#### Tetrahedron: Asymmetry 21 (2010) 2834-2840

Contents lists available at ScienceDirect

Tetrahedron: Asymmetry

journal homepage: www.elsevier.com/locate/tetasy

### Chiral linear polymers bonded alternatively with salen and 1,4-dialkoxybenzene: synthesis and application for Ti-catalyzed asymmetric TMSCN addition to aldehydes

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#### ARTICLE INFO

Article history: Received 20 October 2010 Accepted 25 November 2010 Available online 20 December 2010

#### ABSTRACT

The synthesis of chiral linear polymers **1a–b** having salen and 1,4-dioctyloxybenzene as alternate segments has been accomplished. The GPC analysis showed the molecular weights corresponding to ca. 15 ( $M_w = 10,999$ ,  $M_n = 9165$  and PDI = 1.20) repeating units for **1a** and ca. 8 ( $M_w = 8547$ ,  $M_n = 7883$  and PDI = 1.08) repeating units for **1b**. Polymers **1a–b** have been studied with Ti(O<sup>i</sup>Pr)<sub>4</sub> as a recyclable catalyst for the asymmetric addition of TMSCN to aldehydes while the selectivity of the polymer catalyst is identical to that of the monomer. The reactions are efficient affording the cyanohydrins with up to 88% ee. The selectivity of the polymer based catalyst **9a** is found to be the same to that of the monomer **10a**. The reaction provides the advantages of simplified product isolation and easy recovery and recyclability of polymer catalyst **9a** without any loss of activity or selectivity.

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#### 1. Introduction

The application of chiral macromolecular catalysts in asymmetric synthesis has attracted extensive attention,<sup>1</sup> because they provide the advantages of simplified product isolation, easy recovery, and recyclability of the generally quite expensive chiral catalysts and potential use for continuous production. Chiral macromolecular catalysts can be divided into three classes: (i) polymer anchored chiral catalysts;<sup>2</sup> (ii) chiral dendritic catalysts;<sup>3</sup> and (iii) chiral main chain polymer catalysts.<sup>4</sup> Among these, the last have the advantages of bearing more reactive sites along with the preservation of the microenvironment of the reactive centers which is crucial for the selectivity of the reaction. Herein we report the synthesis and application of new chiral linear polymers **1a–b** bonded alternatively with salen<sup>5</sup> and 1,4-dioctyloxybenzene for the Ti-catalyzed asymmetric TMSCN addition to aldehydes.

#### 2. Results and discussion

The synthesis of 2,5-dioctyloxyphenyldiboronic acid **4** is shown in Scheme 1. The reaction of hydroxyquinone **2** with 1-bromooctane gave 1,4-dioctyloxybenzene in the presence of  $K_2CO_3$  in 80% yield which could be brominated using  $Br_2$  to afford 1,4-dibromo-2,5-dioctyloxybenzene **3** in 90% yield. Compound **3** was reacted with 2.3 equiv of *n*-BuLi followed by 2.5 equiv of trimethylborate

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to give tetramethyl 2,5-dioctyloxyphenyldiboronate, which could be hydrolyzed using 2 N HCl to provide conjugate segment **4** in 80% yield (Scheme 1).<sup>6</sup>



**Scheme 1.** Reagents and conditions: (i)  $C_8H_{17}Br$  (2.5 equiv),  $K_2CO_3$  (2.5 equiv), EtOH, 70 °C, 24 h, 80%; (ii)  $Br_2$ , CHCl<sub>3</sub>, rt, 27 h, 90%; (iii) *n*-BuLi (2.3 equiv), B(OMe)<sub>3</sub> (2.5 equiv), Et<sub>2</sub>O, -20 °C to rt, 12 h, 2 M HCl, rt, 0.5 h, 80%.

The synthesis of aldehyde **7** was next accomplished. Iodination of 3-*tert*-butyl-2-hydroxybenzaldehyde **5** with iodinemonochloride in CH<sub>3</sub>COOH provided 3-*tert*-butyl-2-hydroxy-5-iodobenzaldehyde<sup>7</sup> **6** in 97% yield which could be C–C cross-coupled with **4** using Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> to give the target molecule **7** in 70% yield (Scheme 2).



**Scheme 2.** Reagents and conditions: (i) ICl (1.5 equiv), AcOH, 120 °C, 5 h, 97%; (ii) 3-*tert*-butyl-2-hydroxy-5-iodobenzaldehyde (2.1 equiv),  $Pd(PPh_3)_2Cl_2$  (3 mol %), PPh<sub>3</sub> (9 mol %),  $Cs_2CO_3$  (3 equiv), THF, 60 °C, 24 h, 70%.



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Scheme 3. Synthesis of polymer 1a. Reagents and conditions: (i) 7, CHCl<sub>3</sub>, 45 °C, 5 h, 97%.



Scheme 4. Synthesis of polymer 1b. Reagents and conditions: (i) 7, CHCl<sub>3</sub>, 45 °C, 5 h, 93%.



Figure 1. UV-vis spectra of polymers 1a-b in CHCl<sub>3</sub>.

The synthesis of polymers **1a–b** was then carried out by condensation of **7** with chiral (1*R*,2*R*)-diaminocyclohexane **8a** and (1*R*,2*R*)diphenylethylenediamine **8b** in CHCl<sub>3</sub> (Schemes 3 and 4). The reactions proceeded smoothly to afford polymers **1a–b** in 93–97% yield. Polymers **1a–b** were soluble in common organic solvents, such as THF, CHCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, and toluene. The GPC analysis, with polystyrene as the internal standard and THF as the eluent, exhibited their average molecular weights that corresponded to ca. 15 repeating units for **1a** ( $M_w$  = 10,999,  $M_n$  = 9165 and PDI = 1.20) and ca. 8 repeating units for **1b** ( $M_w$  = 8547,  $M_n$  = 7883 and PDI = 1.08). The <sup>1</sup>H NMR spectra recorded at 400 MHz were consistent with their structure. The UV–vis spectra of the CHCl<sub>3</sub> solutions of **1a–b** exhibited maximum absorptions ( $\lambda_{max}$ ) at 323, 255, and 323, 266 nm, respectively (Fig. 1).



To study their application for asymmetric catalysis, the polymers **1a–b** were reacted with  $Ti(O^iPr)_4$  to afford a Ti–polymer complex **9a–b** as dark yellow solids (Scheme 5).<sup>8</sup> Their catalytic activities were compared in the TMSCN addition to aldehydes (Table 1).<sup>8,9</sup> The reaction conditions were optimized with *p*-methoxy-benzaldehyde as a model substrate. As anticipated, the reaction occurred efficiently with 1 mol % of **9a–b** (with respect to the repeating unit) to afford the desired cyanohydrin with up to 78% ee. The selectivity was similar to that of the monomer catalyst **10a**. Polymer catalyst **9a** was found to be superior to **9b**. The effect of temperature was studied and 0 °C afforded the best results. It was seen that CHCl<sub>3</sub> was the solvent of choice, whereas CH<sub>2</sub>Cl<sub>2</sub>, THF, and toluene gave inferior results. Control experiments confirmed that without Ti, no reaction occurred.

Using the optimized conditions, the scope of the procedure was further explored (Table 2). The reactions of the aryl aldehydes with 2-Br, 2-Cl, 2-OCH<sub>3</sub>, 2-OC<sub>2</sub>H<sub>5</sub>, 2-OC<sub>3</sub>H<sub>5</sub>, 3-Br, and 4-CH<sub>3</sub> substituents were studied. The substrates readily proceeded to react with TMSCN to give the corresponding cyanohydrins with up to 88% ee. Likewise, 2-naphthaldehyde underwent reaction with TMSCN to give the respective cyanohydrin in 90% yield and 74% ee, while



Scheme 5. Synthesis of chiral Ti-polymer complexes 9a-b.

Table 1

Optimization of the reaction conditions



_							
_	Entry	Catalyst	Solvent	Temp. (°C)	Yield (%) <sup>a,b</sup>	ee (%) <sup>c</sup>	Config. <sup>d</sup>
	1	9a	CHCl <sub>3</sub>	0	95	78	(S)
	2	9b	CHCl <sub>3</sub>	0	90	43	(S)
	3	9a	$CH_2Cl_2$	0	90	43	(S)
	4	9a	THF	0	Trace	-	_
	5	9a	Toluene	0	70	16	(S)
	6	9a	CHCl <sub>3</sub>	-5	90	72	(S)
	7	9a	CHCl <sub>3</sub>	25	95	43	(S)
	8	10a	CHCl <sub>3</sub>	0	97	76	(S)
	9	1a	CHCl <sub>3</sub>	0	n.r.	-	-

n.r. = no reaction.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by HPLC analysis of the acetyl derivative of the cyanohydrin with a Chiralcel OD-H column using 99:1 *n*-hexane/2-propanol.

<sup>d</sup> Determined by the sign of the specific rotation.

the aliphatic aldehydes, propanal, isobutanal, and crotonal reacted with TMSCN to afford the corresponding cyanohydrins in 90–95% yield and 40–66% ee.

The advantage of this system is that catalyst **9a** can be recovered and recycled (Table 3). After completion, the reaction mixture was concentrated (ca. 0.5 mL) and the resultant solution was treated with MeOH (ca. 0.5 mL). The precipitated out Ti–polymer catalyst **9a** precipitate was filtered, dried, and reused for a fresh reaction of *p*-methoxybenzaldehyde with TMSCN. This process was repeated for three runs and the reactions occured to afford the target cyanohydrin with 93–95% yield and 78% ee. These results clearly suggest that the catalyst **9a** can be recycled without a loss of activity or selectivity.

#### 3. Conclusions

In conclusion, the synthesis and application of chiral linear polymers 1a-b with  $Ti(O'Pr)_4$  have been described for cyanohydrin synthesis. The system provides the advantages of simplified product isolation, and easy recovery and recyclability of the polymer catalyst **9a**. Further exploration of this procedure for other potential reactions and the mechanism is currently pursued.

#### 4. Experimental section

#### 4.1. General

TMSCN (98%) and aldehydes were purchased from Aldrich. Ti(O<sup>i</sup>Pr) (98%) was procured from Acros Organics. Solvents were purchased from Rankem and purified prior to use by standard procedure.<sup>10</sup> Column chromatography was carried out with Rankem 60–120 mesh silica gel. Analytical TLC was performed with Rankem silica gel G and GF 254 plates. NMR spectra (400 MHz for <sup>1</sup>H and 100 MHz for <sup>13</sup>C) were recorded using a DRX-400 Varian spectrometer using CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> as solvent and Me<sub>4</sub>Si as an internal standard. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were obtained using Perkin–Elmer spectrum one spectrometer. UV–vis spectra were recorded using Perkin–Elmer Lambda 25 UV/vis spectrometer. GPC analysis was performed on Waters-2414 with stationary phase column Styragel<sup>®</sup> WAT044221 using polystyrene as an internal standard and THF as eluent. HPLC analysis was carried out for acetylated cyanohydrin using Waters-2489 with Daicel Chiralcel OD-H column and for benzoylated cyanohydrin using Waters-2489 with Daicel Chiralcel OJ column. Elemental analysis was carried out using a Perkin–Elmer-2400 CHNS analyzer.

#### 4.2. 2,5-Dioctyloxyphenyldiboronic acid 4<sup>6</sup>

At first, *n*-BuLi (11.5 mL, 2.0 M in cyclohexane) was added to a stirred solution of 1,4-dibromo-2,5-dioctyloxybenzene 3 (10 mmol, 4.92 g) in dry  $Et_2O$  (40 mL) at -20 °C under nitrogen atmosphere. After 1 h, trimethylborate (25 mmol, 2.8 mL) was added and the mixture was allowed to warm up to room temperature after which stirring was continued for an additional 12 h. The reaction mixture was then treated with 2 M HCl (25 mL) and the precipitate was collected by filtration and washed successively with water (10 mL) and Et<sub>2</sub>O (20 mL) to give 4 as a colorless solid in 80% (3.37 g) yield. Mp 140 °C, <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$ 7.79 (s, 4H), 7.16 (s, 2H), 3.97 (t, J = 6.4 Hz, 4H), 1.70 (t, J = 7.4 Hz, 4H), 1.38–1.24 (m, 20H), 0.84 (t, J = 6.6 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) & 156.9, 124.5, 118.0, 68.4, 31.1, 28.7, 28.65, 28.59, 25.4, 22.1, 13.9; FT-IR (KBr) 3498, 3362, 2941, 2921, 2870, 2852, 1495, 1470, 1417, 1389, 1299, 1272, 1205, 1127, 1083, 1049, 1002, 887, 804, 722, 652, 566 cm<sup>-1</sup>. Anal. Calcd for C<sub>22</sub>H<sub>40</sub>B<sub>2</sub>O<sub>6</sub>: C, 62.59; H, 9.55. Found: C, 62.55; H, 9.59.

#### 4.3. 3-tert-Butyl-2-hydroxy-5-iodobenzaldehyde 6<sup>7</sup>

To a stirred solution of 3-tert-butyl-2-hydroxybenzalde-hyde 5 (10 mmol, 1.78 g) in glacial CH<sub>3</sub>COOH (15 mL) at room temperature, iodinemonochloride (15 mmol, 2.43 g) in glacial CH<sub>3</sub>COOH (7 mL) was added drop wise. Next, the mixture was refluxed for 5 h, cooled to room temperature, and treated with CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and water (15 mL). The organic layer was separated and washed with brine (10 mL) and water ( $2 \times 10$  mL). Drying  $(Na_2SO_4)$  and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to give 6 as a pale yellow solid in 97% (2.95 g) yield. Mp 55 °C, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  11.72 (s, 1H), 9.78 (s, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.68 (t, *J* = 2 Hz, 2H), 1.37 (s, 9H);  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  195.9, 160.9, 142.6, 141.4, 140.1, 122.6, 80.8, 35.1, 29.2; FT-IR (KBr) 3435, 3088, 2963, 2871, 2728, 1651, 1599, 1475, 1434, 1413, 1350, 1303,1269, 1196, 1163, 1024, 930, 769, 756, 704, 559, 512 cm<sup>-1</sup>. Anal. Calcd for C<sub>11</sub>H<sub>13</sub>IO<sub>2</sub>: C, 43.44; H, 4.31. Found: C, 43.47; H, 4.32.

#### 4.4. Preparation of dialdehyde 7

To a stirred solution of aldehyde 6 (5.25 mmol, 1.6 g), 2,5-dioctyloxyphenyldiboronic acid **4** (2.5 mmol, 1.05 g) and Cs<sub>2</sub>CO<sub>3</sub> (7.5 mmol, 2.4 g) in THF (30 mL) under a nitrogen atmosphere was added Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (3 mol %) and PPh<sub>3</sub> (9 mol %), and the mixture was stirred at 60 °C for 24 h. The solvent was evaporated and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and washed with brine (5 mL) and water  $(2 \times 10 \text{ mL})$ . Drying  $(Na_2SO_4)$  and evaporation of the solvent gave a solid that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to give 7 as a pale yellow solid in 70% (1.21 g) yield. Mp 194 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  11.80 (s, 2H), 9.91 (s, 2H), 7.81 (d, J = 2 Hz, 2H), 7.59 (d, *I* = 2 Hz, 2H), 6.94 (s, 2H), 3.94 (t, *I* = 6.4 Hz, 4H), 1.70-1.66 (m, 4H), 1.45 (s, 18H), 1.34-1.21 (m, 20H), 0.85 (t, I = 6.8 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  197.5, 160.6, 150.4, 137.8, 136.1, 132.6, 129.7, 129.5, 120.6, 115.7, 69.7, 35.2, 31.9, 29.7, 29.53, 29.48, 29.43, 26.4, 22.8, 14.3; FT-IR (KBr) 3433, 2930,

 $<sup>^</sup>a\,$  p-Methoxybenzaldehyde (1 mmol), catalyst (1 mol % with respect to monomeric unit), TMSCN (2 mmol) and solvent (3 mL) were stirred for 48 h under an  $N_2$  atmosphere.

Table 2
Chiral poly-Ti 9a catalyzed TMSCN addition to aldehydes

Entry	Aldehyde	Product	Yield <sup>a,b</sup> (%)	ee <sup>c</sup> (%)	Config. <sup>d</sup>
1	CHO Br		95	50	n.d.
2	CHO	OH CI	97	60	(S)
3	CHO OCH3	OH CN OCH3	95	88	(S)
4	CHO OC <sub>2</sub> H <sub>5</sub>	OH CN OC <sub>2</sub> H <sub>5</sub>	91	78	n.d.
5	CHO OC <sub>3</sub> H <sub>5</sub>	OH CN OC <sub>3</sub> H <sub>5</sub>	90	75	n.d.
6	CHO Br	OH CN Br	90	75	n.d.
7	H <sub>3</sub> CO CHO	H <sub>3</sub> CO	97	78	(S)
8	H <sub>3</sub> C CHO	OH H <sub>3</sub> C	97	68	(S)
9	CHO	OH	90	74	(S)
10	H <sub>3</sub> C CHO		95 <sup>e</sup>	40 <sup>f</sup>	n.d.
11	Н₃С Н₃С	H <sub>3</sub> C OH H <sub>3</sub> C CN	90 <sup>e</sup>	66 <sup>f</sup>	(S)
12	H <sub>3</sub> C CHO		93	55 <sup>f</sup>	(S)

<sup>a</sup> Aldehyde (0.5 mmol), TMSCN (1 mmol), and **9a** (1 mol % with respect to monomeric unit) were stirred at 0 °C for 48 h in CHCl<sub>3</sub> (1.5 mL) under an N<sub>2</sub> atmosphere.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by HPLC analysis of the acetyl derivative of the cyanohydrin using a Chiralcel OD-H column with 99:1 *n*-hexane/2-propanol.

<sup>d</sup> Determined by the sign of the specific rotation.

<sup>e</sup> Reaction carried out on a 2.0 mmol scale of the aldehyde.

<sup>f</sup> Determined by HPLC analysis of the benzoyl derivative of the cyanohydrin using a Chiralcel OJ column with 90:10 *n*-hexane/2-propanol.

2857, 1643, 1514, 1441, 1388, 1366, 1322, 1266, 1234, 1221, 1210, 1168, 1087, 1023, 960, 876, 783, 736, 709, 521 cm<sup>-1</sup>. Anal. Calcd for C<sub>44</sub>H<sub>62</sub>O<sub>6</sub>: C, 76.93; H, 9.10. Found: C, 76.97; H, 9.07.

#### 4.5. Synthesis of polymers 1a-b

#### 4.5.1. Polymer 1a

To a solution of **7** (0.23 mmol, 158 mg) in CHCl<sub>3</sub> (2 mL) was added (1*R*,2*R*)-diaminocyclohexane **8a** (0.23 mmol, 27 mg). The mixture was stirred at 45 °C for 5 h and cooled to room temperature. Next, MeOH was added and the precipitate **1a** was collected by filtration as a yellow powder in 97% (171 mg) yield. GPC:  $M_{\rm w}$  = 10,999,  $M_{\rm n}$  = 9165 (PDI 1.20); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.39 (s, 2H), 7.56 (s, 2H), 7.24 (s, 2H), 6.85 (s, 2H), 3.87–3.81 (m, 4H), 1.94–1.21 (m, 52H), 0.86 (t, *J* = 7.2 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.5, 159.8, 150.4, 136.5, 131.4, 130.6,

#### 4.5.2. Polymer 1b

3.66. Found: C, 78.51; H, 9.45; N, 3.69.

To a solution of **7** (0.23 mmol, 158 mg) in CHCl<sub>3</sub> (2 mL) was added (1*R*,2*R*)-diphenylethylenediamine **8b** (0.23 mmol, 49 mg) and the mixture was stirred at 45 °C for 5 h. Isolation of **1b** was carried out as described for **1a** as a yellow powder in 93% (185 mg) yield. GPC:  $M_w$  = 8547,  $M_n$  = 7883 (PDI 1.08); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.41 (s, 2H), 7.59 (s, 2H), 7.25–7.21 (m, 12H), 6.84 (s, 2H), 4.81 (s, 2H), 3.82–3.79 (m, 4H), 1.63–1.19 (m, 42H), 0.83 (t, *J* = 6 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 167,

130.2, 128.2, 118.6, 116.1, 72.8, 69.7, 35.1, 33.6, 32.0, 29.7, 29.6,

29.5, 26.5, 24.5, 22.8, 14.2; FT-IR (KBr): 3465, 2928, 2857, 1629, 1507, 1465, 1440, 1389, 1264, 1203, 1083, 1035, 973, 862, 802,

707 cm<sup>-1</sup>; UV-vis (CHCl<sub>3</sub>):  $\lambda_{max}$  323, 255 nm;  $[\alpha]_{D}^{20} = +231$  (*c* 

0.026, CHCl<sub>3</sub>). Anal. Calcd for (C<sub>50</sub>H<sub>72</sub>N<sub>2</sub>O<sub>4</sub>)<sub>n</sub> C, 78.49; H, 9.49; N,

### Table 3Recyclability of the catalyst 9a



Run	Catalyst recoverability (%)	Product yield (%)	ee (%) <sup>c</sup>
1 <sup>a</sup>	99	95	78
2 <sup>b</sup>	99	93	78
3 <sup>b</sup>	99	93	78

 $^a\,$  p-Methoxybenzaldehyde (1 mmol),  $9a\,$  (1 mol $\%\,$  with respect to monomeric unit) and TMSCN (2 mmol) were stirred at 0 °C for 48 h in CHCl\_3 (3 mL) under an  $N_2$  atmosphere.

<sup>b</sup> Recovered **9a** used.

<sup>c</sup> Determined by HPLC analysis of the acetyl derivative of the cyanohydrin with a Chiralcel OD-H column using 99:1 *n*-hexane/2-propanol.

159.8, 150.4, 139.9, 136.6, 131.7, 130.8, 130.2, 128.5, 128.2, 127.7, 118.5, 116.1, 80.1, 69.7, 35.1, 31.9, 29.6, 29.5, 26.3, 22.8, 14.2; FT-IR (KBr) 3445, 3062, 3031, 2954, 2926, 2856, 1626, 1507, 1453, 1439, 1390, 1376, 1264, 1202, 1087, 1028, 864, 801, 774, 698, 555 cm<sup>-1</sup>; UV-vis (CHCl<sub>3</sub>):  $\lambda_{max}$  323, 266 nm;  $[\alpha]_D^{20} = +95$  (*c* 0.021, CHCl<sub>3</sub>). Anal. Calcd for (C<sub>58</sub>H<sub>74</sub>N<sub>2</sub>O<sub>4</sub>)<sub>n</sub> C, 80.70; H, 8.64; N, 3.25. Found: C, 80.68; H, 8.60; N, 3.27.

#### 4.6. Preparation of monomer 10

To a stirred solution of the (1R,2R)-diammoniumcyclohexane mono-(+)-tartrate salt (1.97 mmol, 520 mg) and K<sub>2</sub>CO<sub>3</sub> (3.94 mmol, 543 mg) in distilled water (3 mL) was added EtOH (15 mL). The cloudy mixture was heated to 80 °C and an EtOH (5 mL) solution of the aldehyde 5 (3.94 mmol, 702 mg) was added. The resulting yellow colored slurry was stirred for 2 h at the same temperature and water (3 mL) then added. The mixture was then cooled to <5 °C over 2 h and maintained at that temperature for an additional hour. The product was collected by vacuum filtration and washed with EtOH (2 mL). The crude solid was redissolved in  $CH_2Cl_2$  (10 mL) and washed with water (2 × 5 mL) and brine (3 mL). Drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation of the solvent gave **10** as a yellow powder in 97% yield (831 mg). Mp 75 °C; <sup>1</sup>H NMR  $(400 \text{ MHz}, \text{CDCl}_3) \delta 8.21 \text{ (s, 2H)}, 7.18 \text{ (dd, } I = 1.2, 8 \text{ Hz}, 2\text{H}), 6.92$ (dd, J = 1.2, 7.2 Hz, 2H), 6.63 (t, J = 7.2 Hz, 2H), 3.26 (m, 2H), 1.91–1.41 (m, 8H), 1.33 (s, 18H);  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ 165.7, 160.5, 137.2, 129.9, 129.4, 118.8, 117.9, 72.4, 34.9, 33.3, 29.5, 24.4; FT-IR (KBr) 3454, 2959, 2934, 2860, 1629, 1436, 1390, 359, 1306, 1264, 1199, 1144, 1083, 1037, 848, 800, 750, 691 cm<sup>-1</sup>;  $[\alpha]_D^{20} = -433$  (*c* 0.25, CHCl<sub>3</sub>). Anal. Calcd for C<sub>28</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.35; H, 8.76; N, 6.51.

#### 4.7. Preparation of the chiral poly-Ti catalysts<sup>8</sup>

#### 4.7.1. Catalyst 9a

To a stirred solution of **1a** (8.3 µmol, 100 mg) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added a solution of Ti(O<sup>i</sup>Pr)<sub>4</sub> (125 µmol, 35 mg) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at room temperature. After 3 h, water (0.1 mL) was added and the stirring continued for an additional 16 h. The resultant solution was concentrated in vacuo, and the residue was washed with MeOH (5 mL) to afford **9a** as yellow solid (106 mg).

#### 4.7.2. Catalyst 9b

The preparation of **9b** was carried out as described for **9a** from polymer **1b** (14.6  $\mu$ mol, 100 mg) and Ti(O<sup>i</sup>Pr)<sub>4</sub> (117  $\mu$ mol, 33 mg) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and obtained as a yellow solid (108 mg).

#### 4.8. Preparation of 10a

Preparation of **10a** was carried out as described for **9a** from monomer **10** (125  $\mu$ mol, 55 mg) and Ti(O<sup>i</sup>Pr)<sub>4</sub> (125  $\mu$ mol, 35 mg) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) to provide **10a** as a yellow solid (63 mg).

#### 4.9. General procedure for the TMSCN addition to aldehydes

To a stirred solution of aldehyde (0.5 mmol) and **9a** (1 mol % with respect to the monomeric unit) in dry  $CHCl_3$  (1.5 mL) was added TMSCN (1 mmol) and the reaction mixture was stirred for 48 h under nitrogen atmosphere (Table 2). Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then concentrated (ca. 0.5 mL) and MeOH (0.5 mL) was added drop wise. The **9a** precipitate was collected and the filtrate was evaporated to give a residue which was stirred with 2 M HCl (2 mL) in ethyl acetate (5 mL) for 1 h. The resultant solution was extracted with ethyl acetate (2 × 5 mL) and washed with brine (3 mL) and water (5 mL). Drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to afford analytically pure cyanohydrins.

#### 4.10. General procedure for cyanohydrin acylation<sup>11</sup>

To a stirred solution of cyanohydrin (0.5 mmol) and pyridine (0.6 mmol) in CHCl<sub>3</sub> (1 mL) at 0 °C was added Ac<sub>2</sub>O (1.5 mmol) or benzoyl chloride (1 mmol). The mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was passed through a short pad of silica gel using ethyl acetate and hexane to give the acetyl derivative whose ee was determined by HPLC analysis.

### 4.10.1. (+)-2-Hydroxy-2-(2'-bromophenyl)acetonitrile (Table 2, entry 1)<sup>12a</sup>

Colorless solid, yield 95%, mp 58 °C,  $[\alpha]_D^{20} = +6.3$  (*c* 1.09, CHCl<sub>3</sub>). HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2propanol (99:1), wavelength: 254 nm, flow rate: 1 mL/min, retention time: 10.49 min, 13.42 min, 50% ee.

### **4.10.2.** (*S*)-(+)-2-Hydroxy-2-(2'-chlorophenyl)acetonitrile (Table 2, entry 2)<sup>12b</sup>

Colorless oil, yield 97%,  $[\alpha]_D^{20} = +1.6$  (*c* 0.43, CHCl<sub>3</sub>).<sup>12*c*</sup> HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 9.26 min, 11.10 min, 60% ee.

## **4.10.3.** (*S*)-(-)-2-Hydroxy-2-(2'-methoxyphenyl)acetonitrile (Table 2, entry 3)<sup>12d</sup>

Colorless solid, yield 95%, mp 73 °C,  $[\alpha]_D^{20} = -23.9$  (*c* 0.37, CHCl<sub>3</sub>).<sup>12d</sup> HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 12.53 min, 14.22 min, 88% ee.

### 4.10.4. (–)-2-Hydroxy-2-(2'-ethoxyphenyl)acetonitrile (Table 2, entry 4)

Colorless solid, yield 91%, mp 88 °C, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.38–7.34 (m, 2H), 7.0–6.93 (m, 2H), 5.52 (d, *J* = 10.4 Hz, 1H), 4.2–4.14 (m, 2H), 3.63 (d, *J* = 9.2 Hz, 1H), 1.49 (t, *J* = 7 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.2, 131.2, 128.1, 123.9, 121.1, 119.1, 112.1, 64.4, 60.6, 14.8; FT-IR (KBr): 3368, 2982, 2936, 2887, 2251, 1601, 1590, 1494, 1473, 1457, 1391, 1307, 1285, 1258, 1237, 1182, 1160, 1125, 1112, 1060, 1043, 927, 910, 796, 758, 721, 616, 591 cm<sup>-1</sup>,  $[\alpha]_D^{20} = -38$  (*c* 0.61, CHCl<sub>3</sub>). Anal. Calcd for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.32; N, 7.87. HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/

2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 8.78 min, 10.76 min, 78% ee.

### 4.10.5. (+)-2-Hydroxy-2-(2'-allyloxyphenyl)acetonitrile (Table 2, entry 5)

Oil, yield 90%, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.39–7.34 (m, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.10–6.02 (m, 1H), 5.57 (d, *J* = 6.8 Hz, 1H), 5.47–5.42 (td, *J* = 1.6, 9.2 Hz, 1H), 5.35–5.31 (m, 1H), 4.67–4.65 (m, 2H), 3.66 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.6, 132.4, 131, 128, 124, 121.3, 119, 118.3, 112.3, 69.3, 60.0. FT-IR (neat): 3463, 2923, 2855, 2253, 2071, 1650, 1491, 1458, 1287, 1252, 1185, 1162, 1120, 1030, 927, 812, 753, 699 cm<sup>-1</sup>;  $[\alpha]_D^{20} = +22.5$  (*c* 0.75, CHCl<sub>3</sub>). Anal. Calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.79; H, 5.92; N, 7.36. HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 10.55 min, 13.94 min, 75% ee.

# 4.10.6. (-)-2-Hydroxy-2-(3'-bromophenyl)acetonitrile (Table 2, entry 6)<sup>12b</sup>

Colorless oil, yield 90%,  $[\alpha]_D^{20} = -19.5$  (*c* 1.34, CHCl<sub>3</sub>). HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 15.12 min, 16.36 min, 75% ee.<sup>12d</sup>

### 4.10.7. (*S*)-(–)-2-Hydroxy-2-(4'-methoxyphenyl)acetonitrile (Table 1, entry 7)

Colorless solid, yield 97%, mp 67 °C,  $[\alpha]_D^{20} = -32.4$  (*c* 0.55, CHCl<sub>3</sub>).<sup>12d</sup> HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 17.37 min, 19.08 min, 78% ee.

### 4.10.8. (S)-(–)-2-Hydroxy-2-(4'-methylphenyl)acetonitrile (Table 2, entry 8)<sup>12d</sup>

Colorless oil, yield 97%,  $[\alpha]_D^{20} = -31.5$  (*c* 0.51, CHCl<sub>3</sub>).<sup>12d</sup> HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 10.10 min, 12.27 min, 68% ee.

### **4.10.9.** (*S*)-(-)-2-Hydroxy-2-(2'-naphthyl)acetonitrile (Table 2, entry 9)<sup>12e</sup>

Colorless solid, yield 90%, mp 119 °C,  $[\alpha]_D^{20} = -24.6$  (*c* 1.16, CHCl<sub>3</sub>).<sup>12e</sup> HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 26.67 min, 29.65 min, 74% ee.

#### 4.10.10. (-)-2-Hydroxybutanenitrile (Table 2, entry 10)<sup>12b</sup>

Colorless liquid, yield 95%,  $[\alpha]_D^{20} = -10.3$  (c 0.89, CHCl<sub>3</sub>). HPLC of the benzoyl derivative: Chiralcel OJ column, *n*-hexane/2-propanol (90:10), wavelength 254 nm, flow rate: 0.5 mL/min, retention time: 16.57 min, 18.14 min, 40% ee.

## 4.10.11. (S)-(-)-2-Hydroxy-3-methylbutanenitrile (Table 2, entry 11)<sup>12b</sup>

Colorless liquid, yield 90%,  $[\alpha]_D^{20} = -10.5 (c \ 1.19, CHCl_3)$ .<sup>12e</sup> HPLC of the benzoyl derivative: Chiralcel OJ column, *n*-hexane/2-propanol (90:10), wavelength 254 nm, flow rate: 0.5 mL/min, retention time: 12.04 min, 13.11 min, 66% ee.

## **4.10.12**. (*E*)-(*S*)-(+)-2-Hydroxypent-3-enenitrile (Table 2, entry 12)<sup>12b</sup>

Colorless liquid, yield 93%,  $[\alpha]_{20}^{20} = +10.5$  (*c* 0.50, CHCl<sub>3</sub>).<sup>9d</sup> HPLC of the benzoyl derivative: Chiralcel OJ column, *n*-hexane/2-propa-

nol (90:10), wavelength 254 nm, flow rate: 0.8 mL/min, retention time: 9.83 min, 10.36 min, 55% ee.

#### 4.11. Recyclability experiment

To a stirred solution of 4-methoxybenzaldehyde (0.5 mmol) and **9a** (1 mol % with respect to the monomeric unit) in dry  $CHCl_3$  (1.5 mL) was added TMSCN (1 mmol) and the reaction mixture was stirred for 48 h under a nitrogen atmosphere (Table 3). The reaction mixture was then concentrated (ca. 0.5 mL) and MeOH (0.5 mL) was added. The **9a** precipitate was collected and reused for a fresh reaction.

#### Acknowledgments

This work was supported by the Department of Science and Technology, New Delhi, and Council of Scientific and Industrial Research, New Delhi. One of us (S.S.) thanks CSIR for Junior Research Fellowship.

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