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Synthesis of Cinchona Alkaloid-Derived Chiral Polymers by Mizoroki−Heck Polymerization and Their Application to Asymmetric Catalysis

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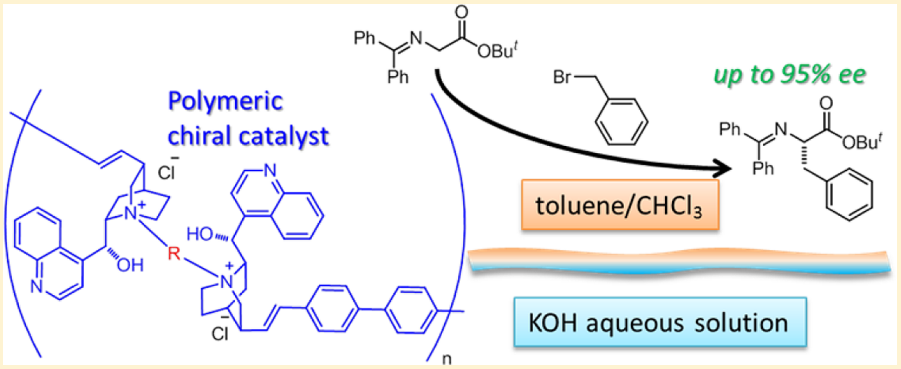

ABSTRACT: To facilitate the asymmetric catalysis process, we designed novel polymeric chiral catalysts. Since quaternary ammonium salts of cinchona alkaloid derivatives show efficient catalytic activity in various asymmetric transformations, we have synthesized novel chiral polymer catalysts containing cinchonidinium moieties in the main chain of the polymer. Repetitive Mizoroki−Heck coupling reactions between the cinchona alkaloid-derived dimer and diiodide afforded the chiral polymer catalysts, which were subsequently used as catalysts in asymmetric benzylation reactions to yield the corresponding phenylalanine derivatives in higher yields and levels of enantioselectivity than can be obtained with a monomeric catalyst. Because of the insolubility of the polymeric catalysts, they were easily recovered from the reaction mixture and reused several times.

INTRODUCTION

Cinchona alkaloids have been utilized for the preparation of various types of chiral catalysts.[1] Some cinchona alkaloid derivatives can be utilized as chiral ligands for transition metal catalysis[2] and organo/metal cooperative catalysis,[3] but the most important application of cinchona alkaloids is their use as chiral organocatalysts.[1,4,5] A number of asymmetric catalysis experiments have been performed with chiral organocatalysts derived from cinchona alkaloids.[5] Typical examples include chiral base catalysis with cinchona alkaloids. A large number of chiral quaternary ammonium salts have also been designed and synthesized from cinchona alkaloids.[6] In most cases, due to the relatively lower catalytic activities of chiral quaternary ammonium salts as compared to transition metal catalysts, over 10 mol % of the catalyst is usually required to facilitate a reaction at a reasonable rate. The amphiphilic nature of these chiral quaternary ammonium salts is necessary for their performance as phase transfer catalysts;[7] however, this property can sometimes complicate isolation of the desired reaction products from the reaction mixture and cause decreases in yield. Moreover, recovery and reuse of the catalyst are usually difficult. One effective solution is to immobilize the catalyst on a solid support, and several approaches to immobilize cinchona-derived organocatalysts onto polymers have been reported.[8] In most cases, the immobilization strategy employed involves attachment of cinchona derivatives onto the side chain of polymers, resulting in chiral polymers containing randomly attached cinchona moieties on the cross-linked polymer supports.[9] However, most of these polymer-immobilized cinchona derivative catalysts possess lower catalytic activities and enantioselectivities as compared with the low-molecular-weight cinchona-derived catalysts in solution.[10]

We have recently investigated novel polymeric cinchona-derivative catalysts, in which the organocatalyst is incorporated into the polymer main chain as a repeating unit.[11] Since cinchona alkaloids contain several functionalities such as a quinuclidine tertiary nitrogen, a secondary alcohol, a quinoline nitrogen, and vinyl group, various types of polycondensation reactions that use these functionalities can be applied to cinchona alkaloid dimers. For example, polymerization between cinchonidine dimers and dihalide linkers yielded a polymer containing cinchonidinium salts in its main chain unit, which we termed quaternization polymerization.[12] By utilizing the secondary alcohol functionality of the cinchona alkaloid, etherification polymerization of cinchona alkaloid dimers and dihalide linkers yielded yet another class of chiral polymer.[13]

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Another method of polymerization is to use an ion exchange reaction between cinchonidinium halide dimers and aromatic dihalide linkers.[14] These chiral polymers were applied to asymmetric catalysis, some of which showed excellent catalytic activity in asymmetric alkylation reactions. However, no other polymerization reaction has been developed by using the vinyl group of cinchona alkaloids except for the radical copolymerization of cinchona alkaloids and acrylonitrile to give chiral polymers possessing cinchona moieties as the side-chain pendant groups.[15]

