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Enantioselective Amination of α-Phenyl-α-cyanoacetate Catalyzed by Chiral Amines Incorporating the α-Phenylethyl Auxiliary

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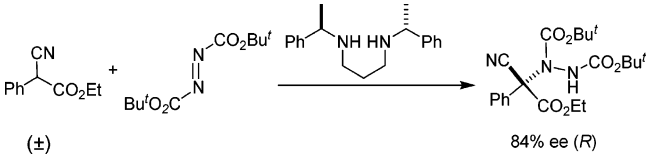

Nineteen chiral amines and their derivatives were prepared and investigated as organocatalytic Lewis bases in the α-amination of ethyl α-phenyl-α-cyanoacetate. For comparison purposes, a few natural products were also examined as catalysts in this study. Among the results obtained, (*R*)-*N*-benzyl-*N*-(1-phenylethyl)-amine and (*R,R*)-*N,N*′-bis(1-phenylethyl)-propane-1,3-diamine as the catalysts afforded the amination products in excellent yields and with up to 84% ee. By contrast, under comparable conditions the two derivatives of natural products $(DHQ)_2PYR$ and $(DHQD)_2PYR$ provided the product of amination with lower than 10% enantiomeric excess.

Ongoing studies in our group on the enantioselective synthesis of amino acids[1] brought our attention to the very recently reported organocatalytic enantioselective electrophilic amination reactions of α-substituted α-cyanoacetates and α-substituted *β*-ketoesters with azodicarboxylates.[2−5] Indeed, the α-aminated products thus formed have the potential to be converted to either α- or *β*-amino acids,[6] which play determinant roles in biology, chemistry, and medicine. In particular, unnatural α,α-disubstituted α- and *β*-amino acids are of increasing importance for the preparation of conformationally restricted peptide libraries as well as intermediates of natural products.[7]

The application of natural products as organocatalysts constitutes a relevant concept in the field of enantioselective organocatalysis;[8] nevertheless, organocatalysis with natural products can suffer from their structural complexity, large molecular weight, and in some cases high cost of isolation. Since one of the challenges in asymmetric catalysis is to develop a highly enantioselective reaction under convenient conditions using a simple catalyst system that is as cheap as possible,[9] development of synthetic structurally simpler organic molecules for organocatalysis is highly desirable. In addition, the main advantages of synthetic over natural molecules are that both enantiomers are readily available and that their structure can be easily modified.

Proline is among the most famous examples of a structurally simple natural catalyst, whose use can be traced even to the 1970s, in applications pioneered by Hajos et al.[10] Although this research then faded away for 25 years, it has reblossomed more recently.[11] In spite of its great efficiency and practicality, proline has its own limitations, and its supremacy is being challenged by new synthetic analogues.[12] Nevertheless, relatively little new work appears on successful enantioselective reactions catalyzed with structurally simple compounds besides proline analogues.

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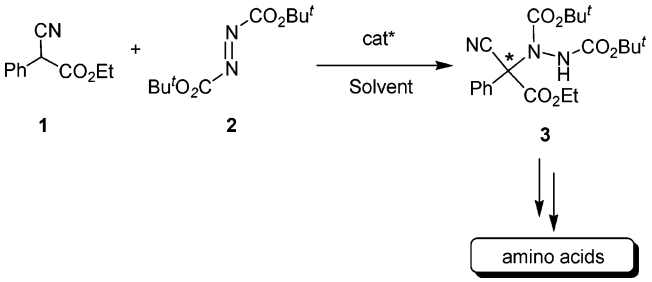
SCHEME 1



Thus, development of new catalysts to meet the demand for enantioselective synthesis is of both scientific and economic importance. Herein we aim to search for practical and simple organocatalysts to promote the enantioselective amination of racemic ethyl α-phenyl-α-cyanoacetate, (±)-**1**, with di-*tert*-butyl azodicarboxylate (**2**), the product thus formed (**3**) being a precursor of amino acids (Scheme 1).

