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Tetrahedron 60 (2004) 10479–10486
Tetrahedron

Development of β-hydroxyamide/titanium complexes for catalytic enantioselective silylcyanation of aldehydes

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Received 24 June 2004; revised 3 August 2004; accepted 23 August 2004

Available online 25 September 2004

Abstract—A highly enantioselective addition of trimethylsilylcyanide to aldehydes catalyzed by chiral titanium complexes is described. The chiral titanium complexes were prepared in situ from $Ti(O^iPr)_4$ and β-hydroxyamide ligands, that could easily be synthesized from ketopinic acid and C_2 symmetrical chiral diamines in a small number of steps.

1. Introduction

Enantiomerically pure cyanohydrins are versatile intermediates,[1,2] useful in the synthesis of a variety of natural and unnatural biologically active molecules owing to their potential for selective transformations given by the presence of a single asymmetric center bearing two reactive functionalities. The cyanohydrin functionality is also a component of commercially important compounds such as the pyrethroid insecticides cypermethrin and fluvalinate.[3,4] Due to their synthetic versatility for the production of pharmaceuticals and agrochemicals, there is currently significant interest in the asymmetric synthesis of cyanohydrins, especially by methods that utilize a chiral catalyst.

A wide range of catalysts are available for this reaction,[5–7] including enzymes, synthetic peptides, chiral Lewis bases, and chiral transition metal complexes. The structural modification of enzymes and peptides to improve their substrate compatibility is a long and difficult undertaking. In contrast, the modification of the structures of chiral transition metal complexes is a straightforward undertaking, thus offering the potential for this class of asymmetric catalysts to generate a desired cyanohydrin with high enantiomeric excess. Of the chiral metal complexes reported so far, titanium-based Lewis acids have attracted the most interest. The chiral ligand for titanium-based catalysts include TADDOLs,[8–10] BINOLs,[11–16] tartrate esters,[17,18] sulfoximines,[19,20] peptides,[21] Schiff bases[22–29] and others.[30–34] In each case, complexation of the ligand to a suitable titanium salt generated a chiral complex that induced the asymmetric addition of hydrogen and/or trimethylsilyl cyanide to aldehydes. Herein we describe an enantioselective silylcyanation of aldehydes catalyzed by $Ti(O^iPr)_4$ and a series of C_2 symmetrical chiral hydroxyamide ligands.

2. Results and discussion

At the outset, we synthesized the dihydroxyamide ligand **4a** and its diastereoisomer **4b** from ketopinic acid chloride **1**[35] and diamine **2** (Scheme 1). On treatment with optically pure (+)- or (−)-*trans*-1,2-diaminocyclohexane in dichloromethane in the presence of triethylamine, ketopinic acid chloride was converted to the *trans*-diketoamide **3a** or **3b**, respectively. Diketoamides **3a** and **3b** could also be obtained in pure form by reacting ketopinic acid chloride with *rac-trans*-1,2-diaminocyclohexane in the same fashion as above followed by separation of the resulting diastereomeric mixture by column chromatography on silica gel. Subsequent reduction of **3a** and **3b** using L-selectride® in tetrahydrofuran at −78 °C for 1 h and then at room temperature for 2 h gave **4a** and **4b** respectively, with the hydroxy group at the *exo*-position.[36] The absolute stereochemistry of ligand **4a** was further confirmed by X-ray crystallographic analysis.[34]

Ligand **4a** was found to be a useful chiral ligand for asymmetric induction. In conjunction with titanium tetraisopropoxide, ligand **4a** was shown to effect the

Keywords: Cyanohydrin; Asymmetric catalysis; Titanium complex; β-Hydroxyamide.
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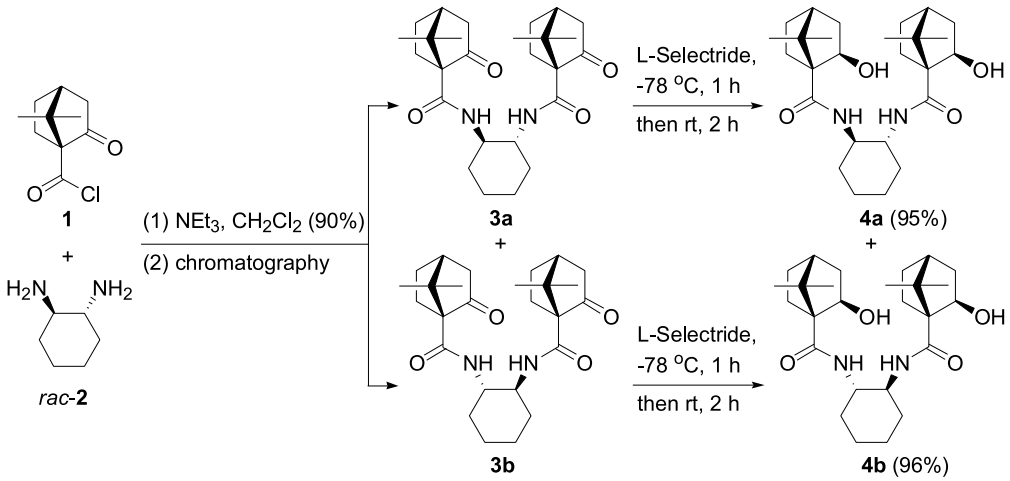
doi:10.1016/j.tet.2004.08.083



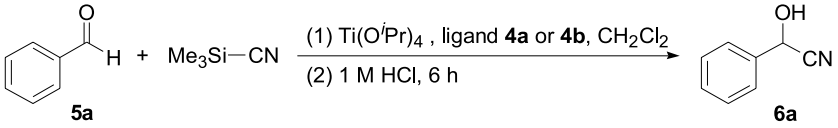
Scheme 1. Synthesis of ligand **4a** and **4b**.

enantioselective addition of trimethylsilyl cyanide to benzaldehyde **5a** (Table 1). Optimum results were obtained when the reaction was carried out at −78 °C in dichloromethane using the complex prepared from 16.5 mol% of ligand **4a** and 15 mol% of titanium tetraisopropoxide in the presence of 4 Å molecular sieves (entry 6). Under these conditions, the desired cyanohydrin was isolated in 79% yield and 94% ee after hydrolysis of the initial addition product with 1 M HCl at room temperature. At the same time, chiral ligand **4a** was recovered in 92% yield. Interestingly, in the absence of molecular sieves, the reaction was extremely slow and no sign of reaction was observed after 24 h at −30 °C (entry 2). This observation is in agreement with those reported previously by Narasaka.[9] It is also noteworthy that the degree of enantioselectivity appears to be proportional to the amount of the complex employed. Thus, when the amount of the catalyst was reduced by half, the enantioselectivity of the reaction was found to depreciate considerably (entries 4 and 5). The selectivity was also found to be temperature dependent as expected; when the reaction was carried out at −30 °C, mandelonitrile was obtained in 71% ee after hydrolysis (entry 5). This level of enantioselectivity was considerably inferior to that observed for the addition reaction carried out at −78 °C. Not surprisingly, however, the improved selectivity at −78 °C was at the expense of the reaction rate. Ligand **4b** was not a useful ligand when applied under the same reaction conditions; only 4% ee was observed in this case (entry 7).

To examine the efficacy of this catalytic process with regards to substrate structure, a variety of aromatic and aliphatic aldehydes were subjected to the conditions optimized in the case of benzaldehyde, employing **4a** with titanium tetraisopropoxide as the catalyst, and the results are summarized in Table 2. The asymmetric induction achieved with both aromatic (>94% ee) and aliphatic aldehydes (>87% ee) is quite high.

It was envisaged that replacement of the cyclohexane ring with two vicinal phenyl groups in the chiral diamide moiety of **4a** would result in a better catalyst which could provide greater facial selectivity in the silylcyanation of the aldehydes. A relatively bulky phenyl group would increase the energy difference between the two diastereomeric transition structure orientations, thereby enhancing the enantioselectivity. Chiral compound **9a** with the desired structural and stereochemical features was prepared starting

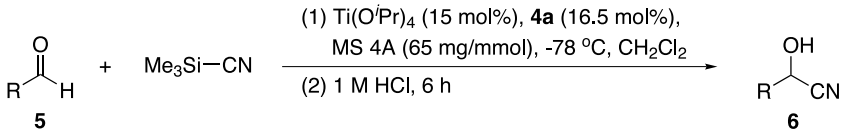
Table 1. Enantioselective addition of TMSCN to benzaldehyde catalyzed by ligand **4** and $Ti(O^iPr)_4$



Entry	Ligand (mol%)	$Ti(O^iPr)_4$ (mol%)	4 Å MS[a] (mg/mmol)	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	**4a** (22)	20	—	0	10	78	20	*S*
2	**4a** (22)	20	—	−30	24	0	—	—
3	**4a** (11)	10	65	30	6	78	48	*S*
4	**4a** (11)	10	65	−30	24	74	55	*S*
5	**4a** (22)	20	65	−30	18	75	71	*S*
6	**4a** (16.5)	15	65	−78	48	79	94	*S*
7	**4b** (16.5)	15	65	−78	48	77	4	*R*

[a] Powder, dried at 300 °C/0.1 mmHg for 24 h before use.
[b] Isolated yield.
[c] Determined by HPLC after being protected as a TBDMS ether.
[d] Absolute configurations were determined by comparison of optical rotations with literature values.

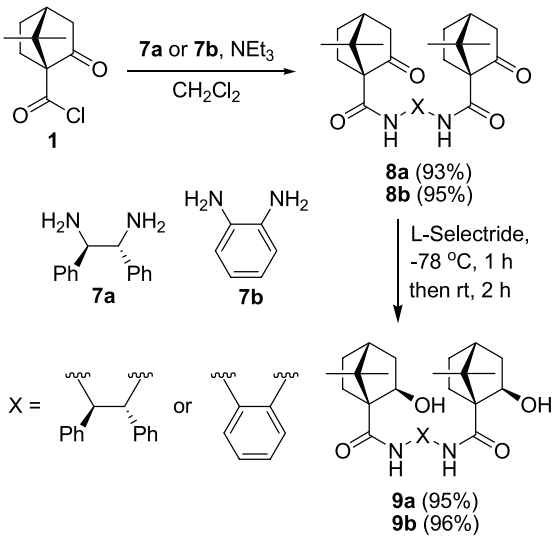
Table 2. Enantioselective addition of TMSCN to aldehydes catalyzed by **4a**/Ti(O^{i}Pr)$_4$ at −78 °C



5 **6**

Entry	Aldehyde	Time (h)	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	Benzaldehyde (**5a**)	48	79	94	*S*
2	3-Phenoxybenzaldehyde (**5b**)	120	57 (76)	97	*S*
3	4-Methoxybenzaldehyde (**5c**)	120	53 (75)	97	*S*
4	2-Naphthaldehyde (**5d**)	120	76 (85)	96	*S*
5	(*E*)-Cinnamaldehyde (**5e**)	120	51 (80)	95	*S*
6	3-Phenylpropionaldehyde (**5f**)	120	62 (78)	98	*S*
7	2-Methylbenzaldehyde (**5g**)	120	68 (85)	97	*S*
8	Cyclohexanecarboxaldehyde (**5h**)	60	94	87	*S*
9	Valeraldehyde (**5i**)	30	96	89	*S*

[a] Numbers in parentheses are percent conversions.
[b] Determined by HPLC after being protected as a TBDMS ether (entry 1) or acetate (entries 2–9).
[c] Absolute configurations were determined by comparison of optical rotations with literature values.



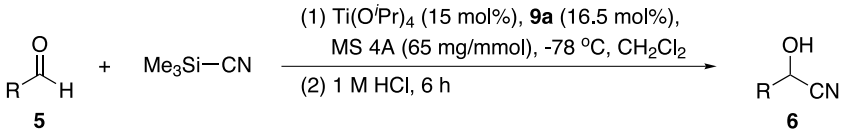
Scheme 2. Synthesis of ligands **9a** and **9b**.

from (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine **7a** in the same manner as described above for ligand **4a** (Scheme 2).

Excellent results were again obtained when the reaction was carried out under the optimum conditions (Table 3). The desired cyanohydrin was isolated with high enantioselectivity using both aromatic (>93% ee) and aliphatic aldehydes (>97% ee) as substrates. Compared to our former ligand **4a**, there is a pronounced enhancement of enantioselectivity in the reaction of aliphatic aldehydes (entries 8 and 9). At the same time, the chiral ligand **9a** was also recovered in high yield.

To ascertain the effect of the chirality of the diamide moiety of **9a** on the extent of enantioselectivity, compound **9b** lacking chirality in the diamide functionality was prepared from 1,2-phenylenediamine **7b** following the same procedure used for **9a**. Ligand **9b** was then employed as a constituent of a catalyst for the silylcyanation of benzaldehyde (Table 4). As expected, the enantioselectivity was significantly lower with a maximum of 61% ee under optimum reaction condition (entry 4). Apparently, chirality in the diamide moiety facilitates the higher

Table 3. Enantioselective addition of TMSCN to aldehydes catalyzed by **9a**/Ti(O^{i}Pr)$_4$ at −78 °C

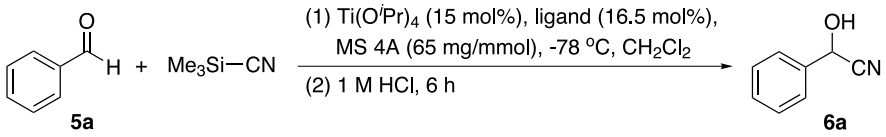


5 **6**

Entry	Aldehyde	Time (h)	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	Benzaldehyde (**5a**)	48	87	93	*S*
2	3-Phenoxybenzaldehyde (**5b**)	120	54 (78)	95	*S*
3	4-Methoxybenzaldehyde (**5c**)	120	47 (72)	99	*S*
4	2-Naphthaldehyde (**5d**)	120	67 (78)	99	*S*
5	(*E*)-Cinnamaldehyde (**5e**)	120	49 (74)	97	*S*
6	3-Phenylpropionaldehyde (**5f**)	120	61 (73)	97	*S*
7	2-Methylbenzaldehyde (**5g**)	120	56 (80)	94	*S*
8	Cyclohexanecarboxaldehyde (**5h**)	48	90	>99	*S*
9	Valeraldehyde (**5i**)	36	92	97	*S*

[a] Numbers in parentheses are percent conversions.
[b] Determined by HPLC after being protected as a TBDMS ether (entry 1) or acetate (entries 2–9).
[c] Absolute configurations were determined by comparison of optical rotations with literature values.

Table 4. Effect of the chirality of ligands on the extent of enantioselectivity



Entry	Ligand	Time (h)	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	**4a**	48	79	94	*S*
2	**4b**	48	77	4	*R*
3	**9a**	48	87	93	*S*
4	**9b**	60	89	61	*S*
5[d]	**3a**	36	73	0	—
6[d,e]	**10**	36	70	0	—
7[d,e]	**11**	36	61	0	—
8[d,e]	**12**	36	72	0	—
9[d]	**13**	24	76	13	*S*
10[d]	**14**	24	73	4	*S*

[a] Isolated yield.
[b] Determined by HPLC after being protected as a TBDMS ether.
[c] Absolute configurations were determined by comparison of optical rotations with literature values.
[d] Reactions were performed at −30 °C.
[e] 33 mol% of ligand was used.

enantioselectivity. Compound **3a** which bears two ketone functionalities instead of the two hydroxy groups of **4a** was also tested as a ligand for the silylcyanation of benzaldehyde. To our surprise, no enantioselectivity was found when ketoamide **3a** was used as the chiral ligand in this reaction (entry 5). We then studied cyclohexanediamides **10**,[37] **11**[38] and **12**[39] as chiral ligands in the same reaction (Fig. 1), but again there was no enantioselectivity under these conditions (entries 6–8). Such results suggested that the hydroxy groups of the chiral ligands play an important role in the construction of the chiral catalysts. A diamide moiety alone might not be efficient enough to coordinate to the titanium(IV) ion, thus no efficient chiral catalyst was generated and the silylcyanation reaction proceeded via a non-stereoselective route.

To further study the influence of ligand structure on the enantioselectivity of the silylcyanation of aldehydes, α-hydroxyamides **13** and **14** were prepared from (1*R*,2*R*)-1,2-diaminocyclohexane and (*R*)- or (*S*)-mandelic acid, respectively according to the literature procedure.[40] Enhancement of reactivity was observed when the titanium complex of either α-hydroxyamide **13** or **14** was used as catalyst for the reaction (entries 9–10). However, low enantioselectivities were obtained in both cases. The low enantioselectivity might result from the sterically less hindered phenyl group when compared to the bornane skeleton of ligands **4a** and **9a** and from the nature of the α- or β-hydroxyamides. More efforts will be needed to understand the nature of the catalysts.

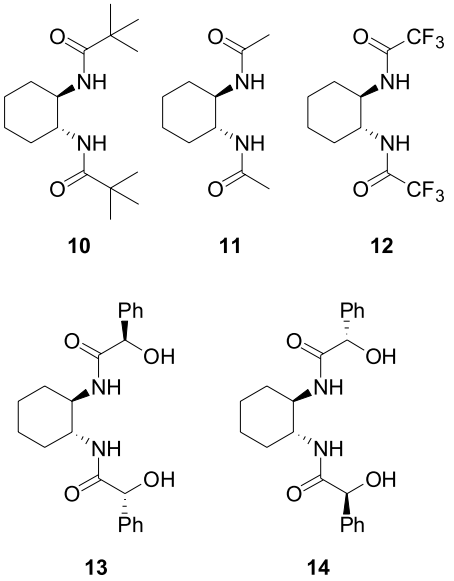


Figure 1.

3. Conclusions

In conclusion, an efficient catalyst for the asymmetric silylcyanation of both aromatic and aliphatic aldehydes with excellent enantioselectivity has been developed. The high degree of enantioselectivity coupled with the high stability and recoverability of chiral component **9a** of the catalyst constitutes a major improvement on existing methods.

4. Experimental

4.1. General

All melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were measured on Varian GEMINI-300, Varian UNITY-400 and Bruker AC-300 MHz NMR spectrometers. HPLC analyses were performed on a HITACHI L-6200 chromatograph fitted with a L-4200 UV detector and a Waters 410 RI detector. Chiracel OD column was purchased from Daicel Chemical Industries, Ltd. Optical rotations were measured with a DIP-1000 polarimeter.

4.2. Materials

CH_2Cl_2 was distilled from CaH_2. THF was distilled from

potassium. $Ti(O^iPr)_4$ and TMSCN were purchased from Aldrich.

4.3. Procedure for the synthesis of 3a and 3b

Ketopinic acid chloride (**1**) (20.1 g, 100 mmol) in CH_2Cl_2 (50 mL) was added to a stirred solution of triethylamine (7.2 g, 100 mmol) and racemic *trans*-1,2-diamino-cyclohexane (**2**) (5.7 g, 50 mmol) in CH_2Cl_2 (50 mL) at 0 °C over a 1 h period. The reaction was then allowed to come to room temperature and then stirred for an additional 1 h period. The reaction was then quenched by pouring into water (200 mL) and extracted with CH_2Cl_2. The organic phase was washed with brine, dried with Na_2SO_4, followed by evaporation and chromatographic separation (EtOAc/hexane=1/2) to give **3a** (9.9 g) and **3b** (9.8 g) (90%).

4.3.1. (1*R*,2*R*)-1,2-*N*,*N*′-Bis[(1*S*,4*R*)-7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptylcarboxyl]cyclohexyldiamine (3a). Mp 153.5–154.3 °C; $[\alpha]_D^{26}=+51.5$ (*c* 1.25, $CHCl_3$); IR (KBr) 3324, 1733, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 6H), 1.18 (s, 6H), 1.20–1.39 (m, 4H), 1.47–1.54 (m, 2H), 1.65–1.70 (brs, 4H), 1.90 (d, $J=20$ Hz, 2H), 2.01–2.10 (m, 6H), 2.40–2.49 (m, 4H), 3.76–3.81 (m, 2H), 7.43 (d, $J=8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.9 (C), 169.0 (C), 64.7 (C), 52.3 (CH), 49.7 (C), 43.6 (CH_2), 43.2 (CH), 32.6 (CH_2), 27.9 (CH_2), 27.4 (CH_2), 24.5 (CH_2), 20.7 (CH_3), 20.4 (CH_3); HRMS (M^+) calcd for $C_{26}H_{38}O_4N_2$ 442.2832, found 442.2846.

4.3.2. (1*S*,2*S*)-1,2-*N*,*N*′-Bis[(1*S*,4*R*)-7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptylcarboxyl]cyclohexyldiamine (3b). Mp 117.3–117.9 °C; $[\alpha]_D^{26}=+55.5$ (*c* 1.5, $CHCl_3$); IR (KBr) 3406, 3343, 3309, 1750, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 6H), 1.18 (s, 6H), 1.20–1.41 (m, 4H), 1.53–1.69 (m, 6H), 1.89 (d, $J=20$ Hz, 2H), 2.01 (t, $J=4$ Hz, 2H), 2.02–2.15 (m, 4H), 2.38–2.46 (m, 4H), 3.75 (brs, 2H), 7.63 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.0 (C), 169.4 (C), 64.7 (C), 52.3 (CH), 49.9 (C), 43.7 (CH_2), 43.2 (CH), 32.1 (CH_2), 28.3 (CH_2), 27.5 (CH_2), 24.3 (CH_2), 20.7 (CH_3), 20.5 (CH_3); HRMS (M^+) calcd for $C_{26}H_{38}O_4N_2$ 442.2832, found 442.2817.

4.4. Procedure for the synthesis of 4a and 4b

To a solution of **3a** or **3b** (4 mmol) in THF (5 mL) at −78 °C was added 1 M L-selectride® in THF (18.0 mL) dropwise. The reaction mixture was stirred at −78 °C for 1 h followed by 2 h at room temperature, then cooled to 0 °C and quenched by the successive addition of H_2O (4.0 mL), EtOH (12 mL), 3 M aq. NaOH (16 mL), followed by the dropwise addition of 30% aq. H_2O_2 (12 mL) over a 30 min period. The aqueous phase was saturated with K_2CO_3 and extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4, and filtered. Evaporation of solvent followed by crystallization (EtOAc/hexane=1/5) from the organic phase gave **4a** (95%) or **4b** (96%).

4.4.1. (1*R*,2*R*)-1,2-*N*,*N*′-Bis[(1*S*,2*R*,4*R*)-7,7,-dimethyl-2-hydroxy-bicyclo[2.2.1]heptylcarboxyl]cyclohexyl-diamine (4a). Mp 208.2–208.3 °C; $[\alpha]_D^{26}=-55.3$ (*c* 1.0, $CHCl_3$); IR (KBr) 3328, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (s, 6H), 0.90–1.02 (m, 4H), 1.14 (s, 6H), 1.16–1.40 (m, 4H), 1.67–1.95 (m, 12H), 2.30–2.38 (m, 2H), 3.70–3.76 (m, 4H), 5.20 (d, $J=6$ Hz, 2H), 6.89 (d, $J=9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7 (C), 77.4 (CH), 58.4 (C), 53.4 (CH), 49.5 (CH), 45.5 (CH), 41.0 (CH_2), 32.4 (CH_2), 29.0 (CH_2), 26.3 (CH_2), 24.9 (CH_2), 21.0 (CH_3), 20.9 (CH_3); HRMS (M^+) calcd for $C_{26}H_{42}O_4N_2$ 446.3145, found 446.3136.

4.4.2. (1*S*,2*S*)-1,2-*N*,*N*′-Bis[(1*S*,2*R*,4*R*)-7,7,-dimethyl-2-hydroxy-bicyclo[2.2.1]heptylcarboxyl]cyclohexyl-diamine (4b). Mp 224.8–225.4 °C; $[\alpha]_D^{26}=-17.8$ (*c* 1.0, $CHCl_3$); IR (KBr) 3367, 3319, 1626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 6H), 1.21 (s, 6H), 1.09–1.40 (m, 6H), 1.60–1.93 (m, 14H), 2.04 (d, $J=12$ Hz, 2H), 3.72 (brs, 2H), 3.96 (dt, $J=3$, 3 Hz, 2H), 5.14 (d, $J=1.5$ Hz, 2H), 6.71 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (C), 78.0 (C), 56.7 (C), 53.3 (CH), 49.8 (CH), 45.6 (CH), 40.8 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 27.4 (CH_2), 24.6 (CH_2), 21.8 (CH_3), 20.8 (CH_3); HRMS (M^+) calcd for $C_{26}H_{42}O_4N_2$ 446.3145, found 446.3115.

4.5. Procedure for the synthesis of 8a and 8b

Ketopinic acid chloride (**1**) (20.1 g, 100 mmol) in CH_2Cl_2 (200 mL) was added to a stirred solution of triethylamine (7.2 g, 100 mmol) and the appropriate diamine (**7a** or **7b**) (50 mmol) in CH_2Cl_2 (50 mL) at 0 °C over a 1 h period. The reaction was then allowed to warm to room temperature and then stirred for an additional 1 h period. The reaction was then quenched by pouring into water (100 mL) and extracted with dichloromethane (2×200 mL). The organic phase was washed with brine (2×200 mL), dried (Na_2SO_4) and concentrated. The residue was purified by passing through a silica column eluting with EtOAc/hexane (1/3 for **8a** and 1/2 for **8b**) to provide **8a** (93%) or **8b** (95%) as a white solid.

4.5.1. (1*R*,2*R*)-1,2-*N*,*N*′-Bis[(1*S*,4*R*)-7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptylcarboxyl]diphenylethylenediamine (8a). Mp 243.5–244.3 °C; $[\alpha]_D^{24}=+39.9$ (*c* 1.46, $CHCl_3$); IR (KBr) 3346, 1740, 1664, 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (s, 6H), 1.11 (s, 6H), 1.34–1.35 (m, 2H), 1.48–1.55 (m, 2H), 1.92–2.08 (m, 6H), 2.36–2.51 (m, 4H), 5.41 (dd, $J=2.0$, 6.0 Hz, 2H), 7.05–7.08 (m, 4H), 7.12–7.19 (m, 6H), 8.41 (d, $J=6.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.9 (C), 168.8 (C), 138.8 (C), 127.9 (2CH), 127.1 (3CH), 64.3 (C), 57.2 (CH), 49.9 (C), 43.5 (CH_2), 43.1 (CH), 28.3 (CH_2), 27.5 (CH_2), 20.6 (CH_3), 20.1 (CH_3); HRMS (M^+) calcd for $C_{34}H_{41}O_4N_2$: 541.2988($M+1$), found 541.3066.

4.5.2. 1,2-*N*,*N*′-Bis[(1*S*,4*R*)-7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptylcarboxyl]phenyldiamine (8b). Mp 136.3–136.8 °C; $[\alpha]_D^{26}=+29.0$ (*c* 1.0, $CHCl_3$); IR (KBr) 3282, 2968, 1730, 1683, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 6H), 1.28 (s, 6H), 1.40–1.49 (m, 2H), 1.74–1.83 (m, 2H), 1.96 (s, 1H), 2.02 (s, 1H), 2.07–2.18 (m, 4H), 2.50–2.65 (m, 4H), 7.12–7.15 (m, 2H), 7.69–7.72 (m, 2H), 9.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.0 (C), 168.2 (C), 129.9 (C), 125.6 (CH), 124.8 (CH), 65.2 (C), 50.4 (C), 43.7 (CH_2), 43.4 (CH), 28.8 (CH_2), 27.7 (CH_2), 20.9 (CH_3), 20.5 (CH_3); HRMS (M^+) calcd for $C_{26}H_{32}N_2O_4$: 436.2362, found 436.2358.

4.6. Procedure for the synthesis of 9a and 9b

To a solution of **8a** or **8b** (4 mmol) in THF (5 mL) at −78 °C was added 1 M L-selectride® in THF (18.0 mL) dropwise. The reaction mixture was stirred at −78 °C for 1 h, followed by 2 h at room temperature, then cooled to 0 °C and quenched by the successive addition of H_2O (4.0 mL), EtOH (12 mL), 3 M aq. NaOH (16 mL), followed by the dropwise addition of 30% aq. H_2O_2 (12 mL) over a 30 min period. The aqueous phase was saturated with K_2CO_3 and extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4, and filtered. Evaporation of solvent followed by crystallization (EtOAc/hexane = 1/5) from the organic phase gave **9a** (95%) or **9b** (96%).

4.6.1. (1*R*,2*R*)-1,2-*N*,*N*′-Bis[(1*S*,2*R*,4*R*)-7,7,-dimethyl-2-hydroxy-bicyclo[2.2.1]heptylcarboxyl]diphenylethylenediamine (9a). Mp 259.7–260.5 °C; $[\alpha]_D^{24} = -222.8$ (*c* 1.00, $CHCl_3$); IR (KBr) 3366, 2936, 1642, 1545, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.78 (s, 6H), 0.94 (s, 6H), 1.02–1.10 (m, 4H), 1.68–1.75 (m, 4H), 1.84–1.97 (m, 4H), 2.38–2.49 (m, 2H), 3.86–3.89 (m, 2H), 5.27 (dd, J = 7.2, 2.6 Hz, 2H), 5.38–5.40 (m, 2H), 7.00–7.03 (m, 4H), 7.12–7.17 (m, 6H), 7.86 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (C), 137.9 (C), 128.4 (2CH), 127.5 (CH), 126.9 (2CH), 77.2 (CH), 59.2 (CH), 58.3 (C), 49.9 (C), 45.2 (CH), 40.9 (CH_2), 28.8 (CH_2), 26.3 (CH_2), 20.6 (CH_3), 20.5 (CH_3); HRMS calcd for $C_{34}H_{44}O_4N_2$: 544.3301, found 544.3301.

4.6.2. 1,2-*N*,*N*′-Bis[(1*S*,2*R*,4*R*)-7,7,-dimethyl-2-hydroxy-bicyclo[2.2.1]heptylcarboxyl]phenyldiamine (9b). Mp 121.1–121.3 °C; $[\alpha]_D^{26} = +4.68$ (*c* 0.52, $CHCl_3$); IR (KBr) 3422, 2940, 1659, 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.08–1.14 (m, 2H), 1.22–1.26 (m, 2H), 1.28 (s, 6H), 1.80–2.03 (m, 8H), 2.28–2.35 (m, 2H), 4.06–4.08 (m, 2H), 4.49 (br, 2H), 7.19–7.21 (m, 2H), 7.42–7.45 (m, 2H), 9.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (C), 130.5 (C), 126.0 (CH), 125.6 (CH), 77.3 (CH), 58.0 (C), 50.5 (C), 45.6 (CH), 41.7 (CH_2), 30.0 (CH_2), 27.2 (CH_2), 21.5 (CH_3), 20.7 (CH_3); HRMS calcd for $C_{26}H_{36}N_2O_4$: 440.2675, found 440.2666.

4.7. General procedure for enantioselective trimethylsilylcyanation of aldehydes

To a stirred solution of compound **9a** (0.180 g, 0.33 mmol) and 4 Å molecular sieves (powder, 130 mg) in dichloromethane (5 mL) was added titanium tetraisopropoxide (0.09 mL, 0.3 mmol) under Ar at room temperature and the mixture was stirred for 1 h. Trimethylsilyl cyanide (0.45 mL, 3.5 mmol) was added to the reaction mixture and stirred for an additional 0.5 h. Then, the reaction mixture was cooled to −78 °C and aldehyde **5** (2 mmol) was added to the reaction mixture. The disappearance of the aldehyde was monitored by thin layer chromatography (EtOAc/hexane = 1/5). The reaction mixture was quenched with 1 M HCl (20 mL) and stirred vigorously at room temperature for 6 h. After being filtered, the mixture was extracted with dichloromethane (5×5 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$, then concentrated in vacuo. The residue was distilled under reduced pressure (100 °C/0.3 mmHg) or purified by column chromatography to afford the corresponding (*S*)-cyanohydrin **6**. Compound **9a** was recovered in 80–92% yield through column chromatography purification of the remaining residue.

4.8. Determination of enantiomeric excess (ee) of the cyanohydrin

Method A (*for 2-hydroxy-2-phenylacetonitrile*, **6a**). The ee of the cyanohydrin was determined by HPLC analysis of the corresponding TBDMS ether (detected by UV detector at 254 nm). The required TBDMS ether was prepared by the following procedure:[27] To a CH_2Cl_2 (2 mL) solution of cyanohydrin (10 mg) was added TBDMSOTf (30 μL) and 2,6-lutidine (30 μL) at 0 °C. The mixture was stirred at room temperature for 1 h, poured into water (5 mL) and extracted with CH_2Cl_2 (2×5 mL). The combined extracts were washed with brine (2×5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatographic separation on a silica gel column (EtOAc/hexane = 1/30) to afford the corresponding TBDMS ether.

Method B (*for other cyanohydrins*, **6b–i**). The ee for the other cyanohydrins was determined by HPLC analysis of the corresponding cyanohydrin acetate (detected by UV detector at 254 nm for **6b–g** and RI detector for **6h–i**) prepared by the following procedure:[41] To a $CHCl_3$ (2 mL) solution of cyanohydrin (10 mg) was added acetyl chloride (0.5 mL) and pyridine (0.1 mL) at 23 °C. The mixture was stirred at 23 °C for 1 h after which it was poured into water (5 mL) and extracted with chloroform (2×5 mL). The combined extracts were washed with brine (2×10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/30) to afford the corresponding cyanohydrin acetate.

4.8.1. 2-Hydroxy-2-phenylacetonitrile (6a). Crude product was purified by bulb-to-bulb distillation (100 °C/0.3 mmHg) to give *S*-enriched product (87%); IR (neat) 3430, 2260, 1700, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.90 (brs, 1H), 5.55 (s, 1H), 7.4–7.6 (m, 5H). The product was determined as 93% ee by HPLC analysis of its *tert*-butyl dimethylsilylether. The t_R of the *R*-isomer is 6.12 min and that of the *S* isomer is 8.02 min [hexane/isopropanol (100/0.25), 1.0 mL/min].

4.8.2. 2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile (6b). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane = 2/1/6) to give *S*-enriched product [54% (78% conversion)]; IR (neat) 3430, 3070, 2250, 1690, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.6 (brs, 1H), 5.47 (s, 1H), 7.0–7.4 (m, 9H). The product was determined as 95% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 18.26 min and that of the *R*-isomer is 26.12 min [hexane/isopropanol (97.5/2.5), 1.0 mL/min].

4.8.3. 2-Hydroxy-2-(4-methoxyphenyl)acetonitrile (6c). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane = 2/1/6) to give *S*-enriched product [47% (72% conversion)]; IR (neat) 3430, 3010, 2250, 1710, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.7 (brs, 1H), 3.84 (s, 3H), 5.49 (s, 1H), 6.96 (d, J = 8.5 Hz, 2H), 7.46

(d, J=8.5 Hz, 2H). The product was determined as 99% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 12.12 min and that of the *R*-isomer is 10.66 min [hexane/isopropanol (95/5), 1.0 mL/min].

4.8.4. 2-Hydroxy-2-naphthylacetonitrile (6d). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane=2/1/6) to give *S*-enriched product [67% (78% conversion)]; IR (neat) 3480, 3060, 2250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.01 (brs, 1H), 5.70 (s, 1H), 7.50–7.60 (m, 3H), 7.80–8.00 (m, 3H), 8.05 (s, 1H). The product was determined as 99% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 12.32 min and that of the *R*-isomer is 14.62 min [hexane/isopropanol/acetonitrile (40/1/1), 1.0 mL/min].

4.8.5. (*E*)-2-Hydroxy-4-phenyl-3-butenenitrile (6e). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane=2/1/6) to give *S*-enriched product [49% (74% conversion)]; IR (neat) 3370, 3030, 2250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.7 (brs, 1H), 5.16 (dd, J=5.7, 1.1 Hz, 1H), 6.25 (dd, J=15.8, 5.7 Hz, 1H), 6.93 (dd, J=15.8, 1.1 Hz, 1H), 7.3–7.5 (m, 5H). The product was determined as 97% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 14.56 min and that of the *R*-isomer is 18.79 min [hexane/isopropanol/acetonitrile (40/1/1), 1.0 mL/min].

4.8.6. 2-Hydroxy-4-phenylbutanenitrile (6f). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane=2/1/6) to give *S*-enriched product [61% (73% conversion)]; IR (neat) 3430, 3050, 2250, 1720, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.0–2.20 (m, 2H), 2.80–2.90 (m, 2H), 4.10 (brs, 1H), 4.43 (t, J= 6.7 Hz, 1H), 7.20–7.40 (m, 5H). The product was determined as 97% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 13.18 min and that of the *R*-isomer is 17.36 min [hexane/isopropanol/acetonitrile (40/1/1), 1.0 mL/min].

4.8.7. 2-Hydroxy-2-(2-methylphenyl)acetonitrile (6g). Crude product was purified by column chromatography (EtOAc/acetonitrile/hexane=2/1/6) to give *S*-enriched product [56% (80% conversion)]; IR (neat) 3400, 3070, 2250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.80 (brs, 1H), 5.65 (s, 1H), 7.21–7.32 (m, 3H), 7.59 (d, J= 6 Hz, 1H). The product was determined as 94% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 19.14 min and that of the *R*-isomer is 21.64 min [hexane/EtOAc (60/1), 1.0 mL/min].

4.8.8. 2-Cyclohexyl-2-hydroxyacetonitrile (6h). Crude product was purified by bulb-to-bulb distillation (120 °C/0.6 mmHg) to give *S*-enriched product (90%); IR (neat) 3450, 2250, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.0–1.40 (m, 5H), 1.60–2.0 (m, 6H), 2.80 (brs, 1H), 4.27 (d, J=6.1 Hz, 1H). The product was determined as >99% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 7.32 min and that of the *R*-isomer is 6.62 min [hexane/isopropanol (60/1), 1.0 mL/min].

4.8.9. 2-Hydroxyhexanenitrile (6i). Crude product was purified by bulb-to-bulb distillation (80 °C/0.6 mmHg) to give *S*-enriched product (92%); IR 3430, 2250, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J=6.0 Hz, 3H), 1.32–1.51 (m, 4H), 1.78–1.86 (m, 2H), 2.92 (brs, 1H), 4.45 (t, J=6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.2 (C), 61.0 (CH), 34.6 (CH_2), 26.5 (CH_2), 21.9 (CH_2), 13.6 (CH_3); HRMS (M^+) calcd for $C_6H_{11}NO$: 113.0841, found 113.0837. The product was determined as 97% ee by HPLC analysis of its acetate. The t_R of the *S*-isomer is 7.09 min and that of the *R*-isomer is 6.45 min [hexane/isopropanol (60/1), 1.0 mL/min].

Acknowledgements

We are grateful to the National Science Council, Republic of China, for the financial support of this work.

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