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New trimeric *Cinchona* alkaloid-based quaternary ammonium salts as efficient chiral phase transfer catalysts for enantioselective synthesis of α-amino acids

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

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

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Abstract

New trimeric quaternary ammonium salts derived from cinchonine or cinchonidine bridging *N*,*N*′-bis(ethyl)-4-(methyl)-phenyl-amine moiety are used as a chiral phase transfer catalysts for the asymmetric alkylation of a *N*-(diphenylmethylene)glycine *tert*-butyl ester with very good chemical yield (up to 97%) and ee's (up to 98%).
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1. Introduction

Optically active α-amino acids are well known interesting compounds for peptide synthesis [1], their synthesis being an important synthetic challenge, which boosted the development of many methodologies. Among these, phase transfer catalysis (PTC) is an attractive field for catalytic asymmetric synthesis especially if the chiral phase transfer catalysts (CPTC) can be derived directly from inexpensive precursors. The use of chiral phase transfer catalysis also offers many advantages over previously developed α-amino acid syntheses, including simple reaction procedure, mild reaction conditions, inexpensive safe reagents and solvents, commercially available starting substrates and the ability to easily scale up the reaction. In particular, since the pioneering work by O'Donnell et al. [2] in 1989 on asymmetric alkylation of glycine imine using benzylammonium salt of *Cinchona* alkaloid **1** (Fig. 1), they achieved a very good chemical yield and enantiomeric excess under CPTC conditions. Corey et al. [3] and Lygo et al. [4] independently reported an improved selectivity of α-amino acids by introducing 9-anthracenylmethyl group on the nitrogen of the quinnuclidine ring of the cinchonidine (CD) **2** (Fig. 1). Maruoka and co-workers [5] reported the chiral binol-based versatile C_2-symmetric spiral ammonium salts, which allow many options for rational design for improving reactivity and enantioselectivity. In addition, many other processes such as Michael addition [6a–c], Darzen's [6d], epoxidation [6e–g], and aldol [6h,i] reactions have been studied recently under chiral phase transfer catalytic conditions. There are several CPTC, viz., spiro-ammonium [7] and phosphonium salts [8], (TADDOL) [9], binaphthyl derived amines [9b,10] and salen-metal complexes [11] used for asymmetric synthesis of α-amino acids. In order to improve the chemical yield and ee's for enantioselective synthesis of α-amino acids, to introduce bulky substituents on N1 of cinchona alkaloids, based on the previous point, dimeric [12] and trimeric [13] cinchona derived catalysts have been reported and also polymer supported cinchonidine or cinchonine based ammonium salts have been employed as recoverable PTC catalysts [14].

Keeping in our mind all the early reported literatures, we have synthesized new versatile trimeric chiral PTCs **6** and **7** derived from *Cinchona* alkaloid. The spacer chain containing CPTCs **6** and **7** quaternised in a different manner could be beneficial for the exploration of efficient chiral PTCs due to extended planarity of the steric bulkiness of the spacer groups. *N*,*N*′-Bis-(2-chloroethyl)-(4-chloromethylphenyl)amine reacts with cinchonine or cinchonidine for about 36 h at 100 °C to give upto 95% yield.

* Corresponding author. Tel.: +91 44 22351137; fax: +91 44 2352494.
E-mail address: ptcsiva@yahoo.co.in (A. Siva).

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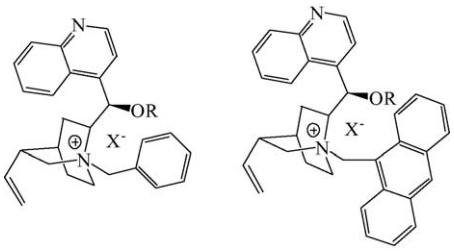


1a R=H, X=Cl-
1b R= allyl, X=Br-
2a R=H, X=Cl-
2b R=allyl, X= Br-

Fig. 1.

2. Experimental

All the melting points are uncorrected. The IR spectra were recorded using a Shimadzu FT-IR 8300 instrument. The ^{1}H and ^{13}C NMR spectra of all compounds in DMSO-d_6 were recorded using a GSX 300 (300, 75 MHz) NMR spectrometer, respectively. The mass spectra were recorded using a HRMS instrument. The column chromatography was performed using silica gel (100–200 mesh size). The enantioselectivities were determined by Chiral HPLC analysis using a chiral column (DAICEL Chiralcel OD).

2.1. Preparation of *N,N′*-bis(2,2-dichloroethyl)-p-toluidine

In a 250 ml RB flask, *N,N′*-bis(2-hydroxy ethyl)-*p*-toluidine **4** (10 g, 51.21 mM) was dissolved in THF (80 ml), then PCl_3 (0.632 ml, 101.41 mM) was added slowly to the flask through an addition funnel and the reaction mixture was stirred vigorously in an ice bath for 12 h. The formation of $POCl_3$ was removed and the resulting solid product *N,N′*-bis(2,2-dichloroethyl)-*p*-toluidine (pale yellow) compound was recrystallised using ethanol (yield 94%, mp 87 °C). FT-IR (KBr) cm^{-1}: 1124, 715; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.62–3.66 (t, 4H, J = 3.6 Hz), 4.01–4.05 (t, 4H, J = 3.6 Hz), 6.47–6.50 (d, 2H, J = 2.7 Hz), 6.86–6.89 (d, 2H, J = 2.7 Hz).

2.2. Preparation of *N,N′*-bis-(2-chloro-ethyl)-(4-chloromethylphenyl)amine (**5**)

N,N′-Bis(2,2-dichloroethyl)-*p*-toluidine was treated with sulfuryl chloride in the presence of benzene to produce compound **5**, viz., *N,N′*-bis-(2-chloroethyl)-(4-chloromethylphenyl)amine (yellow colour). Then it was purified using silica gel column chromatography using hexane:methanol as an eluent. Yield 87%, mp 101–102 °C. FT-IR (KBr) cm^{-1}: 1110, 715; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 3.60–3.65 (t, 4H, J = 4.5 Hz), 3.97–4.01 (t, 4H, J = 3.6 Hz), 4.25 (s, 2H), 6.37–6.40 (d, 2H, J = 2.7 Hz), 6.92–6.95 (d, 2H, J = 2.7 Hz).

2.3. Preparation of trimeric cinchonine derived chiral quaternary ammonium salt (**6a**)

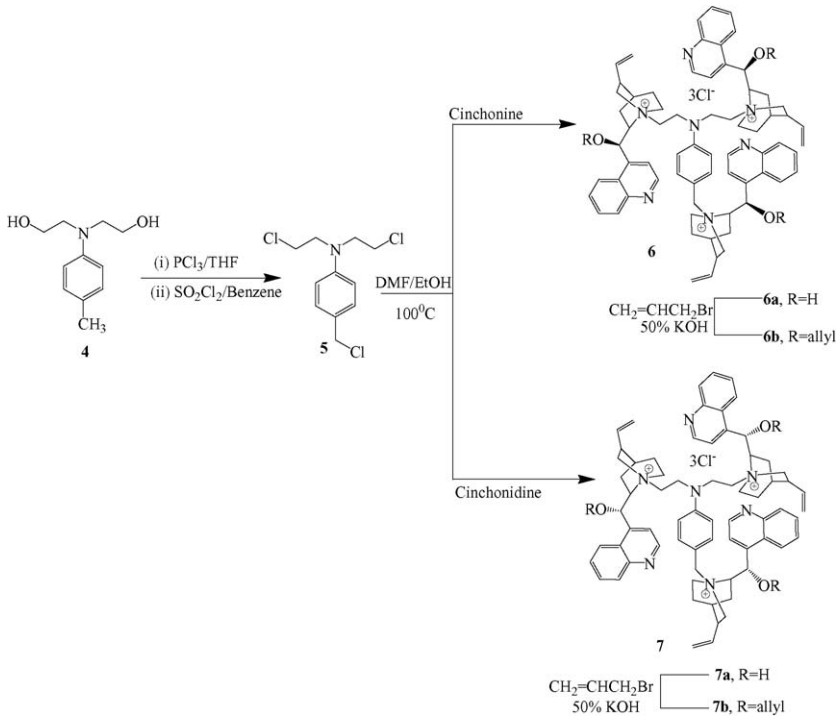
The compound **5**, viz., *N,N′*-bis(2-chloroethyl)-(4-chloromethylphenyl)amine (1.0 g, 3.75 mM) was allowed to react with cinchonine (3.31 g, 11.25 mM, 3 equivalent) in the presence of 50 ml mixture of ethanol/DMF (1:1 ratio). The reaction mixture was stirred at 100 °C for 24 h, the crude product of quaternized salt was washed with 10% $NaHCO_3$ solution followed by chloroform. The quaternized crude salt mixture was purified by silica gel column chromatography using $CHCl_3$:pentane (30:70) mixture as an eluent. The pure colourless solid **6a** was obtained with 88% yield. Decom. temp. 189 °C; FT-IR (KBr) cm^{-1}: 3488, 3035, 1655, 1440, 1087; ^{1}H NMR (300 MHz, DMSO-d^6) δ: 1.5–2.0 (broad s, 3H), 2.17–2.30 (m, 12H), 3.65–3.85 (m, 14H), 4.20–4.35 (m, 8H), 5.00–5.70 (m, 12H), 5.95–6.15 (m, 9H), 6.90–7.10 (d, 6H, J = 9.42 Hz), 7.50–7.60 (d, 3H, J = 10.26 Hz), 7.65–7.80 (dd, 4H, J = 2.70 Hz), 8.15–9.90 (m, 9H); ^{13}C NMR (75 MHz, DMSO-d^6) δ: 23.6, 27.5, 35.4, 36.9, 47.5, 55.7, 62.4, 63.6, 65.3, 66.7, 68.7, 79.6, 114.4, 115.5, 116.4, 120.4, 122.6, 125.5, 126.8, 128.4, 129.4, 130.6, 132.2, 140.6, 143.6, 148.2, 150.1, 151.6; HRMS (ESI) calc. for $[C_{68}H_{80}N_7O_3]^{3+}$: 1043.4063, Found: 1043.3529; Elemental analysis calc. value: C, 71.03; H, 7.01; N, 8.53; Found C, 69.96; H, 6.97; N, 8.42.

2.4. Preparation of trimeric cinchonidine derived chiral quaternary ammonium salt (**7a**)

Prepared from *N,N′*-bis(2-chloro-ethyl)-(4-chloromethylphenyl)amine (1.0 g, 3.75 mM) and cinchonidine (3.31 g, 11.25 mM, 3 equivalent) in 79% yield. Decom. temp. 203 °C; FT-IR (KBr) cm^{-1}: 3436, 3027, 1654, 1435, 1080; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.28–1.34 (m, 3H), 1.65–1.68 (m, 12H), 2.64–2.70 (p, 3H), 3.24–3.33 (m, 12H), 3.40–3.44 (t, 4H, J = 6.38 Hz) 3.79–3.81 (t, 4H, J = 5.49 Hz), 4.04–4.10 (q, 3H, J = 18.39 Hz), 4.51 (s, 2H), 5.12–5.15 (d, 3H, J = 9.64 Hz), 5.34–5.40 (m, 9H), 6.02 (bs, 3H), 6.78–6.82 (dd, 4H, J = 13.68 Hz, 7.05–7.78 (m, 18H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 28.3, 30.5, 38.4, 38.9, 48.7, 58.7, 61.3, 61.6, 65.0, 65.7, 69.2, 79.6, 113.4, 114.4, 114.7, 119.4, 123.6, 125.2, 126.7, 127.4, 128.4, 129.3, 130.2, 141.6, 143.5, 148.4, 149.7, 152.1; HRMS (ESI) Calc. for $[C_{68}H_{80}N_7O_3]^{3+}$: 1043.4063, Found: 1042.8978; Elemental analysis Calc.: C, 71.03; H, 7.01; N, 8.53; Found C, 70.45; H, 6.20; N, 7.68.

2.5. Synthesis of O-allylation of quaternary salts of cinchonine (**6b**)

The RB flask (250 ml) containing compound **6a** (0.7 g, 0.6 mM) was treated with allyl bromide (0.14 g, 1.83 mM) in the presence of 50% aqueous KOH and DMF. Then the reaction mixture was allowed for vigorous stirring for 12 h at room temperature after completion of reaction whole mixture was poured into water. The resulting brown colour precipitate, i.e. allylated ammonium salt **6b** was washed with chloroform three times (3 × 5 ml) and then it was recrystallised in ethanol. The obtained yield was 83% (Scheme 1). Decom. temp. 226 °C; FT-IR (KBr) cm^{-1}; 3425, 3065, 2910, 1465, 1060; ^{1}H NMR (300 MHz, DMSO-d^6) δ: 1.38–1.42 (m, 2H), 1.7–1.89 (m, 2H), 2.14–2.26(m, 2H), 2.54–2.69 (m, 1H), 3.27–3.45 (m, 1H), 3.61–3.74 (m, 3H), 3.84–3.88 (m, 1H), 4.26–4.44 (m, 2H), 4.94–4.99(m, 2H), 5.0–5.09 (t, 2H, J = 6.4 Hz), 5.13–5.25 (m, 2H), 5.31–5.37 (d, 1H, J = 8.4 Hz), 5.58–5.62 (m, 1H), 5.96–6.12 (d, 1H, J = 12.8 Hz), 6.36–6.57 (d,



Scheme 1. A schematic diagram for the synthesis of trimeric chiral phase transfer catalysts (TCPTC).

1H, $J = 12.4$ Hz), 6.77–6.86 (m, 3H), 7.04–7.1 (s, 1H), 7.22 (s, 1H) 7.46–7.55 (m, 3H), 8.1–8.19 (d, 1H, $J = 7.8$ Hz), 8.66–8.79 (d, 1H, $J = 12.6$ Hz), 8.87–8.96 (d, 1H, $J = 7.8$ Hz); ^{13}C NMR (75 MHz, DMSO-d^6) δ: 28.4, 30.0, 37.2, 38.4, 59.6, 61.0, 62.2, 68.8, 78.6, 82.7,113.8, 114.2, 115.6, 117.5, 119.1,122.3, 123.6, 123.9, 125.4, 126.6, 128.4, 129.2, 131.0, 134.4, 137.3, 140.1, 142.6, 147.8, 148.2, 149.7, 151.5; HRMS (ESI) Calc. for $[C_{77}H_{92}N_7O_3]^{3+}$ 1163.5978, Found: 1163.5437; Elemental analysis Calc.: C, 72.82; H, 7.29; N, 7.72; Found: C, 72.68; H, 7.21; N, 7.65.

2.6. Synthesis of O-allylation of quaternary salts of cinchonidine (*7b*)

Prepared from **7a** (0.7 g, 0.6 mM) was treated with allyl bromide (0.14 g, 1.83 mM) in the presence of 50% aqueous KOH and DMF in 90% yield (Scheme 1). Decom. temp. 204 °C; FT-IR (KBr): 3478, 1042; ^{1}H NMR (300 MHz, DMSO-d^6) δ:- 1.40–1.60 (m, 6H), 1.70–1.80 (q, 12), 2.50–2.65 (m, 12H), 3.0 (s, 2H), 3.05–3.25 (m, 8H), 3.35–3.50(m, 6H), 5.63 (d, 6H, $J = 5.85$ Hz), 5.65–5.8 0 (m, 3H), 7.35–7.50 (t, 6H, $J = 8.4$ Hz), 7.6 (m, 8H), 8.10 (dd, 6H, $J = 13.17$ Hz), 8.8 (d, 2H, $J = 7.32$ Hz); ^{13}C NMR (75 MHz):-19.96, 40.02, 104.17, 110.15, 112.42, 114.95, 119.99, 124.38, 126.29, 126.52, 128.09, 128.60, 128.93, 129.24, 132.90, 133.95, 134.74, 136.00, 138.21, 141.63; HRMS (ESI) Calc. for $[C_{77}H_{92}N_7O_3]^{3+}$: 1163.5978; Found 1163.5437.

2.7. Typical alkylation procedure

A solution of glycine *tert*-butyl ester **8** (0.5 mM) in toluene:CH_2Cl_2 (8:2, v/v) was treated sequentially with the appropriate catalyst (5 mole%), alkylating agent (0.5 mM), and 20% aqueous sodium hydroxide (0.5 ml). The resulting mixture was stirred at −10 °C for about 0–15 h (see Table 6). The aqueous layer was then separated with ethyl acetate (5 × 5 ml), and the combined organic layer dried in Na_2SO_4 and concentrated under reduced pressure to give the crude product. This material was dissolved in tetrahydrofuran (5 ml) and 15% aqueous citric acid (1.5 ml) added. The mixture was stirred vigorously at room temperature for 1 h, and then diluted with water (5 ml). The mixture was extracted with diethyl ether (5 × 5 ml) to remove any excess alkylating agent and benzophenone, and then the aqueous layer was basified (K_2CO_3). Extraction with ethyl acetate (5 × 5 ml) followed by drying of the extracts (Na_2SO_4) and concentration under reduced pressure gave the crude product of amino acid *tert*-butyl ester which can be generally purified by passing through a plug of silica.

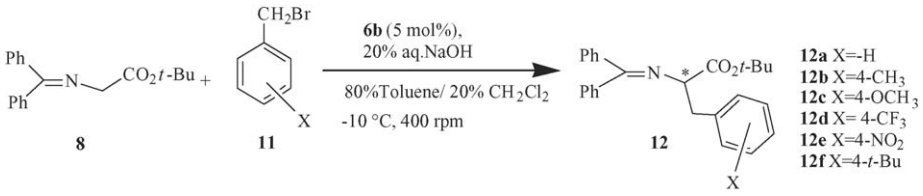
2.7.1. tert-Butyl-3-phenyl-2-diphenylmethyleneamino propanoate (R, *12a*)

Synthesized as 2.7 under the reaction conditions listed in Table 1. Yield 54%. $[\alpha]_D^{25} + 16.4$ ($c = 0.2$, CH_2Cl_2). FT-IR (KBr) cm^{-1}: 3027, 2908, 1713, 1523, 1238; ^{1}H NMR (200 MHz, DMSO-d^6) δ: 1.40 (s, 9H), 3.26–3.30 (d, 2H, $J = 8.0$ Hz), 4.35–4.39 (t, 1H, $J = 4.0$ Hz), 7.12–7.35 (m, 15H); ^{13}C NMR (50 MHz, DMSO-d^6) δ: 27.2, 38.6, 61.7, 73.4, 125.7, 127.3, 128.4, 128.9, 129.5, 130.7, 137.2, 140.6, 164.8, 172.9; *m/z*: $M^+ = 385.19$; HRMS Calcd. for $C_{26}H_{27}NO_2$: 386.2042; Found 386.1897.

2.7.2. tert-Butyl-3-(4-methylphenyl)-2-diphenyl methyleneaminopropanoate (R, *12b*)

Synthesized as 2.7 under the reaction conditions listed in Table 1. Yield 66%. $[\alpha]_D^{25} + 17.3$ ($c = 0.2$, CH_2Cl_2). FT-IR (KBr)

Table 1
Dependence of enantioselection (%) on various substituted benzyl bromide under TCPTC condition



Entry	Electrophiles	Yield (%)	ee (%)	Absolute configuration
12a	—H	54	87	R
12b	—CH_3	66	92	R
12c	—CF_3	87	90	R
12d	—OCH_3	89	96	R
12e	—NO_2	72	65	R
12f	—*t*-Bu	97	98	R

cm^{-1}: 3021, 2876, 1710, 1595, 1227; ^{1}H NMR (200 MHz, DMSO-d^6) δ: 1.37 (s, 9H), 2.22 (s, 3H), 3.01–3.05 (d, 2H, J = 8.0 Hz), 4.38–4.44 (t, 1H, J = 6.0 Hz), 7.07–7.10 (d, 2H, J = 6.0 Hz), 7.24–7.28 (d, 2H, J = 8.0 Hz), 7.51–7.77 (m, 10H); ^{13}C NMR (50 MHz, DMSO-d^6) δ: 23.2, 29.0, 37.6, 65.4, 73.7, 121.2, 129.8, 130.3, 131.5, 132.5, 133.7, 133.5, 142.6, 165.3, 188.2; *m/e*: M^+ = 399.17; HRMS Calcd. for $C_{27}H_{29}NO_2$: 399.2198; Found 399.2101.

2.7.3. *tert-Butyl-3-(4-trifluoromethylphenyl)-2-diphenyl-methyleneaminopropanoate (R, **12c**)*

Synthesized as 2.7 under the reaction conditions listed in Table 1. Yield 87%. $[\alpha]_D^{25}$ + 11.6 (c = 0.2, CH_2Cl_2). FT-IR (KBr) cm^{-1}: 3076, 2904, 1732, 1610, 1230; ^{1}H 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) δ: 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; (MS) *m/e* [M^+] = 453.18.

2.7.4. *tert-Butyl-3-(4-methoxyphenyl)-2-diphenyl methyleneaminopropanoate (R, **12d**)*

Synthesized as 2.7 under the reaction conditions listed in Table 1. Yield 89%. $[\alpha]_D^{25}$ + 13.5 (c = 0.2, CH_2Cl_2). FT-IR (KBr) cm^{-1}: 3042, 2965, 1698, 1555, 1236, 786; ^{1}H NMR (200 MHz, DMSO-d^6) δ: 1.26 (s, 9H), 3.07 (s, 3H), 3.21–3.26 (d, 2H, J = 10.0 Hz), 4.45–4.49 (t, 1H, J = 4.0 Hz), 7.02–7.05 (d, 2H, J = 6.0 Hz), 7.38–7.40 (d, 2H, J = 4.0 Hz), 7.41–7.56 (m, 10H); ^{13}C NMR (50 MHz, DMSO-d^6) δ: 24.2, 37.7, 61.4, 73.4, 120.2, 127.5, 129.4, 130.4, 131.9, 132.5, 133.7, 137.5, 141.6, 166.2, 178.1; (MS) *m/e*: M^+ = 415.18; HRMS calcd. for $C_{27}H_{29}NO_3$: 415.2397 Found 415.2186.

2.7.5. *tert-Butyl-3-(4-nitrophenyl)-2-diphenyl methyleneaminopropanoate (R, **12e**)*

Synthesized as 2.7 under the reaction conditions listed in Table 1. Yield 72%. $[\alpha]_D^{25}$ + 20.1 (c = 0.2, CH_2Cl_2). FT-IR (KBr) cm^{-1}: 3056, 2903, 1723, 1567, 1467, 1223, 1074; ^{1}H NMR (200 MHz, DMSO-d^6) δ: 1.10 (s, 9H), 3.12–3.15 (d, 2H, J = 6.0 Hz), 4.28–4.33 (t, 1H, J = 5.0 Hz), 7.23–7.66 (m, 14H); (MS) *m/e* M^+ = 430.18.

2.7.6. *tert-Butyl-3-(4-tert-butyl-phenyl)-2-diphenyl methyleneaminopropanoate (R, **12f**)*

Synthesized as 2.7 under the reaction conditions listed in Table 1. Yield 94%. $[\alpha]_D^{25}$ + 13.5 (c = 0.2, CH_2Cl_2). FT-IR (KBr) cm^{-1}: 3055, 2910, 1705, 1555, 1450, 1220, 1065; ^{1}H NMR (200 MHz, DMSO-d^6) δ: 1.37 (s, 9H), 2.14 (s, 9H), 3.25 (d, 2H, J = 8.4 Hz), 4.36 (t, 1H, J = 6.2 Hz), 6.92–7.85 (m, 14H), ^{13}C NMR (50 MHz, DMSO-d^6) δ: 23.8, 29.2, 39.5, 65.4, 73.8, 76.4, 122.2, 128.9, 130.2, 131.5, 132.4, 133.7, 133.9, 141.6, 165.2, 186.4; (MS) *m/e*: 441.52.

2.7.7. *tert-Butyl-3-(2-allyl)-2-diphenylmethyleneamino propanoate (R, **13c**)*

Synthesized as 2.7 under the reaction conditions listed in Table 6. Yield 89%. $[\alpha]_D^{25}$ + 15.4 (c = 0.2, CH_2Cl_2). FT-IR (KBr) cm^{-1}: 3060, 2920, 1715, 1625, 1240; ^{1}H NMR (300 MHz, DMSO-d^6) δ: 1.38 (s, 9H), 2.67 (t, 2H, J = 5.7 Hz), 4.21 (t, 1H, J = 6.4 Hz), 4.97 (d, 2H, J = 8.6 Hz), 5.72 (m, 1H), 7.12–7.85 (m, 10H); ^{13}C NMR (75 MHz, DMSO-d^6) δ: 29.3, 34.2, 59.4, 72.9, 115.6, 128.6, 129.2, 130.5, 137.8, 165.7, 175.8; (MS) *m/e*: 321.41.

2.7.8. *tert-Butyl-1-tert-butyloxide-3-(2-diphenyl methylene-tryptophenester (S, **13k**)*

Synthesized as 2.7 under the reaction conditions listed in Table 6. Yield 53%. $[\alpha]_D^{25}$ − 17.3 (c = 0.2, CH_2Cl_2). FT-IR (KBr) cm^{-1}: 3060, 2918, 1720, 1610, 1235; ^{1}H NMR (300 MHz, DMSO-d^6) δ: 1.42 (s, 9H), 1.51 (s, 9H), 3.14 (d, 2H, J = 8.7 Hz), 4.35 (t, 1H, J = 6.4 Hz), 6.12–7.55 (m, 15H); ^{13}C NMR (75 MHz, DMSO-d^6) δ: 28.7, 29.3, 30.4, 62.5, 71.7, 73.2, 111.2, 112.3, 120.3, 121.4, 122.6, 128.6, 129.2, 130.8, 132.7, 137.1, 137.4, 161.7, 164.2, 168.5, 174.0; (MS) *m*/e: 524.62.

2.7.9. *tert-Butyl-3-(2-allene)-2-diphenylmethylene aminopropanoate (S, **13m**)*

Synthesized as 2.7 under the reaction conditions listed in Table 6. Yield 89%. $[\alpha]_D^{25}$ − 13.6 (c = 0.2, CH_2Cl_2). FT-IR (KBr)

cm^{-1}: 3066, 2920, 1722, 1610, 1235; ^1H NMR (300 MHz, DMSO-d^6) δ: 1.26 (s, 9H), 1.82 (s, 1H), 4.38 (d, 2H, $J = 6.4$ Hz), 4.56 (t, 1H, $J = 5.8$ Hz), 6.89–7.56 (m, 10H); ^{13}C NMR (75 MHz, DMSO-d^6) δ: 29.4, 41.5, 58.4, 67.2, 73.4, 85.5, 107.7, 128.6, 129.2, 130.8, 137.4, 146.7, 164.8, 171.5; (MS) *m/e*: 333.42.

*2.7.10. tert-Butyl-3-(2-(2-methyl)-allyl)-2-diphenyl methyleneaminopropanoate (R, **13n**)*

Synthesized as 2.7 under the reaction conditions listed in Table 6. Yield 86%. $[\alpha]_D^{25} + 16.2$ ($c = 0.2$, CH_2Cl_2). FT-IR (KBr) cm^{-1}: 3066, 2912, 1716, 1611, 1230; ^1H NMR (300 MHz, DMSO-d^6) δ: 1.34 (s, 9H, 1.67 (s, 3H, 2.73 (d, 2H, $J = 6.8$ Hz), 4.03 (t, 1H, $J = 6.3$ Hz), 4.72 (dd, 2H, $J = 9.6$ Hz, $J = 8.7$ Hz), 7.14–7.80 (m, 10H); ^{13}C NMR (75 MHz, DMSO-d^6) δ: 23.4, 29.6, 41.5, 56.3, 73.4, 107.7, 128.6, 129.2, 130.8, 137.4, 146.7, 164.8, 170.5; *m/e*: 349.45.

3. Results and discussion

Cinchonine or cinchonidine derived trimeric catalysts were obtained in 80–95% yield. The catalytic efficiency was studied for the alkylation of *tert*-butylglycinate benzophenone imine **8** with various alkyl halides **9** to afford racemic α-amino acids, which is easily hydrolyzed to generate α-amino acids **10**. The highly crystalline glycine imine showed a strong preference for alkylation, since the mono alkylated product gives ester in high yield (Scheme 2).

The induction of chirality in prochiral substance by TCPTC is an attractive process, because of its simplicity and economy. However its success, as measured by the chemical yield and the degree of enantioselection, depends on various factors, such as the nature of the electophiles (steric and electronic), the agitation speed on the alkylation reaction, the structure of the TCPT catalysts, the nature of the counter ion associated with the TCPT catalysts, and the polarity of the solvents; the inorganic base which is associated with the cation of the catalysts (R_4N^+) and its concentration were influenced by the formation of chiral quaternary ammonium hydroxide. We analysed these factors in some depth, with a view to achieving an efficient alkylation of glycine imine **8** using earlier reported procedures [11–16].

3.1. The nature of electrophiles

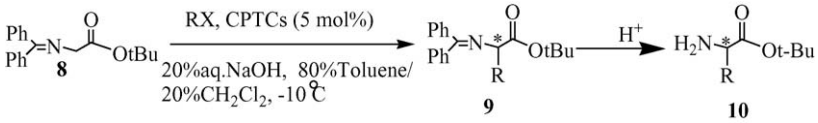
The alkylation of glycine imine **8** was carried out with various substituted benzyl halides in the presence of *Cinchona* derived TCPTCs, viz., **6b** in 20% aqueous NaOH and mixture of solvent medium toluene and CH_2Cl_2 (volume ratio 80:20) at low temperature (−10 °C) (Table 1). From the results, we observed that the enantiomeric excess increases with increasing bulkiness of the substituents on the benzyl moiety, i.e. *t*-Bu > OCH_3 > CF_3 > CH_3 > NO_2 > H, due to the higher optical induction with the catalyst at the chiral environment (entries **12a**–**f**, Table 1). Hence the sterics of the *N*-benzyl group prevent the enolate from docking such that the reface is exposed and also the electron withdrawing substituents on the benzyl group will enhance the π-stacking with the enolate, again promoting binding with the reface exposed. Thus *tert*-butyl substituted benzyl bromide provided higher yield of the product whereas benzyl bromide gave a lower yield (entries **12a** and **12f**, Table 1) since the *N*-benzyl group (electrophile = H) will diminish the π-interaction with the enolate of the substrates. A similar observation was noticed by Arai et al. [15] for the alkylation of α-fluorotetralone in the presence of *Cinchona* based chiral catalyst. It is important to note that the enantiomeric excess of the mixture isolated remained unaltered when resubmitted to conditions that generated it (Table 1).

3.2. Nature of the inorganic bases

Next we carried out the alkylation of glycine imine **8** with 4-*tert*-butylbenzyl bromide in the presence of various inorganic bases like KOH, LiOH, $Ca(OH)_2$ and K_2CO_3 under TCPTC condition. The other parameters such as solvents and temperature were kept constant. From the results, it is clear that the NaOH afforded better results than the other bases (Table 2) due to weak ionic interaction of Na^+ with the substrate. The highest ee's and yield was observed when 20% aq. NaOH solution was used (entry 2, Table 2). The chemical yield as well as the ee were low when KOH, $Ca(OH)_2$, LiOH and K_2CO_3 were used as bases (Table 2) due to the strong ionic interaction between the catalysts and substrates of the enolate anion. When the concentration of aqueous NaOH was increased (more than 20%) the catalyst decomposition had occurred (entries 6–8, Table 2). A similar observation was noticed by O'Donnell et al. [16] for the enantioselective alkylation of ketimine in presence of 50% NaOH as a base.

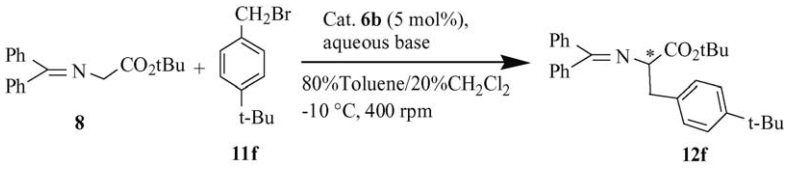
3.3. Effect of solvents and its concentration on enantioselective alkylation of glycine imine

Using solid KOH alone or mixed with K_2CO_3 resulted in a lower enantioselectivity than that obtained with 20% NaOH (entries 9, 10, Table 3). Moderate yield of alkylation was observed in CH_2Cl_2 as solvent due to the solvent react with the base. The alkylation reactions were carried out with several other solvents also. But the enantiomeric efficiency was very low due to the poor solubility of the TCPTC catalyst (Table 3).



Scheme 2. Enantioselective synthesis of α-amino acids under TCPTC condition.

Table 2
Influence of various bases on syntheses of α-amino acids



8 11f 12f

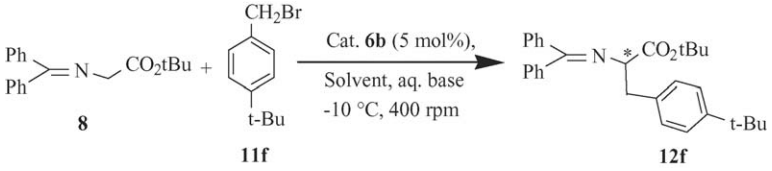
Entry	Aqueous solution (base) (%)	Yield (%)	ee (%)	Absolute configuration
1	KOH (20)	56	64	R
2	NaOH (20)	97	98	R
3	LiOH (20)	67	54	R
4	$Ca(OH)_2$ (20)	30	36	R
5	K_2CO_3 (20)	26	14	R
6	NaOH (30)	78	64	R
7	NaOH (40)	71	52	R
8	NaOH (50)	53	35	R

The reactivity and also enantioselectivity of the TCPTCs are dependent on their solubility and stability in the organic solvent under the PTC reaction conditions. It was found that decomposition of the TCPTC salts in the presence of 20% aqueous NaOH in the non polar solvent, toluene is considerably slower than CH_2Cl_2. Normally, the use of pure toluene solvent is not practical because of the lower solubility of the catalyst in the solvent. Hence, we have carried out the alkylation reaction in the presence of mixture of solvents like toluene and CH_2Cl_2 (8:2, v/v), which can improve the solubility as well as the influence of the enantioselectivity of the alkylation product (entry 6, Table 3). The percentage of ee is decreased by the addition of dichloromethane to toluene in more than 20% (entries 2–5, Table 3). In pure toluene, the rate is almost three fold slower than the mixed solvent (80% toluene:20% CH_2Cl_2) (entries 2, 6, Table 3). The enantioselectivity of the alkylation reaction is strongly dependent on the addition of toluene with the reaction mixture. The increasing toluene amount in the solvent ratio (8:2, v/v), which is influenced the chemical yield (97%) and ee's up to 98%.

3.4. Effect of stirring speed

The formation of higher ee's and chemical yields strongly depends on the stirring speed of the reaction mixture. It was observed that the ratio of volume of the aqueous and organic phase is very important in the alkylation reaction. Increasing either stirring speed of the reaction or the relative amount of the base presumably increases the contact surface area between the aqueous and organic phases, which increases the ee's and chemical yields (entries 1–5, Table 4). From the results, the 400 rpm is the optimum stirring speed for the alkylation reaction due to the perfect collision between the substrates and catalysts (entry 3, Table 4), further increasing the agitation speed 500–600 rpm,

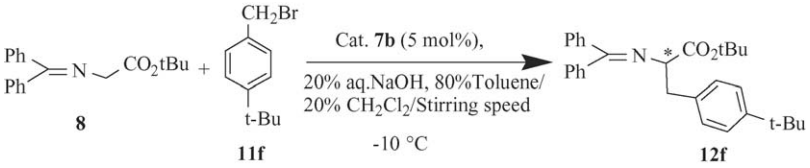
Table 3
Influences of different bases and solvent systems



8 11f 12f

Entry	Reaction solvents	Base	Yield (%)	ee (%)
1	CH_2Cl_2	20%NaOH	12	19 (R)
2	PhMe	20%NaOH	39	36 (R)
3	PhMe/CH_2Cl_2(1:1)	20%NaOH	77	79 (R)
4	30%PhMe/70%CH_2Cl_2	20%NaOH	17	19 (R)
5	70%PhMe/30%CH_2Cl_2	20%NaOH	86	62 (R)
6	80%PhMe/20%CH_2Cl_2	20%NaOH	97	98 (R)
7	90%PhMe/10%CH_2Cl_2	20%NaOH	95	86 (R)
8	80%PhMe/20%CH_2Cl_2	20%KOH	56	64 (R)
9	80%PhMe/20%CH_2Cl_2	NaOH/K_2CO_3(1:1)	42	68 (R)
10	80%PhMe/20%CH_2Cl_2	KOH/K_2CO_3(1:1)	82	64 (R)

Table 4
Effect of stirring speed on the alkylation reaction



8 11f 12f

Entry	Catalysts	Stirring speed (rpm)	Yield (%)	ee (%)
1	**7b**	100	56	65 (S)
2	**7b**	300	60	74 (S)
3	**7b**	400	96	97 (S)
4	**7b**	500	76	80 (S)
5	**7b**	600	73	72 (S)

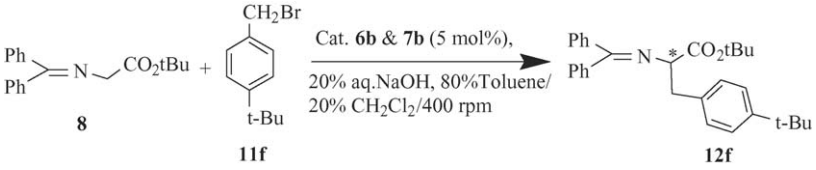
there is no influence of ee's and chemical yield (entries 4 and 5, Table 4).

3.5. Effect of temperature on alkylation of glycine imine

The formation of chemical yield and ee's strongly depends on the temperature. Variation of the reaction temperature also affects the level of the asymmetric induction. From the observed results, the temperature was decreased from 25 to −10 °C, the best results were obtained in the alkylation of glycine imine (entries 1–8, Table 5). Hence the optimum temperature for the alkylation reaction is −10 °C (entries 7, 8, Table 5). However no influence on the ee was observed when the reaction temperature was lowered at −20 to −40 °C (entries 9–12, Table 5) due to the lower induction between the enolate of the substrate and catalysts. The same observation was noticed by Chinchilla et al. [14] for the alkylation of glycine imine in presence of dimeric anthracenyl derived cinchona alkaloid quaternary ammonium salts as phase transfer catalysts and also Park et al. [12b] reported the same observation for the synthesis of α-amino acids at lower temperature −20 °C in presence of *ortho*-fluoro dimeric-cinchona derived phase transfer catalysts.

We have also investigated the monoalkylation of glycine imine **8** with variety of commercially available alkylhalide in presence of trimeric CPTC catalysts such as **6** and **7**. The selected results are given in Table 6. The observed results are generally to give the corresponding amino acids with very good ee's. For the alkylation of simple alkyl halide (entries **13a–i** Table 6) tend to be higher yield and ee's than the benzyl bromide substitution (entries **13a** and **13b**, Table 6). In the case of alkylation of heterocyclic halides (entries **13j** and **13k**, Table 6) gave lower yield and also lower ee's than the benzyl bromide and allylhalide alkylation (entries **13a–i** and **13l–o**, Table 6) due to lower induction between the catalyst and enolates of the substrates. Thus, when the cinchonine derived catalyst **6a** was employed as a TCPTC, the reaction showed a lower enantiomeric efficiency as well as chemical yield of the alkylated product (R)-**13** than that of the reaction when performed in presence of **6b** as a PTC catalyst (entries **13a–e**, **13j13l** and **13n**, Table 6) due to formation of hydrogen bond between the free C_9(O) group of

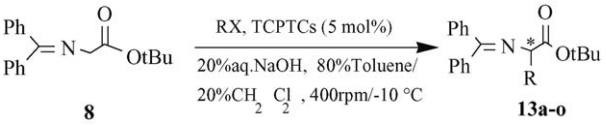
Table 5
Effect of temperature on enantioselective alkylations of glycine imine



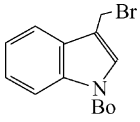
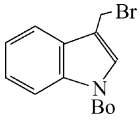
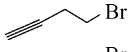
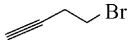
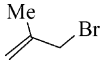
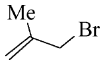
8 11f 12f

Entry	Catalyst	Temperature (°C)	Yield (%)	ee (%)
1	**7b**	25	78	56 (S)
2	**7b**	20	76	71 (S)
3	**6b**	25	80	60 (R)
4	**6b**	20	75	67 (R)
5	**7b**	10	87	83 (S)
6	**7b**	5	89	91 (S)
7	**6b**	−10	97	98 (R)
8	**7b**	−10	96	97 (S)
9	**7b**	−20	81	76 (S)
10	**7b**	−25	78	70 (S)
11	**6b**	−30	72	59 (R)
12	**7b**	−40	50	42 (S)

Table 6
Enantioselective alkylation of α-aminoacids



8 **13a-o**

Entry	R—X	Name of catalyst	Time (h)	Yield[a] (%)	ee[b] (%)
13a	$PhCH_2Br$	6a	1.0	56	62(R)
13b	$PhCH_2Br$	6b	1.5	54	87 (R)
13c	$CH_2{=}CH{-}CH_2Br$	6b	3.0	89	98 (R)
13d	CH_3CH_2Cl	6a	2.5	80	67 (R)
13e	$CH_2{=}CH{-}CH_2Br$	6a	1.0	94	62 (R)
13f	CH_3CH_2Cl	7a	1.0	83	69 (S)
13g	$CH_2{=}CH{-}CH_2Br$	7a	1.0	85	72 (S)
13h	$CH_2{=}CH{-}CH_2Br$	7b	1.5	87	96 (S)
13i	$CH_2{=}CH{-}CH_2Br$	7b	3.0	90	97 (S)
13j		6b	12.0	67	61[c] (R)
13k		7b	12.0	53	63[c] (S)
13l		6b	1.0	94	93 (R)
13m		7b	1.0	89	92 (S)
13n		6b	0.5	86	93 (R)
13o		7b	0.5	90	98 (S)

[a] Isolated crude yield determined by ^{1}H NMR (200 and 300 MHz).
[b] Enantiopurity was determined by HPLC analysis of the alkylated imine **9** using a chiral column (DAICEL Chiralcel OD) with hexane-propane-2-ol (50/2) as a solvent.
[c] Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure [7–16].

the catalyst with enolate of the glycine imine ester **8**, hence the yield and ee's were observed very low. But the *O*-allylated cinchona salts **6b** obtained in higher amount of yield as well as the ee's. The same trend was also observed, when the cinchonidinium salts **7a** and **7b** as a TCPT catalyst in the alkylation of glycine imine **8** was used (entries **13f–i**, **13k**, **13m** and **13o**, Table 6).

To conclude that we have successfully developed new class of trimeric CPT catalysts, which shows higher enantioselectivity for the synthesis of α-amino acids. We are currently involved in the development of the TCPTC catalyst system and investigating their catalytic ability to various organic reactions at lower base and temperature.

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