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Synthesis of chiral quaternary ammonium polymers for asymmetric organocatalysis application

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ABSTRACT

Main-chain chiral quaternary ammonium polymers have been synthesized using cinchonidine or 10,11-dihydrocinchonidine as a chiral source. Since the quinuclidine moiety of cinchonidine is easily quaternized with halide to form cinchonidinium salt, the quaternized reaction (Menshutkin reaction) was applied to the dimeric compound of cinchonidine and dihalide. The quaternization polymerization between cinchonidine dimer and dihalide smoothly occurred to afford the chiral polymers containing cinchonidinium salt structure in its main-chain. This atom economical addition polymerization was also applied to dimer of 10,11-dihydrocinchonidine. The corresponding chiral quaternary ammonium polymers were found to perform as polymeric organocatalysts for enantioselective benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester to afford the desired (*S*)-phenylalanine derivative in high yields and high enantioselectivities (up to 95% ee).

1. Introduction

Chiral quaternary ammonium salts of cinchona alkaloid derivatives are one of the most efficient organocatalyst for various types of asymmetric transformations.[1–3] A typical asymmetric reaction using cinchonidinium salts is asymmetric alkylation of glycinate imines under phase transfer condition, which was successfully introduced by O'Donnel et al.[4] Further improvements have been done by Lygo,[5] Corey,[6] Jew,[7] and Park.[7] Polymer-immobilized cinchona alkaloid based organocatalysts have also been developed mainly due to their easy separation and recyclability.[8] The advantages of polymer-immobilized chiral catalysts are now widely recognized and the progress in the polymeric chiral catalysts has been reviewed in the literature.[9] Some of cinchona alkaloid based chiral quaternary ammonium salts were attached onto the side-chain of polymer-support. For example, cinchonidinium salts were attached onto the side-chain of cross-linked polystyrenes, which were used as polymeric organocatalyst in the same reaction.[10] These classical type of polymeric catalysts worked in the asymmetric alkylation with lowering the catalytic activities. The development of chiral polymer catalysts with rigid and sterically regular structure may have a better defined microenvironment at the catalytic sites and have allowed systematic modification of their catalytic properties. For that purpose, we have demonstrated some chiral main-chain polymers as catalyst for asymmetric reaction.[11] In this article, we have developed atom economical synthesis of chiral polymers by using repetitive quaternization reaction (Menshutkin reaction) between cinchona alkaloid dimer and dihalide. We have examined the catalytic activity of the chiral polymeric catalyst in asymmetric alkylation reaction.

Various kinds of achiral quaternary ammonium polymers called ionene have been synthesized since Gibbs and co-workers found the polymerization of tertiary diamine and dihalide in 1933.[12] The ionene polymers have many potential uses in biomedical application including DNA transfer agents,[13] multifunctional gelators,[14] and antimicrobial applications. Recently pyridinium ionene polymer has been developed to prepare self-assembled supramolecular complex, which was used as a catalyst for organic reactions.[15] However, optically active ionene polymers have not been prepared. We applied this simple polyaddition reaction to the synthesis of optically active quaternary ammonium polymers. By using this polymerization, chiral quaternary ammonium salt structure is regularly incorporated into the polymer main-chain. The catalytic activity of these chiral polymers for enantioselective alkylation of *N*-diphenylmethylene glycine *tert*-butyl ester was discussed.

2. Results and discussion

2.1. Synthesis of chiral quaternary ammonium polymers

The ether-linked cinchonidine dimer **3** was prepared from cinchonidine **1** and dihalide **2**. The cinchona alkaloids react selectively

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at the quinuclidine ring with halide, such as benzyl bromide.[16] The quaternary ammonium salt is quantitatively formed. This quaternization reaction can be applied to the chiral dimeric compounds **3** and dihalide, such as **4**, the chiral polymer should be formed. We found that the copolymerization of **3** and **4** via the intermolecular quaternization reaction smoothly occurred to give the corresponding chiral quaternary ammonium polymer **5**, which we term '*quaternization polymerization*'. We first surveyed the reaction condition of the quaternization polymerization. Quaternization reaction is sometimes sensitive to the solvent used. Table 1

Table 1
Quaternization polymerization of cinchonidine dimer **3a** and dihalide **4b**

Entry	Solvent	Temperature °C	Reaction time h	Yield %
1	DMF	100	21	84
2	DMSO	90	20	96
3	MeOH	70	24	0
4	Toluene	110	24	0
5	DMF/DMSO (1:1)	100	24	55
6	EtOH/DMF/$CHCl_3$ (5:6:2)	100	28	94

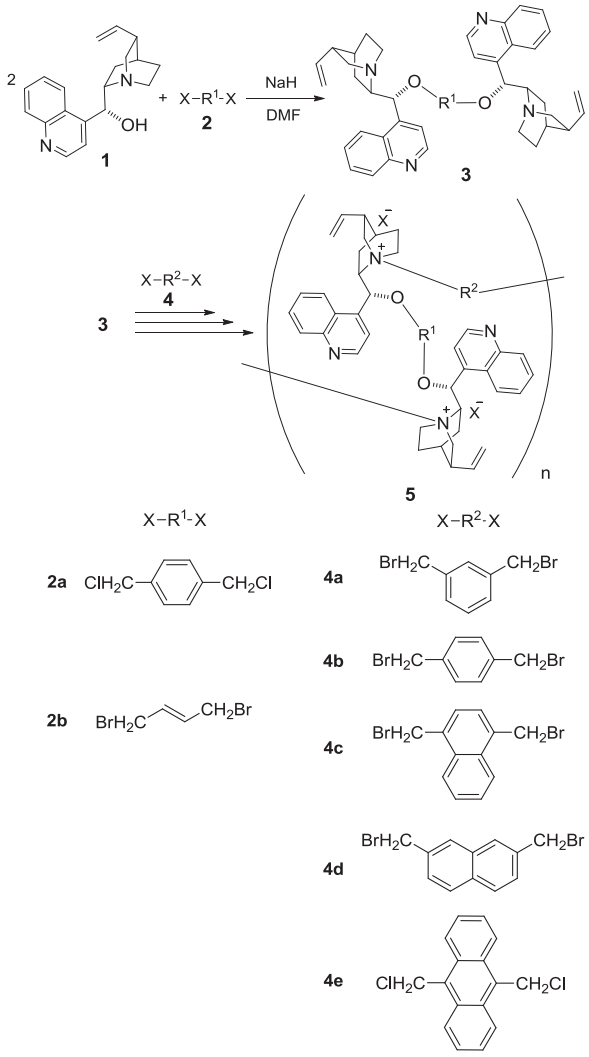
summarizes the result of quaternization polymerization of cinchonidine dimer **3a** and *p*-xylene dibromide **4b**. The polymerization in DMSO gave the chiral polymer **5b** in high yield, while the use of methanol and toluene resulted in no polymer formation. We used DMSO as solvent for the polymerization of other monomer combinations. The chiral polymers **5** were easily isolated by precipitation in ether followed by filtration. This is a highly atom economical addition polymerization to give the chiral polymer (Scheme 1).

In order to evaluate the catalytic activity of the resulting chiral quaternary ammonium polymers, enantioselective alkylation of *N*-diphenylmethylene glycine *tert*-butyl ester **6** was conducted in the presence of the polymer **5** (Fig. 1).

As shown in Table 2, although the polymeric catalyst **5** was not soluble both in the organic solvent and aqueous phase used in this reaction, the enantioselective benzylation of **6** occurred with the polymeric catalyst to give the corresponding chiral product **7** in good yield (Scheme 2). The catalytic activity and enantioselectivity were influenced by the chiral polymer structure. Polymeric catalysts **5c**, **5g** and **5h** having naphthalene derived linkers (R^2 derived from **4c**, **4d**) gave higher enantioselectivities in the asymmetric reaction (entries 3, 9, 10). Organic solvent used in the reaction also influenced on the catalytic activity. In some solvents tested in the reaction, toluene/chloroform mixed solvent system developed by Park and Jew[7] showed higher enantioselectivity (entries 4–6).

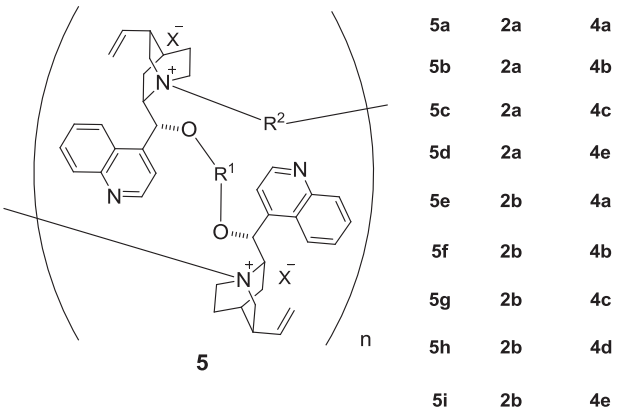
Next, we have prepared 10,11-hydrocinchonidine[17] derived quaternized ammonium polymers **9** by quaternization polymerization method (Scheme 3). 10,11-Hydrocinchonidine dimers **8** were prepared from 10,11-hydrocinchonidine and dihalide **2**. The dimers **8** were then allowed to react with dihalide **4** to give **9**. These chiral quaternized polymers efficiently catalyzed the same asymmetric benzylation reaction of **6**. The results are summarized in Table 3. In most cases, the polymeric catalysts **9** derived from 10,11-hydrocinchonidine gave higher enantioselectivities compared to those obtained using **5**. Naphthalene linked polymer catalyst **9d** gave the highest enantioselectivity (95% ee) in the reaction (Table 3, entry 4). The chiral polymer **9** containing relatively bulky ethyl group instead of vinyl group of **5** in their repeating unit would have a different conformation compared with that of **5**, which might influence on the catalytic activity (Scheme 4).

Since these polymeric catalysts are insoluble in the solvent used, the catalysts were readily removed from the reaction mixture. The recovered polymeric catalyst **9d** was reused for the same reaction. The polymer **9d** was reused twice without any loss of the catalytic activity.



Scheme 1. Quaternization polymerization of chiral diamine and dihalide.

The quaternary ammonium polymers **9** can be prepared by another method, that is, etherification polymerization.[18] The quaternized dimer **10** was treated with dihalide in the presence of NaH to form ether linkages between chiral diol **10** (Scheme 3). The obtained



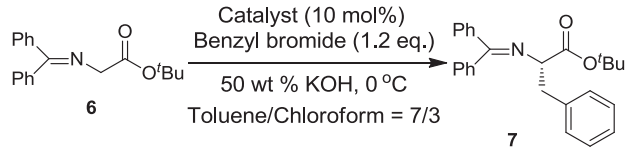
	$X–R^1–X$	$X–R^2–X$
5a	**2a**	**4a**
5b	**2a**	**4b**
5c	**2a**	**4c**
5d	**2a**	**4e**
5e	**2b**	**4a**
5f	**2b**	**4b**
5g	**2b**	**4c**
5h	**2b**	**4d**
5i	**2b**	**4e**

Fig. 1. Structure of Cinchonidium based polymeric catalysts.

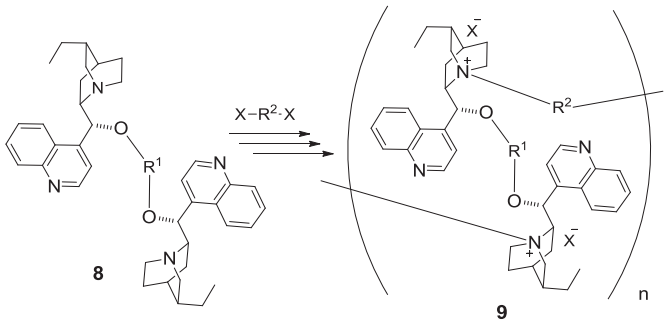
Table 2
Asymmetric alkylation reaction of *N*-diphenylmethylene glycine *tert*-butyl ester by using polymeric catalyst

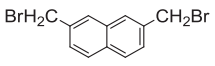
Entry	Catalyst	Time (h)	Yield[a] (%)	ee[b,c] (%)
1	**5a**	4	87	53
2	**5b**	4	76	80
3	**5c**	4	84	84
4	**5d**	4	81	80
5[d]	**5d**	4	44	51
6[e]	**5d**	4	92	74
7	**5e**	4	66	58
8	**5f**	4	72	77
9	**5g**	4	95	88
10	**5h**	4	93	86
11	**5i**	4	66	66

[a] The reaction was carried out with 1.2 equiv of benzyl bromide and 50 wt % aqueous KOH in the presence of 10 mol % of the polymeric catalyst in toluene/chloroform (7:3) at 0 °C.
[b] The yields were determined by ^{1}H NMR spectroscopy.
[c] The ee values were determined by HPLC on a chiral stationary phase using a Chiralcel OD-H column.
[d] Toluene was used as solvent.
[e] CPME was used as solvent.



Scheme 2. Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester.



	X–R^1-X	X–R^2·X		X–R^1-X	X–R^2·X
9a	**2a**	**4a**	**9h**	**2b**	**4c**
9b	**2a**	**4b**	**9i**	**2b**	**4d**
9c	**2a**	**4c**	**9j**	**2b**	**4e**
9d	**2a**	**4d**			
9e	**2a**	**4e**	**9k**		**4a**
9f	**2b**	**4a**		**2c**	
9g	**2b**	**4b**	**9l**	**2c**	**4b**

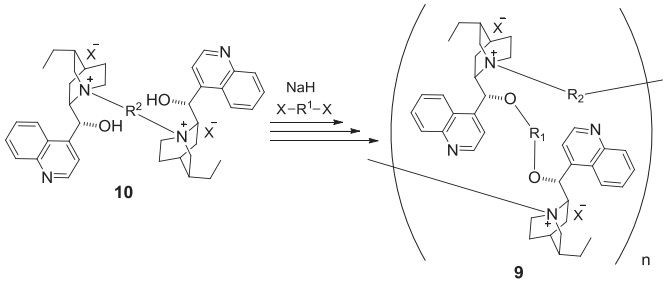
Scheme 3. Quaternization polymerization of hydrocinchonidine dimer **8** and dihalide.

polymer structure is the same as those obtained by quaternized polymerization. However, both the yields and enantioselectivities obtained in the asymmetric benzylation reaction with these polymers **9**(**EP**) were somewhat lower compared with those obtained by using the polymeric catalysts synthesized by quaternization polymerization (entries 10, 12, 14 vs 11, 13, 15).

Table 3
Asymmetric alkylation reaction of *N*-diphenylmethylene glycine *tert*-butyl ester by using polymeric catalyst

Entry	Catalyst	Time (h)	Yield[a] (%)	ee[b,c] (%)
1	**9a**	4	91	73
2	**9b**	4	92	87
3	**9c**	4	92	90
4	**9d**	4	95	95
5[d]	**9d**	4	92	95
6[e]	**9d**	4	93	95
7	**9e**	4	86	89
8	**9f**	4	90	67
9	**9g**	4	92	87
10	**9h**	4	92	90
11	**9h**(**EP**)[f]	12	80	82
12	**9i**	4	92	93
13	**9i**(**EP**)[f]	16	88	90
14	**9j**	4	91	90
15	**9j**(**EP**)[f]	12	68	81
16	**9k**	4	86	82
17	**9l**	4	93	86

[a] Isolated yield was determined by ^{1}H NMR spectrum.
[b] Enantiopurity of the alkylated product was determined by HPLC analysis using Chiral column (Chiralcel (OD-H) with Hexane: IPA (200:1) as solvent).
[c] (*S*) configuration was determined by the relative retention times of the (*R*/*S*)-isomers reported in the literature.
[d] Catalyst recovered from entry 4 was reused.
[e] Catalyst recovered from entry 5 was reused.
[f] EP means etherification polymerization.



Scheme 4. Etherification polymerization of 10,11-hydrocinchonidinium dimer **10** and dihalide.

3. Conclusions

In conclusion, we have successfully synthesized chiral quaternary ammonium polymers by means of quaternization polymerization of cinchonidine dimer **3** or hydrocinchonidine dimer **8** with dihalide **4**. This is an important example of the highly atom economical polymerization method to prepare chiral polymers. In most cases, hydrocinchonidinium polymers **9** gave higher enantioselectivities compared with those obtained from cinchonidinium polymers **5** in the asymmetric benzylation reaction. The structure of spacers (R^1, R^2) between quinuclidine nitrogens in the polymeric catalysts influenced on the enantioselectivity of the polymeric catalyst. The polymeric catalyst was easily recovered from the reaction mixture and reused several times without any loss of the catalytic activity.

4. Experimental section

4.1. General methods

All reagents were purchased from Sigma–Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry Co., Ltd. at the highest available purity and used as is unless noted otherwise. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica-gel plates (Merck 5554, 60F_{254}).

Column chromatography was performed with a silica-gel column (Wakogel C-200, 100–200 mesh). Melting points were recorded using a Yanaco micro-melting apparatus and are uncorrected. ^{1}H NMR (300 MHz) spectra were measured on a Varian Mercury 300 spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University. GC analyses were performed with a Shimadzu Capillary Gas Chromatograph 14B equipped with a capillary column (SPERCO β-DEX 325, 30 m×0.25 mm). HPLC analyses were performed with a JASCO HPLC system comprising a three-line degasser DG-980-50, an HPLC pump PV-980, and a CO-965 column oven equipped with a chiral column (CHIRALCEL OD or AD, Daicel); hexane/2-propanol was used as an eluent. A UV detector (JASCO UV-975 for JASCO HPLC system) was used for peak detection. Optical rotations were recorded with a JASCO DIP-149 digital polarimeter, using a 10-cm thermostated microcell. Size exclusion chromatography (SEC) was obtained with Tosoh instrument with HLC 8020 UV (254 nm) or refractive index detection. DMF was used as a carrier solvent at a flow rate of 1.0 mL/min at 40 °C. Two polystyrene gel columns of bead size 10 μm were used. A calibration curve was made to determine number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) values with polystyrene standards.

4.2. Preparation of cinchonidine dimers 3

*4.2.1. Preparation of **3a**.* To a suspension of sodium hydride (0.49 g, 20.4 mmol) in DMF (20 mL) was added (−)-cinchonidine (3.00 g, 10.2 mmol) under an atmosphere of dry nitrogen, and the mixture was stirred at room temperature for 1 h. The mixture was cooled in an ice-water bath and a solution of α,α′-dichloro-*p*-xylene **2a** (0.89 g, 5.1 mmol) in DMF (15 mL) was added. After 1 h, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 20 h, and then poured into ice-water (70 mL). The mixture was extracted with CH_2Cl_2 (30 mL×2), the combined organic extracts were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure to give a pale yellow solid. The crude solid was washed with hexane (30 mL) on a glass filter to give **3a** as a white solid (2.63 g, 75% yield). Mp 132 °C $[\alpha]_D^{25}$ −1.43 (*c* 1.0 g/dL in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (br, 4H), 1.81 (br, 2H), 2.05 (br, 4H), 2.28 (br, 2H), 2.65 (br, 4H), 3.14 (br, 4H), 3.42 (br, 2H), 4.43 (br, 4H), 4.92 (br, 4H), 5.73 (br, 2H), 7.27 (br, 4H), 7.59 (br, 4H), 7.75 (br, 2H), 8.16 (br, 4H), 8.91 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.84, 28.11, 40.07, 43.44, 57.15, 60.96, 71.28, 114.59, 118.77, 123.39, 126.75, 127.07, 127.99, 129.43, 130.75, 137.62, 141.92, 146.53, 148.79, 150.33. IR (KBr) ν 1584, 1229, 1080 cm^{-1}. Anal. Calcd for $C_{46}H_{50}N_4O_2$: C 79.97, H 7.29, N 8.11; found: C 79.30, H 7.20, N 8.09.

*4.2.2. Preparation of **3b**.* The same procedure was followed as described for **3a** using (−)-cinchonidine (2.00 g, 6.8 mmol) and *trans*-1,4-dibromo-2-butene **2b** (0.73 g, 3.4 mmol). 1.84 g (84% yield) of **3b** was obtained. Mp 205 °C $[\alpha]_D^{25}$ −2.57 (*c* 1.0 g/dL in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.50 (br, 4H), 1.79 (br, 7H), 2.24 (br, 3H), 2.61 (br, 4H), 3.08 (br, 4H), 3.47 (br, 2H), 4.40 (br, 2H), 4.90 (t, *J*=6.0 Hz, 4H), 5.60–5.78 (m, 4H), 7.36 (t, *J*=2.6 Hz, 2H), 7.56–7.68 (m, 4H), 8.01 (dd, *J*=3.0 Hz, 2.8 Hz, 4H), 8.82 (d, *J*=4.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.85, 27.79, 28.10, 40.10, 43.40, 57.17, 60.56, 72.07, 114.58, 118.40, 123.18, 125.86, 126.78, 129.27, 130.47, 141.97, 148.47, 149.47, 150.34. IR (KBr): ν=1633 cm^{-1} (C=C), 1585 cm^{-1} (C=N), 1213 cm^{-1} (C–N), 1098 cm^{-1} (CO). Anal. Calcd for $C_{42}H_{48}N_4O_2$: C 78.71, H 7.55, N 8.74; found: C 78.60, H 7.43, N 8.81.

4.3. Preparation of dihydrocinchonidine dimers 8

*4.3.1. Preparation of **8a**.* To a suspension of sodium hydride (13.6 mmol, 0.326 g, washed by hexane) in DMF (15 mL) was added 10, 11-dihydrocinchonodine (6.78 mmol, 2.0 g) under N_2 atmosphere, and the mixture was stirred at room temperature for 1 h. The mixture was cooled in an ice-water bath and a solution of α,α′-dichloro-*p*-xylene (3.39 mmol, 0.593 g) in DMF (5 mL) was added. After 1 h, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 20 h, and then poured into ice-water (50 mL). The mixture was extracted with CH_2Cl_2 (30 mL×2), the combined organic extracts were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure to give a pale yellow solid. The crude solid was washed with hexane (30 mL) on a glass filter to give **8a** as a white solid (1.77 g, 75% yield). Mp 234 °C $[\alpha]_D^{25}$ +34.77 (*c* 1.0 g/dL in DMSO). ^{1}H NMR (300 MHz, $CDCl_3$): 0.75–0.80 (m, 3H), 1.18–1.22 (m, 2H), 1.39–1.42 (m, 4H), 1.68–1.75 (m, 4H), 1.98 (s, 1H), 2.31–2.36 (m, 1H), 2.54–2.60 (m, 1H), 2.96–3.04 (m, 2H), 3.44 (br, 1H), 4.19 (s, 1H), 5.63 (d, *J*=3.9 Hz, 1H), 7.26–7.40 (m, 1H), 7.57 (d, *J*=4.8 Hz, 1H), 7.61–7.66 (m, 1H), 7.95 (d, *J*=8.70 Hz, 1H), 8.06–8.09 (m, 1H), 8.81 (d, *J*=4.2, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ=0 ($(CH_3)_4Si$)): δ=12.23, 21.48, 25.70, 27.80, 28.44, 37.68, 43.47, 58.77, 60.33, 72.16, 118.42, 123.24, 125.88, 126.79, 129.18, 130.43, 149.61, 150.33. IR (KBr): ν=1590 cm^{-1} (C=N), 1206 cm^{-1} (C–N), 1108 cm^{-1} (C–O). Anal. Calcd for $C_{46}H_{54}N_4O_2$: C 79.44, H 7.77, N 8.05; found C 79.56, H 7.82, N 8.09.

*4.3.2. Preparation of **8b**.* The same procedure was followed as described for **8a** using 10,11-dihydrocinchonidine (6.78 mmol, 2.0 g) and *trans*-1,4-dibromo-2-butene (3.39 mmol, 0.725 g). 1.62 g of **8b** (74%) was obtained. Mp 236 °C $[\alpha]_D^{25}$ −47.00 (*c* 1.0 g/dL in DMSO). ^{1}H NMR (300 MHz, $CDCl_3$): 0.76–0.81 (m, 3H), 1.18–1.27 (m, 2H), 1.41–1.50 (m, 4H), 1.67–1.79 (m, 7H), 2.34–2.38 (m, 1H), 2.56–2.65 (m, 1H), 2.99–3.09 (m, 2H), 3.42–3.51 (br, 2H), 5.63 (d, *J*=3.9 Hz, 1H), 7.26–7.47 (m, 1H), 7.58 (d, *J*=4.8 Hz, 1H), 7.64–7.70 (m, 1H), 7.99 (d, *J*=7.8 Hz, 1H), 8.10 (d, *J*=8.1, 1H), 8.85 (d, *J*=4.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ=0 ($(CH_3)_4Si$)): δ=12.24, 21.62, 25.70, 27.80, 28.46, 37.70, 43.48, 58.786, 60.36, 72.25, 118.38, 123.24, 125.91, 126.81, 129.20, 130.50, 148.43, 149.43, 150.37. IR (KBr): ν=1682 cm^{-1} (C=C), 1590 cm^{-1} (C=N), 1206 cm^{-1} (C–N), 1083 cm^{-1} (C–O). Anal. Calcd for $C_{42}H_{52}N_4O_2$: C 78.40, H 8.96, N 8.71; found C 78.49, H 8.90, N 8.71.

4.4. Preparation of cinchonidinium polymers 5

*4.4.1. Preparation of **5a**.* A solution of cinchonidine dimer **3a** (0.345 g, 0.50 mmol) and α,α′-dibromo-*m*-xylene **4a** (0.132 g, 0.50 mmol) in 4 mL DMSO was heated at 90 °C for 24 h. The whole mixture was concentrated under reduced pressure and the residue was dissolved in methanol (8 mL). The methanol solution of the chiral polymer was poured into ether (200 mL) to precipitate the product. The precipitate was collected on a glass filter and washed with ethyl acetate and hexane. The polymer solid was dried under vacuum to give light brown powder **5a** (0.458 g, 96%). $[\alpha]_D^{25}$ −100.3 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{54}H_{58}Br_2N_4O_2$: C 67.92, H 6.12, N 5.87; found C 67.55, H 6.10, N 5.58. M_n (SEC)=21.0 kg/mol, M_w/M_n=1.43.

*4.4.2. Preparation of **5b**.* The same procedure was followed as described for **5a** using **3a** (0.345 g, 0.50 mmol) and **4b** (0.132 g, 0.50 mmol). **5b** was obtained in 92% yield (0.437 g). $[\alpha]_D^{25}$ −111.45 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{54}H_{58}Br_2N_4O_2$: C 67.92, H 6.12, N 5.87; found C 67.58, H 5.95, N 5.65. M_n (SEC)=8.5 kg/mol, M_w/M_n=1.84.

*4.4.3. Preparation of **5c**.* The same procedure was followed as described for **5a** using **3a** (0.345 g, 0.50 mmol) and **4c** (0.157 g, 0.50 mmol). **5c** was obtained in 90% yield (0.452 g). $[\alpha]_D^{25}$ −67.27 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{58}H_{60}Br_2N_4O_2$: C 69.32, H 6.02,

N 5.58; found C 69.10, H 5.88, N 5.47. M_n (SEC)=9.3 kg/mol, M_w/M_n=1.86.

*4.4.4. Preparation of **5d**.* The same procedure was followed as described for **5a** using **3a** (0.345 g, 0.50 mmol) and **4e** (0.138 g, 0.50 mmol). **5d** was obtained in 71% yield (0.344 g). $[\alpha]_D^{25}$ −8.83 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{62}H_{62}Cl_2N_4O_2$: C 77.08, H 6.47, N 5.80; found C 76.98, H 6.32, N 5.76. M_n (SEC)=7.6 kg/mol, M_w/M_n=2.26.

*4.4.5. Preparation of **5e**.* The same procedure was followed as described for **5a** using **3b** (0.320 g, 0.50 mmol) and **4a** (0.132 g, 0.50 mmol). **5e** was obtained in 87% yield (0.392 g). $[\alpha]_D^{25}$ −83.33 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{50}H_{56}Br_2N_4O_2$: C 66.37, H 6.24, N 6.19; found C 65.98, H 6.14, N 6.02. M_n (SEC)=9.3 kg/mol, M_w/M_n=2.07.

*4.4.6. Preparation of **5f**.* The same procedure was followed as described for **5a** using **3b** (0.320 g, 0.50 mmol) and **4b** (0.132 g, 0.50 mmol), **5f** was obtained in 93% yield (0.422 g). $[\alpha]_D^{25}$ −104.9 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{50}H_{56}Br_2N_4O_2$: C 66.37, H 6.24, N 6.19; found C 66.15, H 6.14, N 5.95. M_n (SEC)=7.1 kg/mol, M_w/M_n=1.84.

*4.4.7. Preparation of **5g**.* The same procedure was followed as described for **5a** using **3b** (0.238 g, 0.372 mmol) and **4c** (0.117 g, 0.372 mmol). **5g** was obtained in 82% yield (0.292 g). $[\alpha]_D^{25}$ −139.30 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{54}H_{58}Br_2N_4O_2$: C 67.92, H 6.12, N 5.87; found C 67.58, H 5.97, N 5.66. M_n (SEC)=4.2 kg/mol, M_w/M_n=2.97.

*4.4.8. Preparation of **5h**.* The same procedure was followed as described for **5a** using **3b** (0.320 g, 0.5 mmol) and **4d** (0.157 g, 0.50 mmol). **5h** was obtained in 84% yield (0.403 g). $[\alpha]_D^{25}$ −139.0 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{54}H_{58}Br_2N_4O_2$: C 67.92, H 6.12, N 5.87; found C 67.58, H 5.89, N 5.80. M_n (SEC)=8.5 kg/mol, M_w/M_n=1.87.

*4.4.9. Preparation of **5i**.* The same procedure was followed as described for **5a** using **3b** (0.320 g, 0.5 mmol) and **4e** (0.138 g, 0.50 mmol). **5i** was obtained in 58% yield (0.266 g). $[\alpha]_D^{25}$ −278.4 (*c* 1.0 g/dL in DMF), Anal. Calcd for $C_{58}H_{60}Cl_2N_4O_2$: C 76.05, H 6.60, N 6.12; found C 75.78, H 6.48, N 6.05. M_n (SEC)=3.7 kg/mol, M_w/M_n=2.49.

4.5. Preparation of dihydrocinchonidinium polymers 9

*4.5.1. Preparation of **9a**.* A solution of 10,11-hydrocinchonidine dimer **8a** (0.347 g, 0.5 mmol) and **4a** (0.132 g, 0.50 mmol) in 4 mL DMSO was heated at 90 °C for 24 h. The whole mixture was concentrated under reduced pressure and the residue was dissolved in methanol (8 mL). The methanol solution of the chiral polymer was poured into ether (200 mL) to precipitate the product. The precipitate was collected on a glass filter and was washed with ethyl acetate and hexane. The polymer solid was dried under vacuum to give light brown powder **9a** (0.422 g, 88%). $[\alpha]_D^{25}$ −102.3 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{54}H_{62}Br_2N_4O_2$: C 67.58, H 6.67, N 5.84; found C 67.45, H 6.46, N 5.81. M_n (SEC)=5.1 kg/mol, M_w/M_n=1.90.

*4.5.2. Preparation of **9b**.* The same procedure was followed as described for **9a** using **8a** (0.347 g, 0.5 mmol) and **4b** (0.132 g, 0.50 mmol). **9b** was obtained in 97% yield (0.465 g). $[\alpha]_D^{25}$ −124.9 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{54}H_{62}Br_2N_4O_2$: C 67.58, H 6.67, N 5.84; found C 67.35, H 6.74, N 5.78. M_n (SEC)=5.4 kg/mol, M_w/M_n=1.51.

*4.5.3. Preparation of **9c**.* The same procedure was followed as described for **9a** using **8a** (0.347 g, 0.5 mmol) and **4c** (0.157 g, 0.50 mmol). **9c** was obtained in 87% yield (0.439 g). $[\alpha]_D^{25}$ −123.4 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{58}H_{64}Br_2N_4O_2$: C 68.99, H 6.34, N 5.55; found C 68.19, H 6.47, N 5.43. M_n (SEC)=5.1 kg/mol, M_w/M_n=1.45.

*4.5.4. Preparation of **9d**.* The same procedure was followed as described for **9a** using **8a** (0.347 g, 0.5 mmol) and **4d** (0.157 g, 0.50 mmol). **9d** was obtained in 88% yield (0.444 g). $[\alpha]_D^{25}$ −93.8 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{58}H_{64}Br_2N_4O_2$: C 68.99, H 6.34, N 5.55; found C 68.74, H 6.49, N 5.42. M_n (SEC)=6.3 kg/mol, M_w/M_n=1.48.

*4.5.5. Preparation of **9e**.* The same procedure was followed as described for **9a** using **8a** (0.347 g, 0.5 mmol) and **4e** (0.138 g, 0.50 mmol). **9e** was obtained in 58% yield (0.282 g). $[\alpha]_D^{25}$ +250.0 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{62}H_{66}Cl_2N_4O_2$: C 76.70, H 6.80, N 5.77; found C 76.51, H 6.60, N 5.73. M_n (SEC)=5.3 kg/mol, M_w/M_n=1.68.

*4.5.6. Preparation of **9f**.* The same procedure was followed as described for **9a** using **8b** (0.321 g, 0.5 mmol) and **4a** (0.132 g, 0.50 mmol). **9f** was obtained in 95% yield (0.431 g). $[\alpha]_D^{25}$ −141.2 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{50}H_{60}Br_2N_4O_2$: C 66.02, H 6.60, N 6.16; found C 67.08, H 7.20, N 7.40. M_n (SEC)=6.0 kg/mol, M_w/M_n=1.63.

*4.5.7. Preparation of **9g**.* The same procedure was followed as described for **9a** using **8b** (0.321 g, 0.5 mmol) and **4b** (0.132 g, 0.50 mmol). **9g** was obtained in 95% yield (0.431 g). $[\alpha]_D^{25}$ −87.44 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{50}H_{60}Br_2N_4O_2$: C 66.02, H 6.60, N 6.16; found C 65.84, H 6.50, N 5.90. M_n (SEC)=8.0 kg/mol, M_w/M_n=1.68.

*4.5.8. Preparation of **9h**.* The same procedure was followed as described for **9a** using **8b** (0.321 g, 0.5 mmol) and **4c** (0.157 g, 0.50 mmol). **9h** was obtained in 77% yield (0.368 g). $[\alpha]_D^{25}$ −164.9 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{54}H_{62}Br_2N_4O_2$: C 67.54, H 6.52, N 5.84; found C 66.72, H 6.32, N 5.57. M_n (SEC)=6.5 kg/mol, M_w/M_n=1.47.

*4.5.9. Preparation of **9i**.* The same procedure was followed as described for **9a** using **8b** (0.321 g, 0.5 mmol) and **4d** (0.157 g, 0.50 mmol). **9i** was obtained in 85% yield (0.406 g). $[\alpha]_D^{25}$ −119.02 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{54}H_{62}Br_2N_4O_2$: C 67.54, H 6.52, N 5.84; found C 66.78, H 6.49, N 5.76. M_n (SEC)=5.7 kg/mol, M_w/M_n=1.65.

*4.5.10. Preparation of **9j**.* The same procedure was followed as described for **9a** using **8b** (0.321 g, 0.5 mmol) and **4e** (0.138 g, 0.50 mmol). **9j** was obtained in 58% yield (0.266 g). $[\alpha]_D^{25}$ −114.02 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{58}H_{64}Cl_2N_4O_2$: C 75.65, H 6.95, N 6.08; found C 75.46, H 6.35, N 6.35. M_n (SEC)=3.5 kg/mol, M_w/M_n=1.20.

*4.5.11. Preparation of **9k**.* The same procedure was followed as described for **9a** using **8c** (0.373 g, 0.5 mmol) and **4a** (0.132 g, 0.50 mmol). **9k** was obtained in 85% yield (0.429 g). $[\alpha]_D^{25}$ +13.56 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{57}H_{60}Br_2N_4O_2$: C 67.79, H 5.94, N 5.55; found C 67.66, H 6.03, N 5.25. M_n (SEC)=5.1 kg/mol, M_w/M_n=1.48.

*4.5.12. Preparation of **9l**.* The same procedure was followed as described for **9a** using **8c** (0.373 g, 0.5 mmol) and **4b** (0.132 g, 0.50 mmol). **9l** was obtained in 91% yield (0.460 g). $[\alpha]_D^{25}$ −25.46 (*c* 1.0 g/dL in DMSO), Anal. Calcd for $C_{57}H_{60}Br_2N_4O_2$: C 67.79, H 5.94, N 5.55; found C 67.61, H 6.18, N 5.05. M_n (SEC)=4.7 kg/mol, M_w/M_n=1.52.

4.6. General procedure for enantioselective benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester (6) using chiral polymeric catalyst 9d

Chiral polymeric catalyst **9d** (0.017 mmol) and *N*-diphenylmethylidene glycine *tert*-butyl ester (**6**: 0.050 g, 0.170 mmol) were added into a mixed solvent of toluene (0.7 mL) and chloroform (0.3 mL). 50 wt % aqueous KOH solution (0.25 mL) was added to the above mixture. Benzyl bromide (0.035 g, 0.203 mmol) was then added dropwise at 0 °C to the mixture. The reaction mixture was stirred vigorously at 0 °C. Saturated sodium chloride solution (2 mL) was then added, and the mixture was subsequently filtered to recover **9d**, which was washed with water and dichloromethane several times. The organic phase was separated, and the aqueous phase was extracted with dichloromethane. The organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of solvents and purification of the residual oil by column chromatography on silica-gel (ether/hexane=1:10 as eluent) gave (*S*)-*tert*-butyl *N*-(diphenylmethylidene) phenylalaninate (**7**) (0.062 g, 0.161 mmol, 95% yield). The enantiomeric excess (95% ee) was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol=100:1, flow rate=0.3 mL/min, retention time: *R* enantiomer=27.6 min, *S* enantiomer=47.9 min).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.03.018. These data include MOL files and InChiKeys of the most important compounds described in this article.

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