# Stereoselective Synthesis of α,β-Diamino Nitriles from Amino Acids

Manfred T. Reetz,*[a] Marcus Hübel,[a] Ralf Jaeger,[b] Renate Schwickardi,[a] Richard Goddard[a]

[a] Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany
[b] Fachbereich Chemie, Universität Marburg, D-35032 Marburg, Germany

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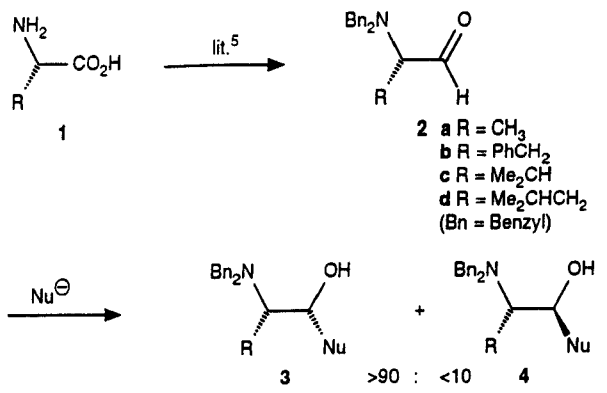
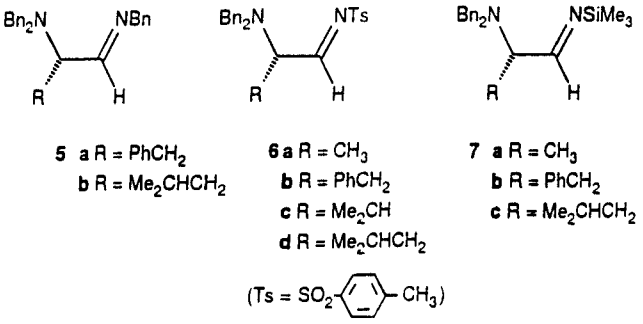
α-Amino acids **1** are readily converted into the corresponding *N,N*-dibenzylamino aldehydes **2** which in turn serve as starting materials for enantiomerically pure α-*N,N*-dibenzylamino aldimines **5**, **6** and **7** having benzyl, tosyl and trimethylsilyl groups, respectively, at the aldimine nitrogen atom. All three classes of chiral aldimines undergo stereoselective Lewis acid promoted $Me_3SiCN$ addition reactions with non-chelation controlled formation of the corresponding α,β-diamino nitriles. All of the reaction sequences occur without any racemization.

Amino acids have long been utilized as chiral building blocks in organic synthesis.[1] In most cases, a particular L-amino acid served as the starting material in the synthesis of a specific target molecule. Alternatively, various classes of compounds have become accessible from the "chiral pool" of amino acids, e.g., amino alcohols via Grignard addition to α-amino aldehydes prepared from amino acids.[2,3] Both strategies are gaining in importance because the number of non-racemic amino acids available to organic chemists has grown beyond the 20 common L-amino acids owing to the development of efficient asymmetric syntheses, enzymatic processes and new antipode separation methods.[1-4]

In 1987 we first described the synthesis and utility of *N,N*-dibenzylamino aldehydes **2**.[5] These compounds are readily accessible from L-amino acids **1** and react stereoselectively without any undesired racemization with a variety of carbon nucleophiles[2] ($Nu^{\ominus}$) such as RLi,[5,6] RMgX,[5,6] $R_2CuLi$,[5,6] Li-enolates,[5,6] enolsilanes/$LiClO_4$,[7] $Me_3SiCN/ZnX_2$[8] and sulfur ylides.[9] Other research groups have utilized *N,N*-dibenzylamino aldehydes **2** in related applications.[10] Surprisingly, in all of these C–C bond forming reactions, non-chelation control in favor of adducts **3** pertains (ds > 90%). Although this observation is in line with the Felkin–Anh model, arguments based on ground state effects have also been considered.[2,11]




Protective group tuning[9] is involved, because α-amino aldehydes having *tert*-butoxycarbonyl (BOC) or benzyloxycarbonyl (Cbz) protective groups react either stereorandomly or favor the chelation controlled products.[2,3,12] Whatever the true source of non-chelation control in reactions of the *N,N*-dibenzylamino aldehydes **2** may be, we envisioned further applications by conversion into the corresponding aldimines followed by nucleophilic addition of appropriate organometallic reagents with formation of vicinal diamines.[2] Indeed, aldimines **5** were shown to react with RLi and $RLi/CeCl_3$ with chelation control, whereas the *N*-tosyl analogs **6** react with Grignard reagents to form the corresponding non-chelation controlled adducts.[13] This is an impressive example of the combination of metal and protective group tuning.[2] In this Feature Article we describe the reactions of the aldimines **5**, **6** and **7** with $Me_3SiCN$ in the presence of Lewis acids as promoters which activate the C–N double bond by complexation. The products in these Strecker-type reactions are *N*-protected α,β-diamino nitriles which are potential building blocks for further synthetic elaboration.




## Synthesis of α-Amino Aldimines

As previously described,[2,13] the aldehydes **2** can be condensed with benzylamine in $CH_2Cl_2$ in the presence of $MgSO_4$ to form the aldimines **5** without any undesired racemization. The crude products contain > 95% of **5** following filtration from $MgSO_4$ and evaporation of the solvent. These materials were used in further reactions without any purification (attempts at chromatography resulted in partial hydrolysis of the aldimine function). In the case of **5a** derived from phenylalanine, a correct CH-analysis was nevertheless obtained. Otherwise only NMR data were recorded.[14] The aldimines **5** can be stored in the refrigerator for a few days, but it is best to utilize them as soon as possible.[14] The *N*-tosyl analogs **6** are accessible in high yield by reacting the aldehydes **2** with *N*-sulfinyl-*p*-toluenesulfonamide (TsN=S=O) according to the method of Weinreb.[15] This process involves [2 + 2] cycloaddition followed by spontaneous $SO_2$ extrusion with formation of the products **6**. Since the aldimines are somewhat unstable, they were not isolated.[16] It should be noted that in previous reports of *N*-tosyl aldimines derived from simple aldehydes, isolation or characterization was also not reported.[15] Thus,

precise structural data are lacking, and it is currently not certain whether the $SO_2$ is actually coordinated to an amine function in **6**.

The *N*-trimethylsilyl aldimines **7** were prepared by reacting the aldehydes **2** with lithium hexamethyldisilamide in THF according to the procedure of Cainelli.[17] This involves an "aza-Peterson" reaction in which the expelled $Me_3SiOLi$ is trapped by $Me_3SiCl$. The crude products **7** were freed from the THF and used in further reactions without any purification.[16] The $^1H$ and $^{13}C$ NMR spectra show single sets of signals in line with the structures **7**.[16]

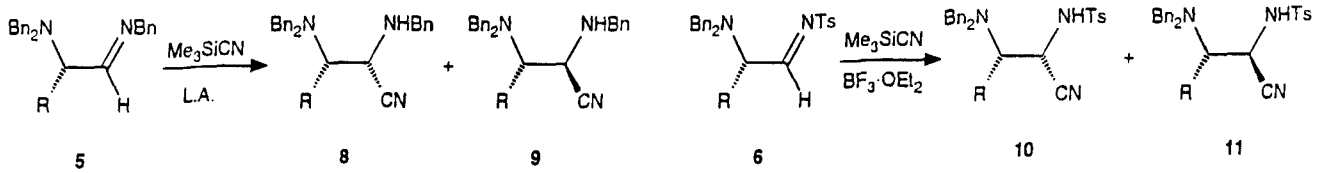
## Cyanide Addition Reactions

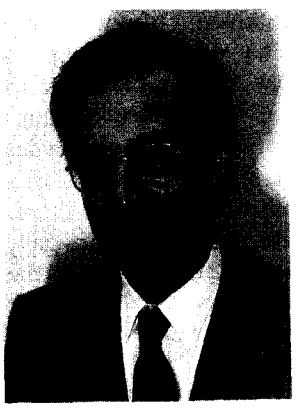
Exploratory experiments were carried out by reacting the aldimine **5a** with $Me_3SiCN$ in the presence of Lewis acids. Table 1 shows that $BF_3 \cdot OEt_2$ and $TiCl_4$ in $CH_2Cl_2$ are the best promoters. Conversion and diastereoselectivity are generally > 90%, but chromatographic isolation of these polar compounds results in loss of material. Interestingly, the same diastereomer is formed preferentially irrespective of the Lewis acid. Since $BF_3$ is not a chelating Lewis acid,[18,19] preliminary configurational assignment of the major product was made in favor of the non-chelation controlled adduct **8a**. This is in line with the observation that the $R_f$-value (TLC) of the minor diastereomer **9a** is larger than that of **8a**. Analogous behavior was observed previously for a large variety of amino alcohols **3/4** and is presumably based on ready intramolecular hydrogen bond formation in the case of chelation controlled adducts **4**.[20] It is interesting to note that upon warming the reaction mixture of the $BF_3$-mediated cyanide addition to room temperature, diastereoselectivity is lost completely. The 50:50 diastereomer mixture clearly indicates $BF_3$-induced equilibration of the diastereomers under thermodynamic control. In the case of aldimine **5b** only $BF_3 \cdot OEt_2$ was tested, resulting in a diastereomer ratio **8b/9b** of > 95:5, but isolation of the analytically pure compound **8b** amounted to only 22%.

**Table 1.** Stereoselective Addition of $Me_3SiCN$ to Aldimines **5**

| Aldimine | Lewis Acid | Solvent | Temp. (°C) | Yield (%) | **8**:**9** |
|---|---|---|---|---|---|
| **5a** | $TiCl_4$ | $Et_2O$ | −78 → 20 | 83 | 83:17 |
| **5a** | $TiCl_4$ | $Et_2O$ | −78 | 83 | 89:11 |
| **5a** | $TiCl_4$ | $CH_2Cl_2$ | −78 → 20 | 81 | >95:5 |
| **5a** | $SnCl_4$ | $Et_2O$ | −78 → 20 | 75 | 81:19 |
| **5a** | $SnCl_4$ | $Et_2O$ | −78 | 75 | 92:8 |
| **5a** | $SnCl_4$ | $CH_2Cl_2$ | −78 → 20 | 78 | 89:11 |
| **5a** | $BF_3 \cdot OEt_2$ | $CH_2Cl_2$ | −78 → 20 | 72 | 50:50 |
| **5a** | $BF_3 \cdot OEt_2$ | $CH_2Cl_2$ | −78 | 76 | 94:6 |
| **5a** | $ZnCl_2 \cdot OEt_2$ | *i*-PrOH | −78 → 20 | 81 | 87:13 |
| **5a** | $ZnI_2$ | *i*-PrOH | −78 → 20 | 84 | 76:24 |
| **5a** | $ZnCl_2$ | $CH_2Cl_2$ | −78 → 20 | 80 | 89:11 |
| **5a** | $Me_2AlCl$ | $Et_2O$ | −78 → 20 | 90 | 73:27 |
| **5b** | $BF_3 \cdot OEt_2$ | $CH_2Cl_2$ | −78 | 22 | >95:5 |

The $Me_3SiCN$ addition to the *N*-tosyl aldimine **6b** was screened for different Lewis acids in a similar manner. $BF_3 \cdot OEt_2$, $TiCl_4$, $Et_2AlCl$, $Me_2AlCl$, $SnCl_4$ and $ZnBr_2$ all led to diastereoselectivities of > 94% in favor of the non-chelation controlled adduct **10b**.[14] Since $BF_3 \cdot OEt_2$ led to the highest isolated yield (83%), this Lewis acid was used in all other cases. Table 2 shows that under such conditions non-chelation control amounts to > 90% in all cases. Configurational stability is surprisingly high, since $BF_3 \cdot OEt_2$ does not cause undesired equilibration **10** ⇌ **11** even at room temperature. This is very likely due to the fact that the *N*-tosyl group does not stabilize the carbocation formed upon cyanide ion-dissociation as effectively as the *N*-benzylamino group in the case of nitriles **8**. Interestingly, the aldimines **6** do not require any Lewis acid for $Me_3SiCN$ to add, although the rate of the reaction is slower. The *N*-tosyl group is electron withdrawing, which increases the electrophilicity and reactivity of the imine function. It is uncertain whether $SO_2$ functions as a Lewis acid in those reactions.



## Biographical Sketch

**Manfred T. Reetz**, born in Hirschberg, Germany in 1943, obtained his PhD under U. Schöllkopf at the Universität Göttingen in 1969. After a post-doctorate in Marburg with R.W. Hoffmann he habilitated there in 1974. From 1978 to 1980 he was professor in Bonn and moved back to the Universität Marburg in 1980. In 1991 he moved to Mülheim/Ruhr and became Director of the Max-Planck-Institut für Kohlenforschung in 1993. His research priorities lie in new methods in synthetic organic chemistry, molecular recognition, and polymer chemistry.

**Table 2.** Stereoselective Addition[a] of $Me_3SiCN$ to Aldimines **6**

| Aldimine | Lewis Acid | Temp.[b] (°C) | Yield (%) | **10** : **11** |
|---|---|---|---|---|
| **6a** | $BF_3 \cdot OEt_2$ | −78 → r.t. | 49 | 90 : 10 |
| **6b** | $BF_3 \cdot OEt_2$ | −78 → r.t. | 83 | 96 : 4 |
| **6b** | $TiCl_4$ | −78 → r.t. | 46 | ≥ 95 : 5 |
| **6b** | $Et_2AlCl$ | −78 → r.t. | 54 | 94 : 6 |
| **6b** | $Me_2AlCl$ | −78 → r.t. | 53 | ≥ 95 : 5 |
| **6b** | $SnCl_4$ | −78 → r.t. | 46 | ≥ 95 : 5 |
| **6b** | $SnCl_4$ | r.t. | 38 | ≥ 95 : 5 |
| **6b** | $MgBr_2$ | 0 → r.t. | 28 | 89 : 11 |
| **6b** | $MgBr_2$ | r.t. | 62 | 83 : 17 |
| **6b** | $ZnBr_2$ | 0 → r.t. | 61 | 83 : 17 |
| **6b** | –[c] | r.t. | 58 | 93 : 7 |
| **6c** | $BF_3 \cdot OEt_2$ | −78 → r.t.[d] | 53 | > 95 : 5 |
| **6d** | $BF_3 \cdot OEt_2$ | −78 → r.t. | 59 | 92 : 8 |

[a] Solvent: $CH_2Cl_2$.
[b] The reaction mixture was allowed to warm up to r.t. overnight.
[c] No Lewis acid.
[d] Additional 4 d at r.t.

Configurational assignment of the major diastereomers **10** was initially based on TLC-behavior (larger $R_f$-value of **11**) and $^1H$ NMR spectroscopy. For example, the geminal coupling constants $J_{AB}$ of the benzyl moieties of the non-chelation controlled adducts **10** are consistently larger than those of adducts **11**,[16] fully in line with previous observations in the case of the amino alcohols **3**/**4**.[5,20] Definite proof was established by X-ray structural analysis of **10c** (Figure 1).

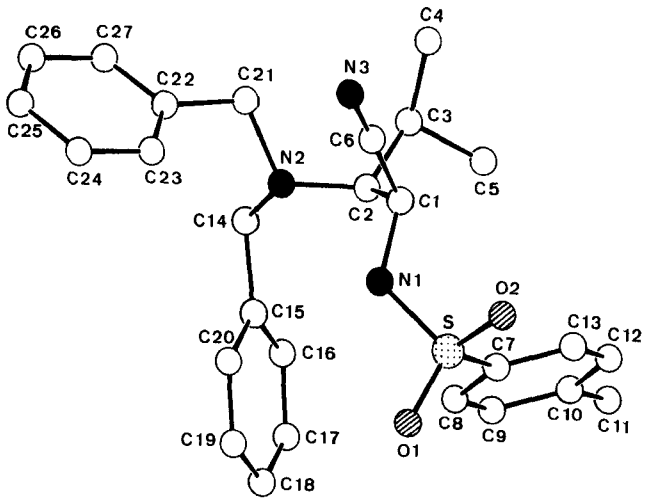
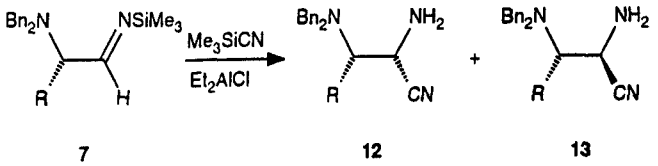



**Figure 1.** The molecular structure of **10c**. Selected distances (Å) and angles (°): N1-C1, 1.471(2); C1-C2, 1.551(2); C2-N2, 1.475(2); S-N1-C1, 119.2(1); C2-N2-C14, 112.3(1); C2-N2-C21, 115.5(1); C14-N2-C21, 109.2(1); N1-C1-C2-N2, 66.1(3); C1-C2-N2-C14, −144.4(4); C1-C2-N2-C21, 89.6(3)

In a final series of experiments the *N*-silyl aldimines **7** were reacted with $Me_3SiCN$ in the presence of various Lewis acids.[16] $Et_2AlCl$ in $Et_2O$ was the Lewis acid of choice, non-chelation control in favor of the adducts **12** being > 90 % at low reaction temperatures (Table 3). The actual immediate products are the *N*,*N*-bistrimethylsilyl derivatives of **12**/**13**. However, partial desilylation is always observed, even upon very careful workup. Therefore, workup conditions were chosen which afford the free amines.




**7** **12** **13**

**Table 3.** $Et_2AlCl$ Promoted Stereoselective Addition[a] of $Me_3SiCN$ to Aldimines **7**

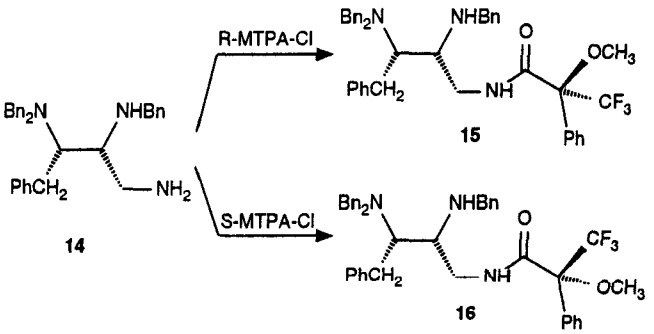
| Aldimine | Temp.[b] (°C) | Yield (%) | **12** : **13** |
|---|---|---|---|
| **7a** | −40 | 72 | 93 : 7 |
| **7a** | 0 | 68 | 71 : 29 |
| **7b** | −40 | 83 | 94 : 6 |
| **7c** | −40 → −20 | 64 | 91 : 9 |
| **7c** | −78 → r.t. | 48 | 77 : 23 |

[a] Solvent: diethyl ether.
[b] Time: 18 h.

The configurational assignment of the major adducts **12** was made, inter alia, by chemical correlation.[16] For example, adduct **12b** was *N*-tosylated, which afforded the previously synthesized compound **10b**. Thus, non-chelation control pertains in all of the described reactions of aldimines **5**, **6** and **7**.

## Determination of Enantiomeric Purity

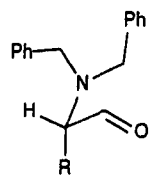
Although the enantiomeric purity of the cyanide addition products was not checked in every case, representative studies were performed for each class of derivatives **8**, **10** and **12** using the method of Mosher.[21] This is illustrated for adduct **8b**. Lithium aluminum hydride reduction afforded the triamine **14** in 55 % having primary, secondary and tertiary amine moieties. Reaction of **14** with *R*-MTPA-chloride and *S*-MTPA-chloride according to Mosher's protocol afforded the diastereomers **15** and **16**, respectively.[14] The $^1H$ and $^{19}F$ NMR spectra showed in each case a single set of signals, as did HPLC studies. Thus, compound **14** is enantiomerically pure (ee > 98 %). Similar studies showed that this also pertains to adducts **10** and **12**.[14,16]



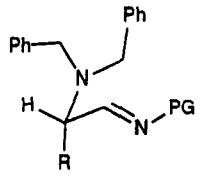
## Discussion

Chelation controlled reactions of α-alkoxy and α-amino aldehydes, are easily explained by invoking cyclic Cram-type intermediates,[2,18,19,22] some of which have been characterized by NMR spectroscopy and X-ray crystallography.[23] In contrast, speculations regarding the origin of non-chelation control are by nature problematical, because many different conformers need to be considered. Indeed, due to different degrees of freedom of the substrates, non-chelation control is generally more difficult to achieve synthetically.[18,19,24] Thus, the fact that effective non-chelation control is observed in the present cyanide addition reactions is remarkable. The source of diastereoselectivity must be related to that for the stereoselectivity in non-chelation controlled reactions of the corresponding *N,N*-dibenylamino aldehydes **2**.[2,5,10] This may involve the electronic effects as defined by the Felkin–Anh model.[2] Alternatively, the ground state geometry may correlate directly with the geometry of the transition state.[11] Indeed, the X-ray structural analysis of aldehyde **2** (R = $PhCH_2$) shows that conformer **17** is involved, in which attack at the sterically non-shielded carbonyl π-face would afford the observed non-chelation controlled adducts **3**.[2] One could therefore postulate a similar conformation **18** in the case of the analogous aldimines. Coordination by a Lewis acid would not change the general picture. Variation of the protective groups at the amino moiety originating from the amino acid (e.g., *N*-BOC) might help in the elucidation of the source of diastereoselectivity. Inverting the sense of diastereoselectivity in cyanide addition reactions in favor of chelation control may become possible by such protective group tuning. These studies are underway in our laboratories.

In conclusion, the present work shows that *N,N*-dibenzylamino aldehydes **2** derived from amino acids **1** are readily transformed into three differently protected aldimines **5**, **6** and **7**. $Me_3SiCN$ additions occur with > 90% non-chelation control under proper conditions to form α,β-diamino nitriles **8**, **10** and **12**, respectively, in enantiomerially pure form. These are synthetically interesting building blocks for further reactions.[25]




**17**




**18** (PG = protective group)

Solvents were dried and distilled before use: THF was distilled from potassium, $Et_2O$ from sodium, and $CH_2Cl_2$ from calcium hydride. All reactions were carried out in flame-dried glassware under Ar. The following NMR instruments were used. $^1H$ NMR, Bruker WH-400 (400 MHz) and Bruker AC-300 (300 MHz); $^{13}C$ NMR, Bruker WH-400 (100 MHz) and Bruker AC-300 (75 MHz); $^{19}F$ NMR, Bruker AC-300 (282 MHz). MS spectra were recorded on Varian CH 7 A, MAT 311 AD and MAT 95. Due to the instability of the aldimines **5**, **6** and **7**, no purifications or microanalyses were attempted, with the exception of **5a** which gave an excellent analysis: C + 0.1, H ± 0.1, N ± 0.12. Satisfactory analyses were obtained for the nitriles **8**, **10** and **12** as well as the triamine **14**: C ± 0.40, H ± 0.20, N ± 0.3 (exceptions: **10a**, **12a** and **12c** for which characteristic mass spectra were recorded and/or satisfactory microanalyses of derivatives, e.g., *N*-BOC derivative of **12a** were obtained).[16]

**Aldimines 5; General Procedure:**
To a solution of an aldehyde **2** (30 mmol) in 150 mL of dry $CH_2Cl_2$ was added benzylamine (3.2 g, 30 mmol) and anhydr. $MgSO_4$ (7.2 g, 60 mmol). The mixture was stirred at r.t. for 4 h. After filtration from the $MgSO_4$, the solvent was removed in vacuo. The aldimines were formed in > 95% yield and were used in further reactions without any purification.

**Aldimines 6; General Procedure:**
Using the procedure of Weinreb,[15] a solution of *N*-sulfinyl-*p*-toluenesulfonamide (600 mg, 2.8 mmol) in 10 mL of dry $CH_2Cl_2$ was treated with a solution of an aldehyde **2** (2 mmol) in 2 mL of $CH_2Cl_2$. After stirring for 3 h (in the case of **2c**, 2 d), the solutions of the aldimines **6** were ready for further reactions. Conversion into **6** was > 90%.

**Aldimines 7; General Procedure:**
Using the procedure of Cainelli,[17] a solution of an aldehyde **2** (2.0 mmol) in 5 mL of dry THF was slowly treated with a THF solution of lithium hexamethyldisilamide (2 mmol) at − 30 °C. After stirring for 1 h, chlorotrimethylsilane (220 mg, 2.0 mmol) was added dropwise. The solution was allowed to stir for an additional 0.5 h at − 30 °C and was then concentrated in vacuo. The light yellow oil was dissolved in 30 mL of dry petroleum ether (40–60), cooled to − 78 °C and filtered from the LiCl through a frit (G4) filled with Celite. The solution was concentrated in vacuo, which also results in the removal of most of the hexamethyldisiloxane. The liquid residues were used without further purification of the aldimines **7** (> 90% conversion).

**$Me_3SiCN$ Addition to Aldimines 5; General Procedure:**
The solution of an aldimine **5** (1 mmol) in 10 mL of a solvent (Table 1) was cooled to − 78 °C and treated with a Lewis acid (1.2 mmol). After stirring for 10 min, cyanotrimethylsilane (198 mg, 2 mmol) was added. The mixture was stirred for 6 h at the temperature given in Table 1 and then treated with sat. aq NaCl (8 mL). The aqueous phases were extracted twice with $Et_2O$ and the combined organic phases were dried ($MgSO_4$). The solvents were removed in vacuo and the crude product was purified by flash chromatography over silica gel (petroleum ether/EtOAc, 2:1) to provide adducts **8** as oils.

*(2S,3S)-2-(N-Benzylamino)-3-(N,N-dibenzylamino)-4-phenylbutanenitrile* (**8a**):
$^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.97 and 3.17 (ABX, 2H, $J_{AB}$ = 13.7, $J_{BX}$ = 9.3, $J_{AX}$ = 5.1 Hz), 3.25 and 3.28 (dt, 1H, $J$ = 5.4, 5.2 Hz), 3.40 (d, 1H, $J$ = 5.6 Hz), 3.51 and 4.07 (AB, 4H, $J$ = 13.6 Hz), 3.59 and 3.86 (AB, 2H, $J$ = 13.0 Hz), 7.11–7.30 (m, 20H).
$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 32.78, 51.29, 51.62, 54.94, 61.31, 119.69, 126.78, 127.39, 127.45, 128.23, 128.53, 128.61, 128.95, 129.28, 129.32, 138.76, 138.83, 139.00.

*(2S,3S)-2-(N-Benzylamino)-3-(N,N-dibenzylamino)-5-methylhexanenitrile* (**8b**):
$^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, $J$ = 5.3 Hz, 6H, $CH_3$), 1.52–1.67 (m, 3H, $CH_2CH$ and $CHCH_3$), 3.01 (m, 1H, $CHNBn_2$), 3.53 and 3.90 (AB, $J_{AB}$ = 13.6 Hz, 4H, $CH_2N$), 3.72 and 3.96 (AB, $J_{AB}$ = 13.2 Hz, 2H, $CH_2N$), 3.53 (d, $J$ = 5.7 Hz, 1H, CHCN), 7.23–7.31 (m, 15H, $C_6H_5$).
$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 22.08 (q, $CH_3$), 22.84 (q, $CH_3$), 24.97 (d, $CHCH_3$), 35.42 (t, $CH_2CH$), 51.04 (t, $CH_2N$), 51.46 (d, $CHCH_2$), 54.37 (t, $CH_2N$), 56.59 (d, CHCN), 119.43 (s, CN), 126.85 (d), 127.00 (d), 127.85 (d), 128.04 (d), 128.11 (d), 128.53 (s), 128.60 (s), 128.83 (d), 138.35 (s), 138.96 (s, $C_6H_5$).

**$Me_3SiCN$ Addition to Aldimines 6; General Procedure:**
A cooled solution of an aldimine **6** (1 mmol) was treated with a Lewis acid (1.4 mmol) (Table 2). After 10 min, cyanotrimethylsilane (2 mmol) was added, and the mixture was allowed to reach r.t. and

stirred overnight (in the case of **5b**, 2 d at −78 °C). The mixture was treated with 10% aq citric acid (2 mL) and extracted twice with EtOAc (40 mL). The combined organic phases were washed with sat. aq NaCl and dried ($MgSO_4$). The solvents were removed in vacuo and the residue flash chromatographed over silica gel (hexane/EtOAc, 4:1) to provide adducts **10** in the isolated yields given in Table 2.

*(2S,3S)-3-(N,N-Dibenzylamino)-2-(tosylamino)butanenitrile* **(10a)**:

Mp 156 °C.

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.16 (d, $J$ = 6.8 Hz, 3 H, $CH_3CH$), 2.34 (s, 3 H, $CH_3C_6H_4$), 2.93 (p, $J$ = 6.8 Hz, 1 H, $CHCH_3$), 3.29 and 3.87 (AB, $J_{AB}$ = 13.4 Hz, 4 H, $CH_2$), 3.87 (d, $J$ = 7.2 Hz, 1 H, CHCN), 7.16–7.31 (m, 12 H, *m*-H in $C_6H_4$ and $C_6H_5$), 7.45 (d, $J$ = 5.7 Hz, 2 H, *o*-H in $C_6H_4$).

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 9.80 (q, $CH_3CH$), 21.55 (q, $CH_3C_6H_4$), 47.46 (d, $CHCH_3$), 54.22 (t, $CH_2$), 54.90 (d, $CHCN$), 117.08 (s, CN), 127.11 (d), 127.64 (d), 128.75 (d), 129.07 (d), 129.82 (d), 136.03 (s), 138.16 (s), 144.12 (s, $C_6H_4$ and $C_6H_5$).

MS (FAB): $m/z$ = 432 (M − 1, 9%), 335 (100).

*(2S,3S)-3-(N,N-Dibenzylamino)-4-phenyl-2-(tosylamino)butanenitrile* **(10b)**:

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.44 (s, 3 H, $CH_3C_6H_4$), 2.84–2.96 (m, 2 H, $CHCH_2$ and 1 H in $CH_2CH$), 3.24 (dd, $J$ = 12.5, 2.6 Hz, 1 H, $CH_2CH$), 3.51 (AB, $J_{AB}$ = 13.3 Hz, 4 H, $CH_2N$), 3.67 (dd, $J$ = 7.1, 4.8 Hz, $CHNH$), 5.65 (d, $J$ = 7.1 Hz, 1 H, NH), 7.03–7.32 (m, 19 H, $C_6H_4$ and $C_6H_5$).

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 21.41 ($CH_3C_6H_4$), 31.15 ($CH_2CH$), 43.90 ($CHCH_2$), 54.43 ($CH_2N$), 61.59 (CHNH), 117.09 (CN), 126.32, 126.89, 127.56, 128.51, 128.93, 128.97, 129.15, 129.57, 134.93, 136.39, 138.00, 143.62 ($C_6H_4$ and $C_6H_5$).

MS (FAB): $m/z$ = 510 (M + 1, 49%), 483 (510-HCN, 100).

*(2S,3S)-3-(N,N-Dibenzylamino)-4-methyl-2-(tosylamino)pentanenitrile* **(10c)**:

Mp 144 °C.

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.88 (d, $J$ = 6.4 Hz, 3 H, $CH_3CH$), 1.23 (d, $J$ = 6.8 Hz, 3 H, $CH_3CH$), 2.40 (s, 3 H, $CH_3C_6H_4$), 2.40 (mc, 1 H, $CHCH_3$), 2.50 (dd, $J_1$ = 10.0 Hz, $J_2$ = 4.8 Hz, 1 H, $CHNBn_2$), 3.66 and 4.11 (AB, $J_{AB}$ = 13.3 Hz, 4 H, $CH_2N$), 4.01 (dd, $J$ = 7.6, 4.8 Hz, 1 H, CHCN), 5.50 (d, $J$ = 7.6 Hz, 1 H, NH), 7.14–7.42 (m, 14 H, $C_6H_4$ and $C_6H_5$).

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 20.63 (q, $CH_3CH$), 21.53 (q, $CH_3C_6H_4$), 22.10 (q, $CH_3CH$), 29.09 (d, $CHCH_3$), 44.19 (d, $CHNBn_2$), 55.22 (t, $CH_2$), 65.28 (d, CHCN), 117.08 (s, CN), 127.15 (d), 127.77 (d), 128.96 (d), 129.40 (d), 129.63 (d), 136.12 (s), 138.55 (s), 143.90 (s, $C_6H_4$ and $C_6H_5$).

MS (FAB): $m/z$ = 462 (M + 1, 26%), 435 (462-HCN, 100).

X-ray crystal structure analysis: Crystals of **10c** were obtained by recrystallization from hexane/EtOAc. $C_{27}H_{31}N_3O_2S$, $M_r$ = 461.6, crystal size 0.28 × 0.02 × 0.72 mm, $a$ = 10.692(1), $b$ = 9.692(1), $c$ = 12.504(1) Å, $\beta$ = 104.95(1)°, $V$ = 1252.0(5) Å$^3$, $T$ = 293 K, $D_c$ = 1.22 g cm$^{-3}$, $Z$ = 2, monoclinic, space group $P2_1$ [No. 4], Enraf-Nonius CAD-4 diffractometer, graphite monochromated Cu-K$\alpha$ radiation, $\lambda$ = 1.54178 Å, scan mode $\omega$-2$\theta$, $\mu$ (Cu-K$\alpha$) = 13.26 cm$^{-1}$, 5284 measured reflections ($\pm h$, $\pm k$, $l$), $[(\sin\theta)/\lambda]_{max}$ 0.63 Å$^{-1}$, analytical absorption correction (min: 1.033, max: 1.487), 5052 independent reflections, 4827 observed reflections [$I > 2.0\sigma(I)$] for 422 refined parameters, structure solution: SHELXS-86 Sheldrick, G.M. *Acta Crystallogr.* **1990**, *A46*, 467; structure refinement: GFMLX, a modified version of ORFLS, Busing, W.R.; Martin, K.O.; Levy, H.A. Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA 1962, non-H atoms anisotropic, H atoms isotropic, absolute configuration determined [Flack parameter = 0.02(1)], $R$ = 0.038, $R_w$ = 0.045, shift/error 0.58, residual electron density 0.33 eÅ$^{-3}$. Further details of the X-ray structure determination may be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany, on quoting the depository number CSD-58153, the names of the authors and the journal citation.

*(2S,3S)-3-(N,N-Dibenzylamino)-5-methyl-2-(tosylamino)hexanenitrile* **(10d)**:

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.60 (d, $J$ = 6.4 Hz, 3 H, $CH_3CH$), 0.92 (d, $J$ = 6.8 Hz, 3 H, $CH_3CH$), 1.37 (mc, 1 H, $CHCH_3$), 1.53–1.70 (m, 2 H, $CH_2CH$), 2.38 (s, 3 H, $CH_3C_6H_4$), 2.70 (dt, $J$ = 10.4, 4.5 Hz, 1 H, $CHNBn_2$), 3.30 and 3.99 (AB, $J_{AB}$ = 13.3 Hz, 4 H, $CH_2N$), 3.87 (dd, $J$ = 7.2, 5.6 Hz, 1 H, CHCN), 5.73 (d, $J$ = 7.2 Hz, 1 H, NH), 7.14–7.41 (m, 14 H, $C_6H_4$ and $C_6H_5$).

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 21.01 (q, $CH_3CH$), 21.47 (q, $CH_3C_6H_4$), 22.82 (q, $CH_3CH$), 24.86 (d, $CHCH_3$), 33.62 (t, $CH_2CH$), 44.50 (d, $CHNBn_2$), 55.28 (t, $CH_2N$), 56.97 (d, CHCN), 117.03 (s, CN), 127.19 (d), 127.76 (d), 128.88 (d), 129.15 (d), 129.73 (d), 135.54 (s), 138.35 (s), 143.98 (s, $C_6H_4$ and $C_6H_5$).

MS (CI): $m/z$ = 476 (M + 1, 44%), 449 (476-HCN, 95), 293 (100).

**$Me_3SiCN$ Addition to Aldimines 7; General Procedure:**

An aldimine **7** (2 mmol) was dissolved in $Et_2O$ (30 mL) and treated with a hexane solution of $Et_2AlCl$ (2.6 mmol) at −40 °C. After 10 min, cyanotrimethylsilane (397 mg, 4 mmol) was added and the mixture stirred for 18 h at −40 °C (in the case of **7c** the temperature was raised to −20 °C). The mixture was treated with 10% aq citric acid (2 mL) and extracted with EtOAc (2 × 40 mL). The combined organic phases were washed with sat. aq NaCl and dried ($MgSO_4$). After filtration from $MgSO_4$ the solvents were removed in vacuo and the crude products were purified by flash chromatography over silica gel (hexane/EtOAc, 1:1) to afford compounds **12** (Table 3).

*(2S,3S)-2-Amino-3-(N,N-dibenzylamino)butanenitrile* **(12a)**:

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.21 (d, $J$ = 6.8 Hz, 3 H, $CH_3$), 1.62 (bs, 2 H, $NH_2$), 2.97 (dt, $J$ = 8.0, 6.8 Hz, 1 H, $CHCH_3$), 3.42 and 3.90 (AB, $J_{AB}$ = 13.7 Hz, 4 H, $CH_2N$), 3.58 (d, $J$ = 8.0 Hz, 1 H, CHCN), 7.24–7.42 (m, 10 H, $C_6H_5$).

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 9.80 ($CH_3$), 48.01 ($CHCH_3$), 54.49 ($CH_2N$), 56.31 (CHCN), 121.96 (CN), 127.27, 128.44, 129.02, 139.00 ($C_6H_5$).

MS (EI): $m/z$ = 224 ($C_{16}H_{18}N$), 91 ($C_7H_7$, 100).

*(2S,3S)-2-Amino-3-(N,N-dibenzylamino)-4-phenylbutanenitrile* **(12b)**:

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.65 (bs, 2 H, $NH_2$), 2.82 and 3.12 (ABX, $J_{AB}$ = 13.3, $J_{AX}$ = 10.2, $J_{BX}$ = 4.5 Hz, 2 H, $CH_2CH$), 3.02 (ddd, $J$ = 10.2, 5.2, 4.6 Hz, 2 H, $CHCH_2$), 3.38 (d, $J$ = 5.2 Hz, CHCN), 3.47 and 4.07 (AB, $J_{AB}$ = 13.6 Hz, 4 H, $CH_2N$), 7.06–7.28 (m, 15 H, $C_6H_5$).

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 32.29 (t, $CH_2CH$), 44.09 (d, $CHCH_2$), 54.82 (t, $CH_2N$), 62.45 (d, CHCN), 121.60 (CN), 126.66 (d), 127.35 (d), 128.24 (d), 128.60 (d), 128.99 (d), 129.13 (d), 138.23 (s), 138.75 (s, $C_6H_5$).

MS (FAB): $m/z$ = 356 (M + 1, 42%), 329 (356-HCN, 7), 300 ($C_{22}H_{22}N$, 100).

*(2S,3S)-2-Amino-3-(N,N-dibenzylamino)-5-methylhexanenitrile* **(12c)**:

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.82 (d, $J$ = 6.0 Hz, 3 H, $CH_3$), 0.85 (d, $J$ = 6.0 Hz, 3 H, $CH_3$), 1.46–1.63 (m, 3 H, $CH_2CH$ and $CHCH_3$), 1.73 (bs, 2 H, $NH_2$), 2.82 (mc, 1 H, $CHNBn_2$), 3.44 and 3.91 (AB, $J_{AB}$ = 13.4 Hz, 4 H, $CH_2N$), 3.59 (d, $J$ = 5.2 Hz, 1 H, CHCN), 7.15–7.30 (m, 10 H, $C_6H_5$).

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 22.29 (q, $CH_3$), 23.28 (q, $CH_3$), 25.21 (d, $CHCH_3$), 35.36 (t, $CH_2CH$), 44.94 (d, $CHCH_2$), 54.65 (t, $CH_2N$), 57.82 (d, CHCN), 121.79 (s, CN), 127.17 (d), 128.30 (d), 129.11 (d), 139.15 (s, $C_6H_5$).

**(2*R*,3*S*)-1-Amino-2-(*N*-benzylamino)-3-(*N*,*N*-dibenzylamino)-4-phenylbutane (14):**

The solution of **5a** (200 mg, 0.45 mmol) in 5 mL of $Et_2O$ was added dropwise to a suspension of lithium aluminum hydride (LAH) (470 mg, 12 mmol) in 15 mL of $Et_2O$. The mixture was stirred overnight at r.t. and was then carefully treated with $H_2O$. After extrac-

tion twice with $Et_2O$, the combined organic phases were washed with $H_2O$ and dried ($MgSO_4$). The solvent was removed in vacuo to afford the triamine **14** (110 mg, 55%).

$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.68 (b, 3 H), 2.30–2.36 (m, 2 H), 2.74–2.84 (m, 2 H), 2.96 and 3.11 (AB, 2 H, $J$ = 13.1 Hz), 3.05 and 3.20 (ABX, 2 H, $J_{AB}$ = 13.5, $J_{AX}$ = 4.7, $J_{BX}$ = 5.1 Hz), 3.47 and 3.77 (AB, 4 H, $J$ = 13.7 Hz), 7.13–7.33 (m, 20 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 32.40, 41.29, 50.99, 55.39, 59.61, 61.04, 125.98, 126.59, 127.29, 128.03, 128.31, 128.44, 128.64, 129.00, 129.11, 139.85, 140.70, 141.25.

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