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Asymmetric Strecker Synthesis of α-Amino Acids via a Crystallization-Induced Asymmetric Transformation Using (*R*)-Phenylglycine Amide as Chiral Auxiliary

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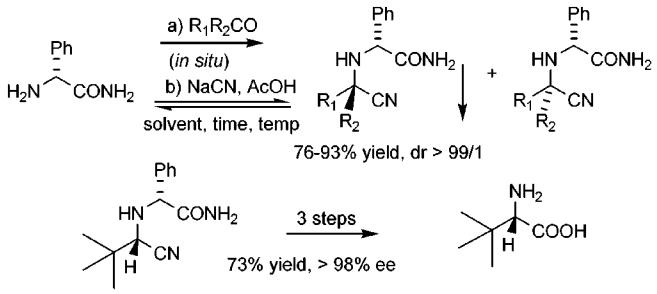
ABSTRACT



Diastereoselective Strecker reactions based on (*R*)-phenylglycine amide as chiral auxiliary are reported. The Strecker reaction is accompanied by an in situ crystallization-induced asymmetric transformation, whereby one diastereomer selectively precipitates and can be isolated in 76–93% yield and dr > 99/1. The diastereomerically pure α-amino nitrile obtained from pivaldehyde (R_1 = *t*-Bu, R_2 = H) was converted in three steps to (*S*)-*tert*-leucine in 73% yield and >98% ee.

The asymmetric synthesis of α-amino acids and derivatives is an important topic as a result of their extensive use in pharmaceuticals and agrochemicals and as chiral ligands. Many highly enantioselective approaches have been reported.[1] Industrial production of α-amino acids via the Strecker reaction is historically one of the most versatile methods to obtain these compounds in a cost-effective manner, making use of inexpensive and easily accessible starting materials.[2] The Strecker reaction is usually followed by resolution of the racemic amino acid or amino acid amide obtained after hydrolysis of the amino nitrile.[3] Either process leads to a maximum yield of 50% if the unwanted enantiomer is not racemized. In principle, asymmetric synthesis ap-

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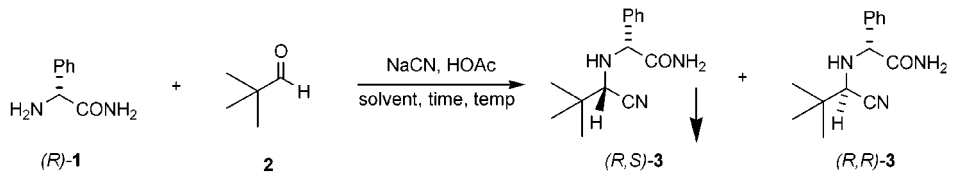
Table 1. Asymmetric Strecker Reactions of (*R*)-Phenylglycine Amide **1** and Pivaldehyde **2**



entry	sovent	temp (°C)	time (h)	yield (%)[a]	dr (*R*,*S*)-**3**/(*R*,*R*)-**3**[b]
1	MeOH	rt	20	80	65/35
2	MeOH/2-PrOH, 1/9[c]	rt	22	51	99/1
3	2-PrOH	rt	22	84	88/12
4	2-PrOH/*t*-BuOH, 4/1[c]	rt	20	65	96/4
5	MeOH/H_2O, 35/1[c]	rt	20	69	81/19
6	H_2O	55	24	81	85/15
7	H_2O	60	24	84	96/4
8	H_2O	65	24	84	98/2
9	H_2O	70	24	93	>99/1

[a] Isolated yield after: evaporation of the solvent (entry 1) or filtration of precipitated amino nitrile **3** (entries 2−9). [b] The dr was determined by ^{1}H NMR spectroscopy. [c] Ratio in volume/volume.

proaches that lead to a maximum yield of 100% of a single enantiomer are more advantageous.

Recently several catalytic asymmetric Strecker reactions leading to N-protected amino nitriles in high ee's and high yields have been published.[4] Alternatively, diastereoselective Strecker syntheses using a broad variety of chiral inducing agents, like α-arylethylamines,[5] β-amino alcohols and derivatives,[6] amino diols,[7] sugar derivatives,[8] and sulfinates[9] have been reported to provide the α-amino nitriles with varying diastereoselectivities. A major drawback of these chiral auxiliaries can be cost and/or availability, because they are used in stoichiometric amounts and in principle lost during the conversion. Furthermore, in many cases the α-amino nitriles need to be purified in a separate step to obtain diastereomerically pure compounds. Purification requires, for example, crystallization or chromatography, which may lead to losses. An interesting solution to these problems would be a crystallization-induced asymmetric transformation,[10,11] in which one diastereomer precipitates and the other epimerizes in solution via the corresponding imine. This would lead both to high yield and high diastereoselectivity in a practical one-pot procedure.

Recently, optically pure (*R*)-phenylglycine amide **1** became readily accessible as a result of application on an industrial scale as key intermediate in the enzymatic synthesis of β-lactam antibiotics.[12] Either aminopeptidase-catalyzed hydrolysis of racemic phenylglycine amide[3] or asymmetric transformation of racemic phenylglycine amide with (*S*)-mandelic acid as resolving agent[13] can be used to prepare **1**. Because of its ready availability on a large scale and its anticipated easy removal via catalytic hydrogenolysis, we decided to investigate the application of (*R*)-phenylglycine amide **1** as chiral auxiliary in asymmetric synthesis.

In this paper, the first two examples of the use of (*R*)-phenylglycine amide in asymmetric Strecker reactions are presented. Pivaldehyde and 3,4-dimethoxyphenylacetone have been used as starting materials, which lead, respectively, to enantiomerically enriched *tert*-leucine and α-methyl-dopa, two important nonproteogenic α-amino acids for pharmaceutical applications. In addition, *tert*-leucine has considerable utility as a chiral building block.[14]

The asymmetric Strecker reaction of (*R*)-phenylglycine amide **1**, pivaldehyde **2** and HCN generated in situ from NaCN and AcOH was studied (Table 1). Amino nitriles (*R*,*S*)-**3** and (*R*,*R*)-**3** were obtained in 80% yield in a ratio of 65:35 by stirring an equimolar mixture of **1** (as AcOH salt)

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with **2** and NaCN in MeOH overnight at room temperature, followed by evaporation of the solvent (entry 1). The diastereomeric ratio of (*R*,*S*)-**3** and (*R*,*R*)-**3** was determined by ^{1}H NMR on the basis of the relative integration between the *t*-Bu signals at 1.05 ppm for (*R*,*S*)-**3** and 1.15 ppm for (*R*,*R*)-**3**. The assignments have been made on the basis of the absolute configuration as established by X-ray analysis and conversion to (*S*)-*tert*-leucine (vide infra).

Because in methanol crystallization of amino nitrile **3** did not take place, first the solvent was varied in order to attempt to find conditions for a crystallization-induced asymmetric transformation. At a MeOH/2-PrOH ratio of 1/9 amino nitrile (*R*,*S*)-**3** was isolated in 51% yield and dr 99/1 (entry 2). Other combinations of alcoholic solvents failed to lead to a higher yield of precipitated (*R*,*S*)-**3** in high dr (entries 3 and 4). On further screening of solvents it was observed that upon addition of H_2O to the methanol solution selective precipitation of amino nitrile (*R*,*S*)-**3** occurred giving (*R*,*S*)-**3** and (*R*,*R*)-**3** in a ratio of 81:19 and 69% yield (entry 5). The asymmetric Strecker reaction was further studied in H_2O alone using temperature as a variable. The results of these experiments are given in Table 1 (entries 6−9). After addition of NaCN/AcOH at 23−28 °C to (*R*)-phenylglycine amide **1** and pivaldehyde **2** in H_2O, the mixture was heated to the indicated temperatures.

After approximately 24 h of stirring, the mixture was cooled to 30 °C and the precipitated amino nitrile filtered and analyzed by ^{1}H NMR to determine the dr. The results in Table 1 show that optimal results were achieved after 24 h of stirring in water at 70 °C. The amino nitrile (*R*,*S*)-**3** was obtained in 93% yield and a dr > 99/1 via a crystallization-induced asymmetric transformation (entry 6). At lower temperatures the epimerization reaction is slower.[15]

The crystallization-induced asymmetric transformation in water at 70 °C is verified further by the observed increase of the dr of (*R*,*S*)-**3** as a function of the reaction time (Figure 1). After 30 h the precipitated (*R*,*S*)-**3** was obtained with a dr > 99/1.

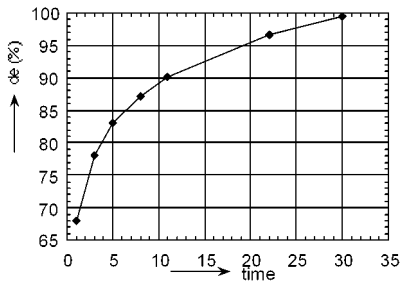


Figure 1. Crystallization-induced asymmetric transformation of amino nitrile **3** in water at 70 °C.

The observed diastereoselectivity in the asymmetric Strecker step via the crystallization-induced asymmetric transformation can be explained as shown in Figure 2. Apparently, the *re*-face addition of CN^- to the intermediate imine **4** is preferred at room temperature in methanol and results in a dr 65/35. At elevated temperatures in water the diastereomeric outcome and yield of the process is controlled by the reversible reaction of the amino nitriles **3** to the intermediate imine and by the difference in solubilities of both diastereomers under the applied conditions.[16,17]

(15) At higher temperatures, lower yields of product were found, probably by degradation of amino nitrile.

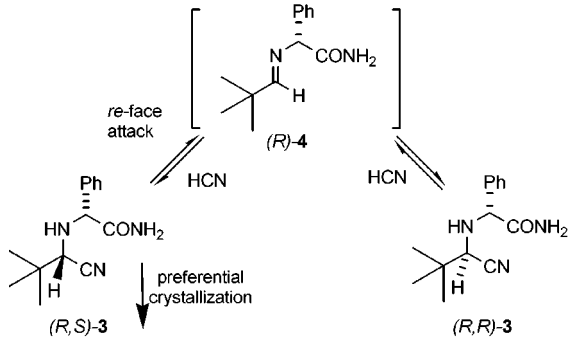


Figure 2. Crystallization-induced asymmetric transformation of amino nitrile **3**.

The absolute configuration of amino nitrile (*R*,*S*)-**3** was confirmed by X-ray analysis as shown in Figure 3[18] and by conversion to (*S*)-*tert*-leucine.

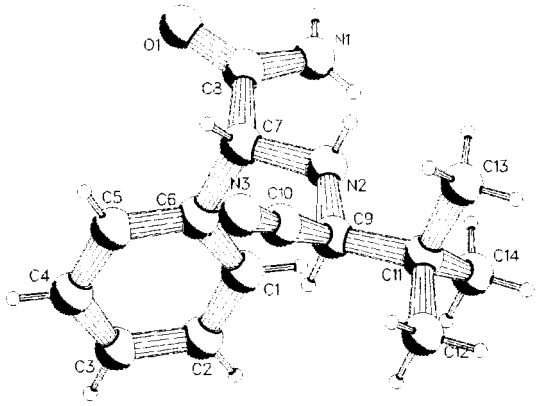


Figure 3. X-ray structure of amino nitrile (*R*,*S*)-**3**.

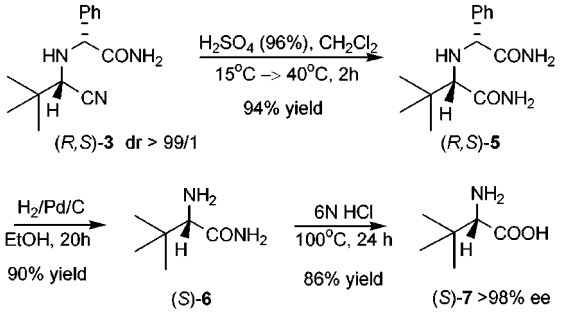
Conversion of the amino nitrile (*R*,*S*)-**3** to (*S*)-*tert*-leucine **7** was accomplished via the reaction sequence shown in Scheme 1. Hydrolysis of (*R*,*S*)-**3** to the diamide (*R*,*S*)-**5**

(16) For example, in the case of phenylacetone (not illustrated) it was found that in solution the initially formed minor isomer preferentially precipitated under crystallization conditions.

(17) For a discussion of asymmetric transformation of α-amino nitriles with mandelic acid, see: Hassan, N. A.; Bayer, E.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3747.

(18) The crystal structure of (*R*,*S*)-**3** has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 154034.

Scheme 1



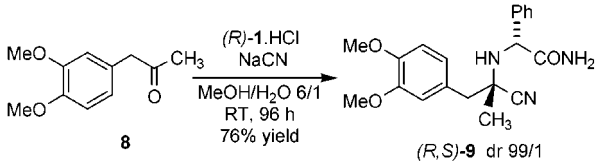
proceeded smoothly in concentrated H_2SO_4 in high yield and without racemization.

Removal of the phenylacetamide group under 2 atm of H_2 with catalytic Pd/C afforded (*S*)-*tert*-leucine amide **6** in 90% yield. Finally, hydrolysis of the amide was accomplished by heating in 6 N HCl at 100 °C to give (*S*)-*tert*-leucine **7** in 86% yield and >98% ee. The absolute configuration assignment, (*S*), was made by comparison with an authentic sample.[3] Obviously, other routes to convert the amino nitrile derivatives to the amino acid can be envisaged and are under investigation.

The crystallization-induced asymmetric transformation, using (*R*)-phenylglycine amide **1** as chiral auxiliary in diastereoselective Strecker reactions, was further explored with 3,4-dimethoxyphenylacetone **8** (Scheme 2).

The optimized asymmetric Strecker reaction of (*R*)-phenylglycine amide **1** (used as HCl salt) and an equimolar amount of 3,4-dimethoxyphenylacetone **8** in MeOH/H_2O (6/1 v/v) gave, after addition of NaCN (30% aqueous solution) and stirring for 96 h at room temperature, the nearly diastereomerically pure (dr > 99/1) amino nitrile **9** as a solid in 76% isolated yield. The dr could easily be determined by

Scheme 2



^{1}H NMR analysis. It was found that in solution at room temperature an equilibrium of 55:45 exists between the two diastereomers (*R*,*S*)-**9** and (*R*,*R*)-**9**. Clearly, again a crystallization-induced asymmetric transformation has occurred.

In summary, (*R*)-phenylglycine amide **1** is an excellent chiral auxiliary in the asymmetric Strecker reaction with pivaldehyde or 3,4-dimethoxyphenylacetone. Nearly diastereomerically pure amino nitriles can be obtained via a crystallization-induced asymmetric transformation in water or water/methanol. This practical one-pot asymmetric Strecker synthesis of (*R*,*S*)-**3** in water leads to the straightforward synthesis of (*S*)-*tert*-leucine **7**. Since (*S*)-phenylglycine amide is also available, this can be used if the other enantiomer of a target molecule is required. More examples are currently under investigation to extend the scope of this procedure.[19]

Acknowledgment. Mr. A. Meetsma of the department of crystallography of the University of Groningen is acknowledged for the X-ray structure of (*R*,*S*)-**3**.

Supporting Information Available: Procedures and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Several other amino nitriles could be obtained as crystalline materials from H_2O/MeOH mixtures, e.g., $R_1 = {}^i$Pr, R_2 = H; R_1 = Ph, R_2 = Me; $R_1 = {}^i$Pr, R_2 = Me. Conditions are being sought to obtain also a crystallization-induced asymmetric transformation in these cases.