Tetrahedron 69 (2013) 3978–3983

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Synthesis of chiral quaternary ammonium polymers for asymmetric organocatalysis application

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ARTICLE INFO

Article history:
Received 7 February 2013
Received in revised form 27 February 2013
Accepted 5 March 2013
Available online 13 March 2013

Keywords:
Quaternary ammonium salt
Organocatalyst
Polymeric catalyst
Asymmetric alkylation
Cinchonidinium salt

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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0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.03.018

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

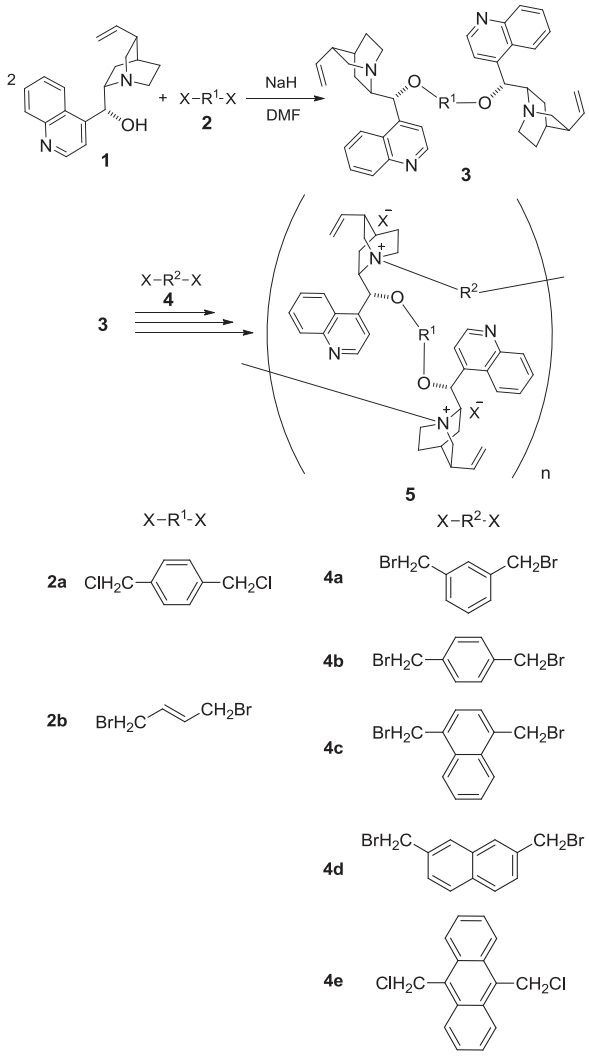
summarizes the result of quaternization polymerization of cinchonidine dimer **3a** and *p*-xylene dibromide **4b**. The polymerization in DMSO gave the chiral polymer **5b** in high yield, while the use of methanol and toluene resulted in no polymer formation. We used DMSO as solvent for the polymerization 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).

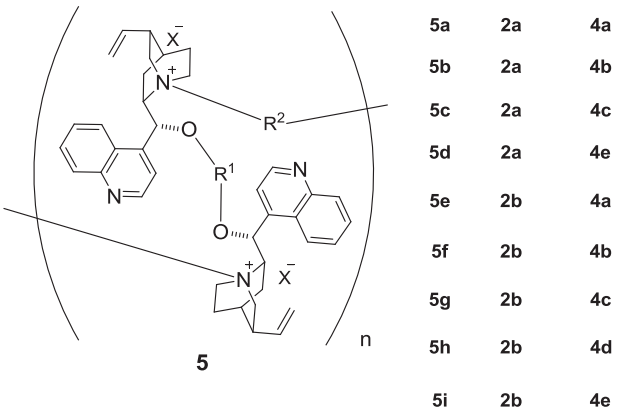
Next, we have prepared 10,11-hydrocinchonidine[17] derived quaternized ammonium polymers **9** by quaternization polymerization method (Scheme 3). 10,11-Hydrocinchonidine dimers **8** were prepared from 10,11-hydrocinchonidine and dihalide **2**. The dimers **8** were then allowed to react with dihalide **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.