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

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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-

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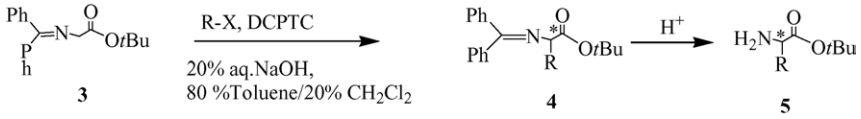



Scheme 1. Mono-alkylation of glycine imine under DCPT catalyst conditions.

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, $CDCl_3$) $\delta$: 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, $CDCl_3$) $\delta$: 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

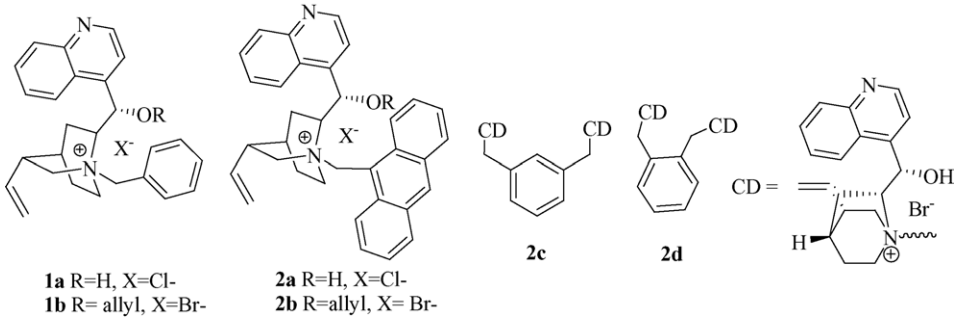



Fig. 1. Different types of chiral phase transfer catalysts synthesized from *Cinchona alkaloid*.

catalytic amount of $NaBH_4$ (0.91 g, 24.05 mmol) with constant stirring for 5 h, and then the solution was extracted with $CHCl_3$ (5 × 30 mL). Adding excess of triethylamine to the above reaction mixture restricted the formation of quaternization **7** with 1,4-dibromobutane. The combined $CHCl_3$ were dried with anhydrous $MgSO_4$ and concentrated under vacuum to give a pale yellow compound of 1,8-[*N*,*N*′-bis(4-bromobutyl)-4,5,5,7,11,12,12,14-octamethyl-1,4,8,11-tetraazacyclotetradecane] formed. The yield was 90%. FT-IR ($cm^{-1}$): 678, 1038, 1224; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.12 (s, 18H, methyl), 1.59 (d 4H, methylene, $J$ = 6.7 Hz), 1.70–1.79 (m, 8H, methylene), 3.30 (t, 2H, methyne, $J$ = 9.1 Hz), 3.35–3.50 (m, 8H, methylene), 3.78–3.88 (m, 8H, methylene); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 20.2, 26.4, 28.1, 31.7, 32.6, 34.2, 46.5, 49.6, 50.4, 51.3, 51.7, 62.3; *m*/*e* (ESI) $M^+$: 554.42.

### 2.4. Synthesis of cinchonine derived dimeric chiral phase transfer catalysts (DCPTC-*9a*)

1,8-[*N*,*N*′-Bis(4-bromobutyl)-4,5,5,7,11,12,12,14-octamethyl-1,4,8,11-tetraazacyclotetradecane] **7** (1.5 g, 2.70 mmol) was treated with cinchonine **8** (2.2 equivalent, 1.75 g, 5.94 mmol) in ethanol/DMF/$CH_2Cl_2$ (volume ratio = 30:50:20) at 100 °C for 12 h. After completion of reaction time, the solvent was removed by vacuum distillation to give the compound **9a**. Then, the crude compound of **9a** was purified by silica gel column chromatography using ethanol:benzene (volume ratio = 20:80) as an eluent. The yield was 94%. Decomposition temperature 274 °C; FT-IR ($cm^{-1}$): 3525, 2657, 1678, 1223; $^1H$ NMR (300 MHz, DMSO $d^6$) $\delta$: 1.13 (s, 18H, $-CH_3$), 1.39–1.44 (d, 4H, $-CH_2$, $J$ = 3.6 Hz), 1.50–1.60 (m, 2H, –CH), 1.65–1.68 (m, 8H, $-CH_2$), 1.71–1.74 (m, 4H, $-CH_2$), 2.15–2.25 (broad, s, 2H, –OH), 2.27 (s, 6H, $-CH_3$), 2.46–2.51 (m, 8H, $-CH_2$), 2.65–2.69 (m, 6H, $-CH_2$), 2.72–2.76 (m, 4H, $-CH_2$), 2.78–2.82 (m, 4H, –CH), 3.24 (m, 4H, $-CH_2$), 3.27–3.40 (m, 4H, $-CH_2$), 3.81–3.90 (m, 2H, –CH), 4.12–4.35 (m, 2H, –CH), 5.13 (d, 4H, $J$ = 6.0 Hz, vinyl), 5.75 (t, 2H, $J$ = 4.5 Hz, –CH), 7.147.56 (m, 8H, aromatic), 8.09–8.36 (m, 4H, aromatic); $^{13}C$ NMR (75 MHz, DMSO $d^6$) $\delta$: 20.5, 22.3, 23.1, 28.4, 28.8, 29.2, 30.6, 34.0, 38.0, 38.9, 43.6, 44.5, 45.7, 51.2, 51.6, 54.2, 59.2, 61.7, 65.7, 69.2, 80.3, 114.4, 119.8, 123.2, 125.5, 126.5, 128.8, 129.7, 140.3, 143.8, 148.3, 149.3; HRMS (ESI): Calc. 984.8, Found 984.7; $C_{62}H_{94}N_8O_2Br_2$: Calc. Value—C 65.13, H 8.29, N 9.80; Found—C 65.35, H 8.10, N 9.39.

### 2.5. Synthesis of cinchonidine based dimeric chiral phase transfer catalyst (DCPTC-*11a*)

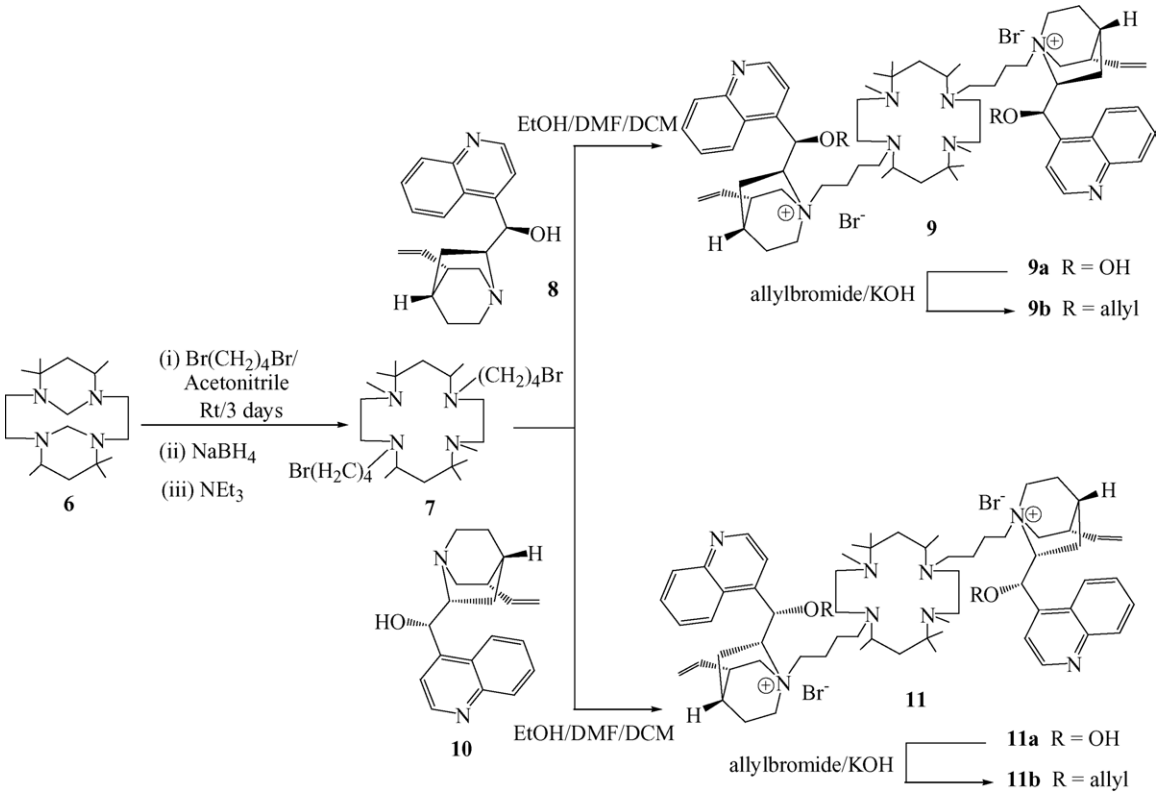
The same procedure (Section 2.4) was followed to synthesize compound **11a** from cinchonidine **10** treated with **7**. The yield was 91%. Decomposition temperature 290–292 °C; FT-IR ($cm^{-1}$): 3525, 2655, 1670, 1225; $^1H$ NMR (300 MHz, DMSO $d^6$) $\delta$: 1.15 (s, 18H, $-CH_3$), 1.35–1.39 (d, 4H, $-CH_2$, $J$ = 12.9 Hz), 1.53–1.61 (m, 2H, –CH), 1.64–1.70 (m, 8H, $-CH_2$), 1.71–1.74 (m, 4H, $-CH_2$), 2.25 (s, 6H, $-CH_3$), 2.45–2.55 (m, 8H, $-CH_2$), 2.65–2.69 (m, 6H, $-CH_2$), 2.74–2.80 (m, 4H, $-CH_2$), 2.82–2.87 (m, 4H, –CH), 3.25–3.30 (m, 4H, $-CH_2$), 3.33–3.40 (m, 4H, $-CH_2$), 3.81–3.92 (m, 2H, –CH), 4.13–4.17 (m, 2H, –CH), 5.10–5.15 (d, 4H, $J$ = 15.96 Hz, vinyl), 5.52 (broad, s, 2H, –OH), 5.75 (t, 2H, $J$ = 5.2 Hz, –CH), 7.10–7.66 (m, 8H, aromatic), 8.12–8.41 (m, 4H, aromatic); $^{13}C$ NMR (75 MHz, DMSO $d^6$) $\delta$: 20.2, 22.5, 24.3, 27.3, 28.4, 29.6, 31.6, 33.2, 38.5, 38.9, 43.7, 45.5, 45.7, 51.4, 51.7, 54.5, 59.7, 61.8, 66.7, 69.6, 81.3, 114.5, 119.9, 123.3, 124.5, 126.7, 127.8, 129.2, 141.3, 145.8, 149.2, 149.8; HRMS (ESI): Calc. 984.8, Found 984.7; $C_{62}H_{94}N_8O_2Br_2$: Calc. Value—C 65.13, H 8.29, N 9.80; Found—C 65.05, H 7.98, N 9.75.

### 2.6. Synthesis of allylated cinchonine derived dimeric chiral phase transfer catalyst (DCPTC-*9b*)

The compound **9a** (0.42 g, 0.36 mmol) was treated with allyl bromide (0.087 g, 0.72 mmol) and 50% aqueous KOH (15 mL) in the presence of DMF/$CH_2Cl_2$ (volume ratio = 40:60) at 100 °C for 18 h. After completion of reaction time, the reaction mixture was poured into ice cold water to remove solvents, and then the crude product of **9b** was purified by silica gel column chromatography using benzene:methanol (volume ratio = 80:20). The yield was 95%. Decomposition temperature 297 °C; FT-IR ($cm^{-1}$): 3045, 2687, 1676, 1225; $^1H$ NMR (300 MHz, DMSO $d^6$) $\delta$: 1.11 (s, 18H, $-CH_3$), 1.35–1.39 (m, 4H, $-CH_2$), 1.57–1.60 (m, 2H, –CH), 1.64–1.67 (m, 8H, $-CH_2$), 1.70–1.74 (m, 4H, $-CH_2$), 2.34 (s, 6H, $-CH_3$), 2.44–2.49 (m, 8H, $-CH_2$), 2.62–2.66 (m, 6H, $-CH_2$), 2.72–2.76 (m, 4H, $-CH_2$), 2.76–2.80 (m, 4H, –CH), 3.21–3.27 (m, 4H, $-CH_2$), 3.29–3.38 (m, 8H, $-CH_2$), 4.12–4.35 (m, 2H, –CH), 5.13–5.37 (m, 6H, vinyl), 5.69–5.73 (m, 3H, –CH), 6.47–6.51 (m, 6H, vinyl), 7.12–7.55 (m, 8H, aromatic), 8.13–8.44 (m, 4H, aromatic); $^{13}C$ NMR (75 MHz, DMSO $d^6$) $\delta$: 21.3, 22.8, 23.4, 28.5, 29.2, 30.4, 32.8, 35.6, 38.5, 40.9, 44.7, 45.5, 47.1, 51.4, 52.6, 54.2, 59.8, 62.7, 66.7, 68.2, 81.3, 82.7, 117.2, 121.7, 124.5, 125.1, 128.5, 130.8, 131.4, 141.2, 145.2, 148.7, 151.5, 154.2; HRMS (ESI): Calc. 1063.8, Found 1063.8; $C_{68}H_{102}N_8O_2Br_2$: Calc. Value—C 66.76, H 8.40, N 9.16; Found—C 66.02, H 8.28, N 8.99.

### 2.7. Synthesis of allylated cinchonidine derived dimeric chiral phase transfer catalyst (DCPTC-*11b*)

The same methodology (Section 2.6) has been adopted for the synthesis of DCPTC catalyst **11b** from cinchonidine based dimeric catalyst **11a** (Scheme 2). The yield was 87%. Decomposition temperature 276 °C; FT-IR ($cm^{-1}$): 3045, 2685, 1676, 1228; $^1H$ NMR (300 MHz, DMSO $d^6$) $\delta$: 1.15 (s, 18H, $-CH_3$), 1.38–1.43 (m, 4H, $-CH_2$), 1.55–1.59 (m, 2H, –CH), 1.65–1.68 (m, 8H, $-CH_2$), 1.70–1.77 (m, 4H, $-CH_2$), 2.40 (s, 6H, $-CH_3$), 2.44–2.49 (m, 8H, $-CH_2$), 2.65–2.70 (m, 6H, $-CH_2$), 2.72–2.76 (m, 4H, $-CH_2$), 2.76–2.80 (m, 4H,




Scheme 2. A schematic diagram for the synthesis of DCPT catalysts.

–CH), 3.21–3.28–3.44 (m, 4H, $–CH_2$), 3.48–3.53 (m, 8H, $–CH_2$), 4.55–4.60 (m, 2H, –CH), 5.12–5.21 (m, 6H, vinyl), 5.42–5.45 (d, 4H, $J = 9.4$ Hz, vinyl), 5.69–5.73 (m, 3H, –CH), 6.47–6.50 (t, 2H, $J = 4.7$ Hz, vinyl), 7.07–7.63 (m, 8H, aromatic), 8.10–8.47 (m, 4H, aromatic); $^{13}$C NMR (75 MHz, DMSO d$^6$) $\delta$: 19.3, 20.4, 22.5, 24.4, 28.6, 28.2, 31.4, 33.8, 35.6, 37.5, 41.3, 44.7, 45.6, 47.5, 51.4, 53.6, 54.2, 58.8, 61.7, 65.7, 67.2, 83.3, 87.4, 116.2, 120.3, 125.1, 125.9, 127.5, 132.8, 133.2, 144.5, 146.3, 148.7, 153.5, 155.6; HRMS (ESI): Calc. 1063.8, Found 1063.6.

### 2.8. Common procedure for enantioselective catalytic alkylation of *3* under DCPTCs conditions

To a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester **3** (50 mg, 0.17 mmol) and DCPT catalyst **9** or **11** (5 mg, $2.5 \times 10^{-3}$ mmol) in toluene:$CH_2Cl_2$ (v/v = 8.0:2.0 mL), benzyl bromide (0.5 g, 2.9 mmol) was added. The reaction mixture was then cooled (−10 °C), and then 20% aqueous NaOH (0.25 mL) was added, stirred at −10 °C until the starting material was consumed (9 h). The suspension was diluted with ether (20 mL), washed with water ($2 \times 5$ mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. The crude product was further purified by column chromatography on silica gel using hexane:ethylacetate (volume ratio = 30:1) as an eluent, to form a desired product **4f** (91% yield and 93% ee) as a colourless oil. Then, the enantioselectivity of that compound was measured by chiral HPLC analysis (DAICEL Chiral OD, hexane:propan-2-ol = 50:2, flow rate 1.0 mL/min, 20 °C, λ = 254 nm; retention time *R* (major) 12.4 min, *S* enantiomer (minor) 22.3 min). The absolute configuration was assigned by the comparison of the HPLC retention time with the authentic sample synthesized by the previous reported procedures [17,18].

#### 2.8.1. tert-Butyl-3-(2-allyl)-2-diphenylmethylene amino propanoate (b, R)

Synthesized as Section 2.8 according to the reaction conditions listed in Table 1. Yield 96%. $[\alpha]_D^{25} + 13.1$ ($c = 0.2$, $CHCl_3$). FT-IR (KBr) cm$^{-1}$: 3065, 2926, 1720, 1629, 1245; $^1$H NMR (300 MHz, DMSO d$^6$) $\delta$: 1.40 (s, 9H), 2.65 (t, 2H, $J = 5.7$ Hz), 4.25 (t, 1H, $J = 6.6$ Hz), 4.95 (d, 2H, $J = 8.4$ Hz), 5.72 (m, 1H), 7.15–7.60 (m, 10H); $^{13}$C NMR (75 MHz, DMSO d$^6$) $\delta$: 28.3, 35.2, 57.4, 71.4, 114.6, 127.6, 128.5, 130.5, 137.8, 161.7, 175.9; *m/e* ($M^+$): 321.4.

#### 2.8.2. tert-Butyl-3-phenyl-2-diphenylmethylene amino propanoate (f, R)

Synthesized as Section 2.8 according to the reaction conditions listed in Table 1. Yield 91%. $[\alpha]_D^{25} + 12.4$ ($c = 0.2$, $CHCl_3$). FT-IR (KBr) cm$^{-1}$: 3025, 2906, 1710, 1525, 1235; $^1$H NMR (200 MHz, DMSO d$^6$) $\delta$: 1.45 (s, 9H), 3.25 (d, 2H, $J = 8.4$ Hz), 4.35 (t, 1H, $J = 4.0$ Hz), 7.12–7.35 (m, 15H); $^{13}$C NMR (50 MHz, DMSO d$^6$) $\delta$: 27.4, 37.6, 61.9, 73.0, 124.7, 125.3, 128.4, 128.9, 129.5, 130.8, 137.5, 141.6, 160.8, 176.9;

Table 1
Alkylation of glycine imine *tert*-butyl ester under DCPTCs conditions

| Entry | RX | Catalysts | Time (h) | Yield[a] (%) | % of ee[b] (configuration)[c] |
|---|---|---|---|---|---|
| a | $CH_2$=$CHCH_2Br$ | **9a** | 13 | 74 | 69(*R*) |
| b | $CH_2$=$CHCH_2Br$ | **9b** | 7 | 96 | 95(*R*) |
| c | $CH_2$=$CHCH_2Br$ | **11a** | 5 | 80 | 76(*S*) |
| d | $CH_2$=$CHCH_2Br$ | **11b** | 3 | 98 | 97(*S*) |
| e | $C_6H_5CH_2Br$ | **9a** | 6 | 76 | 82(*R*) |
| f | $C_6H_5CH_2Br$ | **9b** | 9 | 91 | 93(*R*) |
| g | $C_6H_5CH_2Br$ | **11a** | 10 | 72 | 76(*S*) |
| h | $C_6H_5CH_2Br$ | **11b** | 6 | 98 | 94(*S*) |
| I | 4-$CH_3C_6H_4CH_2Br$ | **9a** | 9 | 79 | 63(*R*) |
| j | 4-$CH_3C_6H_4CH_2Br$ | **9b** | 8 | 100 | 99(*R*) |
| k | 4-$CH_3C_6H_4CH_2Br$ | **11a** | 5 | 74 | 71(*S*) |
| l | 4-$CH_3C_6H_4CH_2Br$ | **11b** | 10 | 99 | 98(*S*) |
| m | 4-$CF_3C_6H_5CH_2Br$ | **9a** | 7 | 90 | 89(*R*) |
| n | 4-$CF_3C_6H_5CH_2Br$ | **9b** | 12 | 93 | 92(*R*) |
| o | 4-$CF_3C_6H_5CH_2Br$ | **11a** | 6 | 95 | 76(*S*) |
| p | 4-$CF_3C_6H_5CH_2Br$ | **11b** | 11 | 98 | 97(*S*) |
| q | 4-$FC_6H_5CH_2Br$ | **9b** | 10 | 95 | 99(*R*) |
| r | 4-$FC_6H_5CH_2Br$ | **11b** | 4 | 90 | 98(*S*) |
| s | 2-$NO_2C_6H_5CH_2Br$ | **9b** | 15 | 99 | 96(*R*) |
| t | 2-$NO_2C_6H_5CH_2Br$ | **11b** | 8 | 95 | 92(*S*) |
| u | 4-$CH_3OC_6H_5CH_2Br$ | **9b** | 10 | 96 | 90(*R*) |
| v | 4-$CH_3OC_6H_5CH_2Br$ | **11b** | 3 | 93 | 95(*S*) |
| w | HC≡$CCH_2Br$ | **9b** | 7 | 94 | 92(*R*) |
| x | HC≡$CCH_2Br$ | **11b** | 3 | 97 | 97(*S*) |
| y | $C_6H_5CH_2Br$ | **1b** | 10 | 76 | 34(*S*) |
| z | $C_6H_5CH_2Br$ | **2b** | 10 | 81 | 27(*S*) |
| $x_1$ | $C_6H_5CH_2Br$ | **2c** | 10 | 89 | 76(*S*) |
| $y_1$ | $C_6H_5CH_2Br$ | **2d** | 10 | 92 | 85(*S*) |

[a] Isolated yield of purified material.
[b] Enantiopurity was determined by HPLC analysis of the alkylated imine **4** using a chiral column (DAICEL Chiralcel OD) with hexane–propan-2-ol (50/2) as a solvent.
[c] Absolute configuration was determined by comparison of the HPLC retention time with the authentic samples independently synthesized by the reported procedure [8a,17,18].

*m*/*z* ($M^+$) 385.19; HRMS calcd. for $C_{26}H_{27}NO_2$: 386.2, Found 386.2.

### 2.8.3. *tert*-Butyl-3-(4-trifluoromethylphenyl)-2-diphenylmethyleneaminopropanoate (m, R)

Synthesized as Section 2.8 according to the reaction conditions listed in Table 1. Yield 90%. $[\alpha]_D^{25}$ + 14.3 ($c$ = 0.2, $CHCl_3$). FT-IR (KBr) $cm^{-1}$: 3076, 2904, 1732, 1610, 1230; $^1H$ NMR (300 MHz, DMSO $d^6$): 1.32 (s, 9H), 3.25–3.29 (d, 2H, $J$ = 12.0 Hz), 4.32–4.38 (t, 1H, $J$ = 9.0 Hz), 7.05–7.09 (d, 2H, $J$ = 12.0 Hz), 7.41–7.44 (d, 2H, $J$ = 9.0 Hz), 7.47–7.76 (m, 10H); $^{13}C$ NMR (75 MHz, DMSO $d^6$) $\delta$: 26.2, 37.3, 61.6, 73.2, 119.6, 125.3, 128.2, 128.6, 129.2, 130.5, 137.4, 143.8, 164.5, 178.2; *m*/*z* ($M^+$) 453.2.

### 2.8.4. *tert*-Butyl-3-(2-nitrophenyl)-2-diphenyl methylene aminopropanoate (t, S)

Synthesized as Section 2.8 according to the reaction conditions listed in Table 1. Yield 95%. $[\alpha]_D^{25}$ − 16.7 ($c$ = 0.2, $CHCl_3$). FT-IR (KBr) $cm^{-1}$: 3055, 2910, 1725, 1560, 1467, 1223, 1075; $^1H$ NMR (200 MHz, DMSO $d^6$) $\delta$: 1.15 (s, 9H), 3.12 (d, 2H, $J$ = 6.0 Hz), 4.25 (t, 1H, $J$ = 5.0 Hz), 7.23–7.66 (m, 14H); $^{13}C$ NMR (75 MHz, DMSO $d^6$) $\delta$: 28.4, 29.5, 60.6, 72.9, 123.6, 126.7, 128.6, 128.9, 129.1, 130.8, 134.2, 135.3, 137.6, 163.8, 176.2; (MS) *m*/*z* ($M^+$) 430.2.

### 2.8.5. *tert*-Butyl-3-(4-methoxyphenyl)-2-diphenyl methyleneaminopropanoate (u, R)

Synthesized as Section 2.8 according to the reaction conditions listed in Table 1. Yield 96%. $[\alpha]_D^{25}$ + 15.3 ($c$ = 0.2, $CHCl_3$). FT-IR (KBr) $cm^{-1}$: 3042, 2965, 1698, 1555, 1236, 786; $^1H$ NMR (200 MHz, DMSO $d^6$) $\delta$: 1.32 (s, 9H), 3.10 (s, 3H), 3.24 (d, 2H, $J$ = 10.0 Hz), 4.45 (t, 1H, $J$ = 4.0 Hz), 7.02 (d, 2H, $J$ = 6.0 Hz), 7.38 (d, 2H, $J$ = 4.0 Hz), 7.47–7.85 (m, 10H); $^{13}C$ NMR (50 MHz, DMSO $d^6$) $\delta$: 24.5, 37.7, 62.3, 71.3, 120.2, 127.5, 129.4, 130.4, 131.9, 132.5, 133.7, 137.5, 141.6, 161.3, 179.0; (MS) *m*/*z* ($M^+$) 415.18; HRMS calcd. for $C_{27}H_{29}NO_3$: 415.2, Found 415.2.

### 2.8.6. *tert*-Butyl-3-(2-propyne)-2-diphenylmethylene amino propanoate (w, R)

Synthesized as Section 2.8 according to the reaction conditions listed in Table 1. Yield 94%. $[\alpha]_D^{25}$ + 11.2 ($c$ = 0.2, $CHCl_3$). FT-IR (KBr) $cm^{-1}$: 3065, 2920, 1730, 1635, 1245; $^1H$ NMR (300 MHz, DMSO $d^6$) $\delta$: 1.43 (s, 9H), 1.87 (s, 1H), 2.73 (d, 2H, $J$ = 10.6 Hz), 4.25 (d, 1H, $J$ = 6.6 Hz), 7.15–7.60 (m, 10H); $^{13}C$ NMR (75 MHz, DMSO $d^6$) $\delta$: 21.3, 27.3, 56.2,

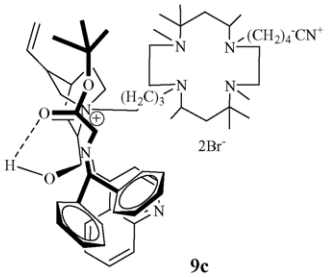
67.6, 73.4, 85.4, 116.8, 124.6, 129.5, 133.5, 137.2, 160.3, 172.1; *m*/*e* ($M^+$): 333.2.

## 3. Results and discussion

The efficacy of the dimeric CPT catalysts was evaluated from the alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **3** with different alkyl halides using $2.5 \times 10^{-3}$ mmol of catalysts **9** and **11** and 20% aqueous NaOH in toluene/$CH_2Cl_2$ (volume ratio = 8:2) at −10 °C for 5–15 h. The selected results are given in Table 1. The enantioselectivities of the alkylated products **4** were determined by chiral HPLC.

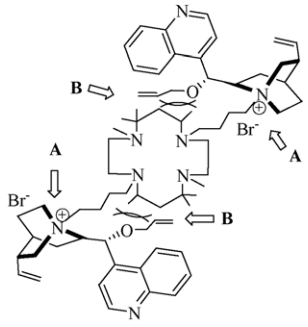
The corresponding amino acids were generally obtained in very good chemical yield and ee's (Table 1, entries a–z, $x_1$ and $y_1$). In all cases, the ee's were determined by HPLC analyses [20,21]. When the cinchonine derived catalyst **9a** was employed as a CPT catalyst for the alkylation of **3**, the reaction showed a lower enantiomeric efficiency of the alkylated product (*R*)-**4** than when performed in the presence of **9b** as a CPT catalyst (Table 1, entries a, b, e, f, i, j, m, n, q, s, u, w) due to the formation of hydrogen bond between the enolate of glycine-imine ester **3** and free –OH present in $C_9$ (O) position of the DCPT catalyst (Scheme 3, **9c**); hence, the formation of ion pair interaction between the enolate of the substrate and $R_4N^+$ of the DCPTC hardly occurred. So very low chemical yield and ee's were observed. But the $C_9$ (O)-allylated cinchona salts **9b** resulted in higher chemical yield as well as the ee's due to the formation of higher induction between the enolate of the substrate and $R_4N^+$ of the DCPT catalyst, i.e. the carbocation of the alkyl halide is brought closely at a bonding distance due to the electrostatic attraction of the positively charged nitrogen of the catalyst and the negatively charged glycine imine. The same trend was also found for the alkylation of glycine-imine *tert*-butyl ester **3** using cinchonidinium salts **11a** and **11b** as a DCPT catalysts (Table 1, entries c, d, g, h, k, l, o, p, r, t, v, x). With the monomeric catalysts **1a** and **2a** much lower yields and enantioselectivities were obtained (Table 1, entries y and z). Further, the newly synthesized DCPT catalysts were compared with the previously reported dimeric catalysts **2c** and **2d** (Fig. 1) [18] under identical reaction conditions. The obtained yield and ee's are higher than those of the **2c** and **2d** DCPTCs due to the steric hindrence being minimized (Table 1, entries $x_1$ and $y_1$). It is known that quaternary ammonium salts derived from cinchona bases suffer base-induced alterations under PTC conditions. In order to maintain their structural integrity, *O*-allylated derivatives have been prepared and they have often provided high enantioselectivity for the alkylation of glycine imine. From the obtained results, the newly synthesized DCPTCs **9b** and **11b** are considered to be the best catalysts for the alkylation of glycine imine under the condition of low base concentrations (20%, w/v).

The predominant formation of alkylated products with *R* and *S* enantiomers is strongly dependent on the respective nature of the two pseudoenantiomeric catalysts such as **9** and **11**, respectively (Table 1, entries a–z). Thus, for the cinchonium and cinchonidinium salts, the molecular assembly during chiral transmission would consist of a contact ion pair formed between the positively charged quaternary nitrogen and the carbanion of the glycine imine with the quinoline part of the former serving as the platform for the aromatic ring of the latter (Scheme 3). There are two most important directions possible for the formation of higher chemical yield and ee such as directions A and B as shown in Scheme 3. The direction A seems to be most preferred for the ion pair interaction between the $R_4N^+$ of the catalyst and enolate of the substrate [22]. The direction B could be less favored due to the steric hindrance between the quinoline part of the cinchona alkaloid and the cyclam group of the catalyst. Further, the dramatic increase in the enantioselectivity for the DCPTC catalysts **9b** and **11b** implies that the cinchona alkaloid moieties and cyclam groups are located near the B site and that the E-enolate of **3** forms an ion pair with **9b** and **11b** from the less hindered direction A (Scheme 3). Furthermore, we expect that as the re-face of the enolate can be effectively blocked by the formation of the ion pair, and hence the alkyl halide can interact only at the si-face of E-enolate to give the *R* and *S* forms, respectively [18,23].




**9c**

Hydrogen bonding between enolate of the glycine imine and free -OH present in $C_9$ (O) position of the catalysts **9a** and **11a**




**11c**

Direction **B**: steric hindrance between the quinoline part of the cinchona alkaloid and cyclam group; direction **A**: most preferential ion-pair formed between $R_4N^+$ of DCPTC **9b** and **11b** with enolate anion of the glycine imine due to electrostatic attraction

Scheme 3. Molecular assembly to enantioselective alkylation of glycine imine under DCPTC condition.

## 4. Conclusion

In conclusion, we prepared cinchona alkaloid based new dimeric chiral phase transfer catalysts **9** and **11** and confirmed by various spectral techniques. These catalysts are more effective for the alkylation of enantioselctive glycine-imine *tert*-butyl ester under lower basic conditions.

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