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SYNTHESIS OF CHIRAL QUATERNARY AMMONIUM POLYMERS FROM CINCHONIDINE DIMER AND THEIR APPLICATIONS IN ASYMMETRIC BENZYLATION OF GLYCINE DERIVATIVE

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Abstract

Quaternization polymerization between cinchonidine dimer and dihalide gives chiral quaternary ammonium polymers. These polymers were used as chiral polymeric organocatalyst in asymmetric benzylation of glycine derivative. High yield and good enantioselectivity was obtained.

Keywords**:** Cinchonidine, Heck coupling, Main-chain chiral polymers, Quaternary ammonium polymers, Asymmetric benzylation.

Introduction

Cinchona alkaloids with pseudoenantiomeric forms such as quinine and quinidine or cinchonine and cinchonidine are one of the most important chirality inducers in the area of asymmetric catalysis (O'Donnell et al., 1989). The quinuclidine nitrogen of the cinchona alkaloid can easily be quaternized and the OH group also can be modified (Lygo et al., 1997; Corey et al., 1997; Jew et al., 2001). The double bond of the cinchona alkaloid also can be hydrogenated (Lee et al., 2007) and dehydrogenated (Park et al., 2001). Thiol-ene click reaction (Park et al., 2002) and Heck coupling (Chinchilla et al., 2002) reaction also can be carried out at the double bond of cinchonidine. We have found that the double bond of cinchonidine can be modified using Heck coupling reaction (Heck et al., 1972). We utilized the double bond of cinchonidine for the synthesis of cinchonidine dimer **(2)** using Heck coupling. Quaternization of **2** gives the polymer **(QP-2).**

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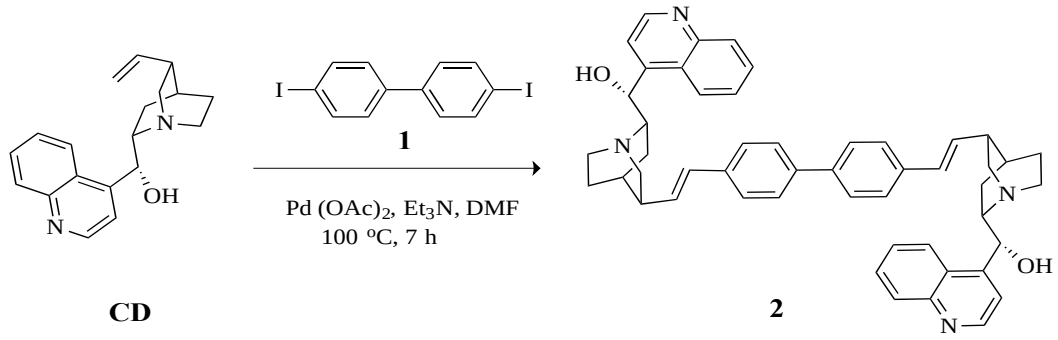
Experimental

