Asymmetric Catalysis of the Strecker Amino Acid Synthesis by a Cyclic Dipeptide

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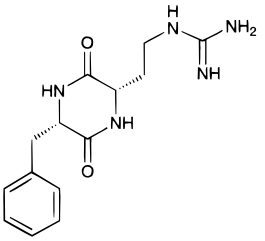
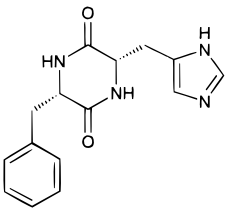
The condensation of aldehydes with ammonia and hydrogen cyanide to form α-amino nitriles followed by hydrolysis of the nitrile groups (the Strecker synthesis) is the oldest known method for the *de novo* synthesis of α-amino acids.[1] The ever-increasing interest in nonproteinogenic α-amino acids in a variety of scientific disciplines has prompted the development of numerous methods for the asymmetric synthesis of α-amino acids.[2] Among the methods developed, several enantioselective versions of the Strecker synthesis in which optically active amines replace ammonia to serve as chiral auxiliaries, with moderate to good levels of asymmetric induction, have been reported.[3−5] To avoid the problems inherent to the use of chiral auxiliaries (e.g., cost) one must instead use a chiral catalyst. In this communication we report a version of the Strecker synthesis employing such a chiral catalyst, permitting the conversion of aldehydes to (*S*)-amino acids in high yield and, in some cases, exceptionally high enantiomeric excess.

The catalyst employed in our studies (**1**) is a cyclic dipeptide composed of (*S*)-phenylalanine and the lower homologue of (*S*)-arginine, (*S*)-α-amino-γ-guanidinobutyric acid. The design of **1** proceeded from *cyclo*[(*S*)-His-(*S*)-Phe] (**2**), a cyclic dipeptide that has previously been shown to catalyze the enantioselective formation of cyanohydrins from aldehydes.[6] While **2** fails to afford any asymmetric induction in the mechanistically similar Strecker synthesis,[7] it was our belief that this resulted from the failure of the imidazole side chain of **2** to accelerate proton transfer in the reaction of HCN with the putative aldimine intermediate in the Strecker synthesis. Replacement of the imidazole of **2** with a more basic guanidine side chain was predicted to afford a catalyst capable of accelerating proton transfer in the Strecker synthesis.

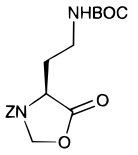


1

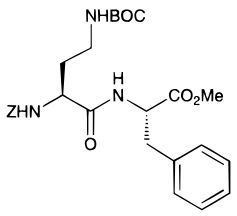


2

The synthesis of **1** begins with benzyloxycarbonyl-(*S*)-glutamic acid, which upon protection as the oxazolidinone and subsequent Curtius rearrangement[8] is converted to the carbamate **3** in 81% yield. Hydrolysis of the oxazolidinone using KOH/MeOH and coupling with (*S*)-phenylalanine methyl ester[9] using 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide/1-hydroxybenztriazole afford the dipeptide **4** (79% yield). The diketopiperazine **5** was formed in quantitative yield by catalytic hydrogenolysis of the benzyloxycarbonyl group of **4** followed by cyclization in refluxing methanol. Deprotection of **5** using HCl in ethyl acetate was followed by guanidylation with 3,5-dimethylpyrazole-1-carboxamidine nitrate[10] to afford the catalyst **1**. Reverse phase HPLC purification of **1** produces the catalyst in 45% yield from **5**.



3
(Z = $CO_2CH_2C_6H_5$; BOC = CO_2tBu)



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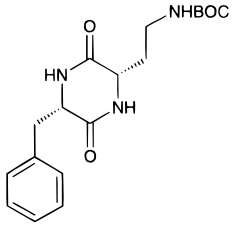

5

Initial experiments involved treatment of benzaldehyde with ammonia and hydrogen cyanide in the presence of 2 mol % of catalyst **1** under a variety of reaction conditions. The enantiomeric purity of the resultant α-amino nitrile was determined by derivatization with (+)-MTPA chloride[11] and comparison

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(9) The possibilty of epimerization during basic hydrolysis of the oxazolidinone was excluded by coupling the resultant acid to both (*S*)- and (*R*)-phenylalanine methyl ester. The diastereomers thus obtained were distinguishable by ^{1}H-NMR and free of diastereomeric impurities.

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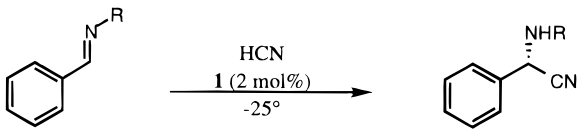
Table 1. Conversion of Substituted Imines to α-Amino Nitriles



R	solvent	yield,[a] %	ee,[b] %
4-OMePhCH$_2$	CH$_3$OH	97	>99
3,4,5-(OMe)$_3$PhCH$_2$	CH$_3$OH	98	>98
Ph$_2$CH	CH$_3$OH	95	>99
t-BuOCO	*i*-PrOH	88	75

[a] Based on ^{1}H-NMR of crude product. [b] Determined by ^{19}F-NMR of (+)-MTPA derivatives.

of the ^{19}F-NMR spectrum of the crude product with that of an authentic racemate derivatized in identical fashion. The configuration of the products was established by conversion of underivatized α-amino nitriles to phenylglycine and determination of the sign of its optical rotation.[12] These experiments proved unsatisfactory due to the unexpected configurational instability of the initial product, 2-aminophenylacetonitrile. As a consequence, the reactions of *N*-substituted imines were studied instead (Table 1).

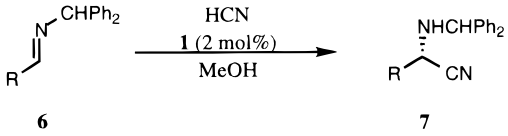
In this version of the reaction, a solution of a preformed imine and **1** (2 mol %) in methanol was treated at −25 °C with hydrogen cyanide (2 equiv). Intriguingly, the presence of alkyl groups on the imine nitrogen resulted in the formation of (*S*)-α-amino nitriles in high yield and exceptionally high enantiomeric excess. Moreover, all the *N*-substituted α-amino nitriles appear to be configurationally stable at room temperature, in marked contrast to the parent 2-aminophenylacetonitrile and in accord with literature precedent.

The various *N*-alkyl α-amino nitriles were hydrolyzed according to literature conditions[12] (6 N HCl, 60 °C, 6 h) to attempt simultaneous hydrolysis of the nitrile and deprotection of the nitrogen. Of the derivatives examined, only the benzhydryl-protected α-amino nitrile proved satisfactory in this regard. When the optically active *N*-benzhydryl-α-amino nitrile was subjected to these conditions, (*S*)-phenylglycine was obtained without loss of optical activity as determined by optical rotation.[13] Benzaldehyde can thus be converted to (*S*)-phenylglycine in three steps, in 92% yield and >99% ee.

The generality of this methodology was explored by subjecting various *N*-benzhydryl imines derived from aromatic and aliphatic aldehydes to the reaction conditions described above (Table 2). Enantiomeric purity of the product α-amino nitriles was determined by chiral HPLC chromatography using a Daicel ChiralPak AD column. Absolute configuration was assigned by hydrolysis of the α-amino nitriles and comparison of the optical rotations of the α-amino acids to literature values.[14−18]

The products derived from aromatic aldehydes (entries 1−7) were obtained generally in high enantiomeric excess, although the electron-deficient 3-nitro (entry 8) and 3-pyridyl (entry 9)

Table 2. Conversion of *N*-Benzhydryl Imines to α-Amino Nitriles



6 **7**

entry	R	temp, °C	yield,[a] %	ee,[b] %
1	Ph (**6**−**7a**)	−25	97	>99
2	4-ClPh (**6**−**7b**)	−25	97	83
3	4-ClPh (**6**−**7b**)	−75	94	>99
4	4-OMePh (**6**−**7c**)	−25	96	64
5	4-OMePh (**6**−**7c**)	−75	90	96
6	3-ClPh (**6**−**7d**)	−75	80	>99
7	3-OMePh (**6**−**7e**)	−75	82	80
8	3-NO$_2$ (**6**−**7f**)	−75	71	<10
9	3-pyridyl (**6**−**7g**)	−75	86	<10
10	2-furyl (**6**−**7h**)	−75	94	32
11	*i*-Pr (**6**−**7i**)	−75	81	<10
12	*t*-Bu (**6**−**7j**)	−75	80	17

[a] Based on ^{1}H-NMR of crude product. [b] Determined by chiral HPLC chromatography using a Daicel ChiralPak AD column.

derivatives afforded essentially racemic products. In light of this striking contrast and the configurational instability of 2-aminophenylacetonitrile (*vide supra*), the question arose as to whether the low enantioselectivities of entries 8 and 9 resulted from racemization of the product α-amino nitriles **7f**,**g**. Although no deuterium exchange was observed when the ^{1}H-NMR spectra of **7f**,**g** were examined, racemization via rapid reversibility of HCN addition cannot be discounted at this point. In contrast to the previous examples, the 2-furyl derivative (entry 10) and the aliphatic examples (entries 11 and 12) afforded low selectivity. In all cases, the enantioselectivity could be improved by lowering the reaction temperature, but preliminary studies indicate that increasing the amount of catalyst did not improve the outcome of any of the problematic reactions. In all cases examined, the (*S*)-isomer was the major product.

Despite the structural resemblance between **1** and **2** and the mechanistic similarities between the reactions they catalyze, several important differences exist which belie the apparent similarity. First, whereas **2** operates as a heterogeneous catalyst, **1** is fully soluble under the conditions of the Strecker synthesis. Second, although both **1** and **2** are composed of (*S*)-amino acids, they catalyze formation of *enantiomeric* products. Additionally, studies conducted on **2** have demonstrated a dependence of the enantioselectivity on the method of crystallization of the catalyst,[6b] solvent viscosity,[6c] and enantioselective autocatalysis by the product itself.[6d] Studies are ongoing in our laboratories to investigate the effects of these and other factors on the enantioselectivity of the Strecker synthesis using catalyst **1**.

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Supporting Information Available: Experimental procedures for the synthesis of **1**, the products listed in Table 2, and characterization of the amino acid products (6 pages). Ordering information is given on any current masthead page.

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