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Direct L-Proline-Catalyzed Asymmetric α-Amination of Ketones

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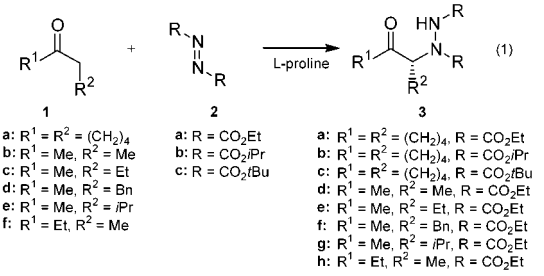
The stereoselective formation of C−N bonds from simple and easily available starting materials is an important task in organic chemistry as molecules containing this functionality are chiral key elements in many important compounds.

There are several catalytic enantioselective procedures for the stereoselective formation of α-amino carbonyl compounds of which the Strecker[1] and Mannich[2] reactions involve the enantioselective addition to imines. However, the direct enantioselective addition of a nitrogen source to a carbon center will be a simple approach for the formation of a chiral carbon atom bound to a nitrogen atom.[3] The first direct metal-catalyzed α-amination of 2-keto esters has recently been presented,[4] which leads to a simple synthetic approach to optically active *syn*-*β*-amino-α-hydroxy esters.

In this communication the first catalytic enantioselective direct α-amination reactions of ketones using azodicarboxylates as the nitrogen source are presented (eq 1). These reactions are catalyzed by L-proline[5] and give access to highly valuable optically active α-hydrazino ketones, which by further transformations can give important optically active compounds such as α-aminated ketones and alcohols.



The results for some of the screening investigations for the enantioselective direct α-amination of cyclohexanone **1a** and butanone **1b** by the azodicarboxylates **2a**−**c** catalyzed by L-proline (eq 1) under various reaction conditions are presented in Table 1.

The L-proline (20 mol %)-catalyzed direct enantioselective α-amination of cyclohexanone **1a** by diethyl azodicarboxylate (DEAD) **2a** proceeds in high yield and the α-hydrazino ketone **3a** is obtained in up to 84% ee in the solvents studied with the best results obtained in 1,2-dichloroethane (Table, 1, entry 1−4). The reaction also proceeds well using the azodicarboxylates **2b**,**c**; however, the enantioselectivities of the corresponding α-hydrazino ketones **3b**,**c** are slightly lower (entry 5,6) compared to those resulting from the use of **2a**. The direct α-amination of butanone **1b** by **2a** proceeds also in high yield and with an improvement of the enantioselectivity compared to **1a**. In acetonitrile as the solvent, the α-hydrazino ketone **3d** is obtained in 96% ee (entry 8). The

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Table 1. Enantioselective α-Amination of Cyclohexanone **1a** and Butanone **1b** by the Azodicarboxylates **2a**−**c** Catalyzed by L-Proline under Various Reaction Conditions at Room Temperature[a]

entry	ketone	azodicarboxylate	cat. load. (%)	solvent	reac. time[b] (h)	product	ee[c] (%)
1	**1a**	**2a**	20	CH_2Cl_2	11	**3a**[d]	79
2	**1a**	**2a**	20	$Cl(CH_2)_2Cl$	44	**3a**	84
3	**1a**	**2a**	20	MeCN	2.5	**3a**	65
4[e]	**1a**	**2a**	20	MeCN	66	**3a**	82
5	**1a**	**2b**	20	MeCN	6	**3b**[d]	59
6	**1a**	**2c**	20	MeCN	52	**3c**[d]	59
7	**1b**	**2a**	20	CH_2Cl_2	76	**3d**	91
8	**1b**	**2a**	20	MeCN	52	**3d**	96
9[f]	**1b**	**2a**	20	Neat	65	**3d**	92
10[f]	**1b**	**2a**	10	Neat	65	**3d**	93
11[f]	**1b**	**2a**	5	Neat	65	**3d**	93
12[g]	**1b**	**2a**	10	MeCN	10	**3d**	95

[a] See Supporting Information for details. [b] After full conversion of **2**. [c] ee determined by chiral GC using Chrompack CP Chiralsil-Dex C*β* or Astec G-TA columns. [d] Approximately 10% of the double addition product is formed. [e] Reaction performed at −24 °C. [f] Reactions are performed with 2 equiv of the ketone. [g] The reaction is performed with 5 equiv of the ketone.

latter reaction can also take place as a neat reaction by just adding **2a** and L-proline to ketone **1b**. Under these conditions the α-aminated adduct **3d** is obtained with excellent enantioselectivities in the presence of only 5 mol % of L-proline as the catalyst (entry 9−11). It should be noted that the reactions are very regioselective as <10% yield of the product obtained from amination of the methyl group is formed.

The simplicity of the reaction conditions for the L-proline-catalyzed direct enantioselective α-amination reaction and isolation procedure should be noted: the reactions are conducted at ambient conditions, and the α-hydrazino ketones are isolated by addition of water to the reaction mixture and extraction with diethyl ether followed by evaporation of the solvent and excess ketone.

The potential and scope of the L-proline (10 mol %)-catalyzed direct enantioselective α-amination is demonstrated by the reaction of the ketones **1a**−**f** with DEAD **2a** (eq 1). The results are presented in Table 2.

The direct α-amination of the various ketones **1a**−**f** by DEAD **2a** in the presence of L-proline takes place with excellent enantioselectivities, and the reaction is highly regioselective as the amination takes place at the highest substituted carbon atom. The α-hydrazino ketone **3a** derived from cyclohexanone **1a** is formed in good yield and with 84% ee (Table 2, entry 1). Butanone **1b** reacts with **2a**, and adduct **3d** is obtained in 80% yield and with 95% ee (entry 2). Increasing the length of the R^2 substituent from methyl to ethyl and benzyl increases the enantioselectivity of the α-hydrazino ketones. For 2-pentanone **1c**, the product (**3e**) is formed with 98% ee (entry 3) and for benzylacetone **1d** the enantiomeric excess of **3f** is 98% ee (entry 4). 4-Methyl-2-pentanone **1e** is aminated by **2a** in a highly enantioselective reaction and the

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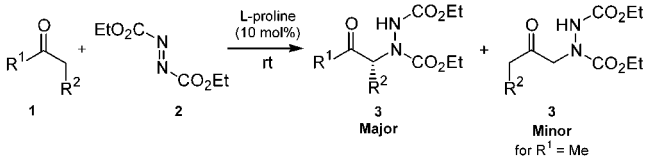
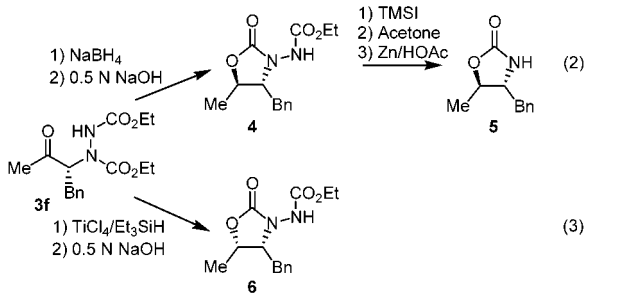
Table 2. L-Proline (10 mol %)-Catalyzed Enantioselective α-Amination of Ketones **1a**−**f** with Diethyl Azodicarboxylates **2a** in MeCN[a]



entry		ketone R1	ketone R2	react. time (h)	ratio[b] (major: minor)	yield[c] (%)	ee[d] (%)
1[e]	**1a**	$(CH_2)_4$		23	−	**3a** − 67	84 (79)
2	**1b**	Me	Me	10	91:9	**3d** − 80[f]	95 (93)
3	**1c**	Me	Et	20	81:19	**3e** − 77[f]	98 (96)
4	**1d**	Me	Bn	24	82:18	**3f** − 92[f]	98 (94)
5	**1e**	Me	*i*Pr	96	76:24	**3g** − 69[f]	99 (99)
6	**1f**	Et	Me	60	−	**3h** − 79	94 (93)

[a] See Supporting Information for details. [b] Determined by ^{1}H NMR. [c] Isolated yield after column chromatography. [d] ee determined after workup by either chiral GC or HPLC. The values in parentheses are the enantiomeric excess after column chromatography. [e] 1,2-Dichloroethane was used as solvent. [f] Isolated total yield of both regioisomers.

Scheme 1

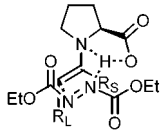


α-aminated adduct **3g** is obtained with 99% ee (entry 5) The symmetric ketone, 3-pentanone **1f**, reacts smoothly with **2a** in the presence of L-proline as the catalyst giving, the corresponding α-hydrazino ketone **3h** in good yield and an excellent enantioselectivity of 94% ee (entry 6).

The stereocenter formed in the reaction should be expected to be prone to racemization due to the electron-withdrawing substituents attached to it. However, as it appears from the results in Table 2, the enantioselectivities of the α-aminated adducts are only reduced by a few percent by purification using silica column chromatography.

Several different valuable optically active products can be obtained from the L-proline-catalyzed direct α-amination reaction of ketones. In Scheme 1, the diastereoselective reduction of the keto functionality is presented. Reaction of the α-aminated adduct **3f** with $NaBH_4$, followed by treatment with NaOH, gives the corresponding *syn*-α-amino alcohol as the *N*-amino oxazolidinone **4** in a diastereomeric ratio of 6.5:1. Further reactions with TMSI, followed by acetone and Zn/HOAc, give the oxazolidinone **5** (eq 2). The absolute configuration of **3f** was assigned (*R*) by its conversion to oxazolidinone **5** having known absolute and relative configuration.[6] The other diastereomer, the *anti*-α-amino alcohol, obtained as the *N*-amino oxazolidinone **6** (diastereomeric ratio 1:7.5) can also be obtained by reduction of **3f** with triethylsilane and $TiCl_4$ (eq 3).[7] The α-hydrazino ketones formed by the direct α-amination of ketones catalyzed by L-proline thus offers a new and simple approach to *syn*- and *anti*-α-amino alcohols, which are highly valuable chiral fragments in many different compounds and very usable as chiral starting materials.[8]

On the basis of the absolute configuration, we propose transition-state model **7** to account for the regio- and enantioselectivity of the α-amination reaction. The enamine-intermediate formed from the ketone and L-proline has the large R_L-substituent *anti* to the carboxylic acid to reduce steric repulsion, and the enamine is formed to the secondary carbon atom due to its higher stability. The approach of the azodicarboxylate from the same face as the carboxylic acid might be directed by interaction of the proton of the carboxylic acid with the nitrogen atom.



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In summary, we have developed the first organo-catalytic direct α-amination of ketones applying azodicarboxylates as the nitrogen fragment and L-proline as the catalyst. The reactions proceed with excellent enantioselectivity and give an easy access to optically active α-hydrazino and α-amino ketones, and *syn*- and *anti*-α-amino alcohols.

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Supporting Information Available: Complete experimental procedure and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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