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Catalytic enantioselective addition of hydrogen cyanide to benzaldehyde and *p*-methoxybenzaldehyde using *cyclo*-His-(α-Me)Phe as catalyst †

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Abstract: Two *cyclo*-dipeptides based on His and the unnatural (αMe)Phe have been examined as catalysts in the enantioselective addition of hydrogen cyanide to benzaldehyde and *p*-methoxy-benzaldehyde. The synthesis, catalytic activity and NMR study towards the mechanism of this reaction are presented. © 1997 Elsevier Science Ltd

Enzymes are useful for the transformations of organic compounds because of their high catalytic efficiencies, their (*enantio*)-specificity and the very mild reaction conditions required.[1] However, only fairly recently have systematic investigations begun to appear on a complementary approach, namely the use of *synthetically obtained* peptides as catalysts in (asymmetric) organic reactions.[2,3] Recent studies involving either or both approaches have been directed chiefly towards asymmetric synthesis involving the formation of carbon–carbon bonds.[4]

The reaction of hydrogen cyanide with benzaldehyde (Scheme 1) as well as other aldehydes is an excellent prototype reaction,[5] both because of the opportunity of direct comparison with the enzyme oxynitrilase, which catalyzes this same reaction, as well as the fact that the resulting *cyanohydrins* **1** are versatile chiral synthons.

Certain alkaloids,[6] *poly*(*L*-iminoisobutylethylene)[7] and cyclodextrines,[8] are known to catalyze this addition reaction although the yields obtained as well as enantiomeric excesses (*e.e.*s) are rather poor. Various synthetic peptides are also active in this capacity,[9] the most successful of which seem to be conformationally restricted *cyclic* (di or tri)-peptides. In 1981, Oku and Inoue[10] and subsequently other groups[11] showed that *cyclo*-[(*S*)-phenylalanyl-(*S*)-histidyl] **2** could be used as a catalyst for the hydrocyanation of various aldehydes.[12,13] Results are excellent both in terms of yield as well as *e.e.*s of the products. The mechanism of this catalytic reaction has been the subject of various studies,[12,13] from which it has been concluded that the imidazole moiety of histidine (His) acts as the basic catalytic group whereas the aromatic ring of the phenylalanine residue blocks the other face of the aldehyde undergoing addition.

We report here the synthesis, use and a mechanistically oriented NMR study of closely analogous *cyclo*-dipeptides based on His and C_α-methyl-phenylalanine [(αMe)Phe]. These are used in the hydrocyanation reaction of benzaldehyde. An unnatural α-alkylated amino acid was incorporated since

† Since submission and acceptance of this article, a paper by C. R. Noe, A. Weigand, S. Pirker and P. Liepart, *Monatshefte für Chemie* **1997**, *128*, 301 has appeared in which a series of compounds including our compound **15** has been investigated. With **15**, Noe *et al.* obtained significantly lower conversions and enantiomeric excesses than reported here.

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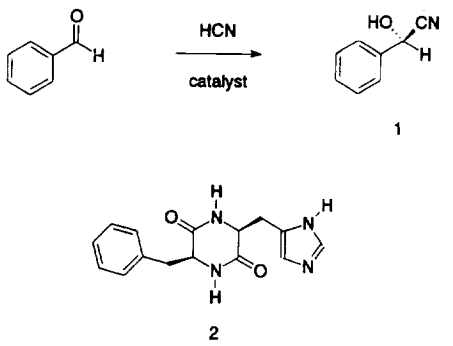
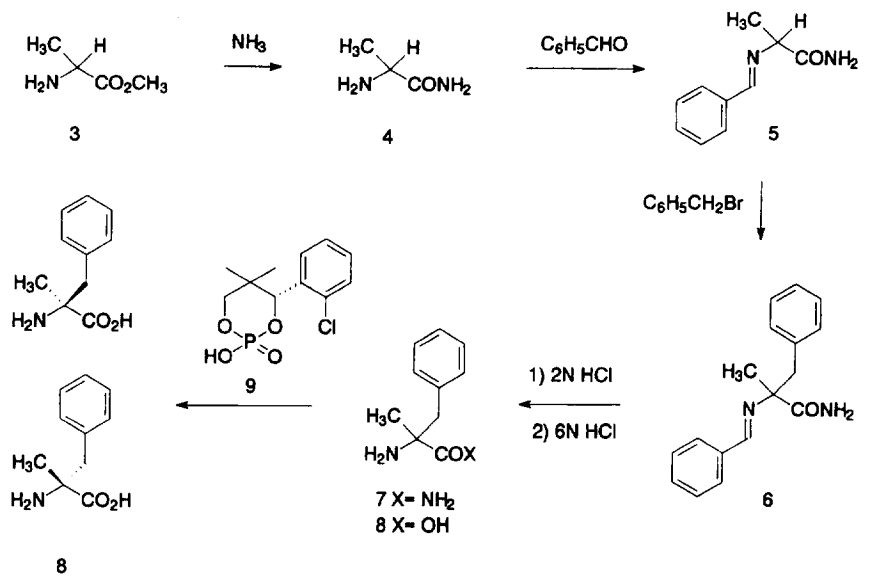


Scheme 1. Hydrocyanation of benzaldehyde. The "Inoue catalyst" **2** is also shown.

they are known to be extremely conformationally restricted and show pronounced tendencies to form folded structures.[14] The manner in which this effect exhibits itself in the catalytic process is described in this article.

Synthesis of the starting materials

Racemic (αMe)Phe was prepared from racemic alanine following literature procedures[15] and subsequently resolved into both enantiomers (Scheme 2).

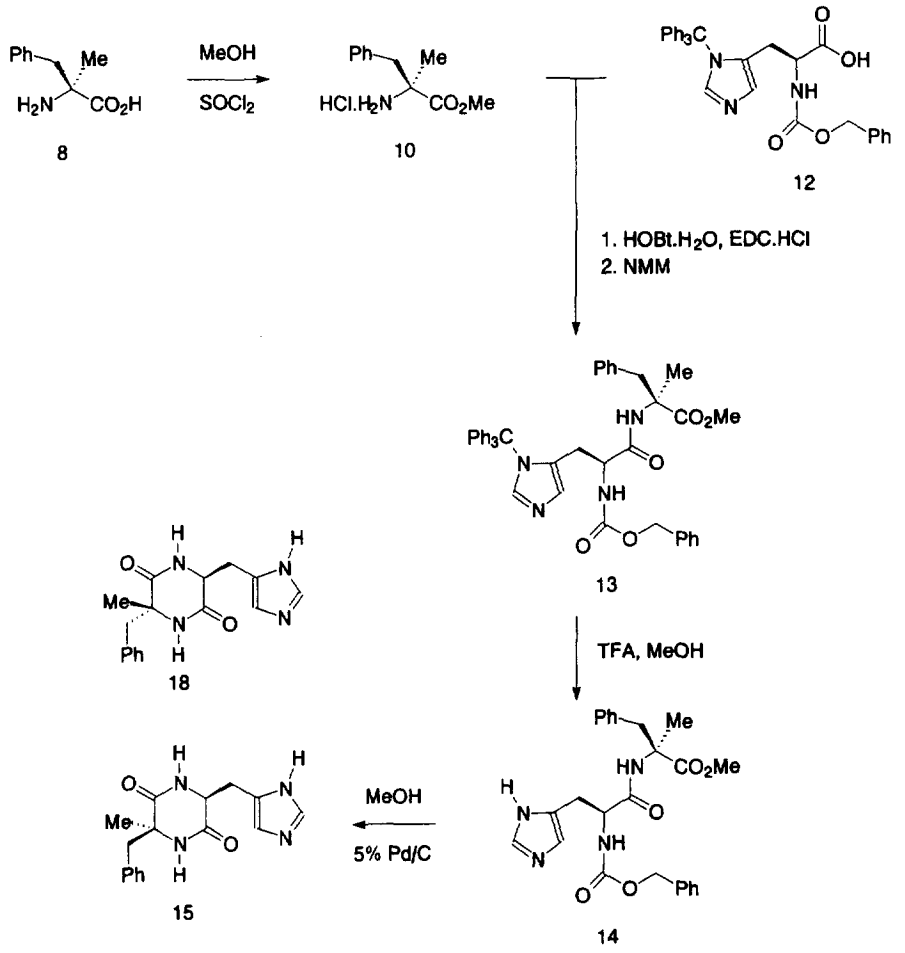


Scheme 2. Synthesis and resolution of (αMe)Phe **8**.

This strategy entails conversion of alanine methyl ester **3** into primary amide **4** in 94% yield by means of a reaction in concentrated ammonia. Subsequently, the Schiff base of **4** was formed using benzaldehyde to afford *N*-benzylidenealanine amide **5** in 68% yield. Benzylation took place readily using benzyl bromide under phase transfer conditions to afford **6** in 90% yield. Acidic hydrolysis (2 N HCl) afforded H-(α-Me)Phe-NH_2 **7** in 68% yield, which was subsequently converted into racemic acid **8** by means of more drastic acidic hydrolysis using boiling 6 N HCl solution in 64% yield. Racemic **8** was resolved into both enantiomers using phosphoric acid (−)-**9** (*Chlocyphos*) according to the procedure described by ten Hoeve and Wynberg.[16] Alternatively, amide **7** can also be resolved

enzymatically into enantiopure *S*-**8** and *R*-**7** using the amidases from *Mycobacterium neoaurum*[17] or *Ochrobactrum anthropi*.[18]

The synthesis of the dipeptides and subsequent cyclization were performed according to the methodologies developed by the Toniolo group[19] (Scheme 3). In this procedure *L*-(αMe)Phe **8** is converted into methyl ester HCl.H-*L*-(αMe)Phe-OMe *L*-**10** in 94% yield.[20] Subsequent peptide formation with bisprotected **12**,[21] obtained from H-*L*-His after protection with Trt- (**11**, 81%) and Z-groups (**12**, 91%), afforded Z-*L*-His(Trt)-*L*-(αMe)Phe-OMe **13** in 92% yield.



8 10 12 13 14 15 18

Scheme 3. Synthesis of cyclic peptides **15** and **18**.

Deprotection of **13** (TFA/MeOH) afforded Z-*L*-His-*L*-(αMe)Phe-OMe **14**, which upon treatment with H_2 on Pd/C cyclized in situ affording *cyclo*-[*L*-His-*L*-(αMe)Phe] **15** in 92% yield. *Cyclo*-[*L*-His-*D*-(αMe)Phe] **18** was obtained from *D*-**10** and **12**, via Z-*L*-His(Trt)-*D*-(αMe)Phe-OMe **16** and Z-*L*-His-*D*-(αMe)Phe-OMe **17** using the same synthetic methodology in 92% yield.

Catalytic and mechanistic studies

The addition of hydrogen cyanide to benzaldehyde and *p*-methoxybenzaldehyde was carried out using 2 mol% (based on the aldehyde used) of **15** or **18**. The conversion and enantiomeric excesses (*e.e.*s) were determined by, respectively, ^{1}H NMR and GC analyses after the transformation of the

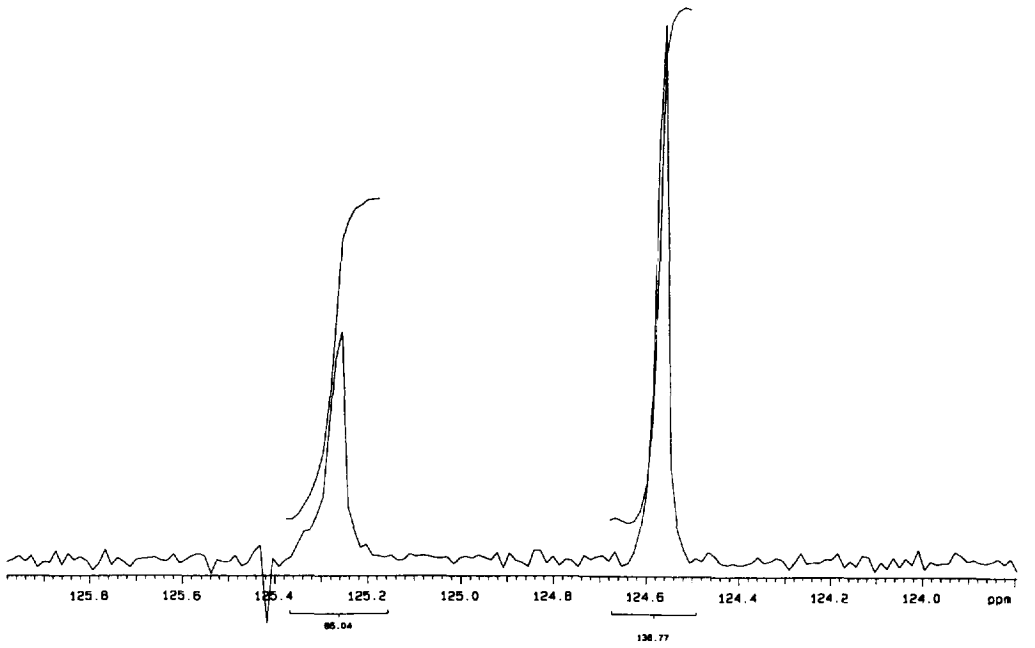
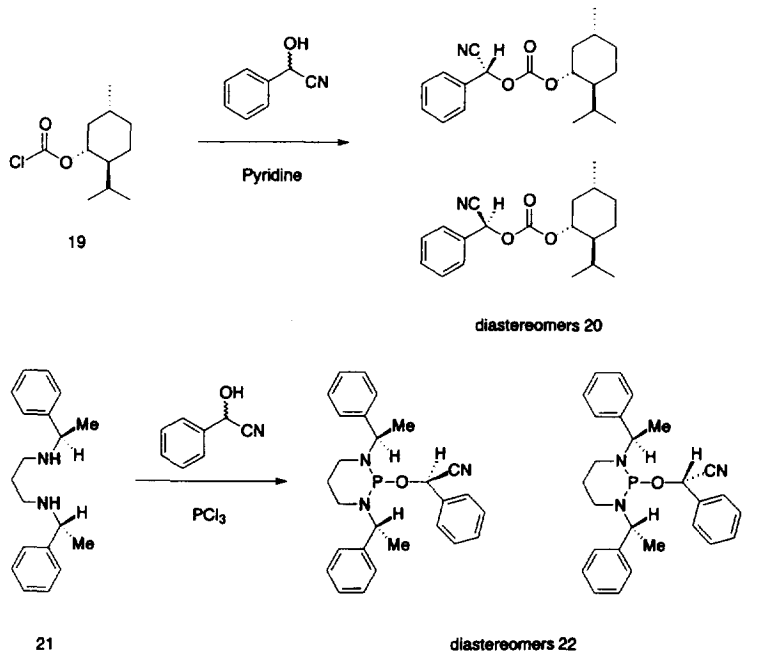


Figure 1. ^{31}P NMR spectrum of **22** with an e.e. of the corresponding cyanohydrin 23%.

cyanohydrins **1** to the corresponding diastereomeric menthyl carbonates **20** upon reaction with **19** (Scheme 4).



Scheme 4. Enantiomeric excess determination by means of derivatization and subsequent ^{1}H, ^{31}P NMR or GC techniques.

Alternatively, ^{31}P NMR could be used after transformation of **1** into the diastereomeric cyclic

phosphorous amidates **22**,[22] applying bisamine **21** and PCl_3 in a slightly modified literature procedure[23] (Scheme 4, Figure 1).

The reaction of benzaldehyde (1 eq), hydrogen cyanide (2 eqs) and 2 mol% **15** (based on the aldehyde) in benzene at 25°C gave (*R*)-mandelonitrile in good enantiomeric excess (94%) in the earlier stages of the reaction (up to 25% conversion). Enantiomeric excesses decreased, however, with increasing conversion (>25%) in agreement with the observations made by Tanaka and co-workers.[12] When *p*-methoxybenzaldehyde was used, comparable results were obtained (77% *e.e.* at 14% conversion, absolute configuration *R*). Change of the solvent to toluene/benzene mixtures or eventually, to toluene exclusively, allowed us to lower the temperature whereby gels were formed: *these gels serve as reaction medium.*

Decrease of the temperature resulted in a marked increase in enantioselectivity. At −40°C benzaldehyde and *p*-methoxybenzaldehyde were converted to the cyanohydrins in 98% and 93% yield, respectively, and moreover, the cyanohydrins were obtained with excellent *e.e.*s: 99% *e.e.* (*R*) for the benzaldehyde and 89% *e.e.* (*R*) for the *p*-methoxybenzaldehyde derivatives. Other solvents were also examined, such as *n*-hexane, diethyl ether, acetonitrile, tetrahydrofuran and methanol. It appeared, however, that the use of toluene at low temperatures afforded the best results.

Counter to our expectations, on use of the diastereomeric catalyst **18** the cyanohydrins were obtained in good yields and with moderate *e.e.*s (90% and 67% yield with 32% and 23% *e.e.* (both *R*) from benzaldehyde and *p*-methoxybenzaldehyde, respectively). These observations are *significantly different* from the results obtained by Tanaka and co-workers,[12] who found that stereoselection vanished nearly completely upon the use of other cyclic dipeptides such as *cyclo*-[(*L*)-Val-(*L*)-His] and *cyclo*-[(*L*)-His-(*L*)-His]. Unfortunately, they did not provide any detailed information about the use of diastereomeric catalytic systems.

NMR spectroscopy is a good tool with which to obtain information about the mechanism of the hydrocyanation of benzaldehyde and *p*-methoxybenzaldehyde using **15** and **18** as catalysts. The ^1H NMR spectra of **15** and **18** recorded in DMSO-d_6 are illustrated in Figure 2. The most remarkable difference between the two spectra is observed in the resonance of one of the β-CH_2 protons (*pro-S*) belonging to the histidine moiety, which shifts upfield from its *normal* position at δ 2.70 ppm to δ 1.21 ppm for the *LL* dipeptide **15**. In the *LD* diastereomer **18**, a similar upfield shift is observed for the α-CH proton belonging to the histidine moiety (from δ 3.84 ppm to δ 2.81 ppm).[24]

Both effects are accounted for by shielding effects on the protons mentioned by the ring current of the phenyl ring system of the (αMe)Phe residue. The respective protons and the phenyl group are on the same average plane of the cyclic dipeptide in the respective diastereomers.

Addition of benzaldehyde to solutions of **15** or **18** did not lead to any through space contacts of interest in the 2D *NOESY* or *ROESY* spectra, even at lowered temperatures in a 1:1 mixture of DMSO-d_6/$CDCl_3$. However, using *p*-methoxybenzaldehyde at −30°C in a 1:1 mixture of DMSO-d_6/$CDCl_3$, through space *NOE* interactions were observed between the methoxy group and the histidine amide *NH* and *pro-S* β-CH_2 protons in **15** (Figs 3 and 4). This orientation is clearly not predicted in the Tanaka model,[12] although it should be noted that Tanaka used the *protonated* cyclic dipeptide rather than the unprotonated counterpart. With *LD* dipeptide **18** under otherwise identical conditions, no interesting through space *NOE* contacts could be observed, indicating the probable importance of the orientation of the phenyl ring system of the (αMe)Phe moiety. Performance of these experiments using one equivalent of acid did not reveal any additional through space contacts of interest, although large shifts were observed in the aromatic region due to the protonation of the histidine moiety.

Unfortunately, using *HCN*, the reaction proceeds too fast to obtain any information of use for the interpretation of the actual hydrocyanation reaction itself.

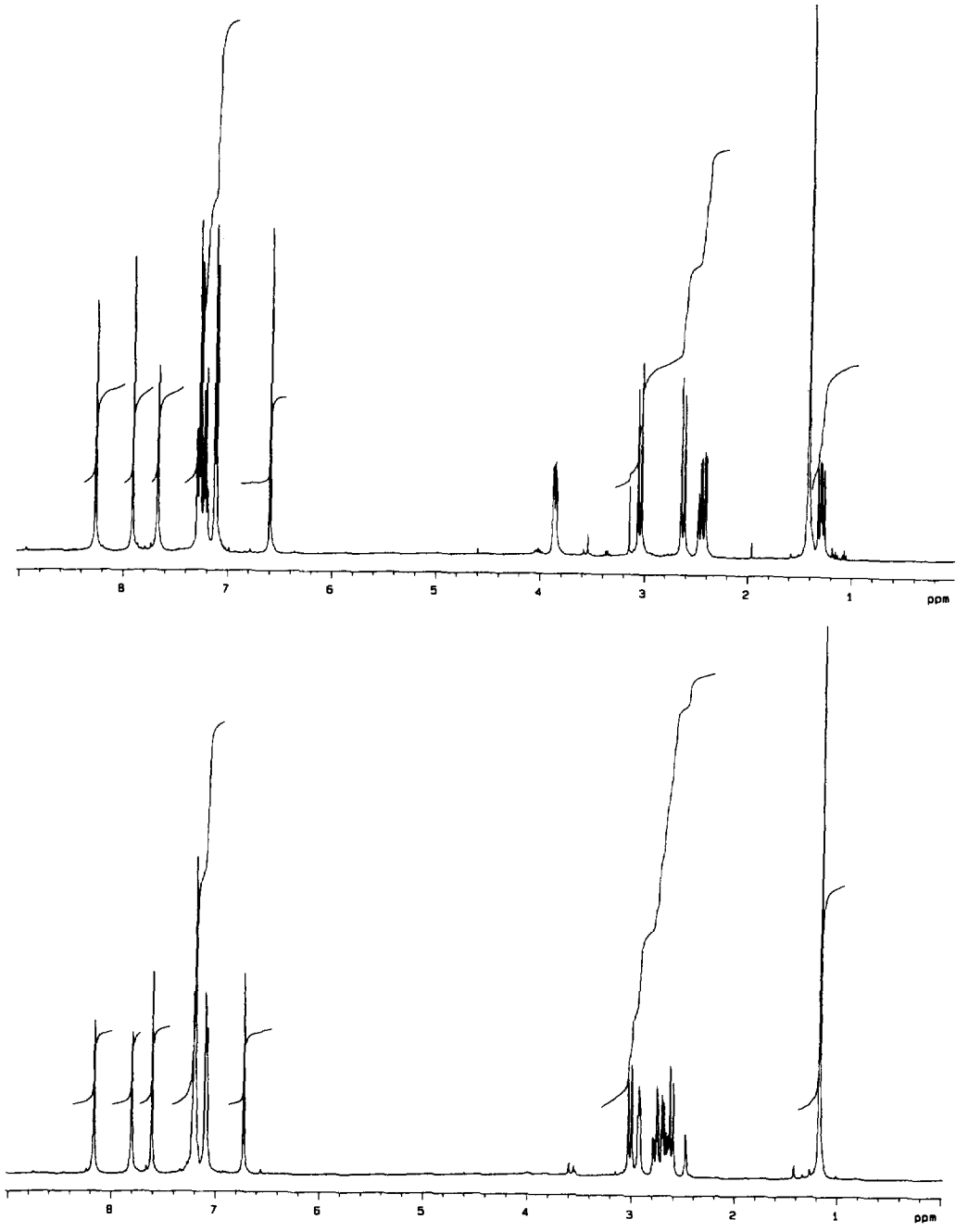


Figure 2. ^{1}H NMR of **15** (upper) and **18** (lower) recorded in DMSO-d_6 (12 mM, 30°C).

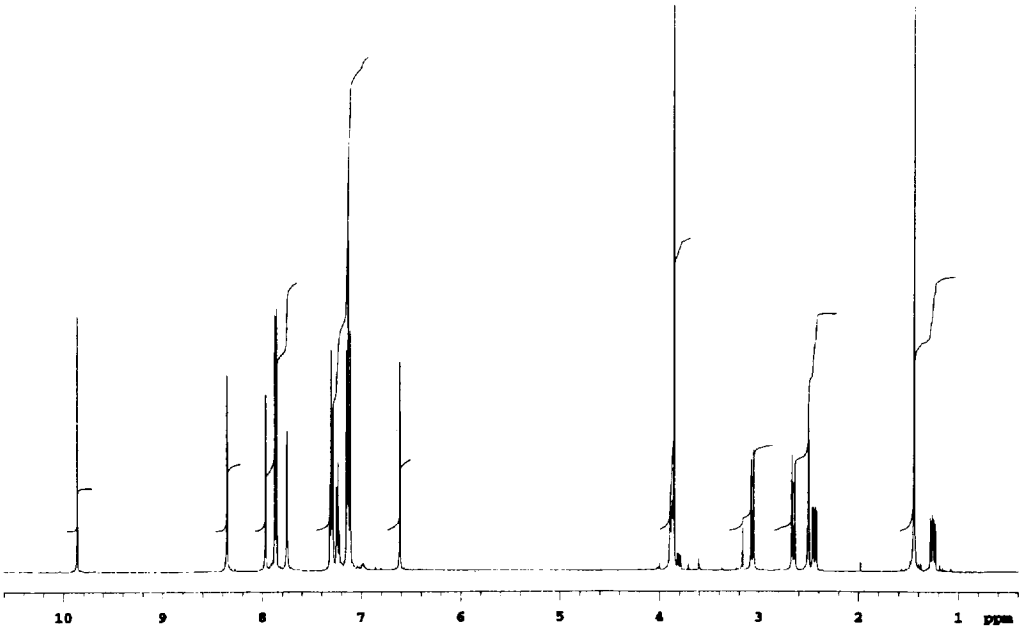


Figure 3. ^{1}H NMR spectrum of **15** with 1 eq of p-methoxybenzaldehyde (DMSO-d_6/$CDCl_3$, −30°C).

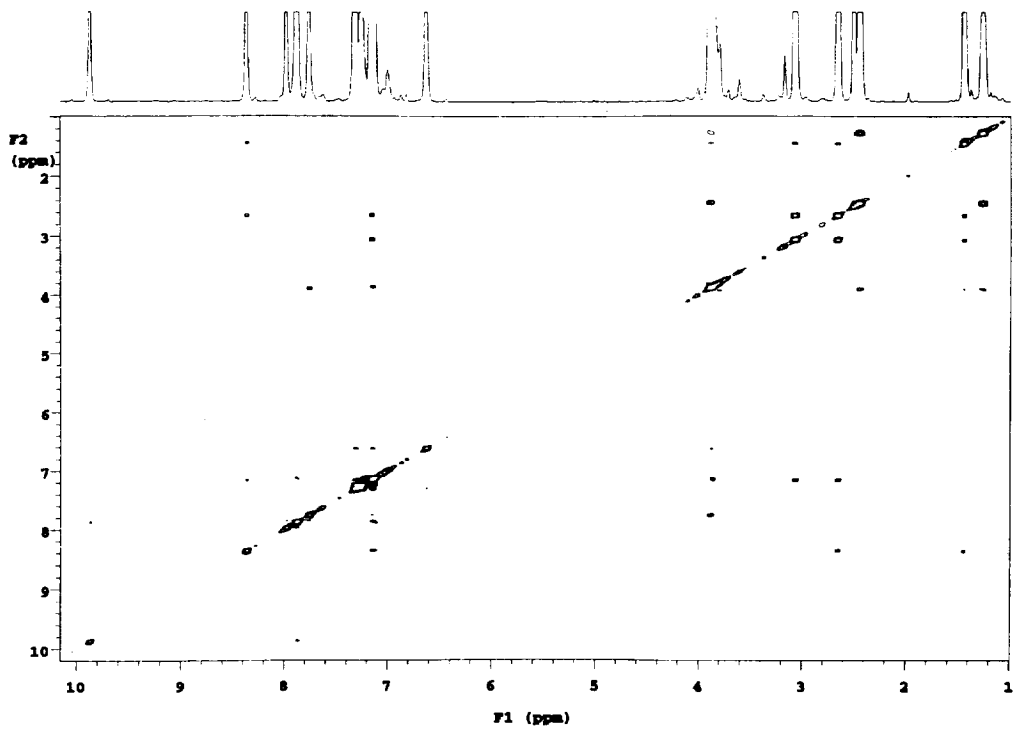
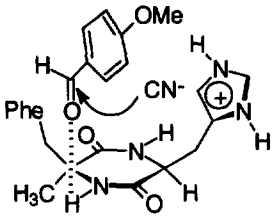


Figure 4. NOESY spectrum of **15** and 1 eq of p-methoxybenzaldehyde (DMSO-d_6/$CDCl_3$, −30°C).

Based on these experiments we postulate that with **15** the orientation of the aldehyde is different from that suggested in the Tanaka model,[12] namely that the aldehyde is hydrogen bonded to the *NH* of the (α-Me)Phe residue and not the histidine residue, as is indicated in Scheme 5.



Scheme 5. Proposed cyanide attack on *p*-methoxybenzaldehyde using **15**.

In this model, *NOE* contacts are expected between the methoxy group and parts of the histidyl moiety, as found. Attack of the cyanide occurs preferentially, in accord with the Tanaka results,[12] from the *si* face leading to the formation of *R* products.

Some caution is necessary, however. It has not been demonstrated that the complex *observed* is indeed the complex that leads to reaction. Secondly, these reactions occur most efficiently in gels. It is unclear what effect this environment may have on stereoselection.

In conclusion, we have shown that cyclic dipeptides, containing conformationally restricted unnatural α-alkylated amino acids like (αMe)Phe, are capable of catalyzing the hydrocyanation reaction of aldehydes in a way comparable with cyclic dipeptides based on naturally occurring amino acids. Moreover, these structural variations should allow modification of the overall conformation of the cyclic dipeptide as well as fine tuning of its catalytic activity.

Experimental

Solvents were dried according to literature procedures. ^1H and ^{13}C spectra were recorded using Varian Unity 500, Unity 400 WB and VXR 300 instruments. The chemical shifts are expressed relative to $CDCl_3$ for ^1H NMR (at δ 7.26 ppm) and ^{13}C NMR (at δ 76.91 ppm). NOESY,[25] ROSEY,[26] TOCSY (MLEV17)[27] and COSY[28] spectra were performed using standard Varian pulse programs. The TOCSY (MLEV17) experiments were performed with mixing times of 30 ms. The mixing times of the NOESY experiments ranged fom 100 to 800 ms. The mixing time of the ROESY experiments consisted of a spin lock pulse of 2 KHz field strength with a duration of 300 ms, typically. All 2D experiments were collected using 2D hypercomplex data[29] and Fourier transformed in the phase-sensitive mode after weighting with shifted square sine-bells or shifted Gaussian functions. NMR data were processed by the standard VnmrS software packages on the Unity 500 or Unity 400 WB host computer (SUN IPX and Sparc stations, respectively). $CDCl_3$ was dried over an Al_2O_3 (activity I) column and DMSO-d_6 was distilled from CaH_2 under an argon atmosphere just prior to use. All reagents were obtained from Aldrich or Acros Chimica and used as received, unless noted otherwise. Starting materials were prepared according to literature procedures.[20]

General procedure for asymmetric addition of hydrogen cyanide to aldehydes

A solution of *cyclo*-[*L*-(αMe)Phe-*L*-His] **15** (0.01 mmol) and freshly purified aldehyde (0.5 mmol) was stirred in 1 mL of toluene and cooled to the desired temperature under an argon atmosphere. Freshly prepared hydrogen cyanide was carefully added dropwise via a precooled syringe (1 mmol), and stirring was continued at that temperature for 30 min. The reaction mixture was quenched by 0.1 N methanolic hydrochloric acid (0.5 mL) and the remaining hydrogen cyanide was removed under reduced pressure. The reaction mixture was washed with 2 N hydrochloric acid and the aqueous layer was extracted three times with CH_2Cl_2 (5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield an oil that was used as such for analysis of the conversion by

means of ^{1}H NMR. The enantiomeric excesses were determined according to the following procedure: bis-amine **21** (1.1 eq) and PCl_3 (1.15 eq) were stirred in dry C_6D_6 (2 mL, distilled from Na/K melt) under an argon atmosphere for 2 min. The crude cyanohydrin (1.0 eq) was added at once, and the solution was stirred for 30 sec. A ^{1}H-decoupled ^{31}P NMR spectrum was then recorded under an argon atmosphere directly.[20,21] The results obtained using this very fast procedure were found to be in excellent agreement with the laborious method described by Tanaka and co-workers.[12]

Resolution of (αMe)Phe **8**

A solution of (−)-*chlocyphos* **9** (4.14 g, 15 mmol) and racemic (αMe)Phe **8** (2.5 g, 14 mmol) was stirred in 125 mL of ethanol (96%) and gently brought to reflux. More ethanol was added if needed to dissolve the mixture completely at boiling point. The solution was then held under reflux for 1 h. After having been stirred for 5 h the solution was slowly cooled to room temperature, and the precipitated material was collected and washed with ethanol–diethyl ether mixtures and shortly dried on the air. The procedure was repeated five times until constant rotation of the solvated crystals was observed. The salt was subsequently hydrolyzed by stirring with 5% aqueous NaOH in CH_2Cl_2 1:1 (500 mL) for 2 h, then neutralized to pH 6, and finally extracted five times with CH_2Cl_2 (250 mL). The combined layers were dried over Na_2SO_4 and taken to dryness. The oil obtained solidified slowly on standing. Crystallization from water (pH 7–7.5) afforded the enantiomerically pure acid as a white solid. The enantiomeric composition was determined by means of ^{31}P NMR after derivatization,[30] and appeared to be over 98%. All the spectroscopic data were found to be in full agreement with the reported values.[18]

*HCl.H-*L*-(αMe)Phe–OMe* L ***10***

H-*L*-(αMe)Phe L-**8** (9.10 g, 51 mmol) was suspended in 120 mL of MeOH and 0.01 mL of DMF and cooled to −15°C and $SOCl_2$ (22.5 mL, 312 mmol) was slowly added to the solution. Subsequently, the mixture was refluxed for 15 h. The solvent was removed under reduced pressure and the residue stripped three times with Et_2O. The white solid material was recrystallized from MeOH/Et_2O, affording a white solid. Yield 10.97 g (48 mmol, 94%). Mp 95–97°C; $[\alpha]_D^{20}$ 8.1 (c 0.5, MeOH); ^{1}H NMR (D_2O, 10 mM): δ 1.54 (s, 3H, CH_3), 3.18 (m, 2H, CH_2), 3.73 (s, 3H, CH_3), 7.10–7.30 (m, 5H, CH); IR (KBr): 3359, 3267, 1754, 1738, 1729, 1634 cm^{-1}.

*H-*L*-His(Trt)-OH* ***11***

To a stirred solution of H-*L*-His (15.5 g, 100 mmol) in 150 mL of CH_2Cl_2 was added Me_2SiCl_2 (12.2 mL, 0.10 mol) and the mixture was refluxed for 4 h. Then, Et_3N (28 mL, 0.20 mol) was added and the mixture was refluxed for 15 min. Subseqeuntly, Et_3N (14 mL, 0.10 mol) followed by a solution of Trt–Cl (28 g, 0.10 mol) in 120 mL of CH_2Cl_2 were added with stirring at room temperature. After 2 h, an excess of MeOH was added and the solvent was evaporated *in vacuo*. H_2O was added to the residue and the pH was adjusted to 8.0–8.5 by dropwise addition of Et_3N. The resulting slurry was shaken with $CHCl_3$ and the insoluble materials were filtered off. The product was further washed with H_2O and Et_2O and dried in vacuo, yielding a white solid material. Yield 32.15 g (80 mmol, 81%). Mp 208–210°C; $[\alpha]_D^{20}$ −1.2 (c 0.5, MeOH); ^{1}H NMR (DMSO-d_6): δ 2.61 (dd, 1H, CH_2), 3.03 (dd, 1H, CH_2), 3.35 (m, 1H, CH), 6.76 (d, 1H, CH), 7.30 (d, 1H, CH), 7.17 and 7.38 (m, 18H, CH and NH_3); IR (KBr): 3402, 1632 cm^{-1}.

*Z-*L*-His(Trt)-OH* ***12***

H-*L*-His(Trt) **11** (20.1 g, 50.6 mmol) was suspended in dioxane (9 mL) and cooled to 0°C. A solution of 2 N NaOH (25.3 mL, 50.6 mmol) was slowly added, followed by $NaHCO_3$ (4.28 g, 51 mmol) and Z-OSu (12.6 g, 50.6 mmol). After stirring the reaction mixture overnight, the solvent was removed under reduced pressure and a solution of 2.5% $NaHCO_3$ (250 mL) was added. The unreacted Z-OSu was extracted with Et_2O. The acqueous solution was acidified with $KHSO_4$ and the product was extracted with AcOEt, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness, yielding

a colorless sticky oil. Yield 24.45 g (46 mmol, 91%). $[\alpha]_D^{20}$ −10.0 (c 0.5, MeOH); ^{1}H NMR ($CDCl_3$): δ 3.08 (dd, 1H, CH_2), 3.31 (dd, 1H, CH_2), 4.42 (m, 1H, CH), 5.02 (dd, 2H, CH_2), 5.91 (d, 1H, NH), 6.63 (d, 1H, CH), 7.14–7.36 (m, 20H, CH), 7.59 (d, 1H, CH), 11.2 (s br, 1H, CO_2H); IR (KBr): 3487, 3300, 1723, 1658 cm^{-1}.

Z-L-*His(Trt)*-L-*(αMe)Phe–OMe* ***13***

Z-*L*-His(Trt)-OH **12** (19.6 g, 36.8 mmol) was dissolved in a CH_3CN:CH_2Cl_2 solvent mixture (200:20 mL) and cooled to 0°C. HOBt.H_2O (5.65 g, 36.9 mmol), followed by EDC.HCl (7.08 g, 36.9 mmol), were added and the mixture was stirred for 1 min. Subseqeuntly, HCl-H-*L*-(αMe)Phe-OMe L-**10** (8.70 g, 37.8 mmol) and NMM (4.2 mL, 37.8 mmol) were carefully added. The mixture was stirred for 12 h, the solvent was removed under reduced pressure and the residue dissolved in AcOEt, washed with 10% $KHSO_4$, H_2O, 5% $NaHCO_3$, H_2O and dried over Na_2SO_4 and taken to dryness. The remaining oil was purified by means of HPLC (eluents: *A* H_2O:TFA 100:0.005; *B* CH_3CN:H_2O:TFA 90:10:0.005; gradient from 60% to 80% of *B* in 30 min). Yield 18.51 g (23.55 mmol, 64%). $[\alpha]_D^{20}$ −18.6 (c 0.5, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 3H, CH_3), 3.20 (m, 4H, CH_2), 3.64 (s, 3H, CH_3), 4.25 (m, 1H, CH), 5.10 (dd, 2H, CH_2), 6.62 (s br, 1H, NH), 6.64 (s, 1H, NH), 7.12–7.29 (m, 27H, CH); IR (KBr): 3310, 1732, 1672 cm^{-1}.

Z-L-*His*-L-*(αMe)Phe-OMe* ***14***

Z-*L*-His(Trt)-*L*-(αMe)Phe-OMe **13** (18.8 g, 26.6 mmol) was dissolved in 75 mL of a TFA:MeOH 95:5 mixture. After stirring for 90 min the solvent was evaporated *in vacuo* and the remainder stripped several times with Et_2O. The residue was taken in Et_2O, filtered and taken to dryness. The oily residue was taken in AcOEt, washed with 5% $NaHCO_3$, H_2O, dried over Na_2SO and taken to dryness. The product was purified by means of flash-chromatography eluting the column with a 95:5 to 90:10 step-gradient mixture of $CHCl_3$:EtOH, affording a white solid material. Yield 6.51 g (11.97 mmol, 45%). Mp 64–65°C; $[\alpha]_D^{20}$ −41.3 (c 0.5, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 3H, CH_3), 3.09 (m, 4H, CH_2), 3.74 (s, 3H, CH_3), 4.50 (m, 1H, CH), 5.08 (s, 2H, CH_2), 5.90 (s br, 1H, NH), 6.84 (d, 1H, CH), 6.95–7.20 (m, 6H, CH and NH), 7.33 (m, 5H, CH), 7.52 (d, 1H, CH); IR (KBr): 3297, 1727, 1665, 1522 cm^{-1}.

Z-L-*His(Trt)*-D-*(αMe)Phe-OMe* ***16***

Z-*L*-His(Trt)-OH **12** (13.8 g, 25.9 mmol) was suspended in a CH_2Cl_2:CH_3CN 1:1 solvent mixture (200 mL) and cooled to 0°C. HOBt.H_2O (4.01 g, 26.2 mmol) and EDC.HCl (4.99 g, 26.0 mmol) were added. H-*D*-(αMe)Phe-OMe (6.15 g, 31.8 mmol, obtained from HCl.H-*D*-(αMe)Phe-OMe *D*-**10** suspended in CH_2Cl_2 and washed with 5% Na_2CO_3, H_2O and dried over Na_2SO_4 and evaporated to dryness) was added as a suspension in CH_2Cl_2. After stirring the reaction mixture for 21 h, the solvent was removed and the residue dissolved in AcOEt, washed with 10% $KHSO_4$, H_2O, 5% $NaHCO_3$, H_2O and dried over Na_2SO_4 and taken to dryness yielding a sticky oil. Yield 13.23 g (16.83 mmol, 65%). $[\alpha]_D^{20}$ 34.2 (c 0.5, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.42 (s, CH_3), 3.10 (m, 4H, CH_2), 3.66 (s, 3H, CH_3), 4.45 (m, 1H, CH), 5.07 (m, 2H, CH_2), 6.60 (s br, 2H, NH), 7.10–7.20 (m, 27H, CH); IR (KBr): 3312, 1721, 1670 cm^{-1}.

Z-L-*His*-D-*(αMe)Phe-OMe* ***17***

Z-*L*-His(Trt)-*D*-(αMe)Phe-OMe **16** (15.8 g, 22.3 mmol) was dissolved in 75 mL of a TFA:MeOH 95:5 mixture. After stirring the reaction mixture for 90 min the solvent was evaporated *in vacuo* and the residue stripped several times with Et_2O. The residue was dissolved in Et_2O, filtered, taken to dryness and redissolved in AcOEt, washed with 5% $NaHCO_3$, H_2O, dried over Na_2SO_4 and evaporated to dryness. The product was purified by flash-chromatography by eluting with a 99:1 to 90:10 step-gradient mixture of $CHCl_3$:EtOH. Oil. Yield 8.25 g (15.16 mmol, 68%). $[\alpha]_D^{20}$ 35.0 (c 0.5, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 3H, CH_3), 2.93 (dd, 1H, CH_2), 3.21 (m, 3H, CH_2), 3.74 (s, 3H, CH_3),

4.40 (m, 1H, CH), 5.07 (s, 2H, CH_2), 5.85 (s br, 1H, NH), 6.79 (d, 1H, CH), 6.94–7.20 (m, 6H, CH and NH), 7.33 (m, 5H, CH), 7.46 (d, 1H, CH); IR (KBr): 3306, 1731, 1663, 1522 cm^{-1}.

Cyclo-*[L-His*-L-*(αMe)Phe] 15*

Z-*L*-His-*L*-(αMe)Phe-OMe **14** (5.07 g, 10.9 mmol) was dissolved in MeOH (250 mL) containing 2.11 g of 10% Pd/C. Hydrogen was bubbled into the solution until the Z-group was completely removed. The catalyst was filtered off, 200 mL of MeOH was added and the clear solution was refluxed for 86 h. The solvent was evaporated under reduced pressure and the product precipitated from a concentrated solution of MeOH affording an off white solid material. Yield 2.99 g (10.03 mmol, 92%). Mp>350°C; $[\alpha]_D^{20}$ −72.7 (c 0.5, MeOH); ^{1}H NMR (DMSO-d_6): δ 1.21 (dd, $^2J_{AB}$=14.65 Hz, ^{3}J=9.28 Hz, 1H, CH_2), 1.43 (s, 3H, CH_3), 2.41 (dd, $^2J_{AB}$=14.65 Hz, ^{3}J=3.41 Hz, 1H, CH_2), 2.63 (d, $^2J_{AB}$=13.19 Hz, 1H, CH_2), 3.04 (d, $^2J_{AB}$=13.19 Hz, 1H, CH_2), 3.82 (m, 1H, CH), 6.61 (s, 1H, CH), 7.02 (m, 2H, CH), 7.22 (m, 1H, CH), 7.31 (m, 3H, CH), 7.76 (s, 1H, NH), 7.98 (s, 1H, NH), 8.38 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 27.96 (CH_3), 30.24 (CH_2), 45.48 (C), 53.98 (CH), 59.81 (CH_2), 116.18 (CH), 126.68 (CH), 127.98 (CH), 130.49 (CH), 132.09 (C), 165.69 (C), 168.47 (C); IR (KBr): 3416, 1667 cm^{-1}.HRMS (*EI*) calcd for $C_{16}H_{18}N_4O_2$ 298.143, found 298.143.

Cyclo-*[L-His*-D-*(αMe)Phe] 18*

Z-*L*-His-*D*-(αMe)Phe-OMe **17** (6.86 g, 14.8 mmol) was dissolved in MeOH (250 mL) containing 2.50 g of 10% Pd/C. Hydrogen was bubbled into the solution until the Z-group was completely removed. The catalyst was filtered off, 400 mL of MeOH was added and the clear solution was refluxed for 40 h. The solvent was evaporated under reduced pressure and the product was precipitated from a concentrated solution of MeOH affording an off white solid material. Yield 4.06 g (13.62 mmol, 92%). Mp 265–266°C; $[\alpha]_D^{20}$ −44.9 (c 0.5, MeOH); ^{1}H NMR (DMSO-d_6): δ 1.17 (s, 3H, CH_3), 2.62 (d, $^2J_{AB}$=13.19 Hz, 1H, CH_2), 2.68 (dd, $^2J_{AB}$=15.14 Hz, ^{3}J=5.86 Hz, 1H, CH_2), 2.76 (dd, $^2J_{AB}$=14.65 Hz, ^{3}J=3.91 Hz, 1H, CH_2), 2.91 (dd, ^{3}J=5.86 Hz, ^{3}J=3.91 Hz, 1H, CH), 3.22 (d, $^2J_{AB}$=13.19 Hz, 1H, CH_2), 6.73 (s, 1H, CH), 7.11 (m, 2H, CH), 7.20–7.25 (m, 4H), 7.60 (s, 1H, NH), 7.87 (s, 1H, NH), 8.22 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 26.90 (CH_3), 29.64 (CH_2), 46.13 (C), 53.88 (CH), 59.76 (CH_2), 116.98 (CH), 126.66 (CH), 127.83 (CH), 130.20 (CH), 132.40 (C), 135.54 (CH), 136.06 (C), 166.28 (C), 168.87 (C); IR (KBr): 3421, 1672, 1562 cm^{-1}; HRMS (*EI*) calcd for $C_{16}H_{18}N_4O_2$ 298.143, found 298.143.

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