Examination of Enantioselective Efficiency of Amination with Selected Natural Products. So far, cinchona alkaloids[2c,3] are reported to be the most efficient organocatalysts for the enantioselective α-amination reaction. Here we further examined the catalytic activity of other natural organocatalysts, such as sparteine[13] and DHQ derivatives,[14] which owing to the structural similarity to cinchona alkaloid and/or to their C_2-symmetry were expected to provide high enantioinduction in the asymmetric amination reaction.

However, although the amination of ethyl α-phenyl-α-cyanoacetate with $(DHQ)_2PYR$ (**4a**) and $(DHQD)_2PYR$ (**4b**) (Figure 1) as catalysts at −78 °C gave high yields of the product, it unfortunately resulted in a disappointingly poor enantioselectivity (<10% ee) (Table 1, entries 1 and 2). Under the same conditions, (−)-sparteine (**5**) afforded higher enantiomeric excess (28%) of the product at −78 °C (Table 1, entry 3), but the amination failed to occur at lower temperature (Table 1, entry 4), at which higher enantioselectivity could be anticipated. The discouraging results listed in Table 1 indicate that natural alkaloids **4** and **5** are not efficient organocatalysts in the present system.

Enantioselective Amination Catalyzed by Unnatural Chiral Amines. To search for structurally simpler inexpensive organocatalysts and to gain understanding of factors affecting the enantioselectivities for the amination, we designed and synthesized a series of 19 chiral amines as the catalyst for screening. Most catalysts investigated incorporate the α-phenylethylamine[15] and include acyclic and cyclic amines, amines with nitrogen as part of a ring, and amines with additional polar functional groups such as hydroxy, ester, etc. The results obtained from this chiral amine-catalyzed amination are summarized in Table 1.

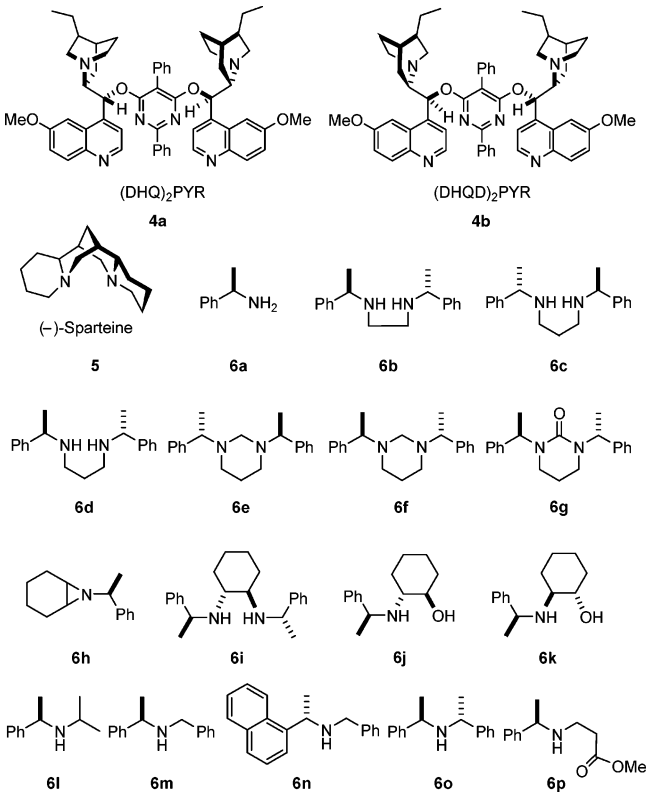


FIGURE 1. Chiral amines examined as potential organocatalysts in the enantioselective amination of ethyl α-phenyl-α-cyanoacetate.

All amines **6a**−**p** proved to be efficient catalysts for the amination of substrate (±)-**1** with electrophile **2**. Remarkably, tertiary amines **6e**, **6f**, and **6h**, as well as urea **6g**, afforded the aminated products **3** in 90−98% yield. This observation is in line with the pioneering work from the Jorgensen[2e] and Deng[3] laboratories showing the efficiency of tertiary amines as organocatalysts in the amination reaction of interest. In those cases where both enantiomeric organocatalysts were used, products of opposite configuration were obtained as anticipated (cf. entries 7 and 8, 9 and 10, 9 and 11 in Table 1). For reactions conducted at different temperature, remarkable improvement in enantioselectivity was observed at −78 °C (cf. entries 10 and 11 in Table 1).