General

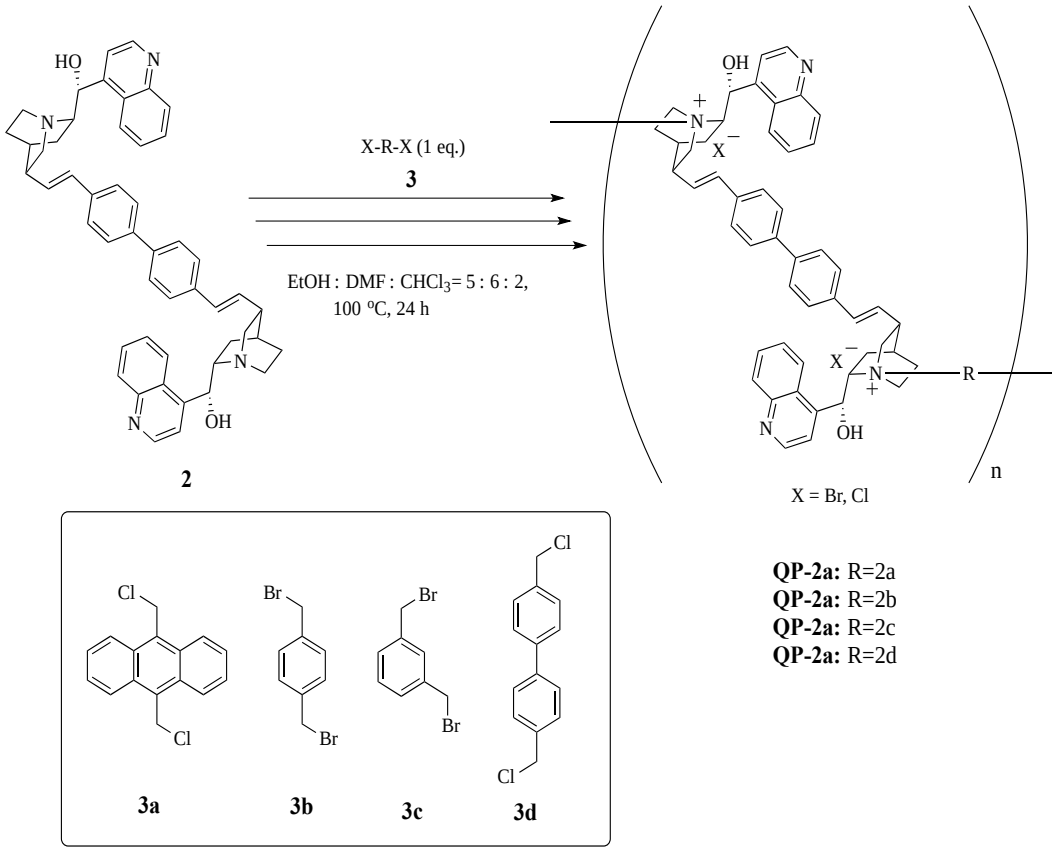
All reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., and Tokyo Chemical Industry Co., Ltd. at the highest available purity and used as is unless noted otherwise. DMF was distilled from calcium hydride before use. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica-gel plates (Merck 5554, 60F254). 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 recorded. ^{1}H (300 MHz and 400 MHz) and ^{13}C NMR (75 MHz and 100 MHz) spectra were measured on Mercury 300 and Jeol ECS 400 spectrometer. Elemental analysis was performed at the Microanalytical Center of Kyoto University. HPLC analysis was 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 ODH); hexane and 2-propanol were 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) and refractive index detection. DMF was used as a carrier solvent at a flow rate of 1.0 mL/min at 40 ^{o}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 cinchonidine dimer and main-chain chiral polymers

Dimer **2**was synthesizedby utilizing the double bond of cinchonidine. Heck coupling reaction between cinchonidine **(CD)** and 4, 4′-diiodobiphenyl gives **2(**Scheme 1). When equimolar amounts of **2** and dihallide **(3)** were allowed to react together and repeated quaternization reaction between **2** and **3** gives the main-chain chiral polymer **(QP-2)** (Scheme 2). The quaternization polymerization occurred smoothly in mixed solvent system to give **QP-2**. The number average molecular weight of the polymers synthesize in this work is in the range of 4600-5200.



Scheme 1. Synthesis of cinchonidine dimer



Scheme 2. Synthesis of main-chain chiral quaternary ammonium polymers

Synthesis of dimer (2)

A mixture of **CD** (0.59 g, 2.0 mmol) with 4, 4'-diiodo biphenyl (**1)** (0.41 g, 1.0 mmol) in 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 ^oC for 12 h. After completion of reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture to room temperature, the reaction mixture was filtered by filter paper and added drop wise to ether (400 mL) with stirring. The solid precipitate was filtered, washed with water, ether, ethyl acetate and hexane, 0.65 g (88 % yield) product was obtained.^{1}H NMR (d^6-DMSO, 300 MHz) δ 8.93 (s,1H), 8.33 (d, J = 7.2 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 6.9, 1H), 7.75~7.66 (m, 3H), 7.60~7.52 (m, 1H), 7.39 (d, J = 6.9 Hz, 1H), 7.25~7.18 (m, 1H), 6.51~6.30 (m, 2H), 5.84 (s, 1H),3.90~3.54 (m, 3H), 3.20~3.15 (m, 2H), 2.83~2.72 (m, 1H), 2.03~1.91 (m, 2H), 1.81~1.71 (m, 2H), 1.55~1.44 (m, 1H), 1.23~0.75 (m, 1H) .^{13}C NMR (d^6-DMSO, 100 MHz) δ 150.22, 147.86, 138.17, 136.16, 129.85, 129.09, 128.76, 128.41, 126.99, 126.67, 126.51, 126.37, 125.50, 123.86, 119.17, 68.73, 60.49, 55.36, 42.35, 38.10, 32.24, 27.64, 26.97. IR (KBr) υ 3315, 2931, 2639, 1653, 1590, 1509, 1456, 1422, 1386, 1237, 1175, 1093, 952, 853. $[\alpha]_D^{25} = +0.32$ (c 1.0, DMSO). Mp = 188~190.

General procedure for the synthesis of QP-2

A mixture of **2** (1 mmol) and **3** (1 mmol) in a mixed solvent EtOH:DMF:$CHCl_3$=5:6:2 (10 mL) were stirred at 100 ^oC for 24 h. After completion of the reaction, the reaction mixture was added dropwise to ether (400 mL) with stirring. The solid precipitate was filtered, washed with water ether and Hexane; dried under vacuum oven to obtain the polymeric product (**QP-2)**.

IR spectral data and values of M_w and M_n of **QP2a-QP2d** are given in the Table 1. IR spectram of all polymers were recorded using KBr plate.

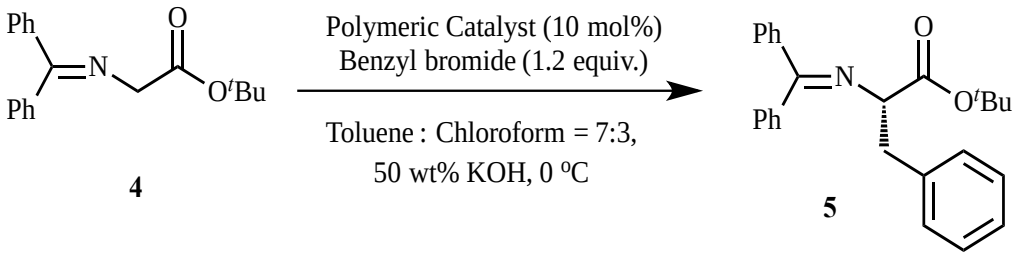
Table 1. IR Spectral data values molecular weight.

Polymer	IR Spectral data/cm^{-1}	M_n	M_w/M_n
QP-2a	3356, 2936, 2766, 1635, 1590, 1509, 1458, 1422, 1314, 1236, 1175, 1021, 952	5200	1.03
QP-2b	3371, 2943, 2761, 1700, 1590, 1509, 1457, 1423, 1236, 1090, 952	5100	1.01
QP-2c	3370, 2942, 1698, 1590, 1508, 1456, 1236, 1090, 1002	4600	1.01
QP-2d	3372, 2931, 1698, 1651, 1615, 1496, 1456, 1395, 1236, 1087, 1003, 952	4500	1.01

Results and Discussion

Applications of main-chain chiral polymers in asymmetric benzylation of glycine derivative

Sincelow molecular weight quaternary ammonium saltsand dimeric quaternary ammonium saltshave catalytic activity in asymmetric benzylation of glycine derivative **(4)** (O'Donnell et al. 1989; Lygo et al. 1997), so **QP-2** prepared from cinchonidine should show some catalytic activity. When **QP-2** was applied in asymmetric benzylation of glycine derivative (Scheme 3), good enantioselectivity was obtined which are summarized in the Table 1.



Scheme 3. Asymmetric benzylation of *N*-diphenylenemethylene glycene *tert*-butyl ester

Table 2. Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester using dimeric[a] and polymeric catalyst[a]

Entry	Catalyst	Time (h)	Yield[b](%)	ee[cd](%)
1	**QP-2a**	6	82	49
2	**QP-2b**	5	82	68
3	**QP-2c**	5	77	54
4	**QP-2d**	6	84	72

[a]The reaction was carried out 1.2 equiv. of benzyl bromide in the presence 10 mol% catalyst in 50 wt% aqueous KOH-toluene-$CHCl_3$ at 0 ^{o}C.[b] Determined by ^{1}H NMR.[c]Determined by HPLC (Chiralcel OD-H). [d]All products have S configuration.

Table 2. shows that main-chain polymer containing anthracenyl moiety **(QP-2a)** gave only 49% enantioselectivity whereas **QP-2b** containing *p*-xylene moiety gave 68% enantioselectivity. In case of *m*-xylene moiety containing main-chain polymer **(QP-2c)** gave 54% enantioselectivity. Polymer **QP-2d** containing biphenyl moiety gave highest, 72% enantioselectivity compare to other polymeric catalyst.

General procedure for catalytic enantioselective benzylation of N diphenylmethylidene glycine tert-butyl ester using chiral polymeric catalyst (QP-2d)

QP-2d (10 mol %) and *N*-diphenylmethylidene glycine *tert*-butyl ester **(4)** (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 drop wise 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. 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 comparing the HPLC retention time with the authentic sample independently synthesized by the reported procedure (O'Donnell et al. 1989).

Conclusion

In this work, we have synthesized a novel type of cinchonidine dimer **(2)** using Heck coupling reaction. Dimer **(2)** has been polymerized using quaternization polymerization to obtain the polymer **(QP-2)**. The polymers were employed as the polymeric organocatalyst in asymmetric benzylation glycine derivative toobtain the phenylalanine derivative **(5)**.

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