In this paper, we report that the vinyl group of cinchonidine easily reacted with aromatic iodide under the conditions of the Mizoroki−Heck coupling reaction. Mizoroki−Heck coupling is one of the most efficient C−C bond formation reactions of olefinic compounds with aromatic halides.[16] Our strategy was to use the Mizoroki−Heck coupling reaction between cinchonidine dimers and diiodide linkers in the presence of $Pd(OAc)_2$. Since the Mizoroki−Heck reaction is relatively tolerant of many functional groups, this polymerization has an advantage in the synthesis of various kinds of cinchona alkaloid polymers including quaternary ammonium catalyst and free amine base catalyst. Repetitive Mizoroki−Heck coupling affords chiral polymers containing the cinchonidine moiety in its main chain. Several examples of Mizoroki−Heck polymerization for achiral monomers have been reported for the synthesis of the corresponding polymers containing *trans* double bonds in the main chain.[17−19] Recently, chiral conjugated polymers have been prepared by Mizoroki−Heck polymerization of divinyl compounds with chiral aromatic dihalide linkers.[20] However, no chiral polymeric catalysts have been synthesized by means of a Mizoroki−Heck polymerization. In this article, we discuss a novel chiral polymer synthesis involving cinchona alkaloid derivatives by using Mizoroki−Heck polymerization and the application of this polymer to asymmetric organocatalysis.

EXPERIMENTAL SECTION

Materials and General Considerations. Unless otherwise stated, all commercial reagents were purchased from Aldrich, Wako, or TCI Chemicals and were used as received. Reactions were monitored by thin layer chromatography using Merck precoated silica gel plates (Merck 5554, 60F254). Column chromatography separations were performed with a silica gel column (Wakogel C-200, 100−200 mesh). Melting points were taken on a Yanaco micro melting apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-140 digital polarimeter with a 10 cm thermostated microcell. NMR spectra were registered in a Varian Mercury 300 (300 MHz (^{1}H)) spectrometer or a JEOL JNM-ECS400 (400 MHz (^{1}H)) spectrometer in $CDCl_3$ or DMSO-d_6 at room temperature operating at 300 or 400 MHz (^{1}H) and 100 MHz (^{13}C{^{1}H}). TMS was used as internal standard for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm referred to TMS, and the *J* values were recorded in hertz. IR spectra were recorded with a JEOL JIR-7000 Fourier transform infrared spectrometer and were reported in reciprocal centimeters (cm^{-1}). Elemental analyses (carbon, hydrogen, and nitrogen) were performed on a Yanaco-CHN coder MT-6 analyzer. GC analyses were performed with a Shimadzu capillary gas chromatograph GC-2014 equipped with a capillary column (SPERCO *β*-DEX 325, 30 m × 0.25 mm). High-performance liquid chromatography (HPLC) analyses were performed with a Jasco HPLC system composed of a DG-980-50 three-line degasser, a PU 980 HPLC pump, and a CO-965 column oven equipped with a chiral column (Chiralcell OD-H, Daicel) with hexane/2-propanol as an eluent. A Jasco UV-975 UV detector was used for the 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.

Synthesis of 2. A mixture of (−)-cinchonidine (1.47 g, 5.0 mmol) with benzyl bromide (0.89 g, 5.2 mmol) was stirred in a mixture of 20 mL (ethanol:DMF:$CHCl_3$/5:6:2) at 100 °C for 6 h. After completion of the reaction, the reaction mixture was cooled to room temperature. After cooling, the reaction mixture was added dropwise to ether (300 mL) with stirring. The solid precipitate was filtered and washed with ether (100 mL) and hexane to afford **1** (2.25 g, 88% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) *δ*: 8.98 (d, *J* = 4.5 Hz, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.11 (d, *J* = 8.4 1H), 7.87−7.80 (m, 2H), 7.77−7.73 (m, 3H), 7.58−7.56 (m, 3H), 6.67 (d, *J* = 4.5 Hz, 1H), 6.56 (d, *J* = 3.6 Hz, 1H), 5.73−5.62 (m, 1H), 5.21−5.13 (m, 2H), 5.05 (d, *J* = 12.3 Hz, 1H), 4.94 (d, *J* = 10.5 Hz, 1H), 4.32−4.25 (m, 1H), 3.97−3.91 (m, 1H), 3.78 (d, *J* = 12.3 Hz, 1H), 3.26−3.18 (m, 2H), 2.69 (s, 1H), 2.15−1.99 (m, 3H), 1.85−1.77 (m, 1H), 1.32−1.24 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 150.1, 147.4, 145.5, 138.0, 133.8, 130.1, 129.6, 129.5, 128.9, 128.0, 127.4, 124.3, 123.9, 120.1, 116.4, 67.5, 64.0, 62.4, 59.1, 50.6, 36.8, 25.9, 24.2, 21.0. IR (KBr) *ν*: 3296, 3090, 2922, 2190, 1967, 1663, 1608, 1587, 1510, 1458, 1343, 1214, 1127, 939, 799. $[\alpha]^{25}_D$ = −123 (*c* 1.0, DMSO).