The highest enantioselectivity (58−68% ee) was observed with secondary amines **6c**, **6m**, and **6n** (entries 7, 19, and 20 in Table 1). It is interesting that, as anticipated, replacement of phenyl by a larger naphthyl group (**6m** → **6n**, entries 19 and 20) leads to a higher ee value.

By contrast, when zinc triflate was added as a potential activator,[17] this failed to produce any encouraging result (entry

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(16) X-ray crystallographic analysis of chloro derivative **A** led Deng et al.[3] to conclude that the dextrorotatory enantiomer presents the (*S*) absolute configuration. The positive optical rotation in analog **3** was assumed to correspond to the (*S*) configured enantiomer as well.[3,4] We are grateful to Professor Yoshiji Takemoto for his advise in this matter.

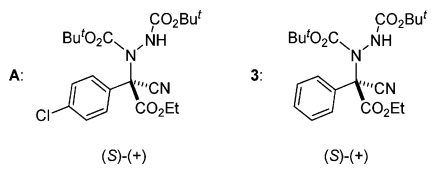
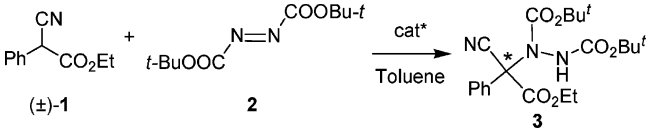


TABLE 1. Amination of α-Phenyl-α-cyanoacetate with Chiral Amines as Catalysts[a]



(±)-**1** **2** **3**

entry	cat*	temp (°C)	time	yield (%)	er[b]	ee (major enantiomer)[c]
1	**4a**	−78	3 h	3	53:47	6 (*R*)-(−)
2	**4b**	−78	3 h	3	48:52	4 (*S*)-(+)
3	**5**	−78	4 h	4	64:36	28 (*R*)-(−)
4	**5**	−100[d]				
5	**6a**	−78	10 min	90	53:47	6 (*R*)-(−)
6	**6b**	−78	30 min	94	35:65	30 (*S*)-(+)
7	**6c**	−78	10 min	97	21:79	58 (*S*)-(+)
8	**6d**/Zn(OTf)$_2$	0[e]	2 days	79	60:40	20 (*R*)-(−)
9	**6e**	−78	2 h	93	31:69	38 (*S*)-(+)
10	**6f**	0	2 h	96	58:42	16 (*R*)-(−)
11	**6f**	−78	2 h	98	74:26	48 (*R*)-(−)
12	**6g**	rt[e]	2 days	90	58:42	16 (*R*)-(−)
13	**6h**	−78	30 h	92	51:49	2 (*R*)-(−)
14	**6i**	−78	3 h	94	41:59	18 (*S*)-(+)
15	**6j**	−78	6 h	91	55:45	10 (*R*)-(−)
16	**6k**	−78	4 h	93	40:60	20 (*S*)-(+)
17	**6l**	0[e]	1 day	91	43:57	14 (*S*)-(+)
18	**6l**	−78[f]				
19	**6m**	−78	1 h	94	20:80	60 (*S*)-(+)
20	**6n**	−78	1 h	95	84:16	68 (*R*)-(−)
21	**6o**	0	2 days	86	38:62	24 (*S*)-(+)
22	**6o**	−78[f]				
23	**6p**	−78	6 h	89	55:45	10 (*R*)-(−)

[a] The reaction was carried out with 0.55 mmol of substrate (±)-**1** and 0.5 mmol of electrophile **2** in the presence of 0.5 equiv (50 mol %) of the organocatalyst. [b] Enantiomeric ratios were determined by chiral HPLC analysis. [c] The assignment of the configuration was based on literature precedent[3,4] (see also ref 16). [d] Sparteine was insoluble at this temperature. [e] No reaction took place at −78 °C. [f] Incomplete reaction.

