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ASYMMETRIC STRECKER SYNTHESIS USING ENANTIOPURE SULFINIMINES: A CONVENIENT SYNTHESIS OF α-AMINO ACIDS

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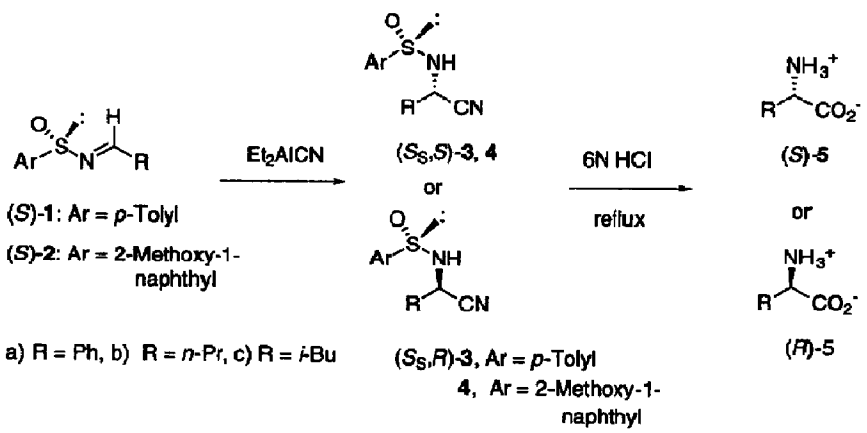
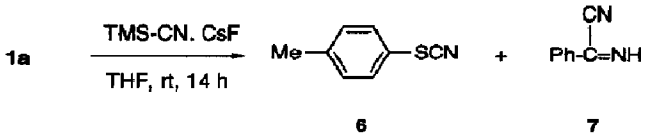
Summary: *Diethylaluminum cyanide adds stereoselectively to enantiopure sulfinimines* ***1*** *and* ***2*** *to give diastereomerically enriched α-amino nitriles* ***3*** *and* ***4*** *which are hydrolyzed in one step to α-amino acids* ***5*** *in >95% ee and good yields.*

The occurrence of protein and non-protein α-amino acids in biological systems[1a] and their exceptional utility as chiral synthons underlie the importance of improved methods for their synthesis in enantiopure form.[1,2,3] This is particularly true for non-proteinogenic or "unnatural" amino acids as their incorporation into peptides can lead to improved bioactivity and stability. The asymmetric Strecker synthesis, reviewed by Williams[2] and Duthaler[3], involves the addition of cyanide [CN] or its equivalent to a chiral imine. In order for this protocol to be generally useful, however, the chiral N-auxiliary needs to be readily available, provide high stereoinduction and be easily removed under nonepimerizing conditions. The 5-amino-4-phenyl-1,3-dioxanes and 1-amino-tetra-*O*-pivaloyl-β-D-glactopyranose auxiliaries, introduced by Weinges[4] and Kunz[5], respectively, afford useful levels of diastereoselection and crystallization often provides the pure diastereoisomers. More recently, de's of 7-80% have been reported for the α-phenylglycinol auxiliary, but yields were modest.[6] In this context we describe a study of the asymmetric Strecker synthesis of α-amino acids using nonracemic sulfinimines **1** and **2** (Scheme). Sulfinimines are chiral ammonia imine synthons important in the asymmetric synthesis of amines,[7] β-amino acids[7b,8] and cis-aziridine 2-carboxylic acids.[9]

Scheme



Under a variety of conditions cyanide (KCN, CuCN) failed to add to (±)-N-(benzylidene)-*p*-tolluenesulfinamide (**1a**) and trimethylsilyl cyanide (TMSCN), in the absence or presence of Lewis acids, gave no reaction or low yields (ca 9-20%) of α-amino nitrile **3a**. Trimethylsilyl cyanide had earlier been reported to be an effective reagent for the Strecker synthesis giving good diastereoselectivity and yields with Lewis acids.[5,6] In these examples the Lewis acid was postulated as coordinating to the nitrogen lone pair, thus activating the C-N double bond for cyanide addition. Despite the fact that organometallic reagents (DIBAL-H, metal enolates, Grignard reagents) add to sulfinimines with high de's the sulfinyl group is apparently not sufficiently activating for CN addition to occur.[7-9] Unexpectedly, however, *p*-toluenethiocyanate (**6**)[10] and 2-imino-2-phenylacetonitrile (**7**)[11] were isolated in 85 and 81% yield respectively, when (±)-**1a** was treated with 2.0 equivalent of TMSCN and cesium fluoride (CsF, 99.9%) in THF at rt for 14 h. The products were isolated by chromatography on silica gel after quenching with aqueous NH_4Cl.



Although the hydrocyanation of enones, ketones[12] and β-ketosulfoxides[13] with diethylaluminum cyanide (Et_2AlCN) has been extensively explored, there is only one report of its addition to imines. In this study the imines of α,β-unsaturated aldehydes were prepared to facilitate 1,4-addition because of the lower reactivity of the C-N double bond.[14] Despite this observation we felt that Et_2AlCN could be an effective reagent for cyanide addition to sulfinimines because of its strong Lewis acidity. Our rational was that this reagent, on complexation at the sulfinyl oxygen in **1** and **2**, will activate the imine for addition, and if intramolecular cyanide transfer occurs the de's could be quite high.

