Chapter V

Discussion
PART I
DISCUSSION

The development of achiral and chiral multi-site phase-transfer catalysts in both soluble and insoluble form that enable rapid and selective chemical transformation is a still field of paramount research interest particularly in organic chemistry. The present study is concerned with the synthesis of new 12 different achiral multi-site phase-transfer catalysts (ACMPTC’s) which include 10 types of soluble and 2 types of insoluble form and also 28 different chiral multi-site phase-transfer catalysts (CMPTC’s). The entire data has been discussed in two parts. Part I describes the synthesis, characterization of 12 types of ACMPTC’s and their catalytic efficiency which were examined by conducting the comparative study of four different organic reactions under pseudo-first order kinetics. Thorough kinetics were again performed for three different reactions using superior ACMPTCs. Part II covers the synthesis, characterization of 28 types of enantioselective CMPTC’s and their applications to two different asymmetric reactions such as C-alkylation of ketimine, aldime and enantioselective synthesis of N-arylaziridines.

PARTI

The main objective of this study was on generating more than one catalytic active site per molecule of catalyst in a simplified synthetic route. We have synthesized 12 different ACMPTC’s which include 2 types of di-site (soluble), 1 type of tri-site (soluble), 5 types of six-site (3 soluble, 2 insoluble) and each one of soluble ten-site, sixteen-site, twenty four-site and thirty two-site. The number of active sites present per molecule (each catalyst) was confirmed using various
spectral techniques. The comparative catalytic ability of these ACMPTC’s was examined through pseudo-first order rate constants of four different organic reactions such as C-alkylation of a-pinene, dichlorocarbene addition to (R)-limonene, Michael addition to cyclopentadiene and Darzen’s condensation to 4-nonanolide. Detailed kinetics of first three reactions were also studied using 4 types of superior six-site ACMPTC’s (2 soluble and its corresponding 2 insoluble) and the variables in the kinetic studies are stirring speed, [substrate], [catalyst], [NaOH] and temperature.

5.1.1. SYNTHESIS AND CHARACTERIZATION OF VARIOUS SOLUBLE AND INSOLUBLE ACHIRAL MULTISITE PHASE TRANSFER CATALYSTS

5.1.1.1. Common blocking agent - 1-(p-hydroxy phenyl)-2,4,8,10-tetraoxaspiro[5,5]undecane (2)

Initially, we prepared general blocking agent as a source reactant for the preparation of ACMPTC’s like di-site, tri-site, six-site, 10-site, 16-site, 24-site and 32-site, /?-Hydroxyacetophenone is taken as a starting material due to its free -OH functionality and it has been converted in to 1-(p-hydroxy phenyl)2,4,8,10-tetraoxaspiro[5,5]undecane 2. The structure of the compound 2 was confirmed by FT-IR spectra, where C-O stretching frequency appeared at 1077.6 cm\(^{-1}\). In the \(^1\)H-NMR analysis, the single methyne proton and four methylene proton appeared as a singlet at 3.15 and 4.29 ppm respectively, the oxaspiro adjacent eight methylene protons and the hydroxyl group appeared as a multiplet and broad singlet at 4.75-4.82 ppm and 1.22 ppm. The aromatic protons appeared as a doublet at 6.49-6.51-6.52 ppm and 7.39-7.42 ppm. Further the undecane compound 2 was confirmed by its molecular ion [M]\(^+\) peak noticed at 242.12.
5.1.1.2. Common blocking agent of 2,2-bis(2,4,8,10-tetraoxaspiro[5,5]undecane-1-(p-hydroxybenzene)-2-ethene (3)

The structure of 3 which was confirmed by the C-Cl stretching frequency at 725.2 cm\(^{-1}\), vinylic group at 1635.5 cm\(^{-1}\), hydroxyl group appeared 3448.5 cm\(^{-1}\) in FT-IR (Fig. 1). Similarly, in the \(^1\)H-NMR analysis (Fig. 2) the four methylene and single methyne proton appeared as singlet at 4.07 ppm and 6.12 ppm respectively. All the aromatic protons appeared as a doublet at 7.25-7.29 ppm (adjacent to phenolic aromatic) and 7.79-7.83 ppm (adjacent to vinylic aromatic) are the further confirmative evidence for compound 3. In \(^{13}\)C-NMR (Fig. 3) seven sharp signals with varied intensities were obtained. The aromatic ring showed four signals at 127.6, 128.7, 135.8 and 156.2 ppm. The olefinic carbon signals are noticed at 115.6 and 124.8 ppm. Alkyllic methylenes gave one signal with high intensities at 43.2 ppm. The molecular ion peak at m/z 216.98, from the mass spectra is an authentic evidence for the formation of dichloro compound 3.

5.1.2.1. Soluble di-site ACMPTC’s of \(\phi[2,2'-\text{bis}(\text{N-triethylammonium methylene chlorido)}-\text{eth}-1\text{-enophenol (4)}\)

The compound 3 viz., 2,2-bis(choloromethyl-3-(p-hydroxybenzene)-2-ethene was quaternised with excess of triethylamine in presence of acetonitrile. The compound 4 was confirmed by the disappearance of C-Cl stretching frequency in FT-IR (700-730 cm\(^{-1}\)) and appearance of C-N stretching frequency at 1056 cm\(^{-1}\). In \(^1\)H-NMR the methyl and methylene proton appeared as triplet and quartet at 0.97-1.01 and 1.86-1.92 ppm respectively. In \(^{13}\)C-NMR, the methyl and methylene carbon showed a high intense peak at 7.9 and 54.6 ppm respectively.
5.1.2.2. **Soluble di-site ACMPTC’s of 4-[(2,2-bis(N-triethylammoniummethylene chloride)eth-1-ene)phenoxymethyl]benzene**

Benzylobromide was condensed with the compound 2,2-bis(chloromethyl)-3-(/?-hydroxybenzene)-2-ethene 3 to give compound 5. The compound 5 was confirmed through FT-IR analysis, i.e. the disappearance of -OH stretching frequency and formation of C-O stretching frequency at 1045 am⁻¹. The condensed product was further quaternised with excess of triethyl amine to obtain the compound 6. As usual, the quaternisation was confirmed by disappearance and appearance of C-Cl and C-N stretching frequency at 700-730 cm⁻¹ and 1165.5 cm⁻¹ respectively. Further, in the case of ¹H-NMR analysis the quaternised ethyl group containing methyl and methylene proton was appeared as triplet and quartet at 1.02-1.05 ppm and 1.92-1.98 ppm respectively, confirming the structure. Furthermore, in ¹³C-NMR methyl and methylene carbon appeared as a high intense peak at 12.4 and 49.8 ppm. Finally the estimation of chloride ion concentration gave a value of 7.26 meq/g, [Calculated value 7.03 meq/g] and also molecular ion peak at m/z 438.32 in the mass spectra confirmed the presence of di-site ACMPTC’s 6.

5.1.3.1. **Soluble six site ACMPTC’s of 1,3,5-tris[(4-(2,2-bis(N-triethylammoniummethylene chloride)eth-1-ene)phenoxymethyl]benzene ([10](TBTEAPMB)]

The compound 3 was condensed with 1,3,5-trichloromethylenebenzene. In the early studies in ACMPTC shows that only two catalytic quaternary onium sites could be obtained using acetophenone as a starting material. Then the compound 9 was prepared by the condensation of 3 with 8 in presence of K₂CO₃. The condensation was ensured from the formation of C-O bond stretching frequency at
The compound 9 was further allowed for quaternization in reaction so as to give six-site ACMPTC’s viz., TBTEAPMB.

The structure of this six-site ACMPTC’s 10 was confirmed by FT-IR, 1H NMR, 13C NMR and MALDI TOF mass techniques along with chloride ion estimation. The disappearance of C-Cl at 700-750 cm\(^{-1}\) and formation of C-N stretching at 1211.2 cm\(^{-1}\) in FT-IR confirmed the quaternization reaction (Fig. 4). This is further confirmed in 1H-NMR analysis; viz., the appearance of methyl proton of the triethylamine unit in catalyst TBTEAPMB 10 as a multiplet at 1.72-2.22 ppm. In the case of 13C NMR, the presence of methyl and methylene group appeared at 9.2 and 10.4 ppm respectively suggested the formation of 10. Compound 10 was further confirmed through MALDI TOF mass analysis (Fig. 5) showing a value of 1159.36 calculated value of 1 159.59 for \([\text{C}_{75}\text{H}_{126}\text{N}_{6}\text{O}_{3}]^{61}\) ion.

Finally, the formation of six quaternised ammonium cation sites was confirmed through estimation of chloride ion concentration by Volhard method and giving a value of 15.15 meq/g, [calcld. value 15.20 meq/g]. The closer agreement values in MALDI TOF analysis and [Cl] in Volhard method were found to be strong evidence for the presence of six-site permolecule of ACMPTC.

5.1.3.2. Insoluble six-site ACMPTC’s of poly(styrene) supported-1,3,5-tris(4-
(2,2-bis(N-triethylammoniummethylene chloride)eth-1-ene) phenoxy methyl] benzene (16) (PSTBTEAPMB)

Insoluble polymer-supported ACMPTC are considered to be attractive much owing to its efficiency, easy reusability after recycling after completion of reaction. Mesitylene was first converted into mesitaldehyde by the method of Gattermann Koch formylation. The formation of aldehyde was confirmed through C=O peak at 1725.2 cm\(^{-1}\) in FT-IR spectra. Then the aldehyde was reduced in presence of
BH$_3$/THF; the formation of alcohol was confirmed by the disappearance of C=O stretching and the formation of broad peak at 3485 cm$^{-1}$ for -OH. Further, the alcoholic compound was converted into tribromo derivative in presence of N-bromosuccinimide, the tribromide was confirmed by the formation of C-Br stretching frequency at 780 cm$^{-1}$ in FT-IR. Furthermore the compound 15 was condensed with 3, the formation of chloride compound was confirmed by the disappearance of C-Br frequency (at 780 cm$^{-1}$) and formation of C-O and C-Cl stretching frequency at 1218 cm$^{-1}$ and 715 cm$^{-1}$ respectively in FT-IR spectrum. Then this blocked compound was condensed with polymer-supported polystyrene co-polymer beads enriched with 25% active site (VBC), +140 -170 mesh size; the condensation was confirmed through disappearance of -OH stretching frequency peak at 3400-3600 cm$^{-1}$ in FT-IR and then the polymer supported chlorine compound was converted in to ACMPTC viz., quaternization; the formation of C-N stretching frequency at 1087.8 cm$^{-1}$ and disappearance of C-Cl stretching frequency at 720 cm$^{-1}$ in FT-IR spectra (Fig. 6) and also in solid $^1$H-NMR (Fig. 7), the ethyl group moiety containing 54 methyl proton appeared as a broad peak (signal) at 1.25-2.5 ppm and 36 methylene proton appeared at 3.13-4.25 ppm. In $^{13}$C NMR (Fig. 8), the presence of N-ethyl group containing methyl and methylene carbon noticed high intense at 11.9 and 43.3 ppm respectively. Finally, the formation of six quaternised ammonium cation sites was confirmed by the chloride ion analysis through Volhard method and showing a value of 12.42 meq./g, [expected value 12.86 meq./g]. The reproducibility of these values [chloride ion] confirmed the presence of 6-active site per molecule or ACMPTC.
5.1.3.3. Soluble six-site ACMPTC of 1,3,5-tris[(4-(2,2-bis(N-
triethylammoniummethylene chloride)eth-l-ene)phenoxy] benzene derived
from phloroglucinol [(TBTEAPB) 18]

The blocking agent 3 was condensed with 1,3,5-trihydroxybenzene
(phloroglucinol) 16. The chlorinated compound 3 was used as a building block for
the synthesis of another six-site ACMPTC viz., TBTEAPB 18 catalyst; the
compound 17 was prepared by condensation of 3 with 16 in presence of
dicyclohexylcarbodiimide (DCC). The condensation product 17 was ensured from
the formation of C-O and C-Cl stretching frequency at 1035.87 cm\(^{-1}\) and 718 cm\(^{-1}\)
respectively and also disappearance of -OH stretching frequency in FT-IR
spectrum. Further the 3 vinylc methyne proton appeared as a singlet at 5.87 ppm,
and allylic 12 methylene proton appeared as a singlet at 4.12 ppm in \(^1\)H-NMR. In
\(^{13}\)C-NMR, the allylic methylene carbon and vinylc methyne carbon appeared at
49.2 ppm and 125.5, 123.2 ppm respectively. The compound 17 was allowed for
quaternization reaction to ACMPTC viz., TBTE APB 18.

The structure of this soluble six-site TBTEAPB catalyst 18 was confirmed
by FT-IR, \(^1\)H NMR, \(^{13}\)C NMR and MALDI TOF mass techniques along with
[chloride ion] estimation. The disappearance of C-Cl at 700-750 cm\(^{-1}\) and
formation of C-N stretching at 1087.8 cm\(^{-1}\) in FT-IR proved the formation of
quaternisation (Fig. 9). It is also confirmed through \(^1\)H-NMR analysis. The 54
methyl proton for triethylamine unit in 18 appeared as multiplet at 1.75-2.2 ppm
and 36 methylene proton appeared as multiplet at 2.73-2.90 ppm, In the case of
\(^{13}\)C NMR, the presence of N-ethyl group containing methyl and methylene carbon
shows intense peaks at 9.2 ppm and 10.4 ppm respectively. The compound 18 was
also confirmed through MALDI TOF for the parent ion viz., \([C_{66}H_{105}N_6O_3]^{+}\); the
obtained experimental value is 1118.75 (Fig. 10) [calculated value 1119.29]. Finally, the presence of six quaternised ammonium cation sites was confirmed by the [chloride ion] analysis and the obtained value is 17.30 meq/g, [expected value 17.35 meq/g]. The obtained experimental results of MALDI TOF and [chloride ion] analyses closely agree with their theoretical values, providing strong evidence for the presence of six-active sites per molecule of ACMPTC.

5.1.3.4. Insoluble six-site ACMPTC of poly (styrene) supported 1,3,5-tris [4-(2,2-bis(N-triethylammoniummethySenechloride)eth-l-ene)phenoxy] benzene (PSTBTEAPB) derived from phuloroglucinol (20)

Phuloroglucinol derived insoluble six-site ACMPTC was synthesized by treating 1,3,5-trihydroxy benzene 16 with the Gatterman Koch formylation to get the 1,3,5-trihydroxy benzaldehyde 19. The formation of the aldehyde was confirmed by the FT-IR technique i.e. the C=O stretching frequency appeared at 1720.4 cm\(^{-1}\) and also in the 'H-NMR, the aldehyde proton appeared as a singlet at 10.33 ppm. The aldehyde was condensed with the three equivalents of blocking agent 3 in presence of DCC, the condensation was confirmed by the appearance of C-O and C-Cl stretching frequency at 1130.2 cm\(^{-1}\) and 715.5 cm\(^{-1}\) respectively. The condensed aldehyde product underwent Merween Pondorf Verly reduction to give the alcoholic product which was confirmed by the disappearance of C=O stretching frequency and appearance of broad -OH band at 3465.7 cm\(^{-1}\). Further, in \(^1\)H-NMR -OH proton appeared as a broad signal at 5.4 ppm; 3 vinylic and 12 allylic protons appeared as singlets at 6.45 ppm and 4.12 ppm respectively. Further, in \(^13\)C-NMR, the vinylic and allylic methylene carbons are noticed at 117.4 ppm, 123.6 ppm and 43.5 ppm respectively. This product was further condensed with polymer supported polystyrene co-polymer beads (+140 +170 mesh size). The condensation
was verified by disappearance of -OH stretching frequency at 3400-3600 cm$^{-1}$ in FT-IR. This polymeric product was quaternised to give the insoluble six-site ACMPTC viz., PTEBTEAPB. The quaternisation was confirmed by solid $^1$H-NMR, $^{13}$C-NMR and [chloride ion] analyses. The C-N stretching frequency appeared at 1087.8 cm$^{-1}$ (Fig. 11). The results of solid $^1$H-NMR (Fig. 12), $^{13}$C-NMR analyses (Fig. 13) confirmed the presence of quaternary ethyl group containing 54 methyl proton and 36 methylene protons showing broad peaks at 1.25-2.5 ppm and 11.9 ppm, 3.13-4.25 ppm and 43.3 ppm respectively. Finally, the presence of six quaternised ammonium cation sites was confirmed by the [chloride ion] showing 15.28 meq/g, [expected value 15.35 meq/g]. The closer agreement of [chloride ion] results both experimentally and theoretically confirmed the presence of six-site per molecule or PTEBTEAPB.

5.1.3.5. Soluble six-site ACMPTC of $a,a,a''$-N-hexakis(triethylammonium methylene chloride)-melamine (24)

Melamine was formylated in presence of 37% formaldehyde to give the compound of N,N,N',N',N'',N''-hexakis-hydroxymethyl-[1,3,5]triazine-2,4,6-triamine 22. The formation of hexamethyol compound 22 was confirmed through FT-IR analysis, the formation of -OH stretching frequency appeared as a broad singlet at 3455 cm$^{-1}$. Further in $^1$H-NMR analysis -OH proton showed broad singlet at 2.1 ppm and methylene carbon observed at 81.53 ppm in $^{13}$C-NMR spectrum. Further, the structure of the compound 22 was chlorinated to give the hexachloro compound of 23. The chloro compound 23 was confirmed through the FT-IR analysis, the disappearace of -OH stretching frequency at 3400-3600 cm$^{-1}$ and appearance of C-Cl stretching frequency at 715 cm$^{-1}$. The compound 23 was treated for quaternization, the quaternization was observed by the FT-IR analysis, the
disappearance of C-Cl stretching frequency and formation of strong C-N stretching frequency at 1100 cm\(^{-1}\). Further, in \(^1\)H-NMR analysis, the quaternised ethyl group containing methyl and methylene proton showed a triplet at 1.47-1.52 ppm and quartet at 3.28-3.35 ppm. In \(^{13}\)C-NMR spectral analysis, the methyl and methylene carbon appeared strong intense peak at 7.46 ppm and 51.6 ppm. Finally, the [chloride ion] of soluble six-site ACMPTC is found 12.40 meq/g, [expected value 12.68 meq/g].

5.1.4.1. Soluble 10-site ACMPTC of 3,5-bis-(4-[bis-[4-(3,3'-triethylammonium chloride)-2-ethene-]-phenoxymethyl]-amino)-phenoxy)-methylbenzoate derived from 3,5-dihydroxybenzoic acid

3,4-Dihydroxy benzoic acid 25 was condensed with the 4,4'-fluoronitrobenzene to give the 3,4-bis(4-nitrophenoxo)benzoic acid and confirmed by FT-IR analysis, viz., C-O stretching frequency at 1280.5 cm\(^{-1}\) and the nitroso compound (1645.5 cm\(^{-1}\)) providing evidence for condensation. Further compound 27 was treated with the methyl iodide and subsequently allowed for reduction using Pd/C in presence of H\(_2\) atmosphere to get the 3,4-bis(4-aminophenoxy)methyl benzoate 28 and it was confirmed from FT-IR analysis i.e. disappearance of nitroso stretching frequency (1645.5 cm\(^{-1}\)) and appearance of N-H broad stretching frequency at 3440 cm\(^{-1}\) and also \(^{1}\)H-NMR analysis, the N-H proton showing a broad singlet at 4.2 ppm. The amino compound 28 was further allowed for formylation/chlorination to give the chlorine containing compound 30 which was confirmed by disappearance of N-H stretching frequency at 3400-3600 cm\(^{-1}\) and appearance of C-Cl and C-N stretching frequency at 715.3 cm\(^{-1}\) and 1075.3 cm\(^{-1}\).

Further the chlorinated compound 30 was confirmed through H-NMR and C\(^{13}\)
NMR analyses, the chloromethylene proton and its carbon noticed as a singlet at 5.45 ppm and 50.4 ppm. Compound 30 was quaternised with excess of triethylamine to give 8-site compound. The 8 site compound was further treated with methyl iodide and then ion exchanged by Amberlite resin to give the 10-site ACMPTCs 31. The quaternization was confirmed through FT-ER analysis (Fig. 14), the disappearance of C-Cl stretching frequency at 700-730 cm$^{-1}$ and appearance of strong C-TSF stretching frequency at 1145.6 cm$^{-1}$ and also the $^{1}$H-NMR analysis (Fig. 15), the ethyl group containing methyl and methylene proton showed triplet and quartet at 1.90-1.92 ppm and 3.96-3.99 ppm respectively and N$^+$-methyl proton was observed at 2.26 ppm. Further in $^{13}$C-NMR (Fig. 16), the methyl and methylene carbon was noticed at 22.1 and 27.8 ppm respectively and also the N$^+$-methyl carbon appeared at 26.2 ppm. Finally the presence of 10-site per molecule was confirmed through MALDI TOF mass (Fig. 17) results i.e. $[C_{114}H_{184}N_{10}O_{8}]^{10+}$ 1828.1 1 ; calculated value 1828.28 and chloride ion concentration found 13.40 meq/g, [expected value 13.68 meq/g]. The closer agreement of [chloride ion] and MALDI ESI mass results both experimentally and theoretically confirmed the presence of ten-site per molecule.

5.1.4.2. Soluble 16-site ACMPTCs of 3,5-bis(4-[bis-\(\text{triethylammonium chloride}\) methylene- amino-phenoxy]-benzoyl]- amino)-phenoxy)-methylbenzoate) derived from 3,5-dihydroxy benzoic acid (34)

The compound 3,5-bis-(4-nitro-phenoxy)benzoic acid 27 was condensed with the 3,5-bis-(4-nitro-phenoxy)methylbenzoate 28 to give the 3,5-bis(4-[bis-[3,5-bis(4-nitro-phenoxy)-benzoyl]-amino]-phenoxy)-methylbenzoate. The resulting nitro compound was confirmed from FT-IR analysis; i.e. the formation of C=0 and C-N stretching frequency were appeared at 1710 cm$^{-1}$ and 1065 cm$^{-1}$
respectively and the disappearance of N-H stretching frequency at 3400-3600 cm$^{-1}$. Further, we confirmed product based on the $^1$H-NMR results; the amide proton appeared as a doublet at 7.56-7.60 ppm and in the case of $^{13}$C-NMR, carbonyl carbon was appeared at 172 ppm providing the strong evidence for the formation of 3,5-bis(4-{bis-[3,5-bis(4-nitro-phenoxy)-benzoyl]-amino}-phenoxy)-methylbenzoate.

Then the nitro compound was reduced to amine in presence of Pd/C and H$_2$ atmosphere; the reduction was confirmed by the appearance of N-H stretching frequency at 3465 cm$^{-1}$ in FT-IR and also amine proton appeared as a broad singlet at 5.16 ppm in $^1$H-NMR is indicative of the formation of 32. Further the compound 32 was allowed for formylation in presence of 37% formaldehyde and 10% aqueous NaOH, the formation of alcoholic compound was confirmed by FT-IR spectrum (-OH stretching observed frequency at 3485 cm$^{-1}$). In $^1$H-NMR analysis, the methylene proton was observed as a singlet at 3.85 ppm, in the $^{13}$C-NMR spectrum, methylene carbon showed at 47.23 ppm indicating the formylation product. Furthermore, the alcoholic compound was chlorinated using PCl$_3$. The chlorination compound 33 was confirmed from the C-Cl stretching frequency at 715 cm$^{-1}$ and disappearance of -OH stretching frequency at 3400-3600 cm$^{-1}$ respectively in FT-IR analysis. Subsequently compound 33 was quaternised to give soluble 16-site ACMPTC viz., 34. The disappearance of C-Cl stretching frequency at 700-730 cm$^{-1}$ and the formation of strong C-N stretching frequency at 1018.3 cm$^{-1}$ in FT-IR proved the catalytic moiety (Fig. 18). The methyl and methylene proton are noticed as a triplet and quartet at 2.61-2.78 and 2.90-3.08 ppm respectively in $^1$H-NMR (Fig. 19) and also methyl and methylene of quaternary ammonium carbon appeared at 37.11 ppm and 37.51 ppm respectively in $^{13}$C-NMR showing further evidence for
the presence of active site (Fig. 20). Furthermore the 16-site per molecule was confirmed using the results of MALDI TOF mass spectra (Fig. 21) giving 3456.08 as m/z for \([\text{C}_{208}\text{H}_{330}\text{N}_{26}\text{O}_{16}]^{16+}\) the calculated value being 3458.26, the chloride anion concentration found 17.36 meq/g. and the theoretical value is 17.87 meq/g. The closer agreement of [chloride ion] and MALDI ESI mass results both experimentally and theoretically confirmed the presence of sixteen active sites per molecule.

5.1.4.3. Soluble 24-site ACMPTC derived from 3,5-dihydroxybenzoic add (35)

The quaternised compound of \(3,5\)-bis\{(4\{-bis\{[3,5-bis(4-bis-N-((triethylammonium chloride) methylene-amino-phenoxy)-benzoyl]-amino}\)-phenoxy)-methylbenzoate\} 34 was further treated with the methyl iodide in presence of acetonitrile to give the aniline nitrogen quaternized compound that contain chloride and iodide as anions. Then this compound was ion exchanged using Amberlite resin. The formation of 24-site quaternised ACMPTC was confirmed by the FT-IR, NMR spectra, MALDI TOF mass and chloride ion estimations. In FT-IR analysis (Fig. 22), the formation of C-N stretching frequency with a strong peak at 1114.8 cm\(^{-1}\) was observed. Further the formation of quaternised ethyl group containing methyl and methylene proton was appeared in the form of triplet and quartet at 1.37-1.44 and 2.47-2.77 ppm respectively and also the quaternised N\(^+\)-CH\(_3\) methyl proton was appeared singlet at 2.50 ppm in \(^{1}H\)-NMR analysis (Fig. 23). In \(^{13}C\)-NMR (Fig. 24) analysis the methyl and methylene carbon appeared at 38.86 ppm and 39.28 ppm respectively and also N\(^+\)-CH\(_3\) carbon noticed at 39.50 ppm. Furthermore the formation of 24-site quaternisation was confirmed by the [chloride ion] estimation and also the FAB mass spectrum (Fig. 25) and observed value of \([\text{C}_{216}\text{H}_{354}\text{N}_{26}\text{O}_{16}]^{24+}\) 3535.33 and
calculated value 3582.16, the chloride anion concentration found 19.89 meq/g and the theoretical value 20.16 meq/g. The closer agreement of [chloride ion] and FAB mass results both experimentally and theoretically confirmed the presence of 24-active site per molecule.

5.1.4.4. Soluble 32-site ACMPTC

3,5-bis(4-{bis-[3,5-bis(4-bis-N-(chloromethylene-amino-phenoxy)-benzoyl]amino)-phenoxy})-methylbenzoate 32 was allowed to formylation reaction in presence of 37 % formaldehyde to give the alcoholic compound and it was confirmed through the formation of -OFI stretching frequency with a broad peak at 3534.25 cm$^{-1}$ in FT-IR analysis. Then this alcoholic compound was chlorinated in presence of PCI3 and the chlorination was confirmed by the disappearance of -OH stretching frequency (3400-3600 cm$^{-1}$) and formation of C-Cl stretching frequency at 704 cm$^{-1}$. Further, the chlorinated compound was condensed with the 2,2-bis(chloromethyl-3-(p-hydroxybenzene)-2-ethene 3 to get compound 36. The compound 36 was confirmed by FT-IR, i.e. formation of C=C stretching frequency appeared at 1680 cm$^{-1}$ Furthermore the allylic methylene proton and vinylic proton was appeared singlet at 3.46 ppm, and 6.15 ppm respectively and also the vinylic aromatic proton appeared multiplet at 7.62-7.75 ppm in $^1$H-NMR analysis. In the case of $^{13}$C NMR analysis, allylic methylene carbon appeared at 44.14 ppm and also the vinylic carbon appeared at 116.75 and 121.40 ppm. Furthermore the condensed compound 36 was quaternised to give the compound 37; the quaternization was confirmed through FT-IR analysis, the disappearance of C-Cl stretching frequency at 700-730 cm$^{-1}$ and formation of C-N stretching frequency observed at 1172.6 ppm (Fig. 26). Further, the quaternisation was proved by the formation of methyl and methylene proton triplet at 2.61-2.68 ppm and quartet at 3.25-3.35 ppm in $^1$H-NMR
analysis (Fig. 27). In the case of $^{13}$C-NMR results (Fig. 28), the methyl and methylene carbon noticed at 17.70 ppm and 30.78 ppm respectively. The MALDI TOF mass spectral result (Fig. 29) of $[C_{46}H_{71}N_{42}O_{32}]^{2+}$ : 7399.76; theoretical value is 7407.39. The chloride anion concentration found 17.24 meq/g; calculated value 17.87 meq/g. The closer agreement of [chloride ion] and MALDI TOF mass values are both experimentally and theoretically confirmed the presence of 32-active site per molecule.

5.1.5. COMPARATIVE STUDY FOR THE EFFICIENCY OF VARIOUS SOLUBLE AND INSOLUBLE ACMPTCS USING DIFFERENT ORGANIC REACTIONS

The catalytic efficiency of these 12 different ACMPTCs (both soluble and insoluble) were examined by conducting comparative studies for four different organic reactions. Commercially available similar catalytic environment single-site (soluble & insoluble) PTCs were also employed to carry out the same organic reaction with a view to compare the efficiency with newly synthesized ACMPTCs. All the reactions were studied under pseudo first order kinetics keeping identical reaction conditions irrespective of the catalysts and using three different concentrations ([N$^+$]). The performance of the ACMPTCs were assessed based on the pseudo first order rate constants for four different organic reactions such as C-alkylation of a-pinene with epichlorohydrin, dichlorocarbene addition to (R)-limonene, Darzen’s condensation to 1,6-dibromohexan-2-one with 4-nonanolide and Michael addition to cyclopentadiene with methylmethacrylate.
5.1.5.1. C-Alkylation of α-pinene with epichlorohydrin under ACMPTCs conditions

The observed rate constants for the C-alkylation of α-pinene using different soluble/insoluble ACMPTCs were found to be in the following order: 32-site > 24-site > 16-site > 10-site > six-site insoluble (PTBTEAPB) > six-site insoluble (PTBTEAPMB) > six-site (HTAMCM) > six-site (TBTEAPMB) > six-site (TBTEAPB) > tri-site (TTEAMCB) > DSPTC II > DSPTC I > PSPTC > TEAC (Table 1). The observed results reveal that the rate constants are proportional to the number of catalytic sites of each ACMPTC’s (per molecule) irrespective of three different $[N^+]$. It is very clear from the early studies that the number of catalytic sites per molecule usually decides the catalytic efficiency of that particular catalyst. The structure of the catalyst and substrates and their proper orientation towards catalytic sites may also play a significant role to influence the rate of reactions. All these ACMPTC’s containing $N^+$ and $Cl^-$ ions act as catalysts irrespective of their soluble and insoluble nature. The enhancement in the rate constants observed in higher numbered active-site ACMPTC’s such as 32, 24, 16 and 10 are not exactly proportional to the number of active sites present in each ACMPTC (per molecule) when compared with the rate constant of single-site PTC (both soluble and insoluble). For instance, although the observed rate constants are not enhanced 32 fold for 32-site ACMPTC or any other ACMPTC in comparison with single-site PTC rate constant, but there is a larger increase in the rate constants with increase in active sites (irrespective of ACMPTC’s). The reason for lack of proportionately in rate constant to number of active site for ACMPTC’s compared to single-site PTC may be due to lower transporting efficiency of cation from...
aqueous phase to organic phase owing to their higher molecular weights of each ACMPTC; complexity of high density molecule of each ACMPTC particularly higher numbered active-site catalysts (or) probably, bands of quaternising site may be less. Further, among the five types of six-site ACMPTC’s, the order of catalytic efficiency in terms of rate constants was observed as PTBTEAPB > PTBTEAPMB > HTAMCM > TBTEAPMB > TBTEAPB. The polymer-supported insoluble six-site ACMPTC derived from phuloroglucinol was assumed to be best when compared to rest of the soluble and insoluble six-site ACMPTC’s. Several reports, including those by Regen et al.\(^2\) Sherrington et al.\(^3\) and Svec et al.\(^4\) in favor of higher catalytic efficiency for insoluble polymer-supported catalysts, that is they have proved that supported polyethylene glycols and crown ethers have been shown to have higher reactivity than their soluble analogues.

Likewise, the six-site insoluble catalysts of PTBTEAPB and PTATEAPMB were synthesized using phuloroglucinol and mesitylene respectively as starting materials with copolymer-beads obtained from styrene, divinylbenzene and vinylbenzyl chloride; as a result, the lipophilicity of these insoluble polymer-supported phase transfer catalyst is increased and thus facilitates the transport of the catalyst into the organic phase, thereby increasing the reaction rate as compared to their respective soluble analogs in the reaction of C-alkylation of a-pinene. This indicates that the polymer-support for the PTC (PSPTC) no longer a constraint as in the case of most heterogeneous catalysts. The present increasing trend in reaction rate for alkylation of a-pinene in the presence of PSPTC’s indicates that support structure can be assertively involved to give maximum conversion for a given time.\(^5\)
Among the three different soluble six-site catalysts, the catalyst derived from melamine (HTAMCM) was found to be more efficient than the catalysts derived from mesitylene (TBTEAPMB) and phloroglucinol (TBTEAPB). The higher rate constant for HTAMCM may be due to in-situ formation of HCl during the alkylation of a-pinene with epichlorohydrin and thus can lead to quaternisation of the free tertiary amine present in HTAMCM catalyst (Scheme 1); in turn there is a formation of additional six active sites added to the regular six site which are actively involved in catalysing the reactions, as a result the rate of the reaction is increased. Further, the molecular mass of the HTAMCM was relatively low when compared with TBTEAPMB and TBTEAPB; as a result this may freely facilitate increase the transport efficiency of anion from aqueous phase to organic phase than the other two soluble six-site catalysts. But this is not observed in the other six-site soluble catalysts. The rate constants of mesitylene derived soluble six-site and phloroglucinol derived catalysts are almost similar owing to the structural similarities.
There are two possibilities available for the formation of monoalkylated epoxide and diol at high concentration of aqueous NaOH. The monoalkylated oxirane has highly strained ring that can be easily hydrolysed to give a diol product (Fig. 30, Scheme 2 and 3). The six-site containing ACMPTCs viz., TBTEAPMB, PTBTEAPMB, TBTEAPB, PTBTEAPB were able to effectively catalyze the reaction at higher [NaOH] at higher rate constants were obtained compared with other experimental variations.

At higher concentration of Q'OH⁻ the monoalkylated oxirane ring was broken easily than the lower concentration of Q'OH⁻ (single-, di- and tri-site). Another possibility for the formation of diol products in the C-alkylation reaction as followed (Scheme 3).
The reason for difference in rate constant particularly with the number of active sites on each ACMPTC’s may be due to high molecular weight and complexity that leads to constraint for transformation of species from aqueous to organic and thus reduce the rate constants.

5.1.5.2. Dichlorocarbene addition to (R)-limonene under ACMPTCs conditions

In the case of dichlorocarbene addition to (R)-limonene, the comparative rate constants for all ACMPTC’s are presented in Table 2: Here too, the observed rate constants lie in the order 32-site > 24-site > 16-site > 10-site > six-site insoluble (PTBTEAPMB) > six-site insoluble (PTBTEAPB) > six-site (TBTEAPB) > six-site (HTAMCM) > six-site (TBTEAPMB) > tri-site (TTEAMCB) > DSPTC II > DSPTC I > PSPTC > TEAC. These results, irrespective of three different [N⁺] each ACMPTC’s reveal that the rate constants increase for di-site and tri-site
ACMPTC’s as compared with the single site ACMPTC. Whereas the increment of rate constant for 32, 24, 16, 10 and six-site ACMPTC’s were not proportional to the number of active sites present as compared with rate constant obtained in single-site catalysts. But however, notable increment of rate constant was observed in each of these high numbered active site than ACMPTC’s with single-site ACMPTCs.

Among the 5 different six-site ACMPTC’s the rate constants are found to be higher for insoluble ACMPTC’s derived from mesitylene (PTBTEAPMB) and phloroglucinol (PTBTEAPB) respectively than with the rest of the soluble ACMPTC’s. The remarkable increase in rate constant observed using insoluble ACMPTCs can be explained as follows; the polymer support to which the catalyst is bound is prepared from styrene-divinylbenzene copolymer which in turn exist as a nonpolar polymer backbone for the active-site moiety. Further, because of presence of more number of pendant methyl chloride in a single molecule, on quaternization with triethylamine leads to afforded the more number of carbon atoms in the respective insoluble ACMPTCs. Therefore, in view of the tendency of nonpolar polymer backbone and presence of more number of carbon atoms both the ACMPTCs, the lipophilicity behavior of the catalyst is increased and this in turn facilitates transport of the organic phase into the catalyst, thereby resulting the enhanced rate constant is noticed in both the ACMPTCs. This observation reveals that, the polymer support is no longer inert as in the case of most heterogeneous catalyst rather this support structure is more useful to manipulated to increase the
maximum catalytic efficiency of the catalyst. Similar observation are already reported by Doraisamy et al. Further, among the 3 different soluble six-site ACMTCs, the rate constants are found to be a little higher for the six-site catalyst derived from phluorogulucinol than the catalysts derived from melamine (HTAMCM) and mesitylene (TBTEAPMB). The difference in the rate constant between HTAMCM and TBTEAPM is not significant. In the C-alkylation of a-pinene although, HTAMCM are observed to be more effective than TBTEAPMB and TBTEAPB due to the increase in number of additional catalytic site (because of instant quaternization in the tertiary amine present in ring) and low molar mass; in the dichlorocarbene addition reaction the efficiency of HTAMCM is low because the formation of highly active species of dichlorocarbene is a strongly ion pairing interaction (R4N3+:CCl2) with the HTAMCM catalyst than the phluorogulucinol derived six-site catalyst.

Furthermore, the comparative study of this reaction under identical condition also reveals that bis addition was observed in GLC particularly in the high numbered active site catalysts viz., six-site to 32-site ACMPTCs; this is not observed in single-site, di-site and tri-site ACMPTCs. The formation of bis-dihalo product (Fig. 31) in the high numbered active site ACMPTCs may be due to bis-dihalocyclopropanation of (R)-limonene owing to the greater number of active site present permolecule (catalyst); whereas only one product is noticed in the case of single site to tri-site ACMPTCs because of mono dihalocyclopropanation of
(R)-limonene. The formation of bis and mono dihalocycloproduct using high numbered active-site and low numbered active site ACMPTCs respectively provides the additional evidence for the presence of their total number of active site in the respective molecule/catalysts.

Further, the rates of the 24 site and 16-site ACMPTCs are almost similar due to instant quaternization of tertiary nitrogen present in 16 site ACMPTCs during the reaction occurs in the medium ((degradation of chloroform) (Scheme 4)). The same observation was noticed in the six-site HTAMCM catalysts.

Further, the dichlorocarbene addition to (R)-limonene has lower rate constant than the other reactions such as C-alkylation of a-pinene, Darzens condensation to 1,6-dibromohexan-2-one and Michael addition to cyclopentadiene due to the formation of highly unstable carbene intermediate directly reacted with the catalysts containing double bond (Scheme 5).
5.1.5.3. **Darzens condensation to 1,6-dibromohexan-2-one with 4-nonanolide under ACMPTCs conditions**

Further, we also ascertained the efficiency of all the ACMPTCs by taking 3 different $[N^+]$ of each of these catalysts using Darzen’s condensation reaction between 1,6-dibromohexan-2-one and 4-nonanolide. The observed in pseudo-first order rate constants are presented in Table 3. Here too, as catalytic efficiency was observed to be in the following decreasing order, 32-site > 24-site > 16-site > 10-site > six-site insoluble (PTBTEAPMB) > six-site insoluble (PTBTEAPB) > six-site (HTAMCM) > six-site (TBTEAPMB) > six-site (TBTEAPB) > tri-site (TTEAMCB) > DSPTC II > DSPTC I > PSPTC > TEAC. For instance in the Darzen’s condensation reaction, the formation of product depend on generation of carbanion from 5-bromo-1-(5-pentyl-1,4-dioxa-spiro[2.4]hept-2-y1)-pentan-1-one, 2-pentyl-1,12-dioxa-dispiro[4.0.5.1]dodecan-7-one which in turn attracted towards 4-nonanolide to give ring substituted product. There are two possibilities available for the formation of carbanion in the Darzen’s condensation reaction (Scheme 6 and 7). Again, the generation of carbanion from 1,6-dibromohexan-2-one depends...
on the number of active catalytic site present per molecule of each ACMPTC catalysts. Particularly, we have noticed the product 2-bromo-2-(2-hydroxy-5-pentyl-tetrahydro-furan-2-yl)-cyclohexanone in the reaction catalysed by high numbers active-site ACMPTCs say from six-site to 32-site; this is because the high numbered active-site catalysts has got large affinity to generate carbanion in the first step leading to formation of product 5-bromo-1-(5-pentyl-1,4-dioxa-spiro[2.4]hept-2yl)-pentan-1-one, again this may under go further alkylation due to the presence of more active site in the respective high numbered catalysts as a result there is a formation of ring closed oxirane product viz., 2-pentyl-1,12-dioxa-dispiro[4.0.5.1]dodecan-7-one (Fig. 32); this inturn undergo acid/base hydrolysis to yield product 2-bromo-2-(2-hydroxy-5-pentyl-tetrahydro-furan-2-yl)-cyclohexanone.

In contrast, there is no hydrolyzed product 2-bromo-2-(2-hydroxy-5-pentyl-tetrahydro-furan-2-yl)-cyclohexanone in the case of single-site, di-site and tri-site ACMPTCs and these catalysts produced only oxirane product 5-bromo-1-(5-pentyl-1,4-dioxa-spiro[2.4]hept-2yl)-pentan-1-one. This trend strongly proves the presence of more number of active site per molecule irrespective of ACMPTCs and the observed rate constants are on par with total number of active site in each catalyst. The difference in rate constant between all the six-site ACMPTCs shows that insoluble ACMPTCs are effective than their respective soluble counterpart, especially the catalysts derived from mesitylene supported polystyrene (PTBEAPMB) are more effective than the insoluble ACMPTC derived from
phluorogulucinol. The rate constant values for soluble six-site viz., HTAMCM and TBTEAPMB are similar irrespective of concentration but higher than the soluble phluorogulucinol based six-site TBTEAPB. This is because, due to existence of low molecular weight and simple structure of HTAMCM and TBTEAPMB than the TBTEAPB.
5.1.5.4. Michael addition to cyclopentadiene with methylmethacrylate under ACMPTCs conditions

Similarly, the effectiveness of all the ACMPTCs (taking three different \([N']\)) were also examined using another reaction such as Michael addition to cyclopentadiene with methylmethacrylate under identical reaction conditions. The pseudo-first order rate constant values for this reaction were also obtained; the trend being similar except for little change in the order of effectiveness among the six-site ACMPTCs. Otherwise, the same trends of efficiency were observed as noted in all
the other three different reactions. That is, the order (Table 4) of the ACMPTCs were found to be as follows; 32-site > 24-site > 16-site > 10-site > six-site insoluble (PTBTEAPMB) > six-site insoluble (PTBTEAPB) > six-site (TBTEAPB) > six-site (TBTEAPMB) > six-site (HTEMCM) > tri-site (TTEAMCB) > DSPTC II > DSPTC I > PSPTC > TEAC. The carbanion reaction with the activated olefins is called Michael addition. The formation of activated olefins is directly proportional to the active site of the catalysts. Thus our findings indicated that the two-cationic moiety of the catalysts simultaneously activated and used to fix the substrates in the same environments (Scheme 8), as a result of the reaction the yield is found to increase. 1
Among the five types of six-site ACMPTC’s, the orders of catalytic efficiency of rate constants were observed as PTBTEAPMB > PTBTEAPB > TBTEAPB > TBTEAPMB > HTAMCM. Here too, the polymer-supported insoluble six-site ACMPTC derived from mesitylene was found to be the best when compared with rest of the soluble and insoluble ACMPTC’s. It is very clear from all the early studies that the number of catalytic sites present per molecule usually decides the catalytic efficiency of each particular ACMPTC. Further, the structure of the catalyst and substrates and their proper orientation towards catalytic sites may also play significant role in influencing the rate of the reactions. Stark’s et al reported that several factors affect the reaction rates; (i) structure of R-groups, (ii) activity of the leaving group X, (iii) nucleophilicity of the displacing group Y (iv) relative ease of transfer of X and Y between the phases (v) reagent concentration (vi) agitation, intensity, (vii) temperature and (viii) catalyst structure. These factors have also been known to effect the reactions that involve triphase catalysis. When all the factors are fixed theoretically the catalyst structure becomes the only factor that differentiates reaction that use a tri-phase catalyst from those that use its soluble analog. In tri-phase catalysis, the active sites of the catalyst are immobilized on the solid support; the catalyst distribution in the reaction system is more restricted. Hence the reactants from both the organic and aqueous phases must migrate from their respective bulk phases to the catalyst surface to contact the catalytic sites.
Furthermore, the reactants also must diffuse within the solid support in order to contact the sites under the surface. These external and intraparticle mass transfer requirements can significantly affect the reaction rate; thus it is commonly believed that tri-phase catalysts have lower reactivity compared to their soluble analogs in two-phase reaction system. However, there are studies reported in the literature where tri-phase catalysts had shown higher reactivity than their soluble analogues; Tundo and Badiali\(^5\) reported that the catalysts made by immobilization of onium salts on inorganic supports (silica and alumina) allow high nucleophilic activity in bromide displacement on octylmethane sulfonate which result in higher reaction rate than for the same reaction in a homogeneous phase. Desikan and Doraiswamy\(^6\) studied the esterification of benzyl chloride with aqueous sodium acetate in the presence of tributylammonium chloride and reported faster reaction rates with the polymer supported form than with its soluble analogues. More recently, Glatzer and Doraiswamy\(^7\) made a comparative assessment of heterogeneous and homogeneous PTCs with different categories of PTC systems. The results suggested that the supported catalyst performed better than the soluble counterpart. Hence, these authors have suggested a methodology for economic choice of PTCs. In view of all these literature study, we strongly proved that the newly prepared insoluble ACMPTCs such as PTBTEAPMB and PTBTEAPB may also be a more economy catalysts.
SECTION II

5.1.6. KINETIC STUDY

Although we have characterized and ascertained the number of active sites present per molecule of each of 12 different ACMPTCs including soluble (10 No) and insoluble (2 No) through different key spectral techniques and [chloride ion] analysis, it is observed that each one have behaved differently in the reaction medium when they were employed in the reaction. Even though, we have synthesized 12 different ACMPTCs containing different number of active-site ranging from 2 to 32, the results from over all comparative study reveal that six-site ACMPTCs derived from mesitylene (both soluble (TBTEAPMB) and insoluble (PTBTEAPMB)) and phluorogulucinol (both soluble (TBTEAPB) and insoluble (PTBTEAPB)) have shown maximum efficiency. Taking into consideration all the above mentioned factors, we chose these four different six-site ACMPTCs viz., TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB as superior catalysts and were employed individually for thorough kinetic study of the following reactions.

1. C-Alkylation of a-pinene with epichlorohydrin
2. Dichlorocarbene addition to (R)-Limonene with excess of chloroform.
3. Michael addition to cyclopentadiene with methylmethacrylate

The detailed kinetic aspects of the chosen three different reactions were studied with a view to optimize the respective reaction and to evolve a suitable mechanism. The effects of various physico-chemical parameters such as stirring speed, [substrate], [catalyst], [NaOH] and temperature were thoroughly ascertained in each reaction with each catalysts.
5.1.6.1. C-Alkylation of α-pinene with epichlorohydrin

Generally, alkylation of any terpenoid provides most useful pharmaceutically valuable intermediate or direct products. Normally, these reactions are performed under strong bases and inert solvent condition. Employing of strong base and inert solvent is a practically difficult process due to pollution of base and cost of the solvent respectively. These problems are solved using phase transfer catalysts. Several procedures have been reported so far in the literature for the alkylation of α-pinene. In the recent past, alkylation of flavanoids are immensely popular owing to its applications in the pharmaceutical industries.

In view of these important applications of alkylated products, we had decided to carry out the C-alkylation of α-pinene with epichlorohydrin and also to investigate the kinetic aspects of this reaction using the 4 types of newly synthesized soluble (2 No.) and insoluble (2No.) six-site ACMPTCs such as TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB (Scheme 9).

![Scheme 9](image)
The kinetic experiments for the C-alkylation of α-pinene were conducted individually under biphasic (using soluble ACMPTCs) and triphasic (using insoluble ACMPTCs) conditions with excess of aqueous sodium hydroxide and epichlorohydrin under pseudo-first-order conditions. The formation of monoalkylated 2-(6,6-dimethyl-2-methylene-bicyclo[3.1.1]hept-3-ylmethyl)-oxirane as a product is noticed and subsequently it is hydrolysed to give the diol product viz., 3-(6,6-dimethyl-2-methylene-bicyclo[3.1.1]hept-3-yl)-propane-1,2-diol. The general reaction condition was studied by fixing the stirring speed at 500 rpm in the temperature 30-50 °C. Before the kinetic run was started, the catalyst was conditioned with aqueous sodium hydroxide and epichlorohydrin for 10 minutes. The substrate α-pinene was preheated at the appropriate temperature and was added to the reaction mixture at 0 time. Then the samples were collected from the organic layer at regular intervals of time. The kinetics of C-alkylation of α-pinene was followed by the disappearance of α-pinene using Gas Chromatograph. The effect of various experimental parameