Asymmetric Strecker Synthesis Using Enantiopure Sulfinimines and Diethylaluminum Cyanide: The Alcohol Effect

Franklin A. Davis,*,† Padma S. Portonovo,† Rajarathnam E. Reddy,‡ and Yu-hung Chiu‡

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, and Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

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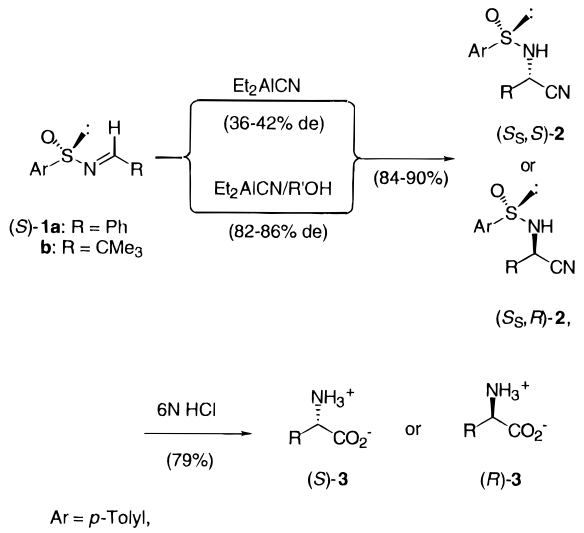
The development of new and improved methods for the asymmetric synthesis of protein and nonprotein α-amino acids is of considerable current interest because of their importance in biological systems and their exceptional utility as chiral building blocks.[1] Of the many methods used to prepare α-amino acids, the asymmetric Strecker synthesis should hold particular prominence because of its simplicity.[2] Unfortunately, the auxiliary-controlled nucleophilic addition of cyanide or its equivalent to enantiopure imines is problematic for several reasons. First, the diastereoselectivity, with rare exception, is mostly modest (22−60% de), although fractionation can often be used to give a diastereomerically pure product.[2] Second, removal of the chiral auxiliary without destroying or epimerizing the α-amino acid is a frequent problem.

Recently, we reported that diethylaluminum cyanide (Et_2AlCN) adds to enantiopure sulfinimines (thiooxime *S*-oxides) **1** to give α-amino nitriles **2** (Scheme 1).[3] Treatment of **2** with acid removes the chiral auxiliary and hydrolyzes the nitrile, affording the α-amino acid **3** in good to excellent yield and without epimerization, thus eliminating one of the problems with the Strecker synthesis protocol. However, as observed in the other procedures, the diastereoselectivities never exceeded 54%.[3,4] We now report that addition of 2-propanol (*i*-PrOH) to the Et_2AlCN−sulfinimine **1** mixture results in a dramatic improvement in the diastereoselectivity and a practical asymmetric Strecker synthesis.

Formation of the amino nitrile **2** typically involved addition of 1.0−1.5 equiv of Et_2AlCN to 1.0 mmol of the sulfinimine **1**[5,6] in THF at −78 °C. When 2-propanol was used it was first added to Et_2AlCN at rt, and this mixture was combined with a −78 °C solution of 1.0 mmol of **1** in THF. After 10 min, the solution was warmed to rt, monitored by TLC, cooled to −78 °C, and quenched by addition of 0.05 N HCl. The reaction mixture was diluted with EtOAc and water and filtered through Celite powder. Drying and removal of the organic solvent afforded the crude amino nitriles **2** (Table 1). A simple crystallization from ether afforded the diastereomerically pure products **2a**,**b** in 80−90% yield.[7] Sulfinimines **1a**[5] and **1b**[6] were prepared in enantiopure form as previously described.

Scheme 1



The results summarized in Table 1 indicate that the de's and yields are highly dependent on the ratio of the sulfinimine **1** to Et_2AlCN and *i*-PrOH. At low ratios of Et_2AlCN the reaction is slow, and optimum results are obtained with an excess (1.5 equiv) of this reagent (compare entries 1 and 8 with 2 and 9). The addition of 1.0 equiv of *i*-PrOH improves the de's from 14−27% to 82−84% (compare entries 2 and 9 with 4, 7, 10, and 14).[8] Addition of **1** to a −78 °C solution of Et_2AlCN/*i*-PrOH had no effect on the selectivity of **2** (entries 5 and 11). The hydrocyanation of **1** appears to be kinetically controlled because increasing the time of reaction has little effect on the diastereoselectivity or yield of **2**. Finally, it is important to note that the rate of hydrocyanation is much faster for the pivalaldehyde sulfinimine **1b** than for **1a**; e.g., hydrocyanation of **1b** was complete within 20 min (entry 10). In a competitive experiment where equal amounts of **1a**/**1b** were treated with 1.5/1.0 equiv of Et_2AlCN/*i*-PrOH, amino nitrile **2a** was not detected; e.g., **2b**:**2a** >95:5.

Consistent with these results is the mechanistic hypothesis outlined in Scheme 2, based in part on the pioneering studies of Nagata et al. on the hydrocyanation of α,β-unsaturated ketones with Et_2AlCN.[9,10] In THF Et_2AlCN exists in equilibrium with the solvated monomer

† Temple University.
‡ Drexel University.

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(2) For excellent reviews on the asymmetric Strecker synthesis see ref 1f−h. See also: Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179.

(3) Davis, F. A., Reddy, R. E.; Portonovo, P. S. *Tetrahedron Lett.* **1994**, *35*, 9351.

(4) A low de of 30% has recently been reported for the addition of Et_2AlCN to an *N*-[1-(triethoxymethyl)ethylidene]sulfinamide. Hua, D. H.; Lagneau, Wang, H.; Chen, C. *Tetrahedron: Asymmetry* **1995**, *6*, 349.

(5) (a) Davis, F. A., Reddy, R. E. Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229. (b) Davis, F. A.; Reddy, R. E. Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037.

(6) Sulfinimine (+)-**1b** has the following properties: mp 73−75 °C: $[\alpha]^{20}_D$ +371.5 (*c* 1.94, $CHCl_3$).

(7) The amino nitriles had the following properties. (S_S,*S*)-**2a**: mp 123−24 °C; $[\alpha]^{20}_D$ +177.4 (*c* 2.2, $CHCl_3$); (S_S,*S*)-**2b**: mp 129−30 °C; $[\alpha]^{20}_D$ +59.2 (*c* 2.2, $CHCl_3$).

(8) Other primary and secondary alcohols behave similarly to 2-propanol. *tert*-Butyl alcohol apparently does not react with Et_2AlCN as evidenced by the lack of ethane formation and the similar de's to those observed in the absence of added alcohol.

(9) Nagata, W.; Yoshioka, M.; Hirai, S. *J. Am. Chem. Soc.* **1972**, *94*, 4635.

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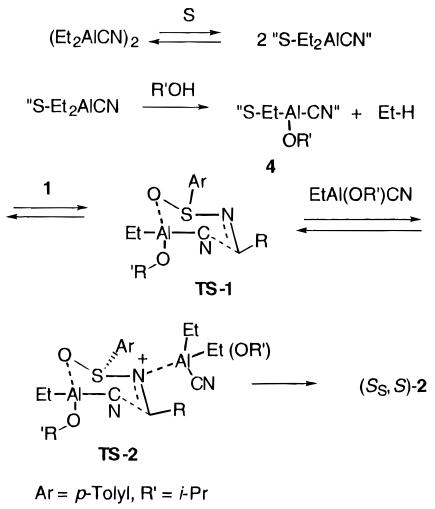
Table 1: Stereoselective Addition of Diethylaluminum Cyanide to Sulfinimimines 1 in THF