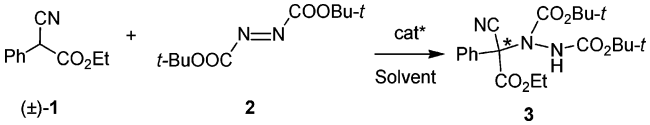
8 in Table 1). In this context, the low efficiency of catalysts **6l** and **6o** (entry 17 and 21) may be attributed to steric hindrance, which prevents effective enantioinduction.

Optimization of Reaction Conditions. The encouraging results shown in Table 1 led us to optimize the reaction conditions for further improvement of the enantioselectivity of the amination protocol. Thus chiral amines **6d**, **6f**, **6m**, and **6n**, which showed better efficiency in the asymmetric amination reaction, were selected as the catalysts for further investigation. It was found that the reaction temperature and the solvent used could influence greatly the enantioselectivity of the amination reaction (Table 2).

When the amination reaction was performed at the finally optimized conditions for **6d** and **6n** (−78 °C, toluene/hexane, Table 2, entries 5 and 8) and for **6f** and **6m** (−100 °C, toluene/hexane, Table 2, entries 10 and 11), the ee of the amination product increased up to 80%. It can also be concluded from Table 2 that the influence of solvent and temperature on the enantioselectivity is dramatic, allowing ee values to reach the 74−84% ee range.

On the other hand, a decrease in catalyst loading is highly desirable for any catalytic reaction. Although organocatalysis has proven successful in many respects, most of the reported processes require 10 mol % or more of the catalyst for sufficient product formation and maintenance of stereoselectivity.[14b] In

TABLE 2. Enantioselective Amination of α-Phenyl-α-cyanoacetate with Selected Chiral Amines as Catalysts under Optimized Conditions[a]

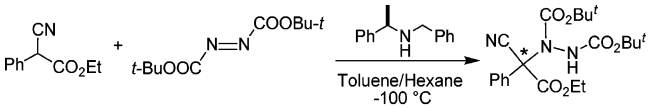


(±)-**1** **2** **3**

entry	cat*	temp (°C)	solvent	time	yield (%)	er[b]	ee (major enantiomer)[c]
1	**6d**	−100	toluene	10 min	95	90:10	80 (*R*)-(−)
2	**6f**	−100	toluene	2 h	94	74:24	48 (*R*)-(−)
3	**6m**	−100	toluene	1 h	95	18:82	64 (*S*)-(+)
4	**6n**	−100	toluene	2 h	96	81:19	62 (*R*)-(−)
5	**6d**	−78	tol/hex[d] (1:1)	30 min	91	92:8	84 (*R*)-(−)
6	**6f**	−78	tol/hex (1:1)	1 h	92	78:22	56 (*R*)-(−)
7	**6m**	−78	tol/hex (1:1)	1 h	95	13:87	74 (*S*)-(+)
8	**6n**	−78	tol/hex (1:1)	2 h	96	88:12	76 (*R*)-(−)
9	**6d**	−100	tol/hex (1:1)	30 min	94	88:12	76 (*R*)-(−)
10	**6f**	−100	tol/hex (1:1)	2 h	95	79:21	58 (*R*)-(−)
11	**6m**	−100	tol/hex (1:1)	1 h	95	10:90	80 (*S*)-(+)
12	**6n**	−100	tol/hex (1:1)	2 h	93	87:13	74 (*R*)-(−)

[a] The reaction was carried out with 0.55 mmol of substrate (±)-**1** and 0.5 mmol of electrophile **2** in the presence of 0.5 equiv (50 mol %) of the chiral amine. [b] Enantiomeric ratios were determined by chiral HPLC. [c] The assignment of the configuration was based on literature precedent.[3,4,16] [d] Toluene/hexane.

TABLE 3. Examination of the Efficiency of Enantioselective Amination with Different Amounts of Specified Catalyst under Similar Conditions[a]



(±)-**1** **2** **3**

entry	amount of **6m** (mol %)	time (h)	yield (%)	er[b]	ee (major enantiomer)[c]
1	1	20	90	18:82	64 (*S*)-(+)
2	5	4	95	18:82	64 (*S*)-(+)
3	10	3	93	18:82	64 (*S*)-(+)
4	20	2	93	19:81	62 (*S*)-(+)
5	50	1	95	10:90	80 (*S*)-(+)
6	100	0.5	94	17:83	66 (*S*)-(+)

[a] The reaction was carried out with 0.55 mmol of substrate (±)-**1** and 0.5 mmol of electrophile **2** in the presence of the specified amounts of organocatalyst **6m**. [b] Enantiomeric ratios were determined by chiral HPLC. [c] The assignment of the configuration was based on literature precedent.[3,4,16]

the present study, amination could be performed without significant loss of enantioselectivity with catalyst loadings as low as 1 mol %. Nevertheless, the use of 0.5 equiv of the (recoverable) chiral amine organocatalyst offers the best combination of enantioselectivity and short reaction times (Table 3).

In summary, this is the first attempt to search for practical and structurally simple organocatalysts as substitutes for natural products in the enantioselective amination of α-substituted α-cyanoacetates with azodicarboxylates. A series of studies on the amination reaction with various chiral amines as catalysts were performed, and efficient optimized reaction conditions were established. The enantioselectivity obtained with the properly designed chiral amines under optimized conditions is satisfactory considering its ready availability and low cost. Furthermore, the amination reaction proceeds smoothly even when the catalyst loading is reduced to 1 mol %. Further exploration of this system is now under way in our laboratory.

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Experimental Section

Compounds **6b**,[18] **6c**,[18] **6d**,[18] **6g**,[19] **6h**,[19b] **6i**,[20a] **6j**,[20a] **6k**,[20b] **6l**,[21] **6m**,[21] and **6o**[22] were synthesized by literature procedures.

General Procedure for Enantioselective Amination, 3. A mixture of ethyl α-phenyl-α-cyanoacetate (0.55 mmol) and catalyst (0.25 mmol) in 2 mL of toluene (or 18 mL of toluene/hexane, 1:1 v/v) was stirred for 1 h at room temperature and then was cooled to −78 °C (or −100 °C) under a nitrogen atmosphere. A solution of di-*tert*-butyl azodicarboxylate (0.5 mmol) in 1 mL of toluene (or 2 mL of toluene/hexane, 1:1 v/v) was added dropwise over a period of 30 min. The reaction mixture was stirred until the yellow color of the solution faded (10 min to 30 h) and then allowed to warm to room temperature. Pure products were isolated by flash chromatography (ethyl acetate/hexane, 1:6). ^{1}H NMR (400 MHz, DMSO): δ 1.20 (t, J = 6.9 Hz, 3H), 1.33 (s, 9H), 1.48 (s, 9H), 4.24 (q, J = 6.9, 2H), 7.45 (s, 3H), 7.63 (s, 2H), 8.70 (br, N-H). ^{13}C NMR (100 MHz, DMSO): δ 13.9, 28.3, 28.5, 63.7, 80.8, 80.9, 83.6, 116.3, 127.2, 128.0, 128.6, 129.1, 130.5, 130.7, 153.9, 154.9, 165.4. Enantiomeric excess determined by HPLC [t_R (−) *levo* enantiomer = 11 min; t_R (+) *dextro* enantiomer = 37 min). Mp: 94−96 °C. IR (CH_2Cl_2) ν (cm^{-1}): 3337, 2982, 2360, 1747, 1716, 1370, 1243, 1154, 1053. $[\alpha]^{20}_D$ = +48.7 (*c* 1, $CHCl_3$) for 84% ee; lit.[3] $[\alpha]^{20}_D$ = +64.0 (*c* 0.175, $CHCl_3$) for 97% ee.

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Supporting Information Available: Experimental details for the preparation of relevant compounds, NMR data for **3**, **6e**, **6f**, **6n**, **6p**, and chromatograms for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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