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Diastereoselective Strecker Reaction of *D*-Glyceraldehyde Derivatives. A Novel Route to *(2S,3S)*- and *(2R,3S)*-2-Amino-3,4-dihydroxybutyric Acid.

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Abstract: Efficient and stereoselective synthetic routes to enantiomerically pure *(2S,3S)*- and *(2R,3S)*-2-amino-3,4-dihydroxybutyric acid have been developed using the stereoselective Strecker type reaction of carbonyl compounds derived from appropriately protected *D*-glyceraldehyde. The stereoselectivity of the cyanide addition was shown to be dependent on the presence of metal complexing agents, which is essential in the case of *(2R)*-2,3-di-*O*-benzyl-*D*-glyceraldehyde. In addition, theoretical calculations to rationalize the stereochemical course of the reaction have been performed. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The stereoselective synthesis of β-hydroxy-α-amino acids has long been of interest,[1] partly due to their presence in a number of biologically active compounds[2] such as peptides, peptidases, polyoxins, and enzyme inhibitors and also the presence of various functional groups which makes them useful synthetic precursors for other biologically active molecules.[3,4]

In recent years, great progress in the asymmetric synthesis of β-hydroxy-α-amino acids has been reported;[1] however, several fundamental problems still remain regarding stereocontrol, racemisation and protecting groups. Moreover, synthetic approaches which make use of readily available chiral building blocks, for example by employing *D*-mannitol[5] as the starting material, are especially attractive.

The Strecker synthesis is interesting from an economic viewpoint and has already been applied to the synthesis of β-unsubstituted-α-amino acids by using chiral amines such as *(4S,5S)*-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane, 2,3,4,6,-tetra-*O*-pivaloyl-β-*D*-galactopyranosylamine, 2,3,4-tri-*O*-pivaloyl-α-*D*-arabinosylamine and benzylic amines as chiral auxiliaries.[6] The use of these chiral matrices has led to optical inductions of up to 86 % diastereoisomeric excess. Nevertheless, to the best of our knowledge, and excluding our work,[7] there are only a few examples,[8] of a Strecker type reaction using chiral imines in which the chiral matrix is the carbonyl moiety.

In a previous communication from this laboratory,[7] it was shown that the stereocontrolled synthesis of *(2S,3S)*-2-amino-3,4-dihydroxybutyric acid is possible, starting from the *N*-benzylimine derived from 2,3-di-*O*-benzyl-*D*-glyceraldehyde and proceeding through a Strecker type reaction using trimethylsilyl cyanide. In this article we have envisaged the stereocontrolled synthesis of *(2S,3S)*-2-amino-3,4-dihydroxybutyric acid and *(2R,3S)*-2-amino-3,4-dihydroxybutyric, both useful synthetic intermediates in the synthesis of β-lactam antibiotics[3f-g] and phytosiderophores.[4] *D*-mannitol is employed as the chiral source and the synthesis is achieved by a diastereoselective Strecker reaction.

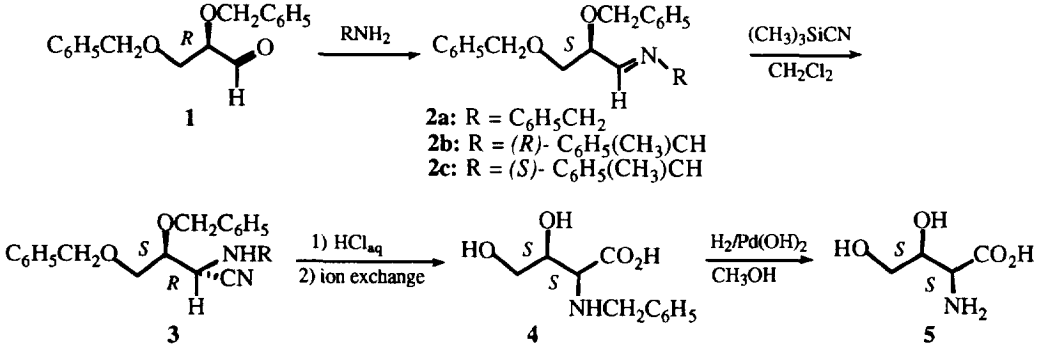
RESULTS AND DISCUSSION

The use of *(2R)*-2,3-di-*O*-benzyl-*D*-glyceraldehyde as starting material means that two hydroxy-substituents and a carbonyl group are present, the later can be transformed, through a Strecker type reaction, to the amino acid in the final product. Protection of the aldehyde as the *N*-benzyl imine, followed by reaction with a nitrile donor will afford the aminonitrile which can subsequently be hydrolysed to give the desired target compound. Reaction of the aldehyde with a nitrile donor will afford the cyanohydrin from which it is possible to obtain the amino acid with inversion of the stereochemistry at C_α.

Diastereoselective Cyanide Addition to Benzylimines Derived from D-Glyceraldehyde.

The reaction between the Schiff base, obtained from 2,3-di-*O*-isopropylidene-*D*-glyceraldehyde, and benzylamine with trimethylsilyl cyanide in methylene chloride at room temperature was studied first. Under these conditions the corresponding amino nitrile with the *(R)*-configuration at C_2 was obtained in good yield. A diastereoisomeric ratio of 90/10 was obtained as determined by integration of the corresponding benzylic protons in the ^1H NMR spectrum of the crude reaction mixture. However, isolation of the major compound could not be achieved as the diastereoisomeric amino nitriles were not separable by either selective crystallisation or column chromatography.

The next reaction investigated was that of the imine derived from 2,3-di-*O*-benzyl-*D*-glyceraldehyde and benzylamine **2a** with trimethylsilyl cyanide under the same conditions as described above. In this case the corresponding amino nitrile **3a** with the *(R)*-configuration at C_2 was formed with an improved yield. The diastereoisomeric ratio in this case was 88/12 as determined by integration of the corresponding benzylic protons in the ^1H NMR spectrum of the crude reaction mixture. On repeating the reaction at a lower temperature (entry 2 Table 1), or increasing the size of the trialkylsilyl reagent (entry 10 Table 1), no perceptible advantage was evident and the reaction yield and diastereoselectivity were in the same range. In this case both diastereoisomeric amino nitriles were oily compounds that could not be recrystallized but could be easily separated by column chromatography using ether/hexane (1:1) as eluent. Thus the benzyl group proved to be a suitable protecting group to afford easily separable diastereoisomeric amino nitriles and has the advantage that it can be easily removed by either acidic hydrolysis under mild conditions or hydrogenolysis. It was therefore decided to continue our studies using 2,3-di-*O*-benzyl-*D*-glyceraldehyde as the starting material.



Scheme 1

Table 1. Diastereoselectivity of the Cyanide Addition to Benzylimines 2a-c Derived from *(2R)*-2,3-Di-*O*-benzyl-*D*-glyceraldehyde.

Substrate	R_3SiCN	Solvent	Lewis Acid[a]	Temp (°C)	Yield[b] (%)	D.r.
2a	$(CH_3)_3SiCN$	CH_2Cl_2	-	r.t.	90	88/12[c]
2a	$(CH_3)_3SiCN$	CH_2Cl_2	-	- 60	96	85/15[c]
2a	$(CH_3)_3SiCN$	2-propanol	-	r.t.	93	82/18[c]
2a	$(CH_3)_3SiCN$	CH_2Cl_2	$ZnCl_2$	r.t.	93	55/45[c]
2a	$(CH_3)_3SiCN$	2-propanol	$ZnCl_2$	r.t.	93	71/29[c]
2a	$(CH_3)_3SiCN$	CH_2Cl_2	$MgCl_2$	r.t.	95	79/21[c]
2a	$(CH_3)_3SiCN$	CH_2Cl_2	$BF_3{\cdot}Et_2O$	r.t.	41	67/33[c]
2a	$(CH_3)_3SiCN$	CH_2Cl_2	Et_2AlCl	- 60	83	61/39[c]
2a	$(CH_3)_3SiCN$	CH_2Cl_2	$TiCl_4$	- 60	-	-
2a	$^tBu(CH_3)_2SiCN$	CH_2Cl_2	-	r.t.	90	88/12[c]
2b	$(CH_3)_3SiCN$	CH_2Cl_2	-	r.t.	95	85/15[c]
2b	$(CH_3)_3SiCN$	CH_2Cl_2	$ZnCl_2$	r.t.	94	64/36[c]
2c	$(CH_3)_3SiCN$	CH_2Cl_2	-	r.t.	94	90/10[c]
2c	$(CH_3)_3SiCN$	CH_2Cl_2	$ZnCl_2$	r.t.	95	81/19[c]

[a] 1.2 equivalents of Lewis acid. [b] Before recrystallization. [c] Determined by ^{1}H-NMR. [d] Determined by ^{13}C-NMR.

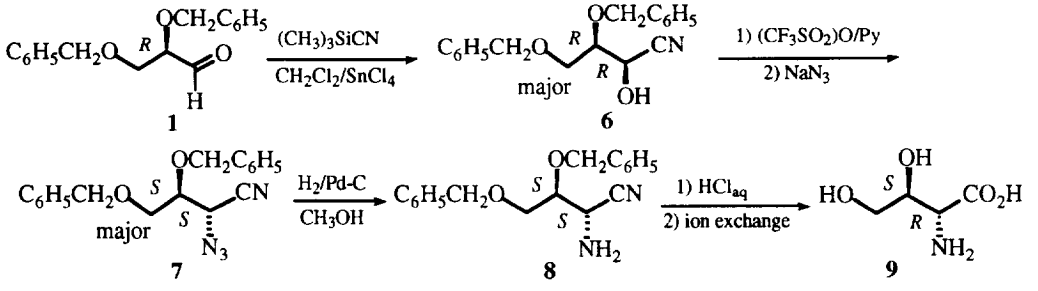
The above synthetic protocol allowed the preparation of the amino acid precursor of *(2S,3S)*-2-amino-3,4-dihydroxybutyric acid in good yield. The next step was to attempt the synthesis of its diastereoisomer with the *(2R,3S)*-configuration by altering the reaction conditions. Firstly, the trimethylsilyl cyanide reaction was investigated both in the presence or absence of zinc chloride as a chelating agent using methylene chloride or isopropanol as the solvent. Two different solvent systems were employed since it has been reported[9] that the direction of asymmetric induction in the Strecker synthesis using 2,3,4,6-tetra-*O*-pivaloyl-β-*D*-galactopyranosylamine can be reversed by changing the solvent. The results in Table 1 show that the use of isopropanol as solvent leads to a somewhat lower diastereoselectivity and that the presence of zinc chloride drastically reduces the diastereoselectivity in both the polar and non polar solvent. However, the sense of induction was not inverted.

It has been reported[10] that the use of other Lewis acids can have a significant influence on the sense and extent of diastereoselectivity in Strecker type reactions. For this reason it was decided to study the trimethylsilyl cyanide addition to imine **2a** in the presence of magnesium chloride, boron trifluoride etherate, diethylaluminum chloride and titanium tetrachloride. The reaction was less selective when the Lewis acids were present and the yield strongly depended on the Lewis acid used, falling to 41 % with the use of boron trifluoride etherate and, in the case of titanium tetrachloride, the corresponding amino nitrile was not detected.

The use of chiral amines as chiral auxiliaries to perform a double asymmetric induction was studied next, and imines derived from 2,3-di-*O*-benzyl-*D*-glyceraldehyde and both *(R)*- and *(S)*-α-methylbenzylamine (**2b** and **2c**) were obtained. These compounds were then submitted to trimethylsilyl cyanide addition in methylene chloride at room temperature in the presence or absence of zinc chloride. As can be seen in Table 1, yields were excellent in all cases, but success was not achieved in increasing the diastereoselectivity of the *(2R,3S)*-amino nitrile formation or inverting the absolute configuration of the newly formed stereogenic centre.

Diastereoselective Cyanide Addition to 2,3-Di-O-benzyl-D-glyceraldehyde.

For the synthesis of *(2R,3S)*-2-amino-3-hydroxybutyric acid, a reversal in the stereochemical course of the cyanide addition to imines derived from suitably protected *D*-glyceraldehyde is necessary. However, all attempts were unsuccessful. Therefore an alternative approach was used based on the stereoselective Strecker reaction of the chiral aldehyde followed by the appropriate transformations of functional groups. Treatment of 2,3-di-*O*-benzyl-*D*-glyceraldehyde **1** with trimethylsilyl cyanide in methylene chloride or isopropanol at room temperature proved unsuccessful in the absence of a catalyst. However, the same reaction was carried out in the presence of zinc iodide and the corresponding cyanohydrin was formed in very high yield when methylene chloride was used as the solvent. Unfortunately there was no selectivity in this addition reaction. Since the presence of a Lewis acid catalyst seemed to be a prerequisite, a study of the Strecker reaction was undertaken using a variety of Lewis acids. Table 2 summarises some of the results obtained in the systematic study of this reaction.



Scheme 2

The behaviour of diethylaluminum chloride as catalyst was similar to that of zinc iodide and the cyanohydrin was produced in very high yield with almost no induction. Cyanide addition to **1** in methylene chloride proceeded much better when titanium tetrachloride, tin tetrachloride or magnesium bromide were used as Lewis acids. Yields were very high and stereoselectivities increased to about 83/17 in favour of the *(2R)*-cyanohydrin when tin tetrachloride was used. An increase in the size of the trialkylsilyl cyanide reagent (entry 10 Table 2) had no influence on the stereochemical course of the reaction.

Remarkably, on using boron trifluoride etherate, the selectivity was reversed in favour of the cyanohydrin of opposite configuration at C_2. Although the level of induction was not good enough to make the reaction useful, it is the only case in which this phenomenon has been observed.

The diastereoisomeric ratio of the products was determined from the spectra of the crude reaction mixture by integration of the ^{13}C NMR (75 MHz) absorption corresponding to the same carbon in each diastereoisomer.

Table 2. Diastereoselectivity of the Cyanide Addition to *(2R)*-2,3-Di-*O*-benzyl-*D*-glyceraldehyde.

Substrate	R_3SiCN	Solvent	Lewis Acid[a]	Temp (°C)	Yield[b] (%)	D.r.[c]
1	$(CH_3)_3SiCN$	CH_2Cl_2	-	r.t.	-	-
1	$(CH_3)_3SiCN$	2-propanol	-	r.t.	-	-
1	$(CH_3)_3SiCN$	CH_2Cl_2	ZnI_2	- 20	96	53/47
1	$(CH_3)_3SiCN$	2-propanol	ZnI_2	- 20	-	-
1	$(CH_3)_3SiCN$[d]	CH_2Cl_2	$TiCl_4$	- 78 → - 20	95	77/23
1	$(CH_3)_3SiCN$	CH_2Cl_2	$SnCl_4$	- 78 → - 20	95	83/17
1	$(CH_3)_3SiCN$	CH_2Cl_2	Et_2AlCl	- 78 → - 20	93	57/43
1	$(CH_3)_3SiCN$	CH_2Cl_2	$BF_3{\cdot}Et_2O$	- 78 → - 20	96	42/58
1	$(CH_3)_3SiCN$	CH_2Cl_2	$MgCl_2$	- 20	94	76/24
1	$^tBu(CH_3)_2SiCN$	CH_2Cl_2	$SnCl_4$	- 78 → - 20	96	85/15

[a] 1.2 equivalents of Lewis acid. [b] Before recrystallization. [c] Determined by ^{13}C-NMR. [d] 2 equivalents of $(CH_3)_3SiCN$.

Isolation of the major compound could not be achieved by either crystallisation or by chromatography, but the synthetic scheme was continued with the diastereoisomeric mixture and the purification of the major diastereoisomer was carried out at a later stage.

Synthesis of (2S,3S)- and (2R,3S)-2-Amino-3,4-dihydroxybutyric Acids.

The next step of the proposed route was the transformation of aminonitrile **3** into the corresponding *(2S,3S)*-2-amino-3,4-dihydroxybutyric acid and the isolation of diastereoisomeric *(2R,3S)*-2-amino-3,4-dihydroxybutyric acid from cyanohydrin **6**.

Treatment of the major isolated amino nitrile with the *(R)*-configuration at C_2 with hydrochloric acid led to nitrile hydrolysis with concomitant deprotection of the O-benzyl groups which afforded, after ion exchange chromatography, *(2S,3S)*-2-benzylamino-3,4-dihydroxybutyric acid **4**. This compound was subsequently submitted to hydrogenolysis in the presence of palladium hydroxide to afford the desired amino acid, whose specific rotation[1a] confirmed both the absolute configuration and optical purity of compound **5**. (Scheme 1).

The synthesis of *(2R,3S)*-2-amino-3,4-dihydroxybutyric acid was easily accomplished by treatment of the diastereoisomeric mixture of cyanohydrins **6** with trifluoromethanesulfonic acid in the presence of pyridine, followed by nucleophilic replacement of the triflate group by reaction with sodium azide to give 2-azido-3,4-dibenzyloxybutyronitrile **7** as an oily, inseparable mixture of diastereoisomers in a diastereoisomeric ratio of 85/15. The catalytic hydrogenolysis of the azido group of **7** with 10 % Pd/C afforded the corresponding amino nitrile **8** as a mixture of diastereoisomers from which the major diastereoisomer could be easily isolated by column chromatography eluting with ether/chloroform 1:1. Consequent acid hydrolysis and ion exchange chromatography afforded the desired *(2R,3S)*-2-amino-3,4-dihydroxybutyric acid, whose measured specific rotation was in total agreement with that described in the literature.[11] (Scheme 2). Moreover, treatment of the

minor diastereoisomer (isolated by column chromatography) with benzyl bromide, followed by nitrile hydrolysis with hydrochloric acid, afforded compound **4** which served to confirm the absolute stereochemistry of compound **8**.

MECHANISTIC CONSIDERATIONS

Since the early 1950's, when Cram proposed a rule to rationalise the stereoselectivities of nucleophilic additions to acyclic chiral carbonyl compounds,[12] many other rules and explanations have been proposed for this and other related phenomena. In particular, in the absence of additional factors, such as the presence of counter ions or Lewis acids, the so-called Felkin–Anh model[13,14] is one of the most successful in explaining this kind of reaction.

Theoretical calculations have often been used to rationalise these models.[15] Very recently, Anh *et al.* have published[16] a thorough study about the factors that influence 1,2-asymmetric induction in the nucleophilic attack of carbonyl compounds. One of the main conclusions of this study is that, in solution, most of the processes are frontier-controlled, so that the best electron acceptor is placed *anti* to the nucleophile in the transition state. Nevertheless, steric and dipolar interactions also play a role in determining the relative stability of diastereoisomeric transition structures.

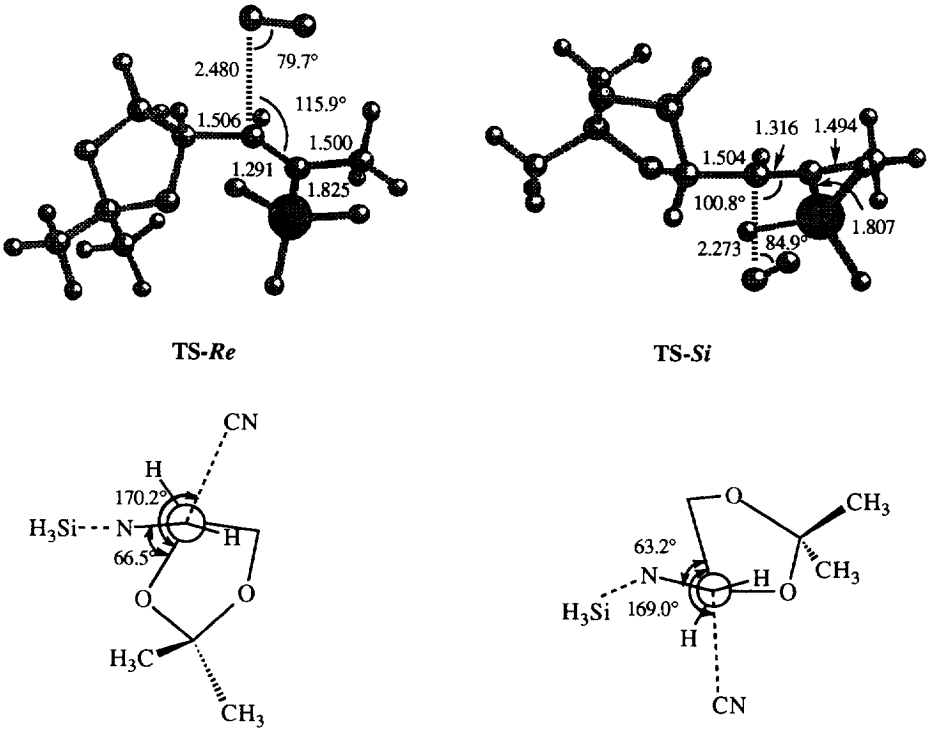


Figure 1

Most of the theoretical studies published deal with very simple carbonyl models, such as substituted propanals, and nucleophiles, such as hydride or cyanide ions, or lithium hydride. In order to get a more realistic picture of the reaction described here, it was decided to perform theoretical calculations on a relatively large system. Thus, the nucleophile considered is silyl cyanide, and the carbonyl derivative is the *(E)*-methyl imine of the di-*O*-isopropylidene-*D*-glyceraldehyde. It has already been shown (Table 1) that the amine moiety of the imine has little or no influence on the asymmetric induction, so it is to be expected that changing the benzyl group to a methyl group will not drastically change the conclusions reached. Moreover, it has also been shown[7] that the use of di-*O*-isopropylidene or di-*O*-benzyl protecting groups leads to virtually identical results, and so the former was chosen for the theoretical study due to its smaller size.

First of all, the reaction surface was thoroughly examined by means of the semiempirical AM1 Hamiltonian,[17] and the transition structures (TS) for the C_1-*Re* and C_1-*Si* nucleophilic attacks were located. From these structures, *ab initio* HF/3-21G calculations were performed, and new TS were located and properly characterised (see the Experimental Section). Several additional TS searches were performed, starting from different C_1–C_2 rotamers, in order to ensure that no other TS exist. A number of significant geometric parameters of both TS (labelled as TS-*Re* ad TS-*Si*) are given in Figure 1. Geometric optimisations were also carried out, with the 3-21G basis set for the reagents and the intermediate products coming from the above-mentioned TS. Single point HF/6-31*//3-21G calculations were also performed on all these structures in order to obtain more reliable energy values. The absolute energies of the reagents, TS and products are gathered in Table 3.

Table 3. Calculated Energies (in hartree) of the Reagents, Transition Structures, and Intermediate Products Discussed in the Text.

Compound	HF/3-21G//3-21G	HF/6-31G*//3-21G
H_3SiCN	- 380.924763	- 382.974153
Imine	- 474.141722	- 476.793285
TS-*Re*	- 855.023826	- 859.701418
TS-*Si*	- 855.009127	- 859.693257
PI-*Re*	- 855.110183	- 859.779923
PI-*Si*	- 855.113101	- 859.779962

As can be seen, both 3-21G and 6-31G* calculations agree with the C_1-*Re* attack being favoured over the corresponding C_1-*Si*, which is in turn in agreement with the absolute stereochemistry of the major product experimentally observed. The question remains as to why the C_1-*Re* attack takes place preferentially. Insights into this matter can be obtained by examining the structures of the TS .

In TS-*Re* the oxygen at C_2 of the imine is placed *anti* with respect to the nucleophile, in accordance with the Anh postulate.[16] Then, due to the chirality at the C_2 atom, C_3 lies *trans* with respect to the nitrogen atom of the imine, far away from the silyl group which is bonded to this nitrogen atom. On the other hand, in TS-*Si* the

C_3 atom is placed *anti* with respect to the incoming nucleophile, whereas the oxygen atom at C_2 is *trans* with respect to the imine nitrogen atom. This situation is not the most favoured, taking the Felkin–Anh model into account. However, it is easy to see why this is the preferred conformation. If the oxygen atom at C_2 was placed *anti* to the nucleophile, then C_3 would lie *gauche* with respect to the imine nitrogen atom, and a significant steric interaction with the silyl group would occur. In conclusion, both electronic and steric factors favour TS-*Re* over TS-*Si*, giving rise to high diastereofacial discrimination. It is important to note that steric interactions will be greater for the bulkier trimethylsilyl reagent. This analysis, derived from the *ab initio* theoretical results is essentially coincident with the model recently postulated by Cainelli *et al.*[8b]

The energy difference between both TS is dependent on the theoretical level used, and decreases on changing from the 3-21G ($\Delta\Delta G^{\ddagger}$=9.22 kcal·mol^{-1}) to the 6-31G* ($\Delta\Delta G^{\ddagger}$=5.12 kcal·mol^{-1}) basis set. This result is in agreement with those previously reported by Anh *et al.*[16] The use of correlation energy corrections or the geometry optimisation at higher theory levels is expected to change the quantitative results somewhat, but we feel that our interpretation of the origin of the asymmetric induction in these systems is essentially correct from a qualitative viewpoint.

A key feature of this model of asymmetric induction is the presence of the trimethylsilyl group linked to the imine nitrogen. As the calculations show, The N–Si bond is almost completely formed in the TS (N–Si bond distance in the product intermediate ≈ 1.770). It seems that the electrophilic attack of the silicon atom on this nitrogen atom is necessary to partially break the silicon–cyanide bond, making the latter group more nucleophilic. As a consequence, it follows that factors affecting the formation of the N–Si linkage also influence the asymmetric induction. In particular, the use of Lewis acids together with the nucleophile dramatically decreases the asymmetric induction observed, which can be related to the preferential coordination of the Lewis acid to the imine nitrogen atom.

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EXPERIMENTAL SECTION

***Apparatus*:** Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FT IR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 spectrometer in deuterochloroform or deuterium oxide using the solvent signal (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C) as the internal standard; chemical shifts (δ) are given in parts per million and the coupling constants *(J)* in Hertz. Elemental analyses were performed with a Perkin-Elmer 2400 analyser. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25 °C.

***Chemicals*:** All reactions were carried out under argon with magnetic stirring. Solvents were dried prior to use. Trimethylsilyl cyanide, Lewis acid catalysts, and hydrogenation catalysts were purchased from Aldrich Chemical Co. *(2R)*-2,3-di-*O*-benzyl-*D*-glyceraldehyde (**1**) was obtained according to the literature procedure.[18] Thin layer chromatography was performed on precoated silica gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was performed using 230-400 mesh (Merck) silica gel.

Theoretical calculations: Semiempirical calculations were carried out using the AM1 Hamiltonian,[17] as implemented in the MOPAC 6.0 program.[19] *Ab initio* calculations were carried out with the GAUSSIAN 92 program,[20] using the 3-21G basis set for geometry optimisations and transition structure searches, and the 6-31G* basis set for single point energy calculations. Transition structures were located by means of Schlegel's algorithm,[21] and were unequivocally characterised by the presence of only one negative eigenvalue of the Hessian, whose corresponding imaginary frequency matched with the NC–C_1 bond formation.

***(2S)*-2,3-Dibenzyloxypropylidene(benzyl)azane (2a).** To a stirred solution of benzylamine (0.535 g, 5 mmol) in dry ether (20 ml) at 0 °C was added a solution of *(2R)*-2,3-di-*O*-benzyl-*D*-glyceraldehyde **(1)** (1.35 g, 5 mmol) in dry ether (20 ml). After 3 h the reaction mixture was dried over anhydrous magnesium sulphate, filtered and evaporated to afford crude imine **(2a)** which was used as such in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70-3.86 (m, 2H), 4.17-4.25 (m, 1H), 4.56 (s, 2H), 4.61 (AB system, 2H), 4.62 (AB system, 2H), 7.20-7.42 (m, 15H), 7.77 (dt, 1H, J = 5.4 Hz, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.8, 71.3, 71.8, 73.4, 79.5, 127.0, 127.6, 127.6, 127.7, 127.9, 127.9, 128.3, 128.4, 128.5, 137.9, 138.0, 138.6, 164.8.

***(2R,3S)*-2-Benzylamino-3,4-dibenzyloxybutyronitrile (3).** A mixture of crude *(2S)*-2,3-dibenzyloxypropylidene(benzyl)azane **(2a)** (1.8 g, 5 mmol) and trimethylsilyl cyanide (0.76 ml, 6 mmol) in dry methylene chloride (50 ml) was stirred under argon at room temperature for 12 h. The reaction mixture was poured into aqueous saturated ammonium chloride solution (5 ml) and the organic phase extracted with ether. The combined organic phases were washed successively with sodium hydrogen carbonate solution and brine, and dried over anhydrous magnesium sulphate. Removal of the solvent *in vacuo* yielded 2-benzylamino-3,4-dibenzyloxybutyronitrile **(3)** as a mixture of diastereoisomers (d. r. 88/12). Purification of the residue by flash chromatography on a silica gel column using ether/hexane 1:1 as eluent afforded 1.29 g (67 % yield) of diastereoisomerically pure *(2R,3S)*-2-benzylamino-3,4-dibenzyloxybutyronitrile **(3)** as a colourless oil. $[\alpha]_D$ = - 62.1 (c = 1 in $CDCl_3$); IR (Nujol) 3334, 2227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (brs, 1H), 3.64 (dd, 1H, J = 9.3 Hz, J = 5.1 Hz), 3.70-3.78 (m, 2H), 3.77 (d, 1H, J = 13.2 Hz), 3.87-3.93 (m, 1H), 4.08 (d, 1H, J = 13.2 Hz), 4.46 (s, 2H), 4.72 (AB system, 2H), 4.62 (AB system, 2H), 7.15-7.32 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.8, 51.4, 68.4, 73.5, 73.6, 76.4, 119.1, 127.4, 127.7, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 137.3, 137.6, 138.3.

***(2S,3S)*-2-Benzylamino-3,4-dihydroxybutyric acid (4).** Hydrogen chloride gas was added to a stirred suspension of *(2R,3S)*-2-benzylamino-3,4-dibenzyloxybutyronitrile **(3)** (0.772 g, 2 mmol) in concentrated hydrochloric acid (30 ml) at room temperature until all the solid had dissolved. The solution was stirred at room temperature for 24 h. After the reaction was over, the hydrochloric acid was evaporated to dryness under reduced pressure. The residue was dissolved in water (15 ml), washed with ether, applied to a Dowex 50W x 8 column (H^+ form, 50 ml) and eluted with 5 % aqueous ammonia. The fractions containing the *N*-benzylamino acid were combined and evaporated under reduced pressure to give a pale yellow solid. Further purification was performed by silica gel column chromatography using acetonitrile/water 2:1 as eluent to afford 0.35 g (78 % yield) of *(2S,3S)*-2-benzylamino-3,4-dihydroxybutyric acid **(4)** as a colourless solid. M. p. 191 °C; $[\alpha]_D$ = - 14.2 (c = 1 in H_2O); IR (Nujol) 3174, 1634 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 3.43 (d, 1H, J = 5.7 Hz), 3.48 (dd, 1H, J = 12 Hz, J = 5.4 Hz), 3.58 (dd, 1H, J = 12 Hz, J = 3.6 Hz), 3.85-3.93 (m, 1H),

4.06 (d, 1H, J = 13.2 Hz), 4.20 (d, 1H, J = 13.2 Hz), 7.34 (m, 5H). ^{13}C NMR (D_2O, 75 MHz) δ 52.8, 65.7, 65.8, 71.8, 131.5, 131.9, 132.3, 132.9, 173.9. Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; C, 6.22. Found: C, 58.81; H, 6.57; C, 6.39.

***(2S,3S)*-2-Amino-3,4-dihydroxybutyric acid (5).** A solution of *(2S,3S)*-2-benzylamino-3,4-dihydroxybutyronitrile **(4)** (0.225 g, 1 mmol) in methanol/water 1:1 (20 ml) was hydrogenated for 12 h using palladium hydroxide on charcoal (0.1 g) as catalyst at room temperature and atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was recrystallized from water/methanol to give 0.128 g (95 % yield) of *(2S,3S)*-2-amino-3,4-dihydroxybutyric acid **(5)** as a colourless solid. M. p. 215 °C, lit.[11] m.p. 214 °C; $[\alpha]_D$ = - 13.4 (c = 2 in H_2O), lit.[11] $[\alpha]_D$ = - 13.5 (c = 2 in H_2O); ^1H NMR (D_2O, 300 MHz) δ 3.49-3.61 (m, 3H), 3.95-4.00 (m, 1H). ^{13}C NMR (D_2O, 75 MHz) δ 55.4, 61.9, 68.4, 172.4.

3,4-Dibenzyloxy-2-hydroxybutyronitrile (6). Trimethylsilyl cyanide (0.76 ml, 6 mmol) was added to a mixture of *(2R)*-2,3-di-*O*-benzyl-*D*-glyceraldehyde **(1)** (1.35 g, 5 mmol) and tin(IV) chloride (6 ml of 1 M solution in methylene chloride, 6 mmol) in dry methylene chloride (50 ml) under argon at -78 °C. The reaction temperature was allowed to rise to -20 °C and stirring was continued for a further 16 h. The reaction mixture was poured into 2 N aqueous hydrochloric acid solution (5 ml), stirred at room temperature for 12 h and the organic phase extracted with ether. CAUTION! it is convenient to carry out this reaction in a forced-draft hood in order to provide protection against hydrogen cyanide. The combined organic phases were washed successively with sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo*. Purification of the residue by flash chromatography on a silica gel column using ether/hexane 1:1 as eluent yielded 1.32 g (89 % yield) of 3,4-dibenzyloxy-2-hydroxybutyronitrile **(6)** as an oily, inseparable mixture of diastereoisomers (d. r. 83/17) which was used as such in the next step. ^1H NMR of major compound ($CDCl_3$, 300 MHz) δ 3.68-3.71 (m, 2H), 3.81-3.84 (m, 1H), 4.53 (AB system, 2H), 4.58-4.63 (m, 1H), 4.70 (s, 2H), 7.36 (m, 10H). ^{13}C NMR of major compound ($CDCl_3$, 75 MHz) δ 62.4, 68.3, 73.4, 73.9, 76.6, 118.6, 127.0, 127.9, 128.1, 128.2, 128.3, 128.6, 136.9, 137.1.

2-Azido-3,4-dibenzyloxybutyronitrile (7). Trifluoromethanesulfonic anhydride (0.76 ml, 4.5 mmol) was added slowly to a solution of 3,4-dibenzyloxy-2-hydroxybutyronitrile **(6)** (1.2 g, 4 mmol) and pyridine (1 ml) in dry methylene chloride (10 ml) under argon at -10 °C. After stirring at -10 °C for 30 min the reaction mixture was warmed to 0 °C and stirred at this temperature for additional 30 min. Ether (25 ml) was added and the mixture was washed with brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo* to afford the crude triflate which was treated with a solution of sodium azide (0.65 g, 10 mmol) in dimethylformamide (5 ml). The reaction mixture was stirred at room temperature for 15 h and ethyl acetate (50 ml) was added. The mixture was washed with brine, dried over anhydrous magnesium sulphate and concentrated *in vacuo*. Purification of the residue by flash chromatography on a silica gel column using ether/hexane 1:1 as eluent yielded 0.70 g (54 % yield) of 2-azido-3,4-dibenzyloxybutyronitrile **(7)** as an oily, inseparable mixture of diastereoisomers (d. r. 85/15). IR (Nujol) 2111 cm^{-1}; ^1H NMR of major compound ($CDCl_3$, 300 MHz) δ 3.55-3.66 (m, 2H), 3.80-3.86 (m, 1H), 4.42 (d, 1H, J = 4.8 Hz) 4.52 (AB system, 2H), 4.70 (AB system, 2H), 7.36 (m, 10H). ^{13}C NMR of major compound ($CDCl_3$, 75 MHz) δ 52.6, 67.5, 73.3, 73.6, 77.4, 114.3, 127.7, 127.9, 128.0, 128.2, 128.5, 128.5, 136.6, 137.0.

***(2R,3S)*-2-Amino-3,4-dibenzyloxybutyronitrile (8).** A solution of 2-azido-3,4-dibenzyloxybutyronitrile (**7**) (0.644 g, 2 mmol) in ethanol (20 ml) was hydrogenated for 2h using 10% palladium on charcoal (0.1 g) as catalyst at room temperature and atmospheric pressure. The mixture was filtered through celite, and the catalyst was washed with ethanol. The combined filtrates were evaporated to dryness to give 2-amino-3,4-dibenzyloxybutyronitrile (**8**) as mixture of diastereoisomers (d. r. 85/15). Purification of the residue by flash chromatography on a silica gel column using ether/chloroform 1:1 as eluent afforded 0.432 g (73 % yield) of diastereoisomerically pure *(2R,3S)*-2-amino-3,4-dibenzyloxybutyronitrile (**8**) as a colourless oil. $[\alpha]_D$ = - 10.3 (c = 1 in $CHCl_3$); IR (Nujol) 3389, 3329, 2231 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.57-3.64 (m, 1H), 3.70-3.77 (m, 2H), 3.97 (d, 1H, J = 3.9 Hz) 4.52 (AB system, 2H), 4.61 (d, 1H, J = 11.7 Hz), 4.74 (d, 1H, J = 11.7 Hz), 7.35 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.8, 68.7, 73.2, 73.7, 78.6, 127.7, 127.9, 127.9, 128.1, 128.5, 128.5, 137.4, 137.5.

***(2R,3S)*-2-Amino-3,4-dihydroxybutyric acid (9).** Hydrogen chloride gas was added to a stirred suspension of *(2R,3S)*-2-amino-3,4-dibenzyloxybutyronitrile (**8**) (0.414 g, 1.4 mmol) in concentrated hydrochloric acid (25 ml) at room temperature until all the solid had dissolved. The solution was stirred at room temperature for 24 h. After the reaction was over, the hydrochloric acid was evaporated to dryness under reduced pressure. The residue was dissolved in water (15 ml), washed with ether, applied to a Dowex 50W x 8 column (H^+ form, 50 ml) and eluted with 5 % aqueous ammonia. The fractions containing the amino acid were combined and evaporated under reduced pressure to give a pale yellow solid. Further purification was performed by silica gel column chromatography using acetonitrile/water 2:1 followed by recrystallization from water/methanol to afford 0.14 g (75 % yield) of *(2R,3S)*-2-amino-3,4-dihydroxybutyric acid (**9**) as a colourless solid. M. p. 194 °C, lit.[11] m. p. 194 °C; $[\alpha]_D$ = + 11.4 (c = 7 in H_2O), lit.[11] $[\alpha]_D$ = + 11.3 (c = 7 in H_2O); ^1H NMR (D_2O, 300 MHz) δ 3.52-3.64 (m, 3H), 3.75-4.00 (d, 1H, J = 3.8 Hz), 3.97-4.01 (m, 1H). ^{13}C NMR (D_2O, 75 MHz) δ 56.1, 61.1, 67.8, 170.0.

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