Typically, the appropriate sulfinimine **1** or **2** (1.0 mmol) was dissolved in 8 mL of solvent (ether and/orTHF, see Table), 1.5 equivalents of Et_2AlCN (1.0 M soln. in toluene) added at -78°C and the reaction mixture warmed to the appropriate temperature. After completion of the reaction (2-4 h), as determined by TLC, the mixture was quenched with sat. NH_4Cl. The major diastereomeric α-amino nitriles **3** and **4** were isolated in high yield by chromatography on silica gel [20% EtOAc-*n*-pentane (**3a**), 35% EtOAc-*n*-pentane (**4a**); 2% acetone-$CHCl_3$ (**3b**); acetone:CH_2Cl_2:*n*-hexane in 5:25:70 ratio (**3c**); ether: $CHCl_3$: *n*-pentane in 1:5:4 ratio (**4b-c**)]. In general the α-amino nitriles having the N-2-methoxy-1-naphthylsulfinyl auxiliary, **4**, proved to be the easiest to separate. Indeed (S_S,*S*)-**4a** was isolated diastereomerically pure (>98% de) in 48% yield in one crystallization from *n*-hexane/EtOAc. Enantiopure sulfinimines **1**[15] and **2**[16] were prepared as previously described.

Gentle refluxing of the appropriate pure isolated diastereomeric α-amino nitriles **3** and **4**[18] in 6 N HCl for 6-8 h followed by washing with ethyl ether (3 x 10 mL) and passing the aqueous solution through a Dowex 50X8-100 ion exchange resin (elution with 1.5 N NH_4OH) gave (*S*)-(+)-phenylglycine (**5a**),[19] (*S*)-(+)-norvaline (**5b**)[20] and (*S*)-(+)-leucine (**5c**)[21] in >95% ee and 71-81%

Table: Stereoselective addition of Diethylaluminum Cyanide to Sulfinimines **1** and **2**

Entry	Sulfinimine (R=)	Solvent /Temp. (°C)	α-Amino Nitriles **3** and **4** %Yield[a]	[(S_S,*S*)/(S_S,*R*)][b]	α-Amino Acid **5** % Yield[c]	%ee[d] (Config.)
1	(±)-**1a** (Ph)	Toluene/rt	<10%			
2		CH_2Cl_2/0	<15%	[40:60]		
3		THF/0 to rt	35	[59:41]		
4	(*S*)-(+)-**1a** (Ph)	Et_2O/-78 to 0	72	[70:30]	71	>95 (*S*)
5	(*S*)-(+)-**1b** (*n*-Pr)	Et_2O/78 to -15	67	[69:31]	79	>95 (*S*)
6	(*S*)-(+)-**1c** (*i*-Bu)	Et_2O/-78 to -15	62	[71:29]	67	>95 (*S*)
7	(*S*)-(+)-**2a** (Ph)	Et_2O-THF/-78 to -10	78	[80:20]	81	>95 (*S*)
8	(*S*)-(+)-**2b** (*n*-Pr)	THF/-78 to -40	75	[83:17]	73	>95 (*S*)
9	(*S*)-(+)-**2c** (*i*-Bu)	THF/-78 to -40	72	[83:17]	71	>95 (*S*)[e]
10	(*R*)-(-)-**2c** (*i*-Bu)	THF/-78 to -40	78	[17:83][f]	75	>95 (*R*)[e]

a) Isolated yields of diastereomeric mixtures . b) Determined by ^{1}H NMR. c) Isolated yield of **5** from the major diastereoisomer. d) Ee's and the configuration were determined by comparison of their optical rotations with authentic samples. e) Ee's determined on the methyl ester using (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. f) The configuration is (R_S,*S*/R_S,*R*).

isolated yields (Table). The ee's and absolute configuration were determined by comparison with authentic samples. Significantly, the conditions for concomitant removal of N-sulfinyl auxiliary and nitrile hydrolysis are exceptionally mild, in comparison with other procedures,[4-6] affording **5** without racemization even for the epimerization sensitive phenylglycine (**5a**).

Interestingly, the highest yields and de's were found in diethyl ether and/or THF (compare entries 1-3 with others) despite the report that Et_2AlCN is more reactive in nonbasic solvents such as toluene.[12] The product stereochemistry, determined by chemical correlation (see above) is consistent with association of Et_2AlCN at the sulfinyl oxygen of the sulfinimine to form a tetracoordinated species followed by intramolecular transfer of cyanide through the usual six-membered chair-like transition state.[8a,9a] However, the reasons for the modest diastereoselectivity (40-60% de) and the somewhat higher de's for **2** (compare entries 4-6 with 7-10) are not readily apparent and under active investigation.

In summary, the facile addition of Et_2AlCN to readily available, enantiopure sulfinimines **1** and **2** represents new and convenient methodology for the asymmetric Strecker synthesis of α-amino acids **5**, in both epimeric forms (see entries 9 and 10).

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