A mixture of **1** (0.93 g, 2.0 mmol) with iodobenzene (0.45 g, 2.2 mmol) in the presence of 3 mol % Pd $(OAc)_2$ (0.06 mmol 0.01 g) and Et_3N (0.2 mL, 2.0 mmol) was stirred in 10 mL of dry DMF at 100 °C for 12 h. After completion of reaction, the reaction mixture was cooled to room temperature. The reaction mixture was filtered by filter paper and poured into ether (300 mL) with stirring. The solid precipitate was filtered, washed with water, ether, ethyl acetate, and hexane to afford **2** (1.09 g, 94% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) *δ*: 8.99 (d, *J* = 4.0 Hz, 1H), 8.36 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 12.2 Hz, 1H), 7.58 (s, 3H), 7.25−7.14 (m, 4H), 6.72−6.50 (m, 2H), 6.23−6.06 (m, 1H), 5.41−4.96 (m, 2H), 4.29−3.84 (m, 2H), 3.45−3.39 (m, 1H), 3.12−3.10 (m, 2H), 2.96−2.91 (m, 2H), 2.08 (d, *J* = 13.2, 2H), 1.86−1.46 (m, 1H), 1.20−1.16 (m, 5H). ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 150.6, 148.0, 146.0, 137.0, 134.3, 131.36, 130.7, 130.4, 130.2, 130.0, 129.5, 128.9, 128.5, 128.0, 127.9, 126.6, 124.9, 124.4, 120.6, 68.4, 64.6, 63.3, 60.4, 51.3, 37.2, 27.0, 24.8, 21.6. IR (KBr) *ν*: 3231, 2943, 1590, 1508, 1388, 1233, 1160, 1032, 758, 701. $[\alpha]^{25}_D$ = 94.70 (*c* 1.0, DMSO).

Synthesis of Cinchonidinium Salt Dimer D1. A mixture of **1** (1.21 g, 2.60 mmol) with 2,7-naphthalene disodium disulfonate (0.42 g, 1.25 mmol) was stirred in a mixture of CH_2Cl_2 (20 mL) and H_2O (10 mL) at room temperature for 30 min. After completion of reaction, the reaction mixture was filtered through a glass filter and washed with CH_2Cl_2, water, and hexane. The solid obtained was dried under vacuum at 40 °C to afford 1.20 g (91% yield) of **D1a**. ^{1}H NMR (DMSO-d_6, 300 MHz) *δ*: 8.98 (d, *J* = 4.5 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 2H), 7.86−7.82 (m, 3H), 7.77−7.69 (m, 4H), 7.56 (s, 3H), 6.79 (d, 1H), 6.57 (s, 1H), 5.76−5.61 (m, 1H), 5.16−5.10 (m, 2H), 4.99−4.92 (m, 2H), 4.24 (s, 1H), 3.94−3.88 (m, 1H), 3.71 (d, *J* = 11.1 Hz, 1H), 3.32−3.20 (m, 2H), 2.68 (s, 1H), 2.15−1.98 (m, 3H), 1.84−1.76 (m, 1H), 1.32−1.24 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 150.2, 147.6, 145.9, 145.4, 138.6, 133.8, 132.6, 131.3, 130.2, 129.9, 129.5, 129.0, 127.9, 127.3, 124.6, 124.4, 123.6, 120.1, 116.4, 67.6, 64.2, 62.9, 59.2, 50.6, 36.9, 25.9, 24.2, 20.9. IR (KBr) *ν*: 3209, 3006, 2849, 1935, 1845.54, 1640, 1590, 1509, 1498, 1459, 1422, 1267, 1062, 779, 698. $[\alpha]^{25}_D$ = −122 (*c* 1.0, DMSO); mp 230−232 °C.

Synthesis of Main-Chain Chiral Polymers P1a from Ionic Dimer D1a Using Mizoroki−Heck Reaction. A mixture of ionic dimer **D1a** (0.53 g, 0.5 mmol) with 4,4′-diiodobiphenyl (0.20 g, 0.5 mmol) in the presence of 3 mol % Pd $(OAc)_2$ and Et_3N (0.07 mL, 0.5 mmol) was stirred in 15 mL of dry DMF at 100 °C for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was then added dropwise into water (400 mL) with stirring. The solid precipitate was filtered and

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washed with water, ether, ethyl acetate, CH_3OH, and hexane to afford 0.42 g (70% yield) of the product. ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 150.2, 147.6, 145.9, 145.5, 138.3, 137.7, 135.6, 133.8, 132.6, 131.3, 130.5, 130.2, 129.9, 129.5, 129.0, 128.6, 127.9, 127.3, 126.7, 126.5, 126.4, 124.6, 123.7, 120.1, 68.0, 64.2, 63.1, 60.0, 50.9, 36.9, 26.5, 24.4, 21.0. IR (KBr) ν: 3230, 2948, 1919, 1700, 1655, 1591, 1508, 1457, 1316, 1217, 1180, 1101, 1026, 699. $[\alpha]^{25}_D = -135$ (c 1.0, DMSO); M_n (SEC) = 7.0×10^3; M_w/M_n = 1.71, dp = 6.

Mizoroki–Heck Phenylation of Cinchonidine Dimer D2b. A mixture of cinchonidine dimer **D2b**[14] (0.85 g, 1.0 mmol) with iodobenzene (0.45 g, 2.2 mmol) in the presence of 3 mol % $Pd(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL dry DMF at 100 °C for 12 h. The reaction mixture was then cooled to room temperature and poured into ether (400 mL) with stirring. The solid precipitated was filtered and washed with water, ether, ethyl acetate, and hexane to afford 0.96 g (96% yield) of **D2bPh**. ^1H NMR (DMSO-d_6, 400 MHz) δ: 8.99 (d, J = 4.4 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.13–8.09 (m, 1H), 8.01–7.93 (m, 1H), 7.84–7.78 (m, 3H), 7.32–7.15 (m, 4H), 7.04–6.20 (m, 3H), 5.39–4.93 (m, 3H), 4.39–3.61 (m, 2H), 3.40 (s, 4H), 3.22–2.91 (m, 1H), 2.29–1.80 (m, 4H), 1.49–1.43 (m, 1H), 1.21–1.16 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 150.3, 147.7, 145.4, 145.0, 136.5, 134.2, 130.8, 129.9, 129.4, 128.5, 128.4, 127.4, 126.1, 124.4, 124.2, 123.8, 120.1, 68.6, 68.1, 64.2, 62.4, 59.8, 36.7, 26.6, 24.1, 21.4. IR (KBr) ν: 3227, 2945, 1653, 1591, 1509, 1455, 1233, 1162, 954. $[\alpha]^{25}_D$ = 50.8 (c 1.0, DMSO).

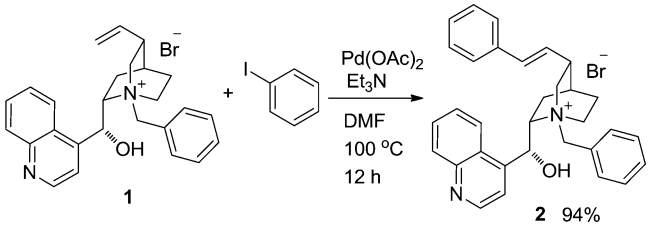
Synthesis of Main-Chain Chiral Polymer P2a from Cinchonidine Dimer D2a Using Heck Reaction. A mixture of cinchonidine dimer **D2a**[14] (0.86 g, 1.0 mmol) with 4,4′-diiodobiphenyl (0.41 g, 1.0 mmol) in the presence of 3 mol % $Pd(OAc)_2$ and Et_3N (0.14 mL, 1.0 mmol) was stirred in 15 mL of dry DMF at 100 °C for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was then added dropwise into water (400 mL) with stirring. The solid precipitate was filtered and washed with water, ether, ethyl acetate, and hexane to afford 0.7 g (71% yield) of the product. ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 150.3, 147.7, 146.7, 138.2, 135.9, 130.5, 129.9, 129.4, 127.1, 127.1, 127.1, 127.0, 126.9,126.8, 126.5, 126.4, 124.7, 123.6, 119.1, 66.2, 59.9, 53.9, 43.0, 37.8, 36.7, 27.3, 27.3, 23.9, 18.1. IR (KBr) ν: 3309, 3024, 2944, 1734, 1699, 1654, 1592, 1508, 1457, 1376, 1024, 807, 755. $[\alpha]^{25}_D$ = 58.7 (c 1.0, DMSO); $M_n = 1.4 \times 10^4$, M_w/M_n = 1.71, dp = 14.

General Procedure for Catalytic Enantioselective Benzylation of *N*-Diphenylmethylidene Glycine *tert*-Butyl Ester. Chiral polymeric catalyst (10 mol %) and *N*-diphenylmethylidene glycine *tert*-butyl ester **6** (0.53 g, 1.78 mmol) were added to a mixed solvent of toluene (7 mL) and chloroform (3 mL). 50 wt % aqueous KOH solution (2.5 mL) was added to the above mixture. Benzyl bromide (0.37 g, 2.14 mmol) was then added dropwise at 0 °C to the mixture. The reaction mixture was stirred vigorously for 8 h. Saturated sodium chloride solution (10 mL) was then added, and the organic phase was extracted with ethyl acetate and concentrated *in vacuo* to give the crude product as colorless oil. Purification of the residual oil by column chromatography on silica gel (ether–hexane = 1:10 as eluent) gave (*S*)-*tert*-butyl *N*-(diphenylmethylidene)phenylalanine **7**. The enantiomeric excess (91% ee) was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane-2-propanol = 100:1, flow rate = 0.3 mL min^{-1}, retention time: *R* enantiomer = 27.6 min, *S* enantiomer = 47.9 min). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[21]

RESULTS AND DISCUSSION

Synthesis of Cinchonidium Dimers and Polymers by Mizoroki–Heck Polymerization. As a model reaction of Mizoroki–Heck polymerization, *N*-benzylcinchonidinium bromide **1** was allowed to react with iodobenzene in the presence of $Pd(OAc)_2$.[22] Mizoroki–Heck coupling occurred smoothly to provide 11-phenyl-modified cinchonidinium salt **2** in 90% isolated yield (Scheme 1).

Scheme 1. Mizoroki–Heck Phenylation of Cinchonidinium Salt 1



In order to apply the Mizoroki–Heck coupling reaction for the synthesis of chiral polymers, cinchonidinium salt dimers **D1** and **D2** were prepared according to literature procedures (Schemes 2 and 3).[14]

In a previous paper, we found that the ion exchange reaction of cinchonidinium bromide **1** and sodium sulfonate occurred smoothly to afford the cinchonidinium sulfonate.[14] When disodium disulfonate **3** was used, the corresponding cinchonidium ionic dimer **D1** was formed in quantitative yield (Scheme 2). Cinchonidinium dimers **D2** were prepared by quaternization of cinchonidine **4** with dihalide **5** (Scheme 3) according to a previously reported procedure.[14] The corresponding phenylated derivative of **D2**, **D2bPh**, was also prepared in 96% yield by using the Mizoroki–Heck reaction (Scheme 4).

Since the Mizoroki–Heck reaction proceeded quantitatively on the vinyl positions in these cinichonidinium salts, we investigated the synthesis of chiral polymers by means of a repetitive Mizoroki–Heck coupling reaction. The Mizoroki–Heck coupling of dimer **D1** and 4,4′-diiodobiphenyl occurred smoothly in DMF to provide chiral polymers **P1** containing cinchonidinium repeating units in its main chain (Scheme 5). Under the same reaction conditions, the Mizoroki–Heck coupling of dimer **D2** with 4,4′-diiodobiphenyl affords chiral polymer **P2** (Scheme 6).

Next, we examined various reaction conditions for the Mizoroki–Heck polymerization of chiral dimer **D2** and 4,4′-diiodobiphenyl. Table 1 summarizes the result of the Mizoroki–Heck polymerization. Polymerization in refluxing THF failed to yield polymer even after 24 h (entry 1). The polymerization proceeded smoothly in DMF to provide the corresponding chiral polymer **P2**. The polymerization temperature was found to significantly influence the degree of polymerization. Lower molecular weight **P2d** (M_n = 5600) was obtained at 80 °C (entry 2), whereas higher molecular weight **P2d** (M_n = 37 000) could be obtained at 100 °C (entry 3). Under this polymerization condition, other dimers **D2** also gave the corresponding polymers **P2** with high molecular weight (entries 4–6). The use of $PdCl_2$ as a catalyst during the reaction at 100 °C afforded a lower molecular weight polymer (entry 7). The polymerization reaction in DMSO at 100 °C resulted in the same chiral polymer with lower molecular weight (entry 8).

In order to evaluate the catalytic activity of the resulting cinchonidinium salts containing chiral polymers **P1** and **P2**, the enantioselective alkylation of *N*-diphenylmethylene glycine *tert*-butyl ester **6** was investigated with these chiral quaternary ammonium salts in a biphasic system comprising organic and aqueous layers. Table 2 summarizes the results for the asymmetric benzylation of **6** with monomeric catalysts **1** and **2**, dimeric catalysts **D1**, and polymeric catalysts **P1**. From entries 1 and 2, it can be seen that the Mizoroki–Heck modification on the cinchonidine double bond (C10–C11)

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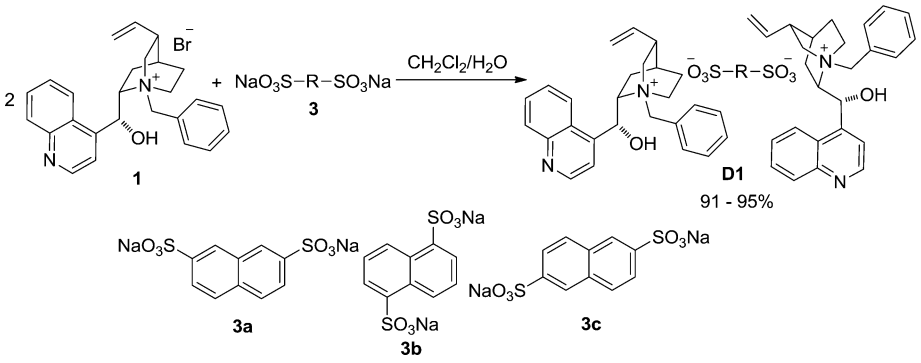
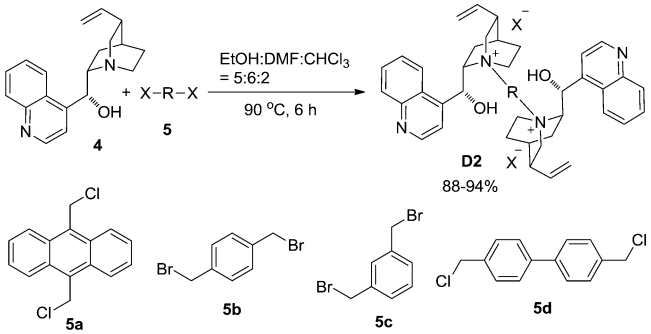
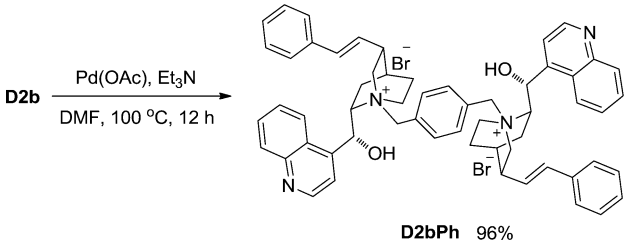
Scheme 2. Synthesis of Cinchonidinium Ionic Dimer D1



Scheme 3. Synthesis of Cinchonidinium Dimer D2



Scheme 4. Mizoroki–Heck Phenylation of D2

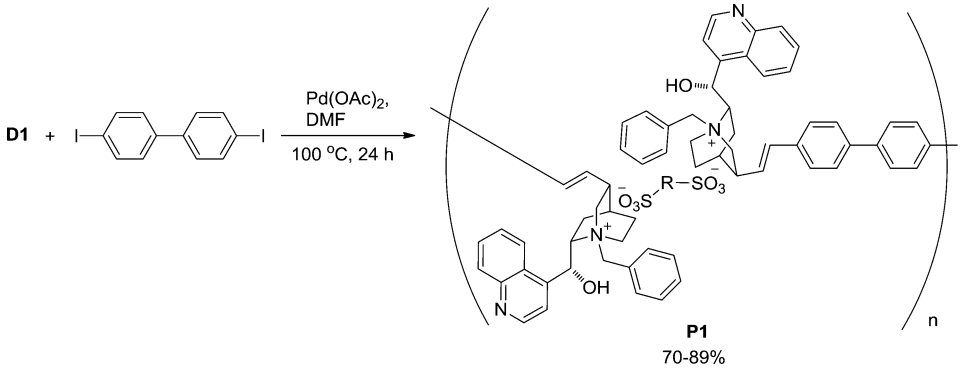


had no significant influence on the asymmetric benzylation reaction. The same enantioselectivity (71%) was observed for either monomeric catalyst. The dimeric catalysts **D1** afforded somewhat higher enantioselectivities (entries 3–5). Chiral polymers **P1** derived from dimer **D1** were then used as catalysts in the same reaction. Although the chiral polymers were not soluble in either the organic or aqueous phase, they showed high catalytic activity in the alkylation reaction. In the presence of the chiral polymeric catalyst **P1**, *N*-diphenylmethylene glycine *tert*-butyl ester **6** was smoothly benzylated to afford the chiral product **7** in quantitative yield although with somewhat decreased enantioselectivities (entries 6–8).

Table 3 summarizes the results for the asymmetric benzylation of **6** with dimeric catalysts **D2** and polymeric catalysts **P2**. Dimeric catalysts **D2** exhibited a better catalytic performance in the enantioselective benzylation of **6** (entries 1–4). Phenylated dimer **D2bPh** also showed high catalytic activity (entry 5). Polymeric catalysts **P2** also demonstrated high levels of catalytic activity similar to the **P1** catalysts. In the presence of **P2b**, ester **6** was asymmetrically benzylated to provide **7** in 83% yield with 91% ee (entry 7), which is much higher than that obtained for the low-molecular-weight catalysts in solution (80% ee for the corresponding dimeric (entry 2) and 71% ee for the monomeric catalyst (Table 1, entry 2)). Although there is no clear explanation why **P2b** showed higher enantioselectivity in the asymmetric reaction, conformational modifications on the catalytic site may occur during polymer formation. **P2b** might have a suitable conformation for the asymmetric catalysis. Moreover, **P2b** was easily separated from the reaction mixture and reused. The polymeric catalyst could be reused at least twice without loss of the catalytic activity (entries 8 and 9).

Chiral polymers **P2** can be prepared by the quaternization polymerization of dimeric cinchonidine **D3** with dihalide instead of the Mizoroki–Heck polymerization of **D2** with diiodide (Scheme 7). Dimer **D3** was prepared by the Mizoroki–Heck reaction of cinchonidine with 4,4′-diiodobiphenyl, and equimolar amounts of dihalide **5d** was allowed to react with **D3** to afford the corresponding quaternized polymer

Scheme 5. Mizoroki–Heck Polymerization of D1



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Scheme 6. Mizoroki–Heck Polymerization of D2

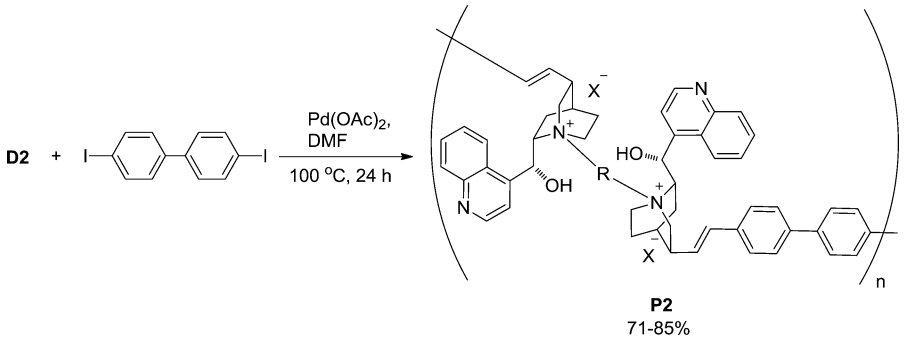
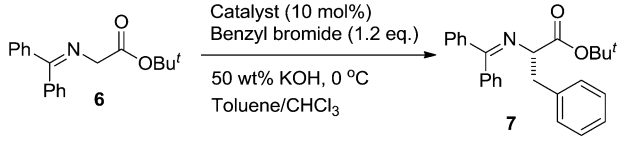


Table 1. Synthesis of Chiral Polymer P2 by Mizoroki–Heck Polymerization

entry	dimer D2	polymer P2	Pd catalyst	solvent	temp (°C)	reaction time (h)	yield (%)	M_n[a]	M_w/M_n[a]
1	**D2d**	**P2d**	$Pd(OAc)_2$	THF	75	24	0		
2	**D2d**	**P2d**	$Pd(OAc)_2$	DMF	80	48	75	5 600	1.21
3	**D2d**	**P2d**	$Pd(OAc)_2$	DMF	100	24	76	37 000	1.43
4	**D2a**	**P2a**	$Pd(OAc)_2$	DMF	100	24	71	14 000	1.71
5	**D2b**	**P2b**	$Pd(OAc)_2$	DMF	100	24	85	29 000	1.66
6	**D2c**	**P2c**	$Pd(OAc)_2$	DMF	100	24	80	24 000	1.58
7	**D2d**	**P2d**	$PdCl_2$	DMF	100	24	70	6 600	1.21
8	**D2d**	**P2d**	$Pd(OAc)_2$	DMSO	100	24	72	6 500	1.20

[a]Determined by SEC measurement using DMF as a solvent at a flow rate of 1.0 mL/min at 40 °C.

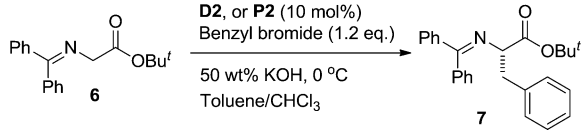
Table 2. Asymmetric Benzylation of *N*-Diphenylmethylene Glycine *tert*-Butyl Ester 6 with Cinchonidine-Based Catalysts[a]



entry	catalyst	time (h)	conv[b] (%)	yield[c] (%)	ee[d] (%)
1	**1**	5	100	91	71
2	**2**	5	100	89	71
3	**D1a**	4	100	88	78
4	**D1b**	4	100	90	79
5	**D1c**	4	100	84	76
6	**P1a**	5	100	83	70
7	**P1b**	5	100	83	66
8	**P1c**	5	100	85	65

[a]Reactions were performed with catalyst (0.178 mmol), *N*-diphenylmethylene glycine *tert*-butyl ester (**6**, 1.78 mmol), and benzyl bromide (2.14 mmol) in toluene/$CHCl_3$ (7/3, 10 mL) in the presence of 50 wt % KOH aqueous solution (2.5 mL). [b]Determined by ^1H NMR spectroscopy. [c]Isolated yield of 7. [d]Determined by HPLC (Chiralcel OD-H).

Table 3. Asymmetric Benzylation of *N*-Diphenylmethylene Glycine *tert*-Butyl Ester 6 with D2 and P2[a]



entry	catalyst	time (h)	conv[b] (%)	yield[c] (%)	ee[d] (%)
1[e]	**D2a**	6	100	88	86
2[f]	**D2b**	8	100	91	80
3[g]	**D2c**	4	100	90	84
4	**D2d**	4	100	89	83
5	**D2bPh**	5	100	85	83
6	**P2a**	6	100	75	64
7	**P2b**	8	100	83	91
8[h]	**P2b**	8	100	85	90
9[i]	**P2b**	8	100	80	91
10	**P2c**	4	100	69	76
11	**P2d**	5	100	83	82
12	**P2d**[j]	5	100	84	72

[a]Reactions were performed with catalyst (0.178 mmol), *N*-diphenylmethylene glycine *tert*-butyl ester (**6**, 1.78 mmol), and benzyl bromide (2.14 mmol) in toluene/$CHCl_3$ (7/3, 10 mL) in the presence of 50 wt % KOH aqueous solution (2.5 mL). [b]Determined by ^1H NMR spectroscopy. [c]Isolated yield of 7. [d]Determined by HPLC (Chiralcel OD-H). [e]Reference 23. [f]Reference 14a. [g]Reference 24. [h]**P2b** used in entry 7 was reused. [i]**P2b** used in entry 8 was reused. [j]Prepared by quaternization polymerization shown in Scheme 7.

P2d. **P2d**, prepared by the quaternized polymerization, was used as a catalyst for the benzylation reaction and lead to lower enantioselectivity (entry 10) when compared with the **P2d** obtained from the strategy employed in Scheme 6 (entry 9).

Having selected chiral polymer **P2b** as the best catalyst, we investigated the effects of reaction temperature and solvent employed in asymmetric benzylation of ester **6**, and the results are summarized in Table 4. Lowering the reaction temperature to −20 °C resulted in a somewhat higher enantioselectivity in toluene–chloroform (entry 3). Further lowering the reaction temperature to −40 °C led to a considerable reduction in the reaction rate, as reflected in the 58% yield with 93% ee after 72 h (entry 4). The toluene:chloroform ratio was also found to affect the catalytic activity. The optimum solvent ratio for the reaction with polymeric catalyst **P2b** was found to be 5:5 toluene:chloroform. In this equivolume mixed solvent system, enantioselective benzylation of **6** provided high yields of product 7 in 95% ee at −20 °C (entry 6).

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Scheme 7. Quaternization Polymerization of D3

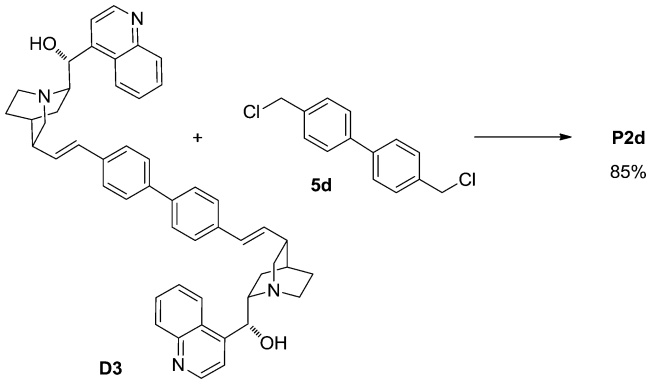
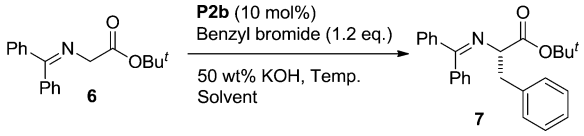


Table 4. Solvent and Temperature Effect on Asymmetric Benzylation of Ester 6 with Catalyst P2b[a]



entry	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	toluene	0	10	84	72
2	toluene:$CHCl_3$ = 7:3	0	8	83	91
3	toluene:$CHCl_3$ = 7:3	−20	24	99	94
4	toluene:$CHCl_3$ = 7:3	−40	72	58	93
5	toluene:$CHCl_3$ = 5:5	0	6	99	93
6	toluene:$CHCl_3$ = 5:5	−20	24	93	95
7	toluene:$CHCl_3$ = 3:7	0	6	84	92
8	$CHCl_3$	0	6	80	90

[a]Reactions were performed with catalyst **P2b** (0.178 mmol), *N*-diphenylmethylene glycine *tert*-butyl ester (**6**, 1.78 mmol), and benzyl bromide (2.14 mmol) in solvent (10 mL) in the presence of 50 wt % KOH aqueous solution (2.5 mL). 100% conversion of **6** was attained for all entries. [b]Isolated yield of **7**. [c]Determined by HPLC (Chiralcel OD-H).

In conclusion, we have successfully synthesized chiral quaternized polymers by means of a Mizoroki−Heck coupling reaction. The alkene moiety of cinchonidinium dimers smoothly reacted with aromatic diiodides to form the chiral polymers. These polymers exhibited excellent catalytic activities in the enantioselective benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester **6**, and high levels of enantioselectivity were obtained from the polymeric catalyst derived from cinchonidinium dimer **D2**. In the presence of **P2b**, the enantioselective benzylation of **6** occurred smoothly to give **7** in higher yields and enantioselectivities (up to 95% ee) than those obtained from the corresponding low-molecular-weight catalyst in solution. We are currently surveying the catalytic activity of the chiral quaternized polymers in various asymmetric transformations other than benzylation.

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Notes

The authors declare no competing financial interest.

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