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The effects of *N*-methylation on the enantioselectivity of catalysis by cyclo[(*R*)-His-(*R*)-Phe] †

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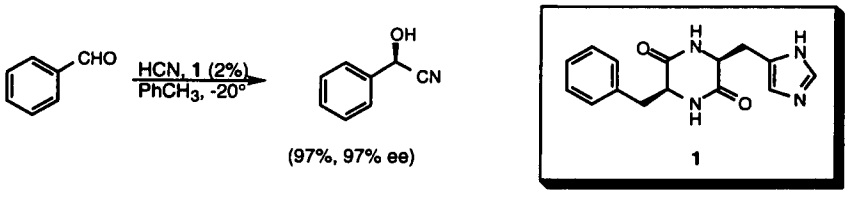
Abstract: The cyclic dipeptide cyclo[(*R*)-His-(*R*)-Phe] **1** has been known since 1981 to catalyze the enantioselective formation of cyanohydrins from aldehydes and HCN. Although **1** has proved to be very effective in the production of optically active cyanohydrins, the precise structure of its catalytically active form remains unresolved. Two derivatives, in which the two amides in **1** were independently *N*-methylated, were synthesized as probes of the structural and functional requirements for catalysis by **1**. Both derivatives were far more soluble in organic solvents and were found to catalyze the formation of *racemic* cyanohydrin, but differed greatly in their turnover rates. Mixtures of the two derivatives with each other and with **1** were also examined as hydrocyanation catalysts. Only the mixtures containing **1** demonstrated any enantioselectivity, but did not appear any more competent as catalysts than reduced quantities of **1**. From these data, it is concluded that both amide bonds are essential for effective catalysis by **1**, but that the amide containing the His N_α appears to be involved in interactions with the substrate while the other amide plays a structural role, possibly for self-associative hydrogen bonding.

In 1981, in an attempt to mimic the activity of the enzyme oxynitrilase, Inoue reported that the cyclic dipeptide cyclo[(*S*)-His-(*S*)-Phe] **1** catalyzed the enantioselective addition of HCN to benzaldehyde to form (*R*)-mandelonitrile in high yield and exceptionally high enantiomeric excess (Scheme 1).[1] In subsequent publications,[2–5] Inoue studied the effects of solvent, temperature and substrate on selectivity; these studies led to the conclusion that, optimally, the reaction should be run at −20°C in toluene and that most aromatic aldehydes performed well as substrates, while aliphatic and heteroaromatic aldehydes reacted with lower selectivity.[6] Inoue's pioneering studies led to the development of cyclo[(*R*)-His-(*R*)-Phe] *ent*-**1** as a catalyst for the enantioselective synthesis of pyrethroid insecticide precursors.[7]



Scheme 1. Asymmetric catalysis of cyanohydrin formation by cyclo[(*S*)-His-(*S*)-Phe] **1**.

Several groups have studied the behavior of **1** since the original work of Inoue. From these studies a picture of a catalytic system has emerged, far more complex than the one originally proposed. Firstly, Inoue found that the morphology of **1** in the solid state strongly affected its ability to catalyze cyanohydrin formation;[5] he further noted that catalytic samples of **1** were amorphous solids that formed

† Dedicated to Professor Herbert C. Brown on the occasion of his 85th birthday.
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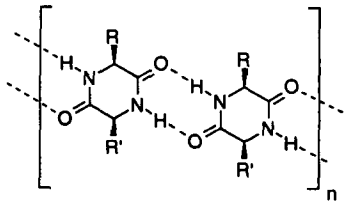
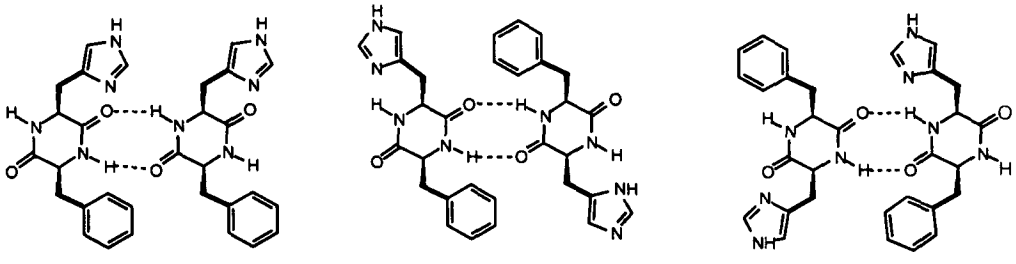


Figure 1. Hydrogen bonded polymer formed by diketopiperazines in the solid state.



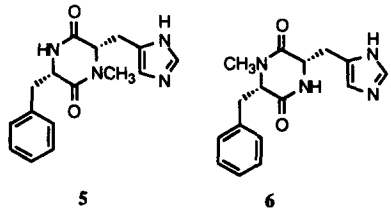
2 **3** **4**

Figure 2. Possible dimeric forms of **1**.

gels in the reaction medium. This same trend was observed independently by researchers at Shell Development[8] and Sumitomo.[9] More recently, Danda has shown that cyanohydrin formation catalyzed by **1** exhibits enantioselective autoinduction, indicating an interaction of cyanohydrin product with **1** that enhances its enantioselectivity of catalysis.[10]

These observations raise the question of whether **1** acts as a homogeneous or heterogeneous catalyst, a question that still remains unresolved. Additionally, the structure of the gel formed by **1** in toluene (or, indeed, in any solvent) remains unspecified, although examination of the solid state structures of related diketopiperazines[11] suggests that the polymer of **1** may be a linear, hydrogen bonded network (Figure 1). This observation, coupled with Danda's observation of enhanced enantioselectivity associated with thixotropy,[12] leads to the possibility that the catalytic species might be a soluble oligomer of **1** created by mechanical disruption of the polymeric gel. Combined with Shvo's recent demonstration of second-order kinetics exhibited by **1**,[13] these findings raise the possibility that a soluble dimer of **1** could be the catalytic species. Such a dimer would be held together by an octacyclic hydrogen bond and could exist as either a head-to-head **2** or one of two head-to-tail dimers **3** or **4**, as shown in Figure 2.

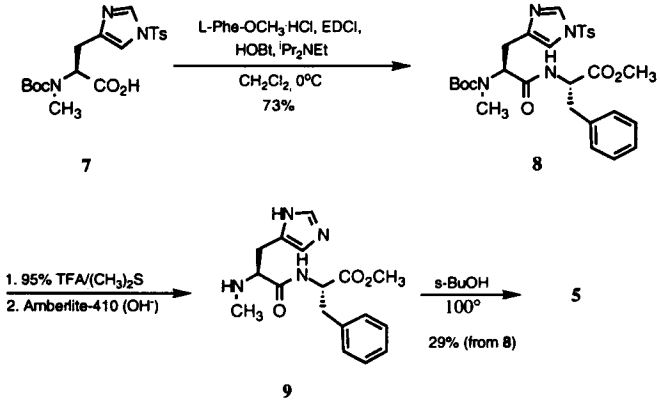
To test this idea, two *N*-methylated derivatives of **1** were synthesized, **5** and **6**.[14] The objective was to selectively disrupt the hydrogen bonding ability of **1** by replacement of an amide hydrogen with a methyl group. It was reasoned that, as a result of their inability to form the tape-like structure shown in Figure 1, **5** and **6** should be substantially more soluble than **1** in organic solvents and each derivative should form only one of the three dimers shown in Figure 2: **5** can only form dimer **3** and **6** can only form **4**. In order to probe the role of the head-to-head dimer **2**, one could examine the catalytic behavior of a 1:1 mixture of **5** and **6** in contrast to that of pure **5** or **6**.



5 **6**

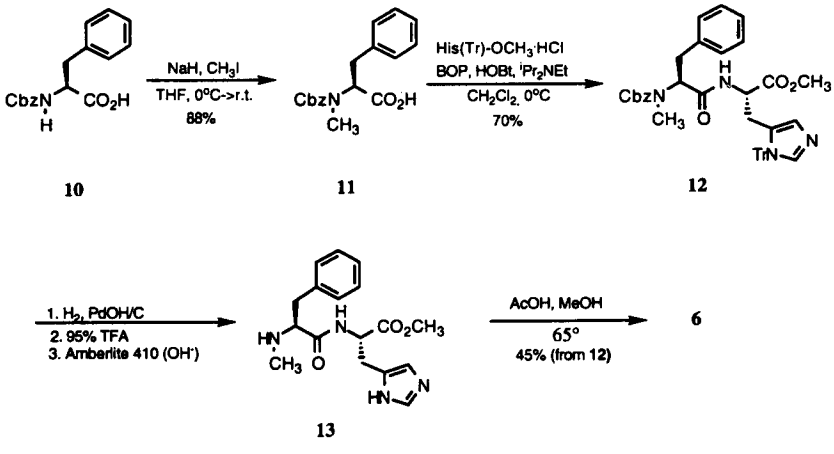
Synthesis of the starting materials

The syntheses of **5** and **6** were carried out in accord with the literature precedent. The synthesis of **5** was complicated by difficulties encountered in the *N*-methylation of various protected histidine derivatives. The final synthesis was begun using the *N*-methyl-L-histidine derivative **7**[15] (Scheme 2) and proceeded without event to afford the acyclic precursor **9**. Cyclization of **9** proved to require much more vigorous conditions than the parent system, as a result of the more hindered nature of the secondary amine, and was found to proceed best in refluxing *sec*-butanol. The product **5** was purified by ion exchange chromatography.



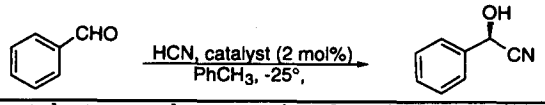
Scheme 2. Synthesis of cyclo[N^{α}-methyl-(*S*)-His-(*S*)-Phe] **5**.

The synthesis of **6** employed a literature *N*-methylation of *Z*-L-phenylalanine **10**, (Scheme 3)[16] followed by peptide coupling of the product **11** to a protected L-histidine derivative, affording the protected dipeptide **12**. Initially, cyclization was attempted after hydrogenolysis of the *N*-terminal benzyloxycarbonyl (Cbz) group to afford the free *N*-terminal amine; however, a complete lack of reactivity of the protected dipeptide was noted, presumably owing to steric hindrance by the N^{π}-trityl group on the histidine sidechain. Thus, the trityl group was removed by acid deprotection and subsequent neutralization, whereupon cyclization to **6** was smoothly accomplished by acid-catalyzed transacylation in acceptable yield.



Scheme 3. Synthesis of cyclo[(*S*)-His-*N*-methyl-(*S*)-Phe] **6**.

Table 1. Evaluation of various catalysts for the asymmetric hydrocyanation of benzaldehyde



catalyst	solvent	time, h	yield, %	ee, %
1	$PhCH_3$	8	95	95
5	$PhCH_3$	3	94	<3
5	$PhCH_3$	4.5	94	<3
5	n-C_6H_6	3	98	<3
5	THF	3	37	<3
6	$PhCH_3$	3.5	15	4
6	$PhCH_3$	19	12	12
6	$PhCH_3$[a]	17	8	4
6	n-C_6H_6	3.5	98	<3
6	CCl_4	3.5	95	<3
6	THF	3.5	43	<3
5, 6 (1:1)	$PhCH_3$	18	85	<3
5, 6 (1:1)	n-C_6H_6	3	27	<3
5, 6 (1:1)	n-C_6H_6[a]	17	62	<3
5, 6 (2:1)	$PhCH_3$	3	29	<3
imidazole	$PhCH_3$	3	61	-

[a] Reaction run at -65°.

Catalysis studies

Because of the known dependence of catalysis by **1** on solid state morphology (*vide supra*), both **5** and **6** were obtained as amorphous solids by lyophilization from aqueous solution. After lyophilization, both diketopiperazines were examined for their ability to catalyze the enantioselective formation of mandelonitrile from benzaldehyde. The results of these studies are shown in Table 1. Both diketopiperazines were far more soluble in organic media than **1**; both were fully soluble even in *n*-hexane after addition of HCN to the reaction medium. In both cases, however, the *N*-methylated derivatives afforded little or no enantioselectivity in all experiments. These findings are in apparent contradiction to those of Noe,[14] who found no catalysis by either **5** or **6**. In our hands, two significant differences between the two diketopiperazines were observed: **5** was a far better hydrocyanation catalyst than **6** in toluene, yet **6** did display a slight amount of enantioselectivity, albeit at low conversion. When a 1:1 mixture of **5** and **6** was examined for catalytic activity, it was found to behave identically to the individual diketopiperazines.

Mixtures of **1** and the two *N*-methylated diketopiperazines were also examined for catalytic ability (Table 2). As a control, varying amounts of **1** were examined for catalytic proficiency. It was found that, even in 0.6 mol% quantity, **1** formed (*S*)-mandelonitrile in 95% ee, albeit in a slightly lower yield. When less **1** was present, however, both yield and enantioselectivity dropped precipitously. In all cases, when either **5** or **6** was added to **1**, the resulting mixture exhibited no cooperative catalysis, thus indicating that **1** was incapable of rescuing either of the crippled catalysts.

It has also recently been demonstrated that (*S*)-1-phenylethanol **14** interacts with **1** and enhances its enantioselectivity.[17] As a consequence, the effect of the addition of **14** to reactions catalyzed by **5** and **6** was examined. Addition of 8 mol% of **14**, enough to enhance the enantioselectivity of reactions catalyzed by **1**, was found to have no effect on the enantioselectivity of reactions catalyzed by either **5** or **6**. Thus, it appears that both **5** and **6** are crippled beyond the ability of either **1** or **14** to repair.

On the basis of these findings, one can conclude that both amide bonds of **1** appear to be critical for enantioselective catalysis. The difference in behavior of **5** and **6** argues that the two amides may play different roles in the behavior of **1**. First, when the His-Phe bond is methylated, the derivative **6** is no more efficient a catalyst for cyanohydrin formation than imidazole, but when the Phe-His amide is methylated enantioselectivity is abolished. The lack of ability of either derivative to interact with either **1** or **14** implies that the amides are essential for enantioselectivity. This observation is

Table 2. Evaluation of mixtures of **1**, **5** and **6** as hydrocyanation catalysts

catalysts, mol %				
1	**5**	**6**	yield, %	ee, %
2	0	0	95	95
1	0	0	80	92
0.6	0	0	72	95
0.2	0	0	9	91
1.6	0	0.4	98	77
1	0	1	98	88
0.4	0	1.6	85	84
1	1	0	86	83
0.4	1.6	0	52	70

consistent with the view that the gel is the catalytic species, although discrete oligomers cannot be rigorously excluded by these results. Further investigations are ongoing to more completely elucidate the structure and behavior of the catalytic complex.

Experimental section

General procedures

All reactions were performed in flame dried or oven dried glassware under a positive pressure of nitrogen. Benzaldehyde was distilled and stored under argon prior to use. Tetrahydrofuran was distilled from benzophenone ketyl. Toluene, methylene chloride, and hexane were distilled from calcium hydride. All other reagents were used without further purification. Flash chromatography was performed using 230–400 mesh silica gel. ^1H and ^{13}C NMR were obtained on a Varian Gemini 200 MHz and a General Electric QE-300 (282 MHz) spectrometer.

N^{α}-(tert-Butyloxycarbonyl)-N^{α}-methyl-N^{τ}-(para-toluenesulfonyl)-(S)-histidyl-(S)-phenylalanine methyl ester **8**

To a solution of *N^{α}*-(*tert*-butyloxycarbonyl)-*N^{α}*-methyl-*N^{τ}*-(*para*-toluenesulfonyl)-(*S*)-histidine[15] **7** (1.23 g, 2.8 mmol) in dichloromethane at 0°C was added (*S*)-phenylalanine methyl ester hydrochloride (0.67 g, 3.1 mmol), HOBt (0.038 g, 0.28 mmol), *i*-Pr_2NEt (0.56 mL, 3.1 mmol), and EDCI (0.67 g, 3.5 mmol). After 2.3 hours the reaction was diluted with CH_2Cl_2 (10 mL) and washed with 10% aqueous citric acid (20 mL) and saturated aqueous sodium bicarbonate (20 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash chromatography (2% $MeOH/CH_2Cl_2$) to yield **5** as a colorless solid (1.2 g, 73%); m.p.: 46–47°C; ^1H NMR (acetone-d_6) δ 8.05 (s, 1H), 7.94 (s, 1H), 7.90 (s, 1H), 7.50 (s, 1H), 7.25 (m, 7H), 4.91 (m, 1H), 4.70 (dq, J=5.1, 2.8, 1H), 3.68 (s, 3H), 3.0 (m, 4H), 2.57, 2.52 (2 s (cis/trans isomers), 3H), 2.43 (s, 1H), 1.34, 1.22 (2 s (cis/trans isomers), 9H); ^{13}C NMR (acetone-d_6) δ 171.7, 170.0, 146.5, 141.7, 137.1, 136.5, 136.4, 136.3, 130.6, 129.3, 128.5, 127.4, 126.7, 114.6, 79.3, 59.1, 57.5, 53.6, 37.1, 27.6, 26.8, 20.8; IR (thin film, cm^{-1}) 2978, 1745, 1687, 1684, 1380, 1175, 1081, 674, 592; HRMS: calculated 585.2383, found 585.2376.

Cyclo[N^{α}-methyl-(S)-histidyl-(S)-phenylalanine] **5**

Protected dipeptide **7** (1.2 g, 2.1 mmol) was dissolved in 95% TFA–dimethyl sulfide (3 mL). After 6 hours, solvent was removed *in vacuo*, yielding a crude oil (1.5 g). The oil was dissolved in distilled water (10 mL) and Amberlite 410 anion exchange resin (^-OH form) was added until the solution reached a pH of 8, after which the solution was stirred for 2 hours. The resin was removed by filtration and the solvent removed *in vacuo*, affording a yellow oil (0.8 g). The oil was dissolved in s-butanol (275 mL) and the solution refluxed for 28 hours. Solvent was evaporated at reduced pressure and the crude material purified by ion exchange chromatography (Amberlite 410), eluting with distilled water. Impure fractions were washed with tetrahydrofuran to dissolve the desired product. All pure fractions were combined, redissolved in water (200 mL) and lyophilized, yielding **5** as a colorless solid (0.17

g, 29%); m.p.: 180–185°C; $[\alpha]^{20}_D$ −106.8 (c=1.8 in methanol); ^{1}H NMR (DMSO-d_6) δ 11.86 (s, 1H), 7.91 (s, 1H), 7.53 (m, 5H), 6.68 (s, 1H), 3.99 (t, J=5 Hz, 1H), 3.94 (s, 1H), 2.65 (s, 3H), 2.57 (dd, J=13, 5 Hz, 2H), 2.2 (m, 1H), 2.06 (dd, J=13, 5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 167.4, 166.4, 136.3, 135.32, 135.27, 129.7, 128.5, 128.0, 126.9, 62.2, 56.6, 40.5, 32.4, 29.5; IR (KBr, cm^{-1}) 3222, 1677, 1639, 1458, 1342, 750, 702; HRMS: calculated 299.1508, found 299.1497.

N-(Benzyloxycarbonyl)-N-methyl-(S)-phenylalanine ***11***

N^{α}-(Benzyloxycarbonyl)-(*S*)-phenylalanine (**10**, 1.95 g, 6.98 mmol) was dissolved in THF (35 mL) and CH_3I (3.5 mL, 55.9 mmol) was added. The solution was cooled to 0°C and transferred via cannula to a flask containing neat NaH (0.44 g, 18.2 mmol), stirring at 0°C. The reaction was allowed to warm to room temperature overnight. The resulting mixture with suspended white precipitate was diluted with distilled H_2O (25 mL) and acidified with HCl (1 N) to a pH of 2. The mixture was washed with ethyl acetate (35 mL) and the organic layer dried over $MgSO_4$. Removal of solvent *in vacuo* and purification by flash chromatography (4% methanol–methylene chloride) afforded **11** as a pale yellow oil (1.5 g, 73%). ^{1}H NMR (acetone-d_6) δ 7.3 (m, 10H), 5.04, 4.97 (2 s [cis/trans isomers], 2H), 4.85 (dd, J=11.3, 4.8 Hz, 1H), 3.25 (dd, J=11.9, 2.2 Hz, 1H), 3.09 (m, 1H), 2.75, 2.72 (2s [cis/trans isomers], 3H); ^{13}C NMR (acetone-d_6) δ 172,6, (156.3, 155.9, cis/trans isomers), 138.4, 137.5, 137.3, 129.3, 128.8, 128.2, 127.7, 127.6, 126.9, (66.8, 66.6, cis/trans isomers), 60.6, 55.4, (34.7, 32.3, cis/trans isomers).

N^{α}-(Benzyloxycarbonyl)-N^{α}-methyl-(S)-phenylalanyl-N^{π}-triphenylmethyl-(S)-histidine methyl ester ***12***

N^{π}-Triphenylmethyl-(*S*)-histidine methyl ester hydrochloride (1.34 g, 3.3 mmol) and **11** (0.92 g, 3.0 mmol) were dissolved in dry CH_2Cl_2 (6.2 mL), HOBt (0.2 g, 1.5 mmol), *i*-Pr_2NEt (0.6 ml, 3.3 mmol), and BOP (1.7 g, 3.8 mmol) were added and the solution stirred for 16 hours. The solution was washed with 10% citric acid (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate, solvent was removed under reduced pressure and the crude product was purified by flash chromatography (2% methanol–methylene chloride), affording **12** as a white solid (1.45 g, 70%): m.p. 66–67°C; ^{1}H NMR (acetone-d_6) δ 8.29 (2 d [1:1, cis/trans isomers], J=8.7 Hz, 1 H), 7.25 (m, 25H), 6.71 (s, 1H), 4.95 (m, 3H), 4.60 (q, J=5.7 Hz, 1H), 3.59 (s, 3H), 3.36 (dt, J=13.4, 3.2 Hz, 1H), 2.95 (m, 3H), 2.82 (s, 3H); ^{13}C NMR (acetone-d_6) δ 172.7, 170.9, 143.8, 139.6, 138.1, 130.9, 130.2, 129.6, 129.4, 129.3, 128.8, 128.6, 128.4, 127.5, 120.7, 76.3, 67.8, 62.2, 61.9, 54.1, 52.7, 35.3, 31.9; IR (thin film, cm^{-1}) 3409, 3031, 2948, 1742, 1678, 1496, 1447, 1209, 1036, 750, 701; HR-FABMS: calculated 707.3233, found 707.3224.

Cyclo[(S)-histidyl-N-methyl-(S)-phenylalanine] ***6***

A degassed solution of **12** (1.45 g, 2.05 mmol) and $Pd(OH)_2$–C (50 mg) in methanol (125 mL) under an atmosphere of hydrogen was stirred for 6 hours. The catalyst was removed by filtration and solvent removed *in vacuo*, affording a pale yellow oil (1.2 g). To this oil (1.0 g) was added 95% aqueous trifluoroacetic acid (5.5 mL). The mixture was stirred for 2 hours, after which solvent was evaporated at reduced pressure, yielding a brownish oil. Removal of solid impurities by dissolution in methanol (100 mL), followed by filtration and evaporation of solvent, yielded the crude product as an oil (0.65 g).

The oil (0.42 g) was dissolved in distilled water (7 mL) and Amberlite 410 anion exchange resin ($^-$OH) was added until the solution reached a pH of 8. After stirring for 2 hours, the reaction was filtered and the filtrate evaporated, yielding a white foam (0.23 g). This material was then refluxed in methanol (110 mL) containing acetic acid (0.04 mL) for 3 days. Solvent was removed *in vacuo*, the oil redissolved in water (200 mL) and lyophilized, yielding **6** (0.175 g, 45% from **12**); m.p.: 218–219°C, $[\alpha]^{20}_D$ −139.0 (c=0.5 in methanol); ^{1}H NMR (DMSO-d_6) δ 11.8 (s, 1H), 7.76 (s, 1H), 7.48 (s, 1H), 7.30 (m, 3H), 7.09 (s, 1H), 7.06 (s, 1H), 6.54 (s, 1H), 4.19 (t, J=4.3 Hz, 1H), 3.79 (dt, J=14.4, 3.0 Hz, 1H), 2.98 (m, 2H), 2.88 (s, 3H), 2.31 (dd, J=14.4, 3.4 Hz, 1H), 0.97 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 168.7, 168.1, 137.2, 137.0, 134.4, 131.7, 130.6, 130.3, 128.9, 119.0, 64.6, 56.4, 37.9, 33.8; IR (KBr,

cm^{-1}) 3210, 168, 1651, 1454, 1336, 1259, 1187, 1095, 723, 666; HRMS: calculated 299.1508, found 299.1497.

Preparation of HCN

Concentrated H_2SO_4 (50 mL) was added dropwise via an addition funnel to an aqueous solution of NaCN (5 M) in a three-necked round bottomed flask connected, by tubing, to a gas weighing flask containing anhydrous $CaCl_2$ and then to a cold finger condenser cooled to −78°C. The HCN was collected as a solid on the surface of the condenser and, once evolution was complete, allowed to slowly warm to 5°C. Liquid HCN was collected in a receiving flask containing anhydrous $CaCl_2$ at −78°C. The HCN was stored as a solid at −78°C until needed, at which point it was warmed to 0°C and transferred via a chilled syringe. EXTREME CAUTION SHOULD BE USED WHEN PREPARING, STORING, AND USING HCN!

Addition of hydrogen cyanide to benzaldehyde

Dry solvent (75 μL) was added to **5** and/or **6** (5.0 mg total catalyst, 17 μmol) under nitrogen and stirred at room temperature for 20 minutes. To this solution was added benzaldehyde (75 μL, 0.74 mmol) and the resulting mixture cooled to −25°C. HCN (0.075 mL, 1.9 mmol) was then added to the mixture via a precooled syringe and the stirring rate increased. At completion the reaction was quenched by addition of 0.1 N methanolic HCl (0.250 mL). The reaction mixture was extracted with ether and water. The organic layer was dried over Na_2SO_4 and solvent was removed *in vacuo* to yield a crude oil that was characterized by ^1H NMR.

Addition of hydrogen cyanide to benzaldehyde in the presence of (S)-1-phenylethanol

Procedure as above except (*S*)-1-phenylethanol was added right after the solvent and the mixture was stirred for 45 minutes at room temperature before benzaldehyde was added.

Determination of optical purity of mandelonitrile

(1*R*,2*S*,5*R*)-(−)-Menthyl chloroformate (0.025 mL, 0.012 mmol) was added to a solution of crude mandelonitrile (7 μL, 57 μmol) in toluene (0.5 mL). Pyridine (15 μL, 19 μmol) was added and the reaction stirred at room temperature for 12 h. The mixture was concentrated *in vacuo* and analyzed by ^1H NMR. The diastereomeric excess was determined by ^1H NMR analysis of signals corresponding to the methine proton α to the cyano group of each diastereomer of the cyanohydrin menthyl carbonate. ^1H NMR ($CDCl_3$): δ 6.28 (minor, s), 6.25 (major, s).

Acknowledgements

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