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

Wilhelmus H. J. Boesten,[†] Jean-Paul G. Seerden,[‡] Ben de Lange,^{*,†} Hubertus J. A. Dielemans,[†] Henk L. M. Elsenberg,[†] Bernard Kaptein,[†] Harold M. Moody,[†] Richard M. Kellogg,[‡] and Quirinus B. Broxterman^{*,†}

DSM Research Life Sciences-Organic Chemistry and Biocatalysis, P.O. Box 18, 6160 MD Geleen, and Syncom B.V., Kadijk 3, 9747 AT Groningen, The Netherlands

rinus.broxterman@dsm-group.com

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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 (R₁ = *t*-Bu, R₂ = 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-

[†] DSM Research Life Sciences-Organic Chemistry & Biocatalysis. E-mail for Ben de Lange: Ben-B.Lange-de@dsm-group.com.

[‡] Syncom B.V.

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

	Ph () I NaCN, HOA	Ph ⊒ HN ∕CO		Ph - CONH₂
		H solvent, time, te			CN
	(<i>R</i>)-1 2		(R,S) -3	(R,I	₹)- 3
entry	sovent	temp (°C)	time (h)	yield (%) ^a	$\mathrm{dr}\;(R,S)\textbf{-}3/(R,R)\textbf{-}3^{b}$
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/ <i>t</i> -BuOH, 4/1 ^c	rt	20	65	96/4
5	MeOH/H ₂ O, 35/1 ^c	rt	20	69	81/19
6	H ₂ O	55	24	81	85/15
7	H ₂ O	60	24	84	96/4
8	H ₂ O	65	24	84	98/2
9	H ₂ O	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 ¹H 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 sulfinates⁹ 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 amide³ or asymmetric transformation of racemic phenylglycine amide with (*S*)mandelic acid as resolving agent¹³ 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 ¹H 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 H₂O 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 H₂O 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 ¹H 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 crystal-lization-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 transfor-



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

mation 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}

The absolute configuration of amino nitrile (R,S)-**3** was confirmed by X-ray analysis as shown in Figure 3¹⁸ 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**

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

⁽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.



proceeded smoothly in concentrated H₂SO₄ in high yield and without racemization.

Removal of the phenylacetamide group under 2 atm of H₂ 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/H₂O (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



¹H 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

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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 H₂O/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.