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Syntheses of new dimeric-*Cinchona* alkaloid as a chiral phase transfer catalysts for the alkylation of Schiff base

Ayyanar Siva [a,*], Eagambaram Murugan [b]

[a] *Department of Chemistry, Gandhigram Rural Institute, Deemed University, Gandhigram 624302, TN, India*
[b] *Department of Physical Chemistry, School of Chemical Sciences, University of Madras, Guindy Campus, Chennai 600025, TN, India*

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Abstract

New dimeric cinchona quaternary ammonium salts have been synthesized and used as efficient chiral phase transfer catalysts for enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester giving very good chemical yield and up to 99% enantiomeric excess. The catalytic efficiency was compared with the previously reported single site chiral phase transfer catalysts.

Keywords: Enantioselection; Dimeric catalyst; Cinchona alkaloid; Phase transfer catalyst; Schiff base

1. Introduction

Phase transfer catalysis (PTC) is a very useful approach that typically involves simple experimental operations, mild reaction conditions, inexpensive, environmentally benign reagents and solvents and large-scale reactions [1]. From the original work of Makosza and Serafinowa [2] and the pioneering efforts of Starks [3] to the asymmetric advances of O'Donnell et al. [4], phase transfer catalysis has played a great role in organic synthesis [5]. The PTC systems have several advantages over single-phase systems including improved reaction rates, lower reaction temperature and absence of expensive anhydrous or aprotic solvents. Achiral phase transfer catalysts can be utilized to synthesize various types of amino acids. Thus, the most promising and widely used methods for the synthesis of α-amino acid derivatives involve the enantioselective alkylation of glycine imine (a Schiff base) with the corresponding alkyl halide under PTC conditions [6]. In addition, many other processes [6f] such as Michael addition [7a–c], Darzen's reaction [7d], epoxidation [7e–g], aldol condensation [7h–j] and fluorination [7k–m] have been studied recently under chiral phase transfer catalytic (CPTC) conditions. There are several CPTC, viz. spiro-ammonium [8] and phosphonium salts [9], TADDOL [10], binaphthyl derived amines [10b,11] and salen–metal complexes [12] used for the asymmetric synthesis of α-amino acids.

Cinchona alkaloid derived quaternary ammonium salts were used as chiral PTC due to their ready availability, low cost and their effectiveness as CPTCs [6]. The synthesis of mono-substituted α-amino acid derivatives via asymmetric phase-transfer catalysed alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **3** (Scheme 1) has been known for some time. The preparation of chiral compounds from achiral substrates with chiral catalysts under PTC condition is a powerful synthetic method for asymmetric synthesis [8a] in which there have been several notable successes [13–16]. Since the first cinchona alkaloid-type PTC **1a** was introduced by O'Donnell et al. [4], more efficient catalysts **2a** and **2b** have been developed independently by Lygo et al. [17a] and Corey et al. [17b,c] by introduction of bulky substituents, viz. *N*-9-anthracenylmethyl group instead of the benzyl group in **1** (Fig. 1). Based on the fact that the introduc-

* Corresponding author. Tel.: +91 451 2452371; fax: +91 451 22453071.
E-mail address: ptcsiva@yahoo.co.in (A. Siva).

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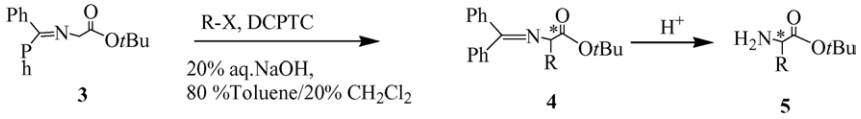

Scheme 1. Mono-alkylation of glycine imine under DCPT catalyst conditions.

tion of a bulky subunit at N1 of cinchona alkaloid leads to an enhancement of the stereoselectivity, recently dimeric [18] and trimeric [19] cinchona derived catalysts were reported for improved enantioselectivity for the alkylation of glycine imine **3**. Further, polymer supported cinchonidine and cinchonine ammonium salts were employed as recoverable PTC catalysts [20]. The *R* and *S* isomers formation of alkylated products would solely depend on chiral transfer between substrate and catalysts.

Systematic literature survey reveals that so far very few reports are available in the enantioselective synthesis of α-amino acids. Further, the catalytic abilities of these catalysts were studied using higher amount of aqueous base to carry out various organic reactions; such a reaction condition is not environmentally acceptable owing to heavy base pollution. It may be expected that the number of active site present per molecule should enhance its catalytic efficiency of reaction yield and ee's. Considering all the early studies, we have synthesized new soluble dimeric chiral phase transfer catalysts (DCPTC) **9** and **11** derived from cinchona alkaloid as a chiral precursor and its catalytic efficiency was studied by the enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **3** under mild reaction conditions.

2. Experimental

2.1. Materials

1,4-Dibromobutane (Merck), cinchonine (Fluka), cinchonidine (Fluka), acetonitrile (AR), dimethylformamide (AR), ethanol (AR), methanol (AR), sodiumborohydride (AR) and triethylamine (Merck). IR spectra were recorded on a JASCO-FT-IR model 5300 spectrometer using KBr pellet. ^{1}H NMR (300 and 200 MHz) and ^{13}C NMR (75 and 50 MHz) spectra were recorded in $CDCl_3$ on a Bruker AC-200 spectrometer using TMS as internal standard. Elemental analyses were recorded on a Perkin-Elmer 240-CHN analyzer. Optical rotations were measured with an Autopol II-automatic polarimeter at room temperature. For TLC analysis, plates coated with silica gel were run in benzene/methanol mixture and spots were developed in the iodine chamber. For column chromatographic separations under gravity, column silica gel (100–200 mesh) was employed.

2.2. 1,8-[N,N′-Bis-(4-bromobutyl)-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane]

5,5,7,12,12,14-Hexamethyl-1,4,8,11-tetraza-tricyclo [9.3.1.1^{4,8}]hexadecane **6** (10 g, 0.03 mol) was dissolved in acetonitrile (30 mL) and 1,4-dibromobutane (13.99 g, 0.066 mol) was rapidly added. This solution was stirred at room temperature (25 °C) for 3 days and the white precipitate formed was filtered, washed with small quantity of acetonitrile and dried under vacuum. This crude product 1,8-[*N*,*N*′-bis-(4-bromobutyl)-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane] was recrystalised from water to give white crystals. The yield was 89%. mp 164 °C (decomposition) $C_{26}H_{54}Br_4N_4$, FT-IR (KBr): 735, 3524 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16 (s, 18H, methyl), 1.63 (d 4H, methylene, J = 4.5 Hz), 1.73–1.76 (m, 8H, methylene), 3.24 (t, 2H, methyne, J = 7.9 Hz), 3.30–3.47 (m, 8H, methylene), 3.82–3.90 (m, 8H, methylene), 4.52–4.60 (m, 4H, methylene); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.5, 22.8, 26.4, 32.7, 41.2, 45.4, 51.3, 55.4, 56.5, 61.7, 79.6; *m*/*e* (ESI) M^+: 742.07.

2.3. Synthesis of 1,8-[N,N′-bis-(4-bromobutyl)-4,5,5,7,11,12,12,14-octamethyl-1,4,8,11-tetraazacyclotetradecane] (7)

1,8-[*N*,*N*′-Bis-(4-bromobutyl)-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane] (3.5 g, 6.03 mmol) was dissolved in acetonitrile (40 mL) and was added

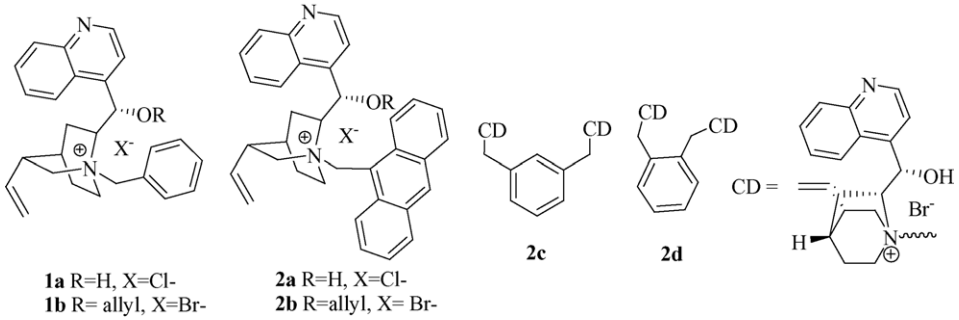

Fig. 1. Different types of chiral phase transfer catalysts synthesized from *Cinchona alkaloid*.