Cinchona Alkaloid Based Quaternary Ammonium Salt as Chiral Phase-Transfer Catalysts: Asymmetric Alkylation Reactions

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***Abstract*-New enantioselective quaternary ammonium salts such as 7-bromo-(cinchoniummethyl)-4-quinazolin-4-ol chloride and 7-bromo-4-chloro-2-cinchoniummethyl)-quinazoline chloride have been prepared and used as efficient phase transfer catalysts for asymmetric monoalkylation of *N*-(diphenyl methylene)glycine *tert*butyl ester to obtain very good yield and high enantioselectivity (98%) under ultrasonic assisted condition.**

***Keywords*-Chiral Phase transfer catalysts, Enatioselective, Glycine imine, Cinchonine.**

I. INTRODUCTION

Phase transfer catalysis (PTC) is one of the most important useful methods in synthetic organic reactions because of its easy reaction workup inexpensive and environmental friendly reagents [1, 2]. The asymmetric version of PTC requiring viz., chiral phase transfer catalysts (CPTC), however has not been extensively studied as compared to general enantioselective catalysts. O'Donnell et al. [3-6] have been reported for the synthesis of α-aminoacids in presence of cinchona alkaloid type PTC 1 (Fig. 1) and found to be poor yield and enantiomeric excess (ee). Consecutively, Corey [7-9] and Lygo [10-12] have been reported independently greatly improved CPTC system [13-16] 2 (Fig. 1). In addition Merrifield resin bound cinchonine and cinchonidine have been employed as insoluble chiral catalysts [17]. Further, various types of chiral phase-transfer catalysts have been developed in recent years and the chiral efficiency of such phase-transfer catalysts was examined by application to the enantioselective synthesis of both natural and unnatural mono, dialkyl α-amino acids. [18-27]. Further, various types of chiral phase-transfer catalysts have been developed in recent years and the chiral efficiency of such phase-transfer catalysts was examined by application to the asymmetric synthesis of both natural and unnatural Jew et al. [28], Park et al. [29] 3 (Fig. 1) and Najera [30] have reported dimeric and trimeric quaternary cinchona based chiral catalysts derived from o-, m-, p-xylene dibromide and mesitylene tribromide respectively. It has been employed as a CPTC to obtain good ee's and chemical yield. But the usage of higher concentration of catalysts and aq. NaOH (more than 50%) by these workers is not environmentally acceptable. Recently, very good enantioselevtity for the alkylation of glycine imine was obtained in presence of low concentration of base and dimeric [31] and trimeric [32-33] CPTCs that were developed by our group. The successes in these studies prompted us to synthesise new CPTCs. This work focusses on the synthesis of 7-bromo-2-(cinchoniummethyl)-quinazolin-4-ol chloride and 7-bromo-4-chloro-2-cinchoniummethyl)-quinazoline chloride. and on their catalytic efficiency for the enantioselective mono alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester under low base/mild CPTC conditions.

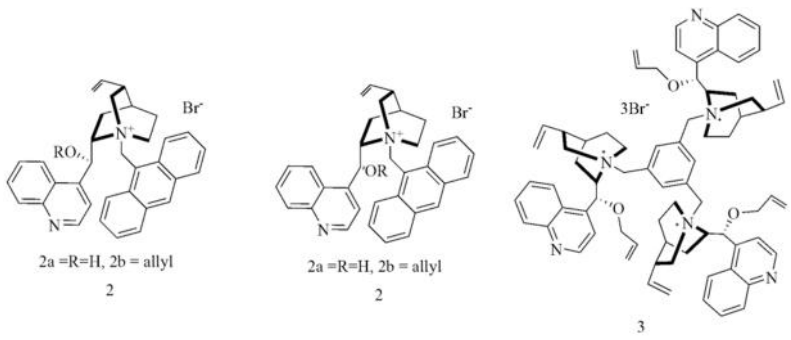


Figure 1. Previously reported CPTC's.

II. EXPERIMENTAL

A. Materials and methods

1,4-Dibromo-2-nitrobenzene (Merck), cuprous cyanide (Merck), hydrazine hydrate (Merck), Raney Ni (Fluka), cinchonine (Fluka), cinchonidine (Fluka), acetonitrile (AR), 2-chloro-1,1-dimethoxyethane (Merck), ethanol (AR) were used in this study without further purification. IR spectra were recorded on a JASCO-FT-IR model 5300 spectrophotometer using KBr pellet method. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded in $CDCl_3$ and DMSO-d^6 on a Bruker AC-300/400 spectrometer using TMS as an 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 chloroform/methanol mixture and spots were developed in the iodine chamber. For column chromatographic separations under gravity, column silica gel (60-120 mesh) was employed.

B. Synthesis of 2-amino-4-bromobenzamide (6)

To a solution of 4-bromo-2-nitrobenzonitrile (5) (3g, 13.22 mmol) in ethanol (25 ml), hydrazine hydrate (85%, 2.6 ml) and highly reactive Raney nickel (0.98g, ~1.5 ml) were added. The temperature was maintained at 60^0C. Then the mixture was refluxed for 2 hrs. The catalyst was filtered at hot condition and washed with hot ethanol. Solvent was removed by vacuum evaporator to give solid, which on charcoaling and crystallization from hot water followed by drying in vacuum gave the compound **6** with the yield of 87%. All the analytical data were in agreement with the reported data [31].

C. Synthesis of 7-bromo-2-(chloromethyl)-quinazolin-4-ol (7a)

A mixture of 2-amino-4-bromobenzamide (6) (1.5g, 6.98 mmol), 2-chloro-1,1,1-trimethoxyethane (20 ml) was refluxed for about 6 hrs. After completion of reaction precipitation formed was filtered; the filtrate was evaporated and washed with ether to get the white solid of title compound. The yield is 79%. ^{1}H NMR (300MHz, $CDCl_3$) δ: 4.55 (s, 2H), 5.52 (bs, 1H), 7.25 (d, 1H, *J*=8.4 Hz), 7.30 (d, 1H, *J*=8.6 Hz), 8.12 (s, 1H); m/z (M^+) 273.5.

D. Synthesis of 7-bromo-4-chloro-2(chloromethyl)quinazoline (7b)

A solution containing 7-bromo-2-(cinchoniummethyl)-quinazolin-4-ol (0.75g, 2.74 mmol) and $POCl_3$ (20 ml) was refluxed for about 6 hrs. The excess of $POCl_3$ was removed under reduced pressure. The mixture was dissolved in ethylacetate and washed with saturated $NaHCO_3$. The organic layer was dried with Na_2SO_4 and concentrated to give yellow solid of title compound with the yield of 85%. ^{1}H NMR (300MHz, $CDCl_3$) δ: 4.52 (s, 2H), 7.12 (d, 1H, *J*=8.2 Hz), 7.33 (d, 1H, *J*=9.3 Hz), 8.17 (s, 1H); m/z (M+1) 293.

E. Synthesis of 7-bromo-2-(cinchoniummethyl)-quinazolin-4-ol chloride (8a)

7-bromo-2-chloromethyl quinazol-4-ol (1.2g, 4.39 mmol) and cinchonine (1.55g, 5.27 mmol) were dissolved in acetonitrile (12 ml) and the reaction mixture was refluxed for about 12 hrs. After completion of reaction, solvent was removed by vacuum to get the quaternised ammonium salt (8a). The crude product was purified by column chromatography using chloroform:methanol (9:1) as an eluent. The yield is 89%. ^{1}H NMR, 400MHz, DMSO-d_6) δ: 0.91 (1H, m), 1.07 (2H, m), 1.15 (1H, m), 1.28 (1H, m), 1.98 (s, 2H), 2.23 (1H, bs), 2.49 (2H, t, *J*=3.44Hz), 3.15 (1H, t, *J*=16.75 Hz), 3.35 (2H, m), 3.56 (1H, m), 4.01 (1H, m), 5.06 (2H, m), 5.12 (2H, m), 7.44 (2H, d, *J*= 4.29 Hz), 7.61 (1H, t, *J*=15.32 Hz), 7.75 (1H, m), 8.03 (2H, dd, *J*=8.57 Hz & 8.21 Hz), 8.18 (1H, d, *J*=8.53 Hz), 8.32 (1H, s), 8.87 (1H, m); ^{13}C NMR, 100 MHz, DMSO-d_6) δ: 12.05, 13.44, 14.04, 15.12, 19.18, 20.71, 23.06, 27.92, 40.14, 42.93, 51.90, 57.54, 59.70, 64.45, 79.18, 115.58, 116.29, 121.24, 125.07, 125.68, 126.98, 129.45, 138.88, 141.94, 147.81, 150.37, 151.08, 170.28; Anal.Calcd. for $C_{28}H_{28}BrClN_4O_2$: C, 59.22; H, 4.97; N, 9.87: Found: C, 58.97; H, 4.92; N, 9.85; LCMS (M+1): 532.17.

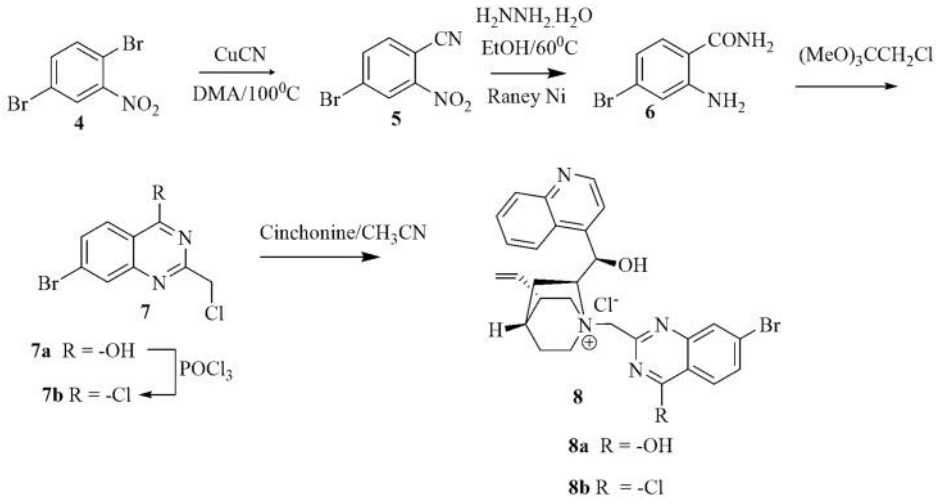
F. Synthesis of 7-bromo-4-chloro-2-cinchoniummethyl)-quinazoline chloride (8b)

The procedure (Section 2.5) adopted for the preparation of 8a was followed to synthesize compound 8b (1.09g, 3.7 mmol) from cinchonine and 7-bromo-4-chloro-2-chloromethyl)-quinazoline 7b **(**0.9g, 3.08 mM). The yield is 92% (Scheme 1). ^{1}H NMR, 400MHz, DMSO-d_6) δ: 1.04 (1H, m), 1.12 (2H, m), 1.21 (1H, m), 1.26 (1H, m), 2.15 (2H, s), 2.69 (2H, m), 3.24 (1H, t, *J*=8.12 Hz), 3.32(2H, m), 3.96 (1H, m), 4.21 (1H, m), 5.24 (2H, m), 5.55 (2H, m), 7.37 (2H, m), 7.71 (1H, t, *J*=16.32 Hz), 7.78 (1H, m), 8.05 (2H, dd, *J*=8.02 Hz & 8.42 Hz),

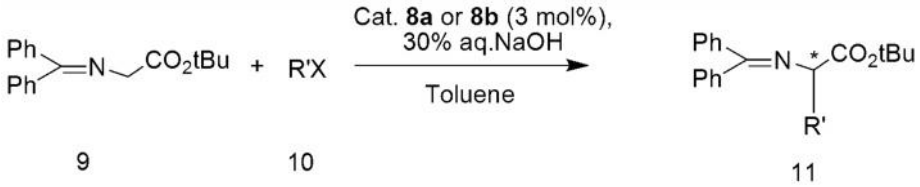
8.22 (1H, d, *J*=8.23 Hz), 8.31 (1H, s), 8.92 (1H, m); ^{13}C NMR, 100 MHz, DMSO-d_6) δ: 13.44, 15.03, 15.13, 19.22, 21.34, 25.56, 27.43, 42.41, 42.56, 51.65, 56.57, 59.76, 64.87, 81.21, 115.89, 119.33, 119.65, 120.38, 123.03 125.13, 127.90, 128.35, 129.21, 143.09, 148.29, 149.57, 150.37, 160.96; Anal.Calcd. for $C_{28}H_{27}BrCl_2N_4O$: C, 57.34; H, 4.64; N, 9.55: Found: C, 57.31; H, 4.59; N, 9.52; LCMS (M+2): 552.81.

G. Typical alkylation procedure

A solution of glycine-imine 9 (0.5 mmol) in toluene (10 ml) was treated sequentially with the appropriate catalyst (3 mol%), alkylating agent (0.5 mmol), and 30% (w/v) aqueous base (0.5ml). The resulting mixture was sonicated with appropriate temperature for about 1-7 h (see Table 1). The aqueous layer was then separated with ethyl acetate (3 x 5 ml), and the combined organic layer was dried in Na_2SO_4 and concentrated under reduced pressure to give the crude product of 11. This material was dissolved in tetrahydrofuran (5 ml) and 15% aqueous citric acid (1.5 ml). The mixture was stirred vigorously at room temperature for about 1 h, then diluted with water (5 ml). The mixture was extracted with diethyl ether (5 x 5 ml) to remove the excess of alkylating agent and benzophenone. Further, the aqueous layer was basified with K_2CO_3 and extracted with ethylacetate (5 x 5ml) subsequently drying with Na_2SO_4 and concentrating under reduced pressure gave the crude product of aminoacid *tert*-butyl ester which was generally purified by passing through a plug of silica. The enantioselectivities were determined by HPLC analysis (chiralcel OD-H with hexane/2-propanol as an eluent at a flow rate of 0.5 mL/min, 25 ^{0}C, λ = 254 nm).



Scheme 1. Synthesis of chiral phase transfer catalysts.



Scheme 2. Enantioselective mono alkylation of glycine imine.

III. RESULTS AND DISCUSSION

7-bromo-2-(cinchoniummethyl)-quinazolin-4-ol Chloride 8a and 7-bromo-4-chloro-2-cinchoniummethyl)-quinazoline chloride 8b were synthesized from cinchonine and 7-bromo-2-chloromethyl quinazol-4-ol 7a and 7-bromo-4-chloro-2-chloromethyl)-quinazoline 7b respectively. The compound 7a and 7b were prepared by earlier reported procedure [31]. Cinchonine (1.0 equ.) with 7-bromo-2-chloromethyl quinazolin-4-ol 7a (1.2 equ.) were dissolved in acetonitrile and the mixture was stirred at 80^{0}C for 7 hrs to get the quaternized cinchonium salt 8a with (89% overall yield) (Scheme 1).

The enantiomeric excess of the alkylated imines 11 were determined by HPLC using CHIRALCEL OD-H and hexane/2-propanol as an eluent. The observed results (shown in Table 1 (entry 1-20)) indicate that

the 80-98% of enantiomeric excess and 70-97% of yields. The enantioselectivity was increased when the temperature decreased from 20^0C to -20^0C. (Table 1, entries 1, 2, 5 and 6). When allylic, benzylic and propargylic bromides were used as electrophiles in the alkylation of glycine-imines as a starting material with reaction temperature at -10^0C, higher reactivity and higher enantioselectivity (Table 1, entries 9-14 and 17-20) were observed due to the formation of ion pair interaction between the R_4N^+ of the catalyst and enolate of the glycine imine. Further, the observed results (Table 1) indicate 8b as a CPTC is highly efficient to give higher chemical yield and ee's when compared to 8a as a CPTC. This may be due to the hydrogen bonding between the free –OH present in the spacer chain and enolate of the glycine imine which restricts the perfect ion pair formation between the glycine anions and quaternary ammonium salt (R_4N^+).

TABLE I. ENANTIOSELECTIVE ALKYLATION OF α-AMINOACIDS.

Entry	R'X	CPTCs	Temp.(^{0}C)	Time (h)	Yield (%)	ee (%)[a]	Absolute Configuration
1	$PhCH_2Br$	8a	20	2.0	82	86	R
2	$PhCH_2Br$	8b	20	2.0	85	88	R
3	$PhCH_2Br$	8a	-20	1.0	94	90	R
4	$PhCH_2Br$	8b	-20	1.0	96	94	R
5	$PhCH_2Br$	8a	25	1.5	91	82	R
6	$PhCH_2Br$	8b	-25	1.5	97	95	R
7	$PhCH_2Br$	8a	-25	1.0	83	92	R
8	$PhCH_2Br$	8b	25	1.0	84	94	R
9	CH_2=$CHCH_2Br$	8a	-10	2.0	88	96	R
10	CH_2=$CHCH_2Br$	8b	-10	2.0	93	98	R
11	4-$FPhCH_2Br$	8a	-10	0.5	60	72	R
12	4-$FPhCH_2Br$	8b	-10	1.5	72	85	R
13	CH≡CCH_2Br	8a	-10	1.5	90	94	R
14	CH≡CCH_2Br	8b	-10	6.5	89	98	R
15	CH_3I	8a	-20	2.0	87	92	R
16	CH_3I	8b	-20	1.5	97	96	R
17	*p*-CH_3PhCH_2Br	8b	-10	4.0	91	98	R
18	*p*-$MeOPhCH_2Br$	8b	-10	12	94	97	R
19	*p*-CF_3PhCH_2Br	8b	-10	2.5	95	98	R
20	2-$NapCH_2Br$	8b	-10	2.5	89	96	R

[a]Determined by HPLC with CHIRALCEL OD-H, hexane/2-propanol as an eluent. Absolute configurations were determined by comparison of HPLC retention time with the reported data. All NMR data's are coincide with the previous reported data's [28, 29, 31].

IV. CONCLUSIONS

In conclusion, we have successfully synthesized new chiral phase transfer catalysts **8a** and **8b** from inexpensive starting materials by easy method. These catalysts from cinchona alkaloid (80-92%) have been found to effective CPTC's for the enantioselective mono alkylation of glycine imine (ee's 98%) under low concentration of aqueous base, catalysts and ultrasonic condition.

V. ACKNOWLEDGMENT

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