		conditions		α-amino nitrile **2**		
entry	sulfinimine **1**	Et_2AlCN/1/R′OH (equiv)	*T* (°C)/time (h)	[S_S,*S*)/(S_S,*R*)][a]	% de	% yield[b]
1	(±)-**1a** (R = Ph)	1.0:1.0:0	−78 to rt/3	71/29	42	76 (18)[c]
2		1.5:1.0:0	−78 to rt/3	64/36	27	94
3		1.5:1.0:1.0 [*i*-PrOH]	−78 to rt/1	90/10	80	64 (33)[c]
4		1.5:1.0:1.0	−78 to rt/3	92/8	84	86
5		1.5:1.0:1.0[d]	−78 to rt/3	92/8	84	83
6		1.5:1.0:1.0	−78 to rt/24	90/10	80	79
7	(+)-**1a** (R = Ph)	1.5:1.0:1.0 [*i*-PrOH]	−78 to rt/3	92/8	84	86
8	(±)-**1b** (R = *t*-Bu)	1.0:1.0:0	−78 to rt/0.5	97/33	33	78 (5)[c]
9		1.5:1.0:0	−78 to rt/0.3	57/43	14	94
10		1.5:1.0:1.0 [*i*-PrOH]	−78 to rt/0.3	89/11	78	91
11		1.5:1.0:1.0[d]	−78 to rt/0.3	89/11	78	91
12		1.5:1.0:1.0	−78 to rt/1	87/13	73	86
13		1.5:1.0:1.0	−78 to rt/24	86/14	72	80
14	(+)-**1b** (R = *t*-Bu)	1.5:1.0:1.0 (*i*-PrOH)	−78 to rt/0.3	90/10	80	91

[a] Determined by ^{1}H NMR on crude material. [b] Isolated material. [c] Recovered starting material **1**. [d] Addition of **1** to Et_2AlCN/*i*-PrOH.

Scheme 2



"S−Et_2AlCN".[10] Addition of 2-propanol to Et_2AlCN results in the irreversible formation of ethyl aluminum cyanide alkoxide **4** as evidenced by the evolution of ethane. We suggest that this species sheds its aluminum-coordinated solvent and forms cyclic **TS-1** which ultimately delivers cyanide to the *Si*-face of the C−N double bond of **1**.[11] However, activation of the imine double bond by a second Lewis acid aluminum species is first required; e.g., **TS-2**. Formation of the iminum ion species **TS-2** explains the higher reactivity of **1** in the presence of excess Et_2AlCN and the fact that **1b** is much more reactive than **1a**.[12,13] The reason for the improved diastereoselectivity of aluminum alkoxide **4** compared to Et_2AlCN is uncertain but may be related to it lower Lewis acidity[14] which enhances selectivity. Furthermore, in addition to highly stereoselective 1,4-hydrocyanation via **TS-1**, 1,2-addition from **TS-2** to the opposite face of the C−N bond by the more reactive Et_2AlCN is also possible. This would result in a deterioration in the selectivity. Additional studies will be necessary to confirm this mechanistic scenario.

Finally, refluxing diastereomeric pure α-amino nitriles **2a**,**b** with 6 N HCl followed by purification on Dowex 50 × 8−100 ion exchange resin afforded enantiomerically pure (>95%) (*S*)-(+)-phenylglycine (**3a**)[15] and (*S*)-(+)-*tert*-leucine (**3b**)[16] in 78% yield. Earlier asymmetric synthesis of *tert*-leucine (**3b**), an important chiral auxiliary,[17] involved more lengthy routes.[18]

In summary, the diastereoselective addition of Et_2AlCN/*i*-PrOH to enantiopure sulfinimines, ammonia imine building blocks,[19] results in a practical asymmetric Strecker synthesis. Studies are currently underway extending this protocol to the asymmetric synthesis of other α-amino acids.

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Supporting Information Available: Experimental details for the preparation of **1a**,**b**, **2a**,**b**, and **3a**,**b** and their ^{1}H and ^{13}C NMR spectra are provided (3 pages).

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(11) Shift reagents studies with tris[3-heptafluoropropylhydroxymethylene-(+)-camphorato]europium(III) indicates that the sulfinyl oxygen is the site of greatest Lewis basicity in **1**.

(12) Under similar conditions, the *N*-(*p*-nitrobenzylidene)sulfinamide **1** (R = *p*-nitrophenyl) fails to react within 3 h. Davis, F. A.; Portonovo, P. S; Fanelli, D. Unpublished results.

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