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Towards the Synthesis of Highly Functionalized Chiral α-Amino Nitriles by Aminative Cyanation and Their Synthetic Applications

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The cyanobis(dibenzylamino)borane-mediated transformation of chiral aldehydes into the corresponding α-amino nitriles is described. Starting from these compounds short synthetic routes can be envisaged for obtaining diastereomerically pure functionalized 1,2-diamines and hydroxylated α-amino acids that are of interest as core key units of biologically active substances or as potential ligands for asymmetric catalysis. The stereochemical outcome of the aminative cyanation reaction is discussed.

Introduction

Compounds with highly versatile functional groups such as α-amino nitriles are extremely useful synthetic intermediates and a number of strategies have been devised for their preparation.[1] Besides the classical Strecker reaction,[2] which relies upon treatment of aldehydes with ammonia and hydrogen cyanide, and its catalytic and asymmetric variants,[3] alternative routes to α-amino nitriles involve the oxidation of secondary and tertiary amines.[4] Furthermore, a Strecker-type aminative cyanation of aldehydes and ketones has been recently devised[5] by Suginome et al. using cyanobis(dialkylamino)boranes.

We have already reported[6] that by using the procedure by Suginome et al., both the amino and the cyano moieties can be transferred to the carbonyl carbon atom of the aldehydes and ketones in a highly efficient way, irrespective of the nature of easily removable or reactive protecting groups at the nitrogen atom, to generate a wide range of α-amino nitriles in nearly quantitative yields. On these grounds we have now decided to apply this protocol to the preparation, starting from suitable aldehydes, of a series of polyfunctional homochiral α-amino nitriles which can be considered versatile building blocks for the synthesis of biologically active compounds and/or as intermediates for the synthesis of new ligands for asymmetric catalysis.

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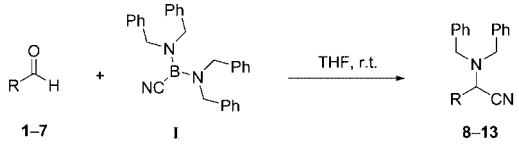
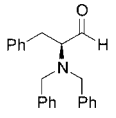
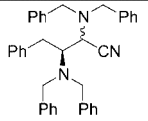
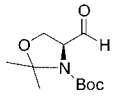
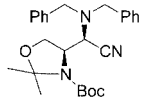
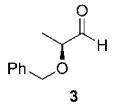
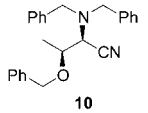
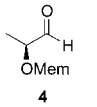
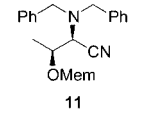
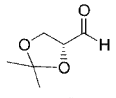
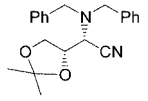
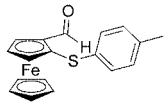
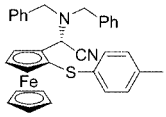
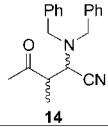
Results and Discussion

Aldehydes **1**–**6**, mostly derived from the chiral pool of natural products and prepared according to literature methods or by employing slightly modified procedures, were treated with 1.25 equiv. of cyanobis(dibenzylamino)borane (**I**) in THF as the solvent to yield after variable reaction times (Table 1) the corresponding *N*,*N*-disubstituted α-amino nitriles **8**–**13** in satisfactory to good isolated yields. The stereoselectivity of the reaction turned out to be closely related to the rigidity of the motif adjacent to the carbonyl moiety of the starting material. As a matter of fact, Garner's aldehyde (**2**), D-glyceraldehyde (**5**) and (S_{Fc})-2-[(4-methylphenyl)sulfanyl]ferrocenecarbaldehyde (**6**) (Entries 2, 5 and 6), which all possess a rigid framework at the α-position, gave much better results in terms of diastereoselectivity than other aldehydes with linear or more flexible scaffolds.

In addition to the different aldehydes used for the synthesis of α-amino nitriles with cyanoborane **I** we also considered the dicarbonyl compound **7** whose preparation was accomplished in two steps from 2-butanone and ethyl formate.[7] The reaction carried out under standard conditions led to unsatisfactory results, but by using 2 equiv. of cyanoborane **I**, to our delight we finally isolated the expected product **14** in a satisfactory yield (Entry 7). Note that the reaction is completely chemoselective with only the aldehydic carbonyl function being involved in the aminative cyanation step. We inferred from this that the first equivalent of cyanobis(dibenzylamino)borane (**I**) might act as a protecting group,[8] with the second adding selectively to the more reactive aldehyde function (Scheme 1). According to this hypothesis, the diastereoselectivity of the reaction would be established during the aqueous quenching of the

Table 1. Synthesis of α-amino nitriles **8**–**14** by the reaction of aldehydes **1**–**7** with cyanobis(dibenzylamino)borane (**I**).



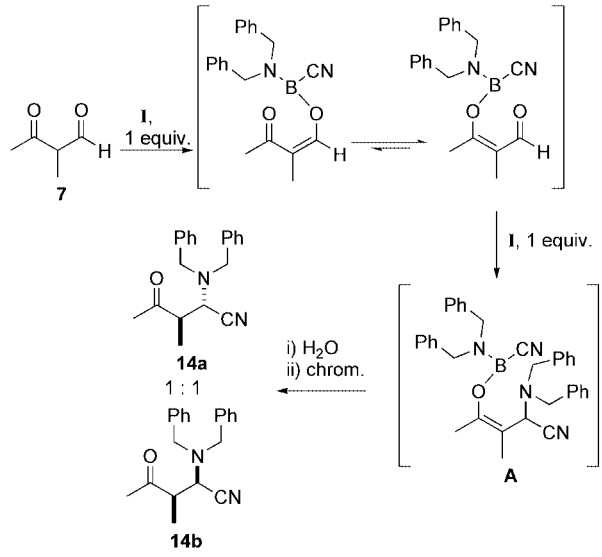
Entry	Aldehydes	α-Amino nitriles	Reaction time [h]	Yield [%][a]	d.r.[b]
1	 **1**	 **8**	24	52	70:30
2	 **2**	 **9**	5	68	>98:2[c]
3	 **3**	 **10**	24	74	66:34[c]
4	 **4**	 **11**	6	43	70:30[c]
5	 **5**	 **12**	18	75	86:14[c]
6	 **6**	 **13**	48	80	>98:2[d]
7	 **7**	 **14**	24	60[e]	50:50

[a] Isolated yield. [b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c] The *syn* isomer prevails. [d] (R,S_{Fc}) stereoisomer. [e] The reaction was conducted at reflux temperature with 2 equiv. of **I**.

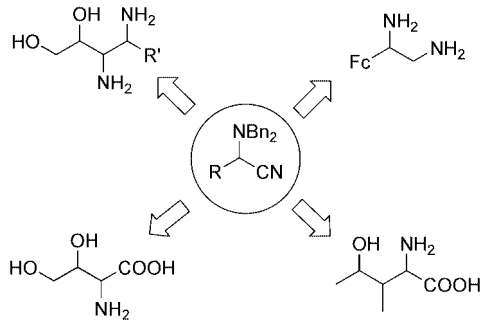
boron enolate moiety in the α-amino nitrile **A**, and this accounts for the generation in a 1:1 ratio of the two diastereoisomers **14a** and **14b** which were easily separated by chromatography on silica gel.

Some of the new chiral α-amino nitriles shown in Table 1 were then chemically manipulated to demonstrate their synthetic utility as valuable building blocks for target compounds. Starting from α-amino nitriles **12**–**14** expeditious routes were envisaged to functionalized 1,2-diamino and α-amino acid moieties that are of potential interest as ligands for asymmetric catalysis and as core key units of biologically active substances (Scheme 2).

The various reaction modes involved the interconversion of the nitrile functional group with preservation of the original carbon atom connectivity[9] and the synthetic elaboration of the diastereomerically enriched α-amino nitriles was performed along two different lines involving the hydrolysis and reduction of the CN moiety. Several synthetic applications focused towards target compounds are described below.



Scheme 1. Proposed mechanism for the aminative cyanation of **7**.

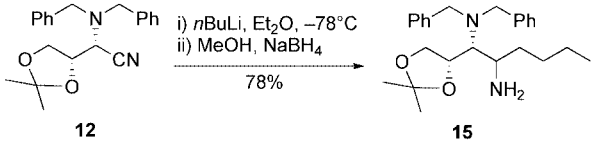


Scheme 2. Core units derived from α-amino nitriles.

Synthesis of 1,2-Diamino Derivatives

Many natural products that have valuable biological properties contain the 1,2-diamino moiety. Moreover, vicinal diamine derivatives also find increasing utilization in organic synthesis, either as chiral auxiliaries or ligands for metal ions, especially in the field of asymmetric synthesis.[10] Starting from **12**, we envisioned a simple entry to 1,2-diamino-3,4-diols by alkylmetalation/reduction of α-amino nitriles, as reported by Mangeney and co-workers.[11] Addition of *n*BuLi to **12** followed by highly stereoselective reduction with $NaBH_4$ after methanolysis of the intermediate imine led to the protected 1,2-diamino-3,4-diol **15** as a single diastereoisomer in 78% yield after chromatography on silica gel (Scheme 3).[12] The use of this kind of derivative in the assembly of (diamine)platinum analogs of cisplatin with antitumor and antimicrobic activities has previously

been reported,[13] highlighting the beneficial role played by hydrophilic OH functionalities in improving water solubility.



Scheme 3. Rapid access to 1,2-diamino-3,4-diol **15**.

In view of our interest in ferrocene chemistry,[14] we then investigated the synthetic applicability of the easily accessible homochiral α-amino nitrile **13**, which has central and planar chirality, and we devised a straightforward chemical elaboration of **13** into a 1,2-disubstituted α,β-diaminoferrocenyl derivative by reduction of the cyano group. Relatively few examples of ferrocenes with reactive functional groups in the α,β-positions of a ferrocene side-chain have been reported and even less known are 1,2-disubstituted derivatives of this type that have both planar and central chiralities. Moreover, the preparation of ferrocene compounds containing diamino motifs is a goal of major interest[15] in view of the widespread application of polyfunctional homochiral ferrocenyl derivatives as ligands in asymmetric catalysis.[16] For this purpose, chiral 1-ferrocenyl-1,2-diamines have recently been prepared by asymmetric reduction of a halo ketone, derivatization of the alcoholic function and nucleophilic substitution with a nitrogen nucleophile.[15a] Although the reduction of **13** with $LiAlH_4$ in THF at room temperature gave mainly the product resulting from the loss of the cyano group, reduction with $LiAlH_4$ in refluxing Et_2O occurred smoothly leading after Boc protection of the new amino functionality of **16** to the diamino derivative **17** as a single stereoisomer in 69% overall yield from the starting α-amino nitrile (Scheme 4).

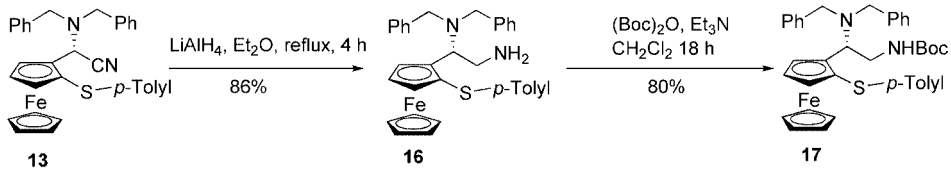
The absolute configuration at the newly created chiral center in **17** was assigned by comparison with compound **21** obtained from the amino alcohol **18** whose absolute configuration has previously been reported[14h] to be (S,S_{Fc}). Treatment of (S,S_{Fc})-**18** with $(Boc)_2O$ followed by Ac_2O led to the acetylated *N*-Boc-protected amino alcohol **20**. Nucleophilic substitution at the α-ferrocenylic position occurred with complete retention of configuration[17] and the (*S*) configuration of the diamine **21** resulting from acetyl displacement in **20** by dibenzylamine could consequently be assigned by chemical correlation with the amino alcohol **18** (Scheme 5).

By comparison of the NMR spectra of **21** and **17**, the configuration of the newly formed stereogenic center in the latter was established to be (*R*).

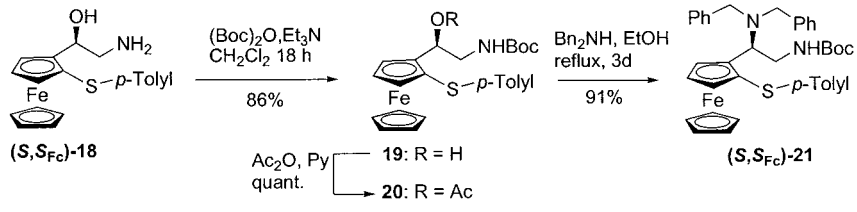
Synthesis of α-Amino Hydroxy Acids

Hydrolysis of the nitrile group in order to generate α-amino acids is perhaps the most important use of α-amino nitriles. We decided to expose α-amino nitriles **12** and **14** to hydrolytic conditions with the aim of obtaining variously substituted α-amino hydroxy acids. These are interesting compounds both as constituents of biologically active non-proteinogenic peptides and as precursors of β-lactam antibiotics.[18] Hydrolysis of α-amino nitrile **12** in a basic oxidizing medium[19] led to the corresponding amide **22** in 95% yield and with the same diastereomeric ratio as the starting material (Scheme 6).

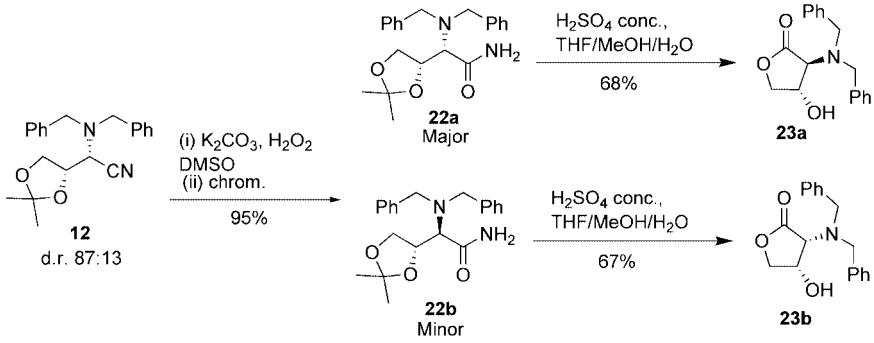
The diastereoisomers were easily separated by column chromatography on silica gel to afford **22a** and **22b** which, subjected separately to acidic hydrolysis, gave the enantiopure *N*-protected 3-hydroxyhomoserine lactones **23a** and **23b**. The relevance of these compounds stems from the role they play as central scaffolds in the construction of the quorum-sensing autoinducers used by Gram-negative bacteria to control transcription of specific genes in relation to population density.[20,21] The absolute configuration of the stereogenic center at the C-3 atom that bears the amino group in the two lactones **23a** and **23b** was tentatively assigned by means of NOE experiments, which suggested a *trans* relationship between the 3-H and 4-H atoms in **23a** and a *cis* arrangement in **23b**. Therefore a prevailing *syn* configuration for the open-chain amide **22a** and consequently for the starting α-amino nitrile **12** could be assumed.



Scheme 4.



Scheme 5.



Scheme 6. Hydrolysis of α-amino nitrile **12** to the corresponding lactones **23a** and **23b**.

The suitability of α-amino nitriles for conversion into highly valuable building blocks or into biologically active substances was further demonstrated by the chemical manipulation of **14**. It has recently been reported[22] that (2*S*,3*R*,4*S*)-4-hydroxyisoleucine (Figure 1), extracted from the seeds of fenugreek, possesses interesting insulinotropic properties since it stimulates glucose-induced insulin secretion in the micromolar concentration range.

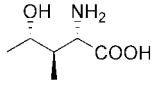
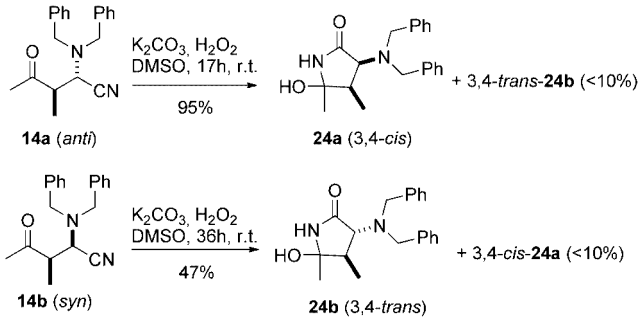


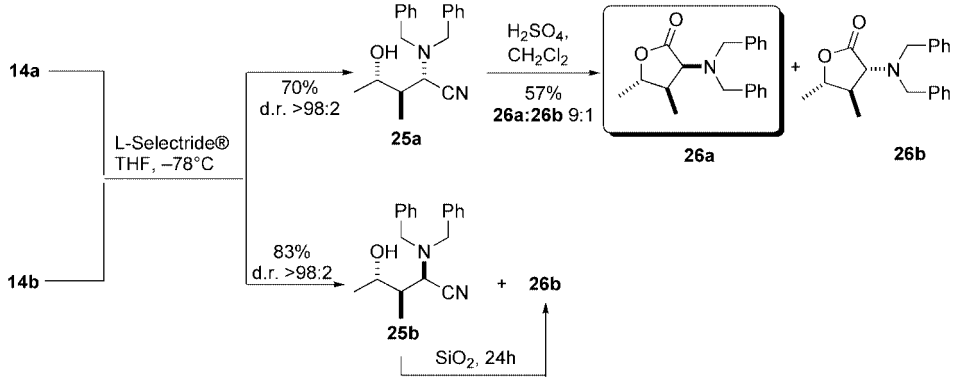
Figure 1. The structure of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine.

Although the stereoselective synthesis of this compound has recently been achieved,[23] as a result of its promising pharmaceutical properties, the development of new shortcut synthetic routes to this nonproteinogenic α-amino acid would appear highly desirable. Considering the structure of **14** we envisioned that hydrolysis of the cyano group followed by reduction of the keto moiety might provide the α-amino γ-hydroxy acid structure of the natural product. After several attempts we switched to the use of H_2O_2 in the presence of K_2CO_3 in DMSO for the hydrolysis of the cyano group.[19] Basic hydrolysis of the diastereomerically pure **14a** and **14b** (Scheme 7) did not afford the linear amide, however, but the cyclic aminals **24a** and **24b** in 95 and 47% yields, respectively, together with very minor amounts of the corresponding diastereoisomers derived from partial epimerization at the α-position to the cyano moiety.



Scheme 7.

Although this reaction turned out to be useless with respect to the synthesis of the desired amide, that both pyrrolidin-2-ones **24a** and **24b** could be obtained has allowed us to assign the relative configuration of the parent compounds **14a** and **14b** by means of NOE experiments. Moreover, this result demonstrates the effectiveness of the synthetic sequence as an entry to 5-hydroxypyrrolidin-2-ones. These systems, extremely stable to hydrolysis under the aforementioned reaction conditions, are rather important compounds as herbicides[24] and in medicinal chemistry as they exhibit interesting activity on the CNS.[25] The formation of aminals **24** can be explained by considering the proposed mechanism for the H_2O_2-promoted hydrolysis of nitriles.[26]



Scheme 8. Synthesis of 3,4-*cis*-4,5-*trans*-3-(dibenzylamino)-4,5-dimethyldihydro-2(3*H*)-furanone (**26a**).

To obtain the target compound, we decided to reverse the sequence of synthetic events and to anticipate the carbonyl reduction step by using L-Selectride® whose steric hindrance, avoiding Lewis acid–Lewis base interactions, should prevent the reported reduction or loss of the cyano group.[9] The choice of reagent turned out to be successful as alcohol **25a**, derived from ketone **14a**, was generated in a fairly good yield and as a single diastereoisomer (Scheme 8).

The cyano group on **25a** was subsequently subjected to acid hydrolysis using concentrated H_2SO_4 in CH_2Cl_2 leading in moderate yield to amino lactones **26a** and **26b** as a 90:10 diastereomeric mixture in favour of **26a** with the correct stereochemistry. The assignment of the relative configuration in lactones **26a** and **26b** was accomplished by means of NOE experiments. To gain further proof of the stereochemical assignment, the α-amino nitrile **14b** was also reduced to furnish in good yield the diastereomerically pure alcohol **25b**, which partially cyclized spontaneously in the reaction medium and could be converted quantitatively into lactone **26b** by simply standing on silica for 24 h.

Stereochemical Considerations

The stereochemistry of α-amino nitrile **9**, as well as the configuration of **12** and **13**, deduced from their conversion into the configurationally defined **17** and **23**, deserves some comment also related to the mechanism of the aminative cyanation reaction.

The prevailing *syn* relative stereochemistry of α-amino nitrile **12** fits well the Strecker-type transformations performed on imines derived from α-alkoxy aldehydes, which all gave the corresponding *syn* diastereoisomer in excess.[27] Considering the proposed mechanism for the addition of cyanobis(dialkylamino)boranes to aldehydes,[5] in an early step of the reaction sequence leading to **12** a four-membered oxazaboretidine ring is formed whose final evolution can be postulated to be an intermediate free iminium ion (Scheme 9, path *a*).[28]

This latter intermediate is likely to adopt the most favorable conformation in which the *N*,*N*-dibenzyl moiety lies far away from the rigid and sterically demanding dioxolane system. In a similar manner to the model proposed for the Strecker reaction of D-glyceraldehyde derivatives,[27b–27d] attack by the nucleophile in a stereodetermining step takes place[29] at the *Re* face *anti* with respect to the oxygen atom at the C-2 atom of the imine to give the *syn* adduct selectively (Figure 2).

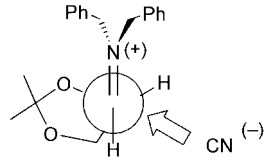
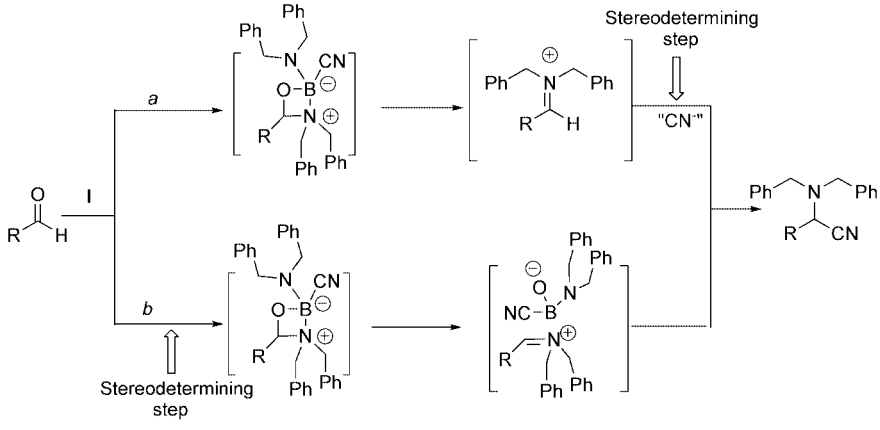


Figure 2. Cyanide attack on the *Re* face of the iminium ion.

The configuration of α-amino nitrile **9**, derived from Garner's aldehyde (**2**), unambiguously assigned as *syn* by means of X-ray analysis (Figure 3),[30] provides further support for a reaction path involving attack of the cyanide on the less hindered face of a putative iminium ion (Scheme 9, path *a*). On the other hand, literature precedents on nucleophilic additions to imines derived from aldehyde **2**,[31] as well as on cyanide additions to the corresponding nitrones,[32] indicate a strong preference for a relative *syn* stereochemistry in the products. However, the possibility that addition to the *Re* face might also occur by assuming precomplexation of the boron reagent with an acetal oxygen atom cannot be ruled out.

With regard to the stereochemistry in the ferrocenyl-derived α-amino nitrile **13**, all the previous reports on nucleophilic additions to imines derived from (S_{Fc})-2-[(4-methylphenyl)sulfanyl]ferrocenecarbaldehyde (**6**) are consistent with an attack of the nucleophile on the less hindered *Si* face of the imine[14g] and this implies the opposite stereochemistry with respect to that observed in the case of **17**. To account for this different stereochemical outcome, we can speculate that the four-membered cyclic intermediate postulated by Suginome[5] generated by the attack of the



Scheme 9. Proposed reaction pathways for the formation of α-amino nitriles.

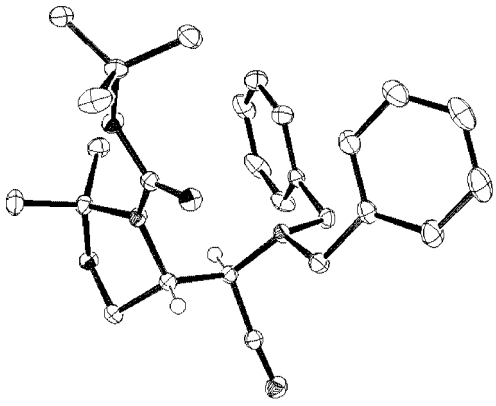
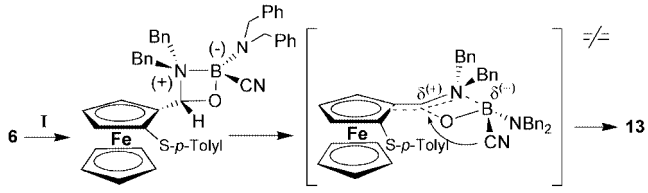


Figure 3. Molecular structure of **9** according to single-crystal X-ray analysis.

cyanobis(dibenzylamino)borane on the less-hindered *Si* face of aldehyde **6** might evolve via a cyclic transition state with the ferrocenyl scaffold stabilizing the positive charge (Scheme 10).[33]



Scheme 10.

This arrangement or a closely related compact ion pair formed between the iminium and the boron-bound cyanide ion might favor delivery of the CN anion to the electrophilic carbon atom from the *Re* face. According to this hypothesis, the stereochemical outcome of the whole Strecker process would be established during the first attack of the cyanoborane on the aldehyde, the second step being stereospecific, and account for the observed stereochemistry (Scheme 9, path *b*) irrespective of the configuration at the stereogenic boron center bearing the CN group.

Conclusions

In summary, we have succeeded in devising a practical method based on the Suginome amino cyanation reaction for the asymmetric synthesis of α-amino nitriles starting from chiral aldehydes. The variable stereoselectivity observed depends upon the rigidity of the motif α to the carbonyl moiety in the starting aldehyde. The compounds obtained represent valuable starting points for the development of compounds of biological interest and for the synthesis of ligands for asymmetric catalysis by interconversion of the nitrile functional group with preservation of the original carbon atom connectivity. An insight into the aminative cyanation mechanism is given that is based on the stereochemical outcome of these reactions.

Experimental Section

General Methods and Materials: Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. Reactions were conducted in oven-dried (120 °C) glassware under a positive pressure of nitrogen. The transfer of anhydrous solvents or mixtures was accomplished using oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under argon. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Cyanobis(dibenzylamino)borane (**I**) was prepared according to a literature procedure.[5] (2*S*)-*N*,*N*-Dibenzylphenylalaninal (**1**),[34] Garner's aldehyde (**2**),[35] (2*S*)-2-(benzyloxy)propanal (**3**), (2*S*)-2-[(2-methoxyethoxy)methoxy]propanal (**4**),[36] D-glyceraldehyde acetonide (**5**),[37] (S_{Fc})-2-[(4-methylphenyl)sulfanyl]ferrocenecarbaldehyde (**6**)[38] and β-keto aldehyde **7**[7] were prepared according to literature or modified procedures. Thin-layer chromatography (TLC) was performed on plastic plates coated with silica gel 60 F_{254} (0.20 mm). Column chromatography was carried out on 70–230 mesh silica gel. Melting points were obtained using an Electrothermal apparatus, and are uncorrected. IR spectra were performed using a Perkin Elmer FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded using Varian Gemini instruments, at 20 °C in $CDCl_3$ or [D_6]acetone at 300 and 400 MHz and 75 and 100 MHz, respectively. Chemical shifts are reported on the δ scale relative to residual $CHCl_3$ (δ = 7.26 ppm) or acetone (δ = 2.05 ppm) for ^1H NMR spectroscopy and relative to the central line of $CDCl_3$ (δ =77.0 ppm) or [D_6]-acetone (δ =29.8 ppm) for ^{13}C NMR spectroscopy. Mass spectra (ESIMS) were obtained using an electrospray ionization source with MeOH as solvent, using a VG 770-E instrument. Optical rotations were obtained at 20 ± 2 °C, with a Perkin Elmer 341 polarimeter. New oily products were characterised by accurate mass measurements [high-resolution mass spectra (HRMS)]. Elemental analyses were performed using a Flash EA1112 Automatic Elemental Analyser CE instrument.

General Procedure for the Synthesis of α-Amino Nitriles 8–13: A solution of the aldehyde **1**–**6** (4.0 mmol) in dry THF (4 mL) was slowly added to a stirred suspension of cyanobis(dibenzylamino)-borane (**I**) (2.15 g, 5.0 mmol) in dry THF (5 mL) under nitrogen. The reaction mixture was then stirred at room temperature until the starting aldehyde had disappeared (TLC, *n*-hexane/EtOAc mixtures) and then filtered through a short plug of Florisil®. After evaporation of the solvents, the resulting crude mixture was purified by chromatography on silica gel (*n*-hexane/EtOAc mixtures).

2,3-Bis(dibenzylamino)-4-phenylbutanenitrile (8): According to the general procedure, compound **8** was obtained, after 24 h of reaction, as a pale yellow oil in 52% yield (1.11 g) as a mixture of diastereoisomers (70:30 diastereomeric, ^1H NMR of the crude reaction mixture). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–6.80 (m, 25 H_{maj}, 25 H_{min}), 4.10 (d, J = 5.0 Hz, 1 H_{maj}), 3.81 (d, J = 13.6 Hz, 2 H_{maj}), 3.80–3.60 (m, 3 H_{min}), 3.56 (d, J = 13.8 Hz, 2 H_{maj}), 3.42–3.38 (m, 1 H_{maj}), 3.60–3.30 (m, 7 H_{min}), 3.28 (d, J = 13.3 Hz, 2 H_{maj}), 3.27 (d, J = 13.9 Hz, 2 H_{maj}), 3.08 (dd, J = 13.9, 8.9 Hz, 1 H_{maj}), 3.00 (dd, J = 13.9, 5.0 Hz, 1 H_{maj}), 2.60–2.55 (m, 2 H_{min}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) [minor isomer in brackets]: δ = [140.2], 139.5, 139.2, [138.8], 138.4, 130.2, 129.7, 129.4, 128.7, 127.0, 126.8, [117.1], 116.5, 60.6, [58.4], [58.0], [56.5], 56.0, 53.1, 36.8, [34.5] ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 2221 cm^{-1}. HRMS: exact mass calcd. for $C_{38}H_{38}N_3$ $[M + H]^+$ 536.3066; found 536.3068.

***tert*-Butyl (4*R*)-4-[(*R*)-Cyano(dibenzylamino)methyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate (9):** According to the general pro-

cedure, compound **9** was obtained, after 5 h of reaction, as a white solid in 68% yield (1.18 g) and as a single diastereoisomer (^{1}H NMR of the crude reaction mixture); m.p. 85–87 °C. $[\alpha]_D^{rt}$ = +40 (c = 0.897, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.15 (m, 10 H), 4.47 (dd, J = 9.0, 5.1 Hz, 1 H), 4.06 (d, J = 13.2 Hz, 2 H), 3.98 (t, J = 9.9 Hz, 1 H), 3.90 (dt, J_t = 9.9, J_d = 5.1 Hz, 1 H), 3.76 (d, J = 6.9 Hz, 1 H), 3.24 (d, J = 13.2 Hz, 2 H), 1.48 (s, 9 H), 1.40 (s, 3 H), 0.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 137.5, 129.3, 128.3, 127.4, 115.8, 94.6, 80.5, 65.5, 58.1, 55.8, 55.5, 28.4, 27.1, 24.4 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 2225, 1696 cm^{-1}. MS (ESI): m/z = 435 $[M]^+$. $C_{26}H_{33}N_3O_3$ (435.25): calcd. C 71.70, H 7.64, N 9.65; found C 71.69, H 7.64, N 9.68.

(2*S*,3*S*)- and (2*R*,3*S*)-3-(Benzyloxy)-2-(dibenzylamino)butanenitrile (10): According to the general procedure, compound **10** was obtained, after 24 h of reaction, as a pale yellow oil in 74% yield (1.10 g) as a mixture of diastereoisomers [66:34 diastereomeric ratio favouring the (2*S*,3*S*) isomer, ^{1}H NMR of the crude reaction mixture]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 15 H_{maj}, 15 H_{min}), 4.52 (d, J = 11.1 Hz, 1 H_{min}), 4.50 (d, J = 12.0 Hz, 1 H_{maj}), 4.47 (d, J = 11.1 Hz, 1 H_{min}), 4.44 (d, J = 11.7 Hz, 1 H_{maj}), 4.07 (d, J = 14.1 Hz, 2 H_{maj}), 3.83 (d, J = 13.5 Hz, 2 H_{min}), 3.77–3.71 (m, 1 H_{maj}, 1 H_{min}), 3.59 (d, J = 5.7 Hz, 1 H_{maj}), 3.40 (d, J = 9.3 Hz, 1 H_{min}), 3.38 (d, J = 13.5 Hz, 2 H_{min}), 3.33 (d, J = 13.8 Hz, 2 H_{maj}), 1.23 (d, J = 6.0 Hz, 3 H_{maj}), 1.15 (d, J = 6.0 Hz, 3 H_{min}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) [minor isomer in brackets]: δ = 137.9, [137.8], 137.3, 128.8, [128.7], 128.6, [128.5], 128.4, [116.6], 115.9, 74.4, [73.8], [72.0], 71.6, [59.0], 58.1, 56.4, [56.1], [17.3], 17.1 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 2228 cm^{-1}. HRMS: exact mass calcd. for $C_{25}H_{26}N_2NaO$ $[M + Na]^+$ 393.1943; found 393.1948.

(2*S*,3*S*)- and (2*R*,3*S*)-2-(Dibenzylamino)-3-[(2-methoxyethoxy)methoxy]butanenitrile (11): According to the general procedure, compound **11** was obtained, after 6 h of reaction, as a pale yellow oil in 43% yield (0.63 g) as a mixture of diastereoisomers [70:30 diastereomeric ratio favouring the (2*S*,3*S*) isomer, ^{1}H NMR of the crude reaction mixture]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 10 H_{maj}, 10 H_{min}), 4.74 (d, J = 7.5 Hz, 1 H_{min}), 4.72 (s, 2 H_{maj}), 4.68 (d, J = 7.2 Hz, 1 H_{min}), 4.11 (d, J = 13.8 Hz, 2 H_{maj}), 4.08–3.96 (m, 1 H_{maj}, 1 H_{min}), 3.86 (d, J = 13.5 Hz, 2 H_{min}), 3.84–3.60 (m, 2 H_{maj}, 3 H_{min}), 3.57 (d, J = 5.4 Hz, 1 H_{maj}), 3.52–3.42 (m, 2 H_{maj}, 2 H_{min}), 3.40–3.30 (m, 2 H_{maj}, 2 H_{min}), 3.30 (s, 3 H_{maj}), 3.29 (s, 3 H_{min}), 1.24 (d, J = 6.3 Hz, 3 H_{maj}), 1.17 (d, J = 6.0 Hz, 3 H_{min}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) [minor isomer in brackets]: δ = 137.7, [137.1], [128.6], 128.5, 128.4, [128.3], [127.5], 127.3, [116.3], 115.6, 94.2, [93.7], 72.5, 71.4, [71.1], [67.1], 67.0, 58.8, 57.7, 56.3, [55.9], [17.6], 17.3 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 2229 cm^{-1}. HRMS: exact mass calcd. for $C_{22}H_{29}N_2O_3$ $[M + H]^+$ 369.2178; found 369.2175.

(2*R*)- and (2*S*)-2-(Dibenzylamino)-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanenitrile (12): According to the general procedure, compound **12** was obtained, after 18 h of reaction, as a white solid in 75% yield (1.01 g) as a mixture of diastereoisomers [86:14 diastereomeric ratio favouring the (2*R*) isomer, ^{1}H NMR of the crude reaction mixture]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.24 (m, 10 H_{maj}, 10 H_{min}), 4.37 (q, J = 6.0 Hz, 1 H_{maj}), 4.28–4.21 (m, 1 H_{min}), 4.06 (dd, J = 8.7, 6.3 Hz, 1 H_{maj}), 4.00 (d, J = 13.2 Hz, 2 H_{maj}), 3.95 (dd, J = 8.7, 5.6 Hz, 1 H_{maj}), 4.04–3.93 (m, 3 H_{min}), 3.77 (d, J = 6.3 Hz, 1 H_{maj}), 3.67 (dd, J = 8.8, 5.5 Hz, 1 H_{min}), 3.54 (d, J = 7.5 Hz, 1 H_{min}), 3.45 (d, J = 13.8 Hz, 2 H_{min}), 3.42 (d, J = 13.5 Hz, 2 H_{maj}), 1.32 (s, 3 H_{maj}), 1.28 (s, 6 H_{min}), 1.25 (s, 3 H_{maj}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) [major isomer]: δ = 137.4, 128.8, 128.5, 127.6, 115.3, 110.3, 74.6, 66.5, 56.1, 56.0, 26.3, 25.0 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 2225 cm^{-1}. MS (ESI): m/z = 359 $[M + Na]^+$. $C_{21}H_{24}N_2O_2$ (336.18): calcd. C 74.97, H 7.19, N 8.33; found C 74.88, H 7.20, N 8.38.

(2*R*)-2-(Dibenzylamino)-2-{(S_{Fc})-2-[(4-methylphenyl)sulfanyl]-ferrocenyl}ethanenitrile (13): According to the general procedure, compound **13** was obtained, after 48 h of reaction, as a red solid in 80% yield (1.74 g) and as a single diastereoisomer (^{1}H NMR of the crude reaction mixture); m.p. 150–154 °C. $[\alpha]_D^{rt}$ = –54 (c = 0.797, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.92 (m, 14 H), 4.92 (s, 1 H), 4.63 (br. s, 1 H), 4.44 (br. s, 1 H), 4.36 (br. s, 1 H), 4.15 (s, 5 H), 3.87 (d, J = 13.5 Hz, 2 H), 3.20 (d, J = 13.8 Hz, 2 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3, 136.7, 134.5, 129.3, 128.8, 128.1, 127.2, 125.5, 116.0, 84.0, 77.3, 76.4, 71.4, 71.1, 69.7, 55.0, 53.1, 21.0 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 2225 cm^{-1}. MS (ESI): m/z = 542 $[M + H]^+$. $C_{33}H_{30}FeN_2S$ (541.14): calcd. C 73.06, H 5.57, N 5.19; found C 73.12, H 5.60, N 5.20.

***anti*- and *syn*-2-(Dibenzylamino)-3-methyl-4-oxopentanenitrile (14a and 14b):** Freshly prepared β-keto aldehyde **7** (1.00 g, 10.0 mmol) was added in one portion to a stirred suspension of cyanobis(dibenzylamino)borane (**I**) (8.60 g, 20.0 mmol) in dry THF (20 mL) under nitrogen. The mixture was then refluxed with stirring for 24 h. The reaction mixture was then cooled to room temperature, poured onto satd. NH_4Cl and then extracted with EtOAc. The organic extracts were dried with $MgSO_4$, filtered and concentrated, and the crude product containing **14a** and **14b** in a 1:1 ratio (^{1}H NMR) was purified by chromatography on silica gel (*n*-hexane/EtOAc mixtures) to afford compounds **14a** and **14b** as single diastereoisomers in 60% overall yield (1.84 g) as pale yellow solids.

14a: M.p. 75–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 10 H), 3.93 (d, J = 13.6 Hz, 2 H), 3.89 (d, J = 11.2 Hz, 1 H), 3.38 (d, J = 13.6 Hz, 2 H), 3.03 (dq, J_q = 7.0, J_d = 11.2 Hz, 1 H), 1.83 (s, 3 H), 1.17 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 137.0, 129.1, 128.5, 127.7, 115.6, 56.6, 55.9, 47.5, 27.0, 14.6 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 2226, 1724 cm^{-1}. MS (ESI): m/z = 329 $[M + Na]^+$. $C_{20}H_{22}N_2O$ (306.17): calcd. C 78.40, H 7.24, N 9.14; found C 78.32, H 7.18, N 9.15.

14b: M.p. 60–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 10 H), 3.90 (d, J = 13.6 Hz, 2 H), 3.73 (d, J = 10.8 Hz, 1 H), 3.41 (d, J = 13.6 Hz, 2 H), 3.09 (dq, J_q = 7.0, J_d = 11.2 Hz, 1 H), 2.20 (s, 3 H), 1.21 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8, 137.2, 128.8, 128.6, 127.7, 116.5, 55.6, 53.8, 47.6, 29.2, 14.1 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 2226, 1724 cm^{-1}. MS (ESI): m/z = 329 $[M + Na]^+$. $C_{20}H_{22}N_2O$ (306.17): calcd. C 78.40, H 7.24, N 9.14; found C 78.41, H 7.18, N 9.21.

(1*R*)-N^1,N^1-Dibenzyl-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,2-hexanediamine (15): *n*BuLi (1.25 mL, 1.6 M in hexanes, 2.0 mmol) was slowly added to a stirred solution of α-amino nitrile **12** (336 mg, 1.00 mmol) in Et_2O (10 mL) under nitrogen cooled to –78 °C. After stirring at the same temperature for 2 h, MeOH (10 mL) was added, followed by $NaBH_4$ (150 mg, 4.0 mmol). The reaction mixture was warmed to room temperature, stirred for 48 h and then quenched by the addition of H_2O. The mixture was then transferred into a separating funnel and the products extracted with $CHCl_3$. The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel ($CHCl_3$/MeOH mixtures) gave compound **15** as a colorless viscous oil in 78% yield (309 mg) as a single diastereoisomer; $[\alpha]_D^{rt}$ = +32 (c = 1.17, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 10 H), 4.57 (q, J = 7.7 Hz, 1 H), 4.06 (dd, J = 7.8, 6.1 Hz, 1 H), 4.05 (d, J = 13.5 Hz, 2 H), 3.87 (d, J = 13.5 Hz, 2 H), 3.62 (t, J = 7.9 Hz, 1 H), 2.60–2.48 (m,

2 H), 1.54 (s, 3 H), 1.44 (s, 3 H), 1.38 (br. s, 2 H), 1.28–0.80 (m, 6 H), 0.75 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 129.3, 128.2, 126.8, 108.3, 76.6, 68.5, 63.2, 56.2, 52.7, 35.6, 28.6, 26.8, 25.3, 22.7, 14.0 ppm. HRMS: exact mass calcd. for $C_{25}H_{37}N_2O_2$ [M + H]$^+$ 397.2855; found 397.2859.

(1*R*)-N^1,N^1-Dibenzyl-1-{(S_{Fc})-2-[(4-methylphenyl)sulfanyl]-ferrocenyl}-1,2-ethanediamine (16): A solution of α-amino nitrile **13** (131 mg, 0.24 mmol) in dry Et_2O (16 mL) was added to a stirred solution of $LiAlH_4$ in Et_2O (1.20 mL, 1 M, 1.20 mmol) under nitrogen. The reaction mixture was then refluxed with stirring for 4 h. Then, while stirring at the same temperature, the reaction mixture was cooled to 0 °C and then quenched by the addition of a 10% aq. solution of Na/K tartrate. The aqueous phase was extracted with EtOAc and the organic extracts were then dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (CH_2Cl_2/MeOH mixtures) afforded diamine **16** as a viscous orange oil in 86% yield (113 mg). $[\alpha]_D^{r.t.}$ = –105 (c = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–6.98 (m, 14 H), 4.66 (dd, J = 2.3, 1.1 Hz, 1 H), 4.48 (t, J = 2.6 Hz, 1 H), 4.33 (br. s, 1 H), 4.21 (s, 5 H), 3.83 (br. d, J = 9.6 Hz, 1 H), 3.41 (d, J = 13.5 Hz, 2 H), 3.28 (br. d, J = 12.1 Hz, 1 H), 3.11 (d, J = 13.6 Hz, 2 H), 2.94 (br. t, J = 12.1 Hz, 1 H), 2.50 (br. s, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4, 137.7, 134.3, 129.6, 129.1, 128.1, 126.8, 125.1, 88.8, 74.7, 70.7, 69.7, 69.3, 59.0, 53.9, 44.1, 20.8 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 3375, 3308 cm^{-1}. HRMS: exact mass calcd. for $C_{33}H_{34}FeN_2NaS$ [M + Na]$^+$ 569.1690; found 569.1691.

(1*R*)-N^2-(*tert*-Butoxycarbonyl)-N^1,N^1-dibenzyl-1-{(S_{Fc})-2-[(4-methylphenyl)sulfanyl]ferrocenyl}-1,2-ethanediamine (17): Boc_2O (15 mg, 0.07 mmol) was added to a stirred, cooled (0 °C) solution of monoprotected diamine **16** (33 mg, 0.06 mmol) and Et_3N (10 μL, 0.07 mmol) in dry CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at room temperature overnight, then quenched with HCl (0.2 M) and extracted with CH_2Cl_2. The organic extracts were then dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (*n*-hexane/EtOAc mixtures) afforded diamine **17** as a viscous colourless oil in 80% yield (31 mg); $[\alpha]_D^{r.t.}$ = –61 (c = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.02 (m, 14 H), 4.91 (br. s, 1 H), 4.64 (br. s, 1 H), 4.47 (t, J = 2.5 Hz, 1 H), 4.35 (dd, J = 2.5, 1.5 Hz, 1 H), 4.24 (s, 5 H), 3.94–3.82 (m, 2 H), 3.40 (d, J = 13.8 Hz, 2 H), 3.32 (br. t, J = 12.3 Hz, 1 H), 3.10 (d, J = 13.8 Hz, 2 H), 2.28 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 140.4, 137.8, 134.3, 129.6, 129.1, 128.2, 126.8, 125.1, 88.2, 76.6, 70.9, 69.5, 69.3, 56.5, 53.7, 42.7, 28.5, 20.8 ppm. MS (ESI): m/z = 668 [M + Na]$^+$. $C_{38}H_{42}FeN_2O_2S$ (645.23): calcd. C 70.58, H 6.55, N 4.33; found C 70.60, H 6.54, N 4.38.

(1*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-{(S_{Fc})-2-[(4-methylphenyl)-sulfanyl]ferrocenyl}ethan-1-ol (19): According to the procedure used for the synthesis of compound **17**, starting from (1*S*)-2-amino-1-{(S_{Fc})-2-[(4-methylphenyl)sulfanyl]ferrocenyl}ethan-1-ol (**18**) (0.22 mmol, 81 mg), compound **19** was obtained as a colourless oil in 86% yield (88 mg) after chromatography on silica gel (*n*-hexane/EtOAc mixtures). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (d, J = 8.4 Hz, 2 H), 6.92 (d, J = 8.4 Hz, 2 H), 4.75 (br. s, 1 H), 4.65 (br. s, 1 H), 4.50 (br. s, 1 H), 4.46 (br. s, 1 H), 4.38 (br. s, 1 H), 4.29 (s, 5 H), 3.42 (br. s, 1 H), 3.16 (ddd, J = 14.3, 6.3, 2.8 Hz, 1 H), 3.03 (br. s, 1 H), 2.22 (s, 3 H), 1.42 (s, 9 H) ppm. MS (ESI): m/z = 468 [M + H]$^+$.

(1*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-{(S_{Fc})-2-[(4-methylphenyl)-sulfanyl]ferrocenyl}ethyl Acetate (20): Ac_2O (90 μL, 0.90 mmol) was added to a stirred solution of compound **19** (88 mg, 0.19 mmol) in dry pyridine (1 mL). After stirring at room temperature overnight, pyridine and excess Ac_2O were removed by evaporation under reduced pressure to afford acetylated derivative **20** as a visvous yellow oil in quantitative yield. Crude **20** was used in the next step with no further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (d, J = 8.1 Hz, 2 H), 6.89 (d, J = 8.1 Hz, 2 H), 6.00 (br. s, 1 H), 4.51–4.45 (m, 3 H), 4.38 (t, J = 2.7 Hz, 1 H), 4.20 (s, 5 H), 3.20–3.08 (m, 2 H), 2.22 (s, 3 H), 2.17 (s, 3 H), 1.38 (s, 9 H) ppm. MS (ESI): m/z = 532 [M + Na]$^+$.

(1*S*)-N^2-(*tert*-Butoxycarbonyl)-N^1,N^1-dibenzyl-1-{(S_{Fc})-2-[(4-methylphenyl)sulfanyl]ferrocenyl}-1,2-ethanediamine (21): Bn_2NH (14 μL, 0.07 mmol) was added to a stirred solution of crude compound **20** (18 mg, 0.035 mmol) in EtOH (0.5 mL). The resulting solution was then refluxed with stirring for 3 d. The solvent was then removed by evaporation under reduced pressure and the residue purified by preparative TLC (*n*-hexane/EtOAc mixture), to afford compound **21** as a yellow viscous oil in 91% yield (21 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 10 H), 7.12 (d, J = 8.2 Hz, 2 H), 6.98 (d, J = 8.2 Hz, 2 H), 5.05 (br. s, 1 H), 4.58 (br. s, 1 H), 4.42 (br. s, 1 H), 4.22 (s, 6 H), 4.05–3.98 (m, 2 H), 3.68 (d, J = 14.5 Hz, 2 H), 3.61 (dd, J = 10.2, 3.8 Hz, 1 H), 3.08 (d, J = 14.5 Hz, 2 H), 2.22 (s, 3 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 139.9, 136.1, 135.1, 129.4, 129.1, 128.4, 128.2, 126.7, 85.2, 78.7, 77.5, 76.0, 72.1, 70.7, 69.0, 59.4, 53.7, 41.8, 28.5, 20.8 ppm. MS (ESI): m/z = 668 [M + Na]$^+$.

(2*S*)- and (2*R*)-2-(Dibenzylamino)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamide (22a and 22b): α-Amino nitrile **12** (500 mg, 1.49 mmol) was dissolved in a DMSO/THF mixture (2:1, 4.5 mL) containing K_2CO_3 (69 mg, 0.5 mmol). After cooling of the solution to 0 °C, an aqueous H_2O_2 solution (0.5 mL, 11 M, 5.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 24 h, then quenched by the addition of brine and extracted several times with Et_2O. The organic extracts were dried with $MgSO_4$, filtered and the solvents evaporated. The crude product containing mainly **22a** and **22b** in an 87:13 ratio (^{1}H NMR) was purified and the two isomers separated by chromatography on silica gel (*n*-hexane/EtOAc mixtures) to give **22a** (435 mg) and **22b** (66 mg) as white solids in a 95% overall yield.

22a: M.p. 83–85 °C. $[\alpha]_D^{r.t.}$ = +17 (c = 0.600, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.22 (m, 10 H), 7.05 (br. s, 1 H), 5.90 (br. s, 1 H), 4.68 (dt, J_d = 9.6, J_t = 7.4 Hz, 1 H), 4.38 (dd, J = 8.8, 5.9 Hz, 1 H), 4.02 (d, J = 12.9 Hz, 2 H), 3.88 (d, J = 12.9 Hz, 2 H), 3.64 (dd, J = 8.7, 7.4 Hz, 1 H), 3.35 (d, J = 9.6 Hz, 1 H), 1.54 (s, 3 H), 1.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 139.1, 129.0, 128.5, 127.3, 108.4, 75.1, 69.7, 54.8, 26.7, 25.1 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 3504, 3383, 1687 cm^{-1}. HRMS: exact mass calcd. for $C_{21}H_{27}N_2O_3$ [M + H]$^+$ 355.2022; found 355.2022.

22b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.21 (m, 10 H), 6.34 (br. s, 1 H), 5.57 (br. s, 1 H), 4.39 (dt, J = 8.9, 6.8 Hz, 1 H), 4.14 (dd, J = 8.7, 6.3 Hz, 1 H), 3.89 (s, 4 H), 3.71 (t, J = 9.1 Hz, 1 H), 3.17 (d, J = 9.1 Hz, 1 H), 1.31 (s, 3 H), 1.22 (s, 3 H) ppm. MS (ESI): m/z = 377 [M + Na]$^+$.

(3*S*,4*S*)-3-(Dibenzylamino)-4-hydroxy-4,5-dihydro-2(3*H*)-furanone (23a): Concd. H_2SO_4 (1.9 mL, 35 mmol) was slowly added over the course of 2 h to a cooled (0 °C), stirred solution of amide **22a** (411 mg, 1.2 mmol) in an MeOH/H_2O/THF mixture (2:2:1, 12.5 mL). After the addition of the acid was complete, the mixture was stirred at 0 °C for a further 30 min and then at room temperature for 2 d. Afterwards, the reaction was quenched by the addition of satd. $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were dried with $MgSO_4$, filtered and concentrated

under reduced pressure. Purification by chromatography on silica gel (CH_2Cl_2/MeOH mixtures) gave lactone **23a** in 68% yield (242 mg) as a white solid; m.p. 176–177 °C. $[\alpha]_D^{rt}$ = –83 (*c* = 0.220, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.51–7.45 (m, 4 H), 7.35–7.20 (m, 6 H), 4.91 (br. s, 1 H), 4.81 (q, *J* = 7.4 Hz, 1 H), 4.41 (dd, *J* = 8.9, 7.4 Hz, 1 H), 3.91–3.82 (m, 1 H), 3.88 (s, 4 H), 3.66 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 174.5, 140.1, 129.6, 129.0, 127.9, 71.2, 69.2, 66.2, 55.4 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 3595, 1777 cm^{-1}. MS (ESI): *m*/*z* = 320 [M + Na]$^+$. $C_{18}H_{19}NO_3$ (297.14): calcd. C 72.71, H 6.44, N 4.71; found C 72.60, H 6.41, N 4.82. The relative stereochemistry of the product was tentatively assigned as 3,4-*trans* by means of NOE experiments: Irradiation at δ = 4.81 ppm (4-H) gave mainly an enhancement of the singlet at δ = 3.88 ppm (CH_2N).

(3*R*,4*S*)-3-(Dibenzylamino)-4-hydroxy-4,5-dihydro-2(3*H*)-furanone (23b): According to the procedure used for the synthesis of compound **23a**, lactone **23b** was obtained starting from amide **22b** (38 mg, 0.11 mmol) in 67% yield (22 mg) as a white solid after purification by preparative TLC (CH_2Cl_2/MeOH mixtures); m.p. 105–107 °C. $[\alpha]_D^{rt}$ = –18 (*c* = 0.200, MeOH). ^{1}H NMR (400 MHz, [D$_6$]-acetone): δ = 7.50 (d, *J* = 7.3 Hz, 4 H), 7.37–7.18 (m, 6 H), 5.22 (br. d, *J* = 4.0 Hz, 1 H), 4.73 (m, 1 H), 4.30 (dd, *J* = 10.2, 3.3 Hz, 1 H), 4.17 (br. d, *J* = 10.2 Hz, 1 H), 4.01 (d, *J* = 13.8 Hz, 2 H), 3.95 (d, *J* = 13.8 Hz, 2 H), 3.66 (d, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 175.2, 141.0, 129.6, 129.4, 127.9, 74.4, 70.7, 62.4, 56.8 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 3590, 1774 cm^{-1}. MS (ESI): *m*/*z* = 320 [M + Na]$^+$. $C_{18}H_{19}NO_3$ (297.14): calcd. C 72.71, H 6.44, N 4.71; found C 72.63, H 6.48, N 4.80. The relative stereochemistry of the product was tentatively assigned as 3,4-*cis* by means of NOE experiments: Irradiation at δ = 4.73 ppm (4-H) gave rise to an increase in the intensity of the signal at δ = 3.66 ppm (3-H).

3,4-*cis*-3-(Dibenzylamino)-4,5-dimethyl-5-hydroxy-2-pyrrolidinone (24a): K_2CO_3 (6 mg, 0.04 mmol) and an aqueous H_2O_2 solution (0.05 mL, 11 M, 0.55 mmol) were sequentially added to a stirred solution of α-amino nitrile **14a** (40 mg, 0.13 mmol) in DMSO (0.3 mL) cooled to 10 °C. After stirring at room temperature for 17 h, H_2O was added (1.5 mL) and the product extracted with EtOAc. The combined organic extracts were washed with satd. NH_4Cl, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by preparative TLC (*n*-hexane/EtOAc mixture) gave **24a** as a viscous colorless oil in 95% yield, together with small amounts (ca. 10%) of **24b**. ^{1}H NMR (400 MHz, $CDCl_3$, 3,4-*cis* isomer **24a**): δ = 7.47–7.19 (m, 10 H), 6.59 (br. s, 1 H), 4.09 (d, *J* = 14.3 Hz, 2 H), 3.81 (d, *J* = 14.3 Hz, 2 H), 3.46 (d, *J* = 10.3 Hz, 1 H), 2.70 (br. s, 1 H), 2.33 (dq, J_q = 7.7, J_d = 9.9 Hz, 1 H), 1.48 (s, 3 H), 1.20 (d, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 3,4-*cis* isomer **24a**): δ = 176.7, 140.0, 128.7, 128.2, 123.8, 86.1, 60.5, 55.4, 43.8, 28.4, 8.9 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 3411, 1702 cm^{-1}. HRMS: exact mass calcd. for $C_{20}H_{24}N_2NaO_2$ [M + Na]$^+$ 347.1735; found 347.1738. The relative configuration at C-3 and C-4 was tentatively assigned as *cis* by means of NOE experiments: Irradiation at δ = 1.20 ppm (4-CH_3) gave rise to a significant enhancement in the signal at δ = 4.09 ppm (NCH_2Ph), while irradiation at δ = 3.46 ppm (3-H) gave rise to an increase in the intensity of the signal at δ = 2.33 ppm (C_4H).

3,4-*trans*-3-(Dibenzylamino)-4,5-dimethyl-5-hydroxy-2-pyrrolidinone (24b): According to the procedure used for the synthesis of compound **24a**, pyrrolidinone **24b** was obtained after 36 h of reaction in 47% yield as a viscous oil, together with small amounts (ca. 10%) of its isomer **24a**. ^{1}H NMR (400 MHz, $CDCl_3$, 3,4-*trans* isomer **24b**): δ = 7.42–7.17 (m, 10 H), 6.63 (br. s, 1 H), 3.92 (d, *J* = 14.3 Hz, 2 H), 3.75 (d, *J* = 13.8 Hz, 2 H), 3.64 (br. s, 1 H), 3.37 (d, *J* = 10.2 Hz, 1 H), 2.15 (dq, J_q = 6.8, J_d = 10.2 Hz, 1 H), 1.44 (s, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 3,4-*trans* isomer **24b**): δ = 177.0, 139.8, 128.7, 128.2, 127.0, 84.7, 64.2, 54.9, 43.8, 26.5, 11.3 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 3425, 1702 cm^{-1}. HRMS: exact mass calcd. for $C_{20}H_{24}N_2NaO_2$ [M + Na]$^+$ 347.1735; found 347.1730. The relative stereochemistry at C-3 and C-4 was tentatively assigned as *trans* by means of NOE experiments: Irradiation at δ = 1.06 ppm (4-CH_3) gave rise to an enhancement of the signal at δ = 3.37 ppm (2-H), while irradiation at δ = 2.15 ppm (4-H) gave rise to an enhancement of the signal at δ = 3.75 ppm (NCH_2Ph).

2,3-*anti*-3,4-*anti*-2-(Dibenzylamino)-4-hydroxy-3-methylpentanenitrile (25a): L-Selectride® (1.17 mL, 1 M in THF, 1.17 mmol) was slowly added to a stirred solution of α-amino nitrile **14a** (144 mg, 0.47 mmol) in dry THF (5.0 mL), cooled to –78 °C. After 2 h of stirring at the same temperature, the reaction was quenched by the addition of a satd. NH_4Cl solution. After acidification with 1 M HCl (pH ≈ 0), the product was extracted with Et_2O. The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (*n*-hexane/EtOAc mixtures) to afford compound **25a** as a viscous oil in 70% yield (101 mg) and as a single diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 10 H), 5.50 (br. s, 1 H), 4.12 (d, *J* = 13.0 Hz, 2 H), 3.54 (d, *J* = 10.9 Hz, 1 H), 3.45–3.33 (m, 1 H), 3.33 (d, *J* = 13.0 Hz, 2 H), 2.09 (m, 1 H), 1.06 (d, *J* = 6.1 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 129.3, 128.9, 128.1, 115.1, 72.4, 59.9, 55.9, 39.2, 20.5, 14.1 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 3328, 2227 cm^{-1}. HRMS: exact mass calcd. for $C_{20}H_{24}N_2NaO$ [M + Na]$^+$ 331.1786; found 331.1784.

2,3-*syn*-3,4-*anti*-2-(Dibenzylamino)-4-hydroxy-3-methylpentanenitrile (25b) and 3,4-*trans*-4,5-*trans*-3-(Dibenzylamino)-4,5-dimethyl-4,5-dihydro-2(3*H*)-furanone (26b): According to the procedure used for the reduction of compound **14a**, the reaction of α-amino nitrile **14b** (153 mg, 0.50 mmol) with L-Selectride® followed by chromatography on silica gel (*n*-hexane/EtOAc mixtures) gave compound **25b** (69 mg) in 45% yield and lactone **26b** (59 mg) in 38% yield as viscous colorless oils. Compound **25b** was quantitatively converted into the corresponding lactone **26b** upon standing on SiO_2 at room temperature for 24 h.

25b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 10 H), 3.96 (d, *J* = 13.7 Hz, 2 H), 3.94 (q, *J* = 6.3 Hz, 1 H), 3.46 (d, *J* = 9.5 Hz, 1 H), 3.38 (d, *J* = 13.6 Hz, 2 H), 2.11 (m, 1 H), 1.69 (d, *J* = 5.0 Hz, 1 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 128.9, 128.6, 127.7, 116.8, 68.8, 55.8, 54.9, 41.2, 19.0, 12.2 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 3328, 2224 cm^{-1}. MS (ESI): *m*/*z* = 331 [M + Na]$^+$.

26b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 10 H), 3.99 (d, *J* = 13.7 Hz, 2 H), 3.88 (dq, J_q = 6.2, J_d = 9.7 Hz, 1 H), 3.84 (d, *J* = 13.7 Hz, 2 H), 3.28 (d, *J* = 11.8 Hz, 1 H), 2.05 (m, 1 H), 1.35 (d, *J* = 6.2 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 139.3, 128.8, 128.3, 127.2, 79.5, 65.3, 54.8, 42.0, 18.8, 14.0 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 1774 cm^{-1}. HRMS: exact mass calcd. for $C_{20}H_{23}NNaO_2$ [M + Na]$^+$ 332.1626; found 332.1629. The relative stereochemistry of lactone **26b** was tentatively assigned as 3,4-*trans*-4,5-*trans* by means of NOE experiments: Irradiation at δ = 3.28 ppm (3-H) gave rise to an enhancement of the signals at δ = 3.88 ppm (5-H) and 1.01 ppm (4-CH_3), while irradiation at δ = 1.01 ppm (4-CH_3) gave rise to an increase in the intensity of the signals at δ = 3.88 ppm

(5-H) and 3.28 ppm (3-H). The signals were assigned on the basis of a gCOSY experiment.

3,4-*cis*-4,5-*trans*-3-(Dibenzylamino)-4,5-dimethyl-4,5-dihydro-2(3*H*)-furanone (26a): Concd. H_2SO_4 (0.30 mL, 4.8 mmol) was slowly added to a stirred, cooled (0 °C) solution of compound **25a** (45 mg, 0.14 mmol) in CH_2Cl_2. The reaction mixture was then stirred at room temperature overnight, quenched by the addition of a satd. Na_2CO_3 solution, further basified with NaOH (pH ≈ 12) and finally extracted with CH_2Cl_2. The combined organic phases were then dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (*n*-hexane/EtOAc) afforded lactone **26a** as a colorless viscous oil in 57% yield (25 mg), together with its epimer **26b** (10%). ^{1}H NMR (400 MHz, $CDCl_3$, 3,4-*cis*-4,5-*trans* isomer **26a**): δ = 7.47–7.22 (m, 10 H), 4.25 (dq, J_q = 6.1, J_d = 8.6 Hz, 1 H), 3.78 (s, 4 H), 3.58 (d, J = 10.1 Hz, 1 H), 2.11 (m, 1 H), 1.34 (d, J = 6.1 Hz, 3 H), 1.23 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 3,4-*cis*-4,5-*trans* isomer **26a**): δ = 175.7, 138.7, 128.6, 128.5, 127.3, 83.2, 59.6, 55.8, 41.3, 20.5, 11.5 ppm. IR (CCl_4, NaCl plate): $\tilde{\nu}_{max}$ = 1763 cm^{-1}. HRMS: exact mass calcd. for $C_{20}H_{23}NNaO_2$ $[M + Na]^+$ 332.1626; found 332.1629. $C_{20}H_{23}NO_2$ (309.17): calcd. C 77.64, H 7.49, N 4.53; found C 77.63, H 7.40, N 4.62. The relative stereochemistry of the product was tentatively assigned as 3,4-*cis*-4,5-*trans* by means of NOE experiments: Irradiation at δ = 4.25 ppm (5-H) gave rise to an enhancement in the signals at δ = 1.23 ppm (4-CH_3) and 3.78 ppm (NCH_2Ph), while upon irradiation at δ = 3.58 ppm (3-H) an increase in the intensity of the signal at δ = 2.11 ppm (4-H) was observed. Finally, irradiation at δ = 3.78 ppm (NCH_2Ph) induced an enhancement of the signals at δ = 4.25 ppm (5-H) and 1.23 ppm (4-CH_3). The signals were assigned on the basis of a gCOSY experiment.

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[30] CCDC-268138 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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