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Amino acid-catalyzed asymmetric α-amination of carbonyls

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Abstract—Electrophilic amination of ketones and aldehydes in the presence of dibenzylazodicarboxylate in dichloromethane, using L-azetidine carboxylic acid as a catalyst, is described. Yields and ee are discussed in comparison with the corresponding L-proline-catalyzed reaction.

Electrophilic amination of sp^3 hybridized carbon atoms is one of the most attractive reaction to generate C–N bonds in organic synthesis. The methods for α-amination of carbonyl compounds using the 'NH_2^+' synthon have been recently reviewed.[1,2] In particular, it has been shown that asymmetric electrophilic amination is possible in the presence of chiral promoters, leading to the expected aminated products with high stereoselectivities. The α-amination of carbonyls in the presence of a chiral catalyst was introduced by Evans et al. in 1997,[3] who added a magnesium-bis(sulfonamide) complex to the reaction mixture for the enantioselective amination of *N*-acyloxazolidinones. Later, combinations based on copper(II)[4] and silver[5] catalysts with azodicarboxylate reagents were explored. In particular, the former are more efficient for the formation of α-hydrazino carbonyl compounds and β-amino-α-keto esters from the corresponding enolsilanes or β-ketoesters, respectively.

Pihko et al.[6] showed the importance of cinchonine and cinchonidine alkaloids in the α-amination of β-ketoesters and β-ketolactones. Later, Jorgensen et al.[7] reported the first quinidine-derived catalyst allowing the amination of substituted α-cyanoacetates and β-dicarbonyl compounds, with very high enantioselectivities. Very recently, it has been shown[8] that 6′-OH modified cinchona alkaloids derived from either quinine and quinidine provide easy access to both enantiomers, respectively, in the formation of a quaternary center by electrophilic amination of α-cyanoacetates.

The direct amination of aldehydes using azodicarboxylates as the nitrogen source, and L-proline (**1a**) as the catalyst has been described in 2002 concomitantly by List[9] and Jorgensen.[10] This reaction was the first one which required a relatively low amount of an inexpensive and non-toxic catalyst available in both enantiomeric forms. Later, the reaction was extended to ketones, and produced the α-hydrazino adducts in good yields and enantioselectivities.

The observed enantioselectivity was explained with a proline–enamine involving transition state, in which the approach of the azodicarboxylate is directed by an interaction between the incoming nitrogen atom and the proton of the carboxylic acid.[10,11] Duthaler[12] has proposed a chair conformation that could explain the mechanism for L-proline-catalyzed reactions—including amination reactions—of ketones or aldehydes with electrophiles. In this model, interactions between the azodicarboxylate moiety, the acidic proton of the carboxylic acid, and the nitrogen atom of the enamine intermediate may account for the regio- and stereoselectivities observed. Thus, changing the nature and the size of the catalytic heterocycle may induce a modification of the conformation of the transition state and thereby the stereochemical outcome. In particular, we have tested the effect of the corresponding four-membered ring heterocycle, namely L-azetidine carboxylic acid (**1b**), for electrophilic α-amination of carbonyl compounds. The general transition state model may still be applicable (Fig. 1), the more constrained ring should only induce modified conformational angles. We described in this letter the synthesis of several α-hydrazinoketones by electrophilic amination in the presence of **1b** as a catalyst.

Keywords: Amination; Organocatalysis; Enantioselectivity; L-Azetidine carboxylic acid; Azodicarboxylates.
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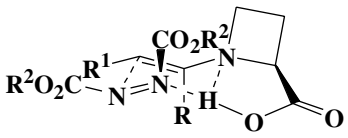


Figure 1.

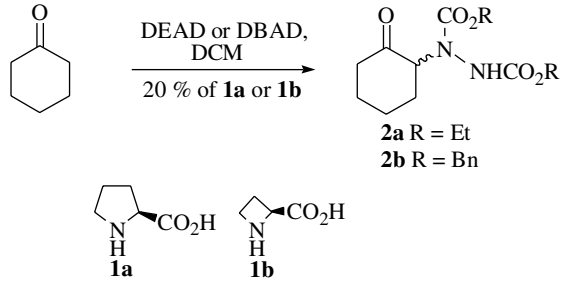
The Jorgensen et al.[11] experimental procedures have been followed using 20 mol % catalyst in dichloromethane. All reactions were stirred until yellow color of the azodicarboxylates had faded.

First, we compared the ee obtained from the symmetric cyclohexanone in the presence of DEAD (Scheme 1). Jorgensen et al.[11] obtained the expected hydrazines **2a** (R = Et) in 79% ee in dichloromethane, and the yield was not reported. We first repeated this experiment and obtained **2a** with a comparable ee, and an isolated yield of 46%. The same conditions (20% catalyst, room temperature, DEAD) in the presence of L-azetidine carboxylic acid led to the α-hydrazino ketone after 24 h with a yield of 73% and an increased ee: 85%.

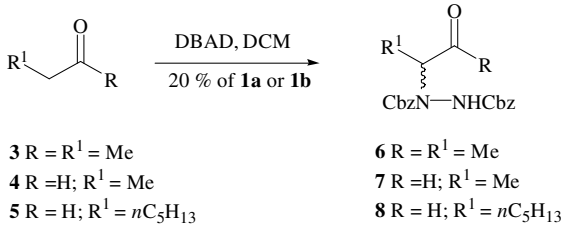
Encouraged by this result, we have decided to test the reaction with DBAD (Table 1), which has the advantage of being easily detected by UV for HPLC analyses. Moreover, it is known that α-hydrazinoketones derived from DBAD can be easily hydrogenolized in a one-step process in the presence of hydrated platinium oxide to obtain the corresponding amino ketone.[13] The reaction with cyclohexanone, and later with other substrates, was first performed with DL-proline leading to the racemic amination product. Purification over silica gel allowed its use as a reference for HPLC analyses.[14] After 24 h of stirring the symmetric ketone with DBAD in dichloromethane, the isolated yield of **2b**[15] was essentially the same whether organocatalyst **1a** or **1b** was used: 56% and 60%, respectively (entries 1 and 3). But we noticed a remarkable increase in the enantiomeric excess, gaining a 29% increase in ee when the smaller N-heterocycle was used. Importantly, after 8 h of reaction time an isolated yield of 50% can be achieved with the same ee (entry 2). Cooling the reaction mixture to 0 °C did not influence the enantioselectivity: ee = 88% and afforded **2b** in a low yield: 25% (entry 4). A higher reaction temperature as 40 °C induced an important decrease of the enantiomeric excess 6%.

Several complementary assays have been performed, confirming the catalyst efficiency not only with other ketones, but also with aldehydes (Scheme 2 and Table 2). We have aminated butanone, propanal, and heptanal first with the racemic proline, leading to the racemic mixture for HPLC analysis, then with **1a** and **1b**, in the presence of DBAD.[14]

Electrophilic amination of butanone **3** by DEAD in the presence of L-proline has been described by Jorgensen et al.[11] leading to an inseparable mixture of the expected 3-hydrazino ketone and its 1-hydrazino regioisomer (91% and 9% yield, respectively). In our case, the electrophilic amination of butanone **3** using DBAD give α-hydrazinoketone **6** as a sole product. The experiments were run at room temperature in dichloromethane in the presence of 20 mol % catalyst, **6** was obtained with yields of 49% and 54% and enantiomeric excesses of 94% and 90% using, respectively, **1a** and **1b** as organocatalyst (entries 1 and 2). Aldehydes such as propanal (entries 3 and 4) and heptanal (entries 5 and 6) also react with DBAD in the presence of the α-amino acids. Reaction times are shorter with L-proline, but after decoloration the yields are comparable. In the presence of L-azetidine carboxylic acid, the enantiomeric excesses were in both cases ranging from 72% to 74%.



Scheme 1.



Scheme 2.

Table 1. Enantioselective α-amination of cyclohexanone by DBAD catalyzed by L-proline **1a** or L-azetidine carboxylic acid **1b**

Entry	Reagent	Catalyst	Time (h)	Temperature (°C)	Product	Yield[b] (%)	ee[c] (%)
1	DBAD	**1a**	24[a]	25	**2b**	56	61
2	DBAD	**1b**	8[a]	25	**2b**	50	90
3	DBAD	**1b**	24	25	**2b**	60	90
4	DBAD	**1b**	48[a]	0	**2b**	25	88

Conditions: Reactions mixtures were stirred in DCM. The time indicates the disappearance of the yellow color.
[a] Decoloration was not complete.
[b] Isolated yield after column chromatography.
[c] Ee determined after workup by chiral HPLC.

Table 2. Enantioselective α-amination of ketones and aldehydes by DBAD catalyzed by L-proline **1a** or L-azetidine carboxylic acid **1b**

Entry	Substrate	Catalyst	Time (h)	Product	Yield (%)	ee (%)
1	**3**	**1a**	114[a]	**6**	49	94
2	**3**	**1b**	114[a]	**6**	54	90
3	**4**	**1a**	3.5	**7**	62	54
4	**4**	**1b**	22	**7**	60	74
5	**5**	**1a**	1.25	**8**	62	91
6	**5**	**1b**	15	**8**	69	72

Conditions: Reactions mixtures were stirred at rt in DCM.
[a] Decoloration was not complete.

In summary, we have shown that L-azetidine carboxylic acid can be used as a catalyst for the asymmetric electrophilic amination of aldehydes and ketones by DBAD. Generally, if the yields are comparable to those obtained by using L-proline, the enantiomeric excesses are increased for substrates such as cyclohexanone and propanal.

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14. The enantiomeric excess (ee) of the products were determined by HPLC using a JACSO PU2089plus apparatus and a column Chiralcel OD. Eluant: heptane/*i*-PrOH: 93/7; flow 0.9 ml/min; λ 260 nm. Compound **2b** (T 45 °C): $\tau_{minor} =$ 18.52 min and $\tau_{major} = 24.91$ min; **6** (T 30 °C): $\tau_{minor} =$ 21.45 min and $\tau_{major} = 25.01$ min; for **7** (T 45 °C): $\tau_{minor} = 16.02$ min and $\tau_{major} = 17.19$ min; for **8** (T 45 °C): $\tau_{minor} = 30.14$ min and $\tau_{major} = 38.38$ min.
15. Compound **2b** was purified by flash chromatography (Et_2O/pentane, 2/1): yield 60%; mp 103 °C; as reported before,[11] the enantioselectivity of the α-aminated product is only reduced by a few percent by purification using silica column chromatography: $[\alpha]_D^{25}$ −24.1 (*c* 0.1, DCM, 81% ee); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32 (m, 10H, Ar), 6.88 (s, 1H, NH), 5.10 (m, 5H, CH_2Ph and H-2), 2.47–1.65 (m, 8H, H-3, H-4, H-5, and H-6); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 207.54 (C-1), 156.09 (CO), 135.63–127.52 (Ar), 68.21, 67.56 (*C*H_2Ph), 65.73 (C-2), 41.28 (C-6), 30.64, 26.88, 26.66, 24.22 (C-2, C-3, C-4, and C-5); Anal. Calcd for $C_{22}H_{24}N_2O_5$ (396.17): C, 66.65; H, 6.10; N, 7.07. Found C, 66.39; H, 5.88; N, 7.19.