2**, 0.2 mmol of **3**, and 0.002 mmol of (*R*)-**1a** (1 mol%), in 2 mL of DME/Et_2O = 3:1 mixed solvent at −80 °C.
[b] Enantiomeric excess was determined by chiral stationary phases HPLC analysis.
[c] In DME/acetone = 3:1 mixed solvent.
[d] 1 mol% of catalyst (*R*)-**1b**.
[e] In DME at −50 °C.
[f] 4.4 mmol of **2a** (0.96 g), 4.0 mmol of **3** (0.92 g), and 0.004 mmol of (*R*)-**1a** (0.1 mol%), in 12 mL of DME/Et_2O = 3:1 mixed solvent.

subsequent investigations as it gave the amination product **4a** quantitatively.

Having identified the optimal reaction conditions, we then investigated the substrate scope of the enantioselective amination of α-cyanothioacetates **2** bearing a variety of substituents at the α-position. As shown in Table 2, the present enantioselective catalysis is applicable to a range of aliphatic substituents. It is noteworthy that excellent enantioselectivities were achieved for primary alkyl substituents (entries 1–7).[10] The methyl-substituted cyanothioacetate **2b** exhibited slightly lower enantioselectivity under the optimized conditions (entry 1), however, the selectivity could be improved by further screening of solvents and catalysts **1** (entries 2 and 3), with the DME/acetone mixed solvent system giving the highest enantioselectivity (entry 2). In addition, modification of the catalyst by introduction of a trimethylsilyl substituent at the 3,5-positions of the terminal phenyl of the bi-

phenyl, giving **1b**, further improves the enantioselectivity (entry 3), reaching 91% *ee*. Unfortunately, the catalyst **1b** was not useful in reaction of the benzyl-substituted **2a**, giving a lower enantioselectivity (87% *ee*) than that observed in catalysis by **1a** (98% *ee*: see Table 1, entries 5 and 6). In contrast to the primary alkyl substituents, the amination of cyanothioacetates having secondary alkyl and aromatic substituents, isopropyl (**2f**) and phenyl (**2g**), respectively, was seriously compromised, giving the products (**4f** and **4g**) in moderate enantioselectivities (entries 8 and 9). Moreover, the reaction of **2g** proceeded sluggishly, giving the product **4g** in moderate yield even for a prolonged reaction period. This observation is in striking contrast to the parent cyanoacetate **2g′**, the oxygen analogue of **2g**, which underwent the reaction to completion within 6 h, giving the product **4g′** in 88% *ee* (entry 10). This enantioselectivity was much higher than that obtained in the reaction of the corresponding thioester **2g** (entry 9). To evaluate the catalytic efficiency of **1a**, we attempted a large-scale experiment with reductions in catalyst loading (entry 11). Gratifyingly, the reaction proceeded smoothly without any detrimental effect even on a gram scale of **2a** and the catalyst loading could be decreased to 0.1 mol%, giving **4a** in high yield with excellent enantioselectivity. To further expand the scope of the present enantioselective amination, we turned our attention to α-cyanothioacetates **2** having a functionalized primary alkyl substituent (Figure 1). Excellent yields and enantioselectivities were achieved under the optimized conditions [1 mol% of (*R*)-**1a**, DME/Et_2O = 3:1, −80 °C] in all cases.

In order to demonstrate the synthetic potential of this methodology and to determine the absolute configuration of the amination product, we transformed **4b** to the stereochemically known *N*-Boc-protected amino acid derivative **5** *via* a four-step chemical transformation (Scheme 2). Derivatization of **4b** was performed by reduction of the thioester moiety by $NaBH_4$, followed by acid hydrolysis of the nitrile and

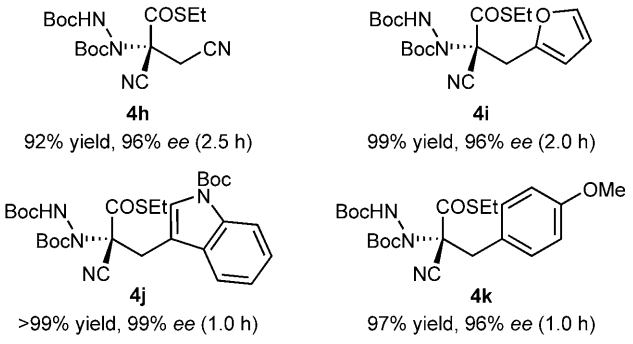
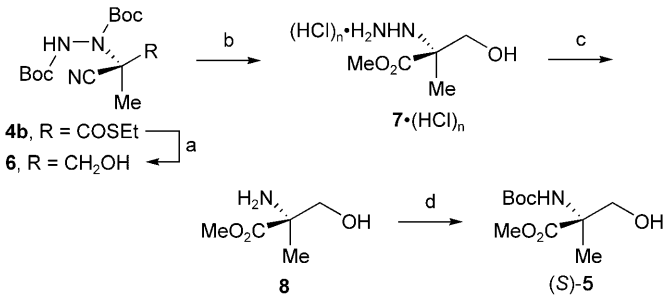


Figure 1. Enantioselective amination of functionalized α-cyanothioacetates.



Scheme 2. Transformation of amination product **4a** to an α-amino acid derivative. *Reagents and conditions:* a) $NaBH_4$, EtOH, room temperature, 1 h (83%); b) HCl, MeOH, reflux, 48 h; c) H_2, PtO_2, MeOH, room temperature, 15 h; d) Boc_2O, MeOH, room temperature, 12 h (15% from **6**).

N-Boc protective groups in MeOH, to afford the HCl salt of the α-hydrazinyl ester **7**. Subsequent hydrogenolysis of the hydrazine moiety was conducted using PtO_2 catalyst to give the serine derivative **8**.[1a] Introduction of a Boc group to the nitrogen atom of **8** then afforded the *N*-Boc-protected serine derivative **5**. The absolute stereochemistry of **5** was determined to be the (*S*)-configuration by comparison of the optical rotation with the literature value.[11] Thus it was confirmed that the electrophilic amination catalyzed by (*R*)-**1a** gave the (*R*)-isomer as the major product.

The stereochemical outcome of catalysis by the axially chiral guanidine **1** is highly dependent on the steric demand of the substituent introduced at the α-position of the cyanothioacetate. When a primary alkyl substituent was used, excellent enantioselectivities were observed for a variety of substituent patterns, including those having functionalized alkyl termini. Moreover, an entirely different effect was observed for the α-substituent of the parent cyanoacetates, oxygen analogues of thioesters **2** (see Table 2, entries 9 and 10).[10] Although the precise mechanism of the enantiofacial selection has not yet been clarified, the fact that subtle differences in not only steric congestion but also the electronic property at the reaction site, that is, the α-position of the cyano(thio)acetates, affect the stereochemical outcome would be ascribed to the intrinsic flexibility of the O···H···N hydrogen bond formed between the enolate of the cyanothioacetate and the chiral guanidinium ion.

In conclusion, we have demonstrated the highly enantioselective electrophilic amination of α-cyanothioacetates with azodicarboxylates catalyzed by axially chiral guanidines. The method facilitates the highly enantioenriched synthesis of α-amino acid derivatives having a quaternary stereogenic center at the α-position, an important class of compounds for the preparation of peptide analogues and biologically

active molecules. Further studies utilizing the activation of α-cyanoacetates by axially chiral guanidines to develop valuable enantioselective transformations will be explored in due course.

Experimental Section

General Procedure

To a test-tube equipped with a magnetic stirring bar was added dimethoxyethane (1.5 mL), diethyl ether (0.5 mL), *S*-ethyl 2-cyano-3-phenylpropanethioate (**2a**; 48.3 mg, 0.22 mmol), and (*R*)-**1a** (1.73 mg, 0.002 mmol). The tube was capped, and stirred at room temperature for 15 min. After that, the mixture was cooled to −80 °C and di-*tert*-butyl azodicarboxylate (DBAD, **3**; 46.1 mg, 0.20 mmol) was added. The resulting yellow solution was stirred until the yellow color had disappeared. After completion of the reaction, the resulting solution was quenched with saturated aqueous NH_4Cl solution (a few drops) and solvent was removed. The residue was purified by column chromatography (hexane/AcOEt 12/1 to 6/1) to afford **4a**; yield: >98%. The enantiomeric excess was determined to be 98% *ee* by chiral stationary phase HPLC analysis.

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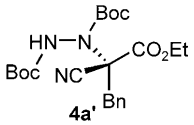

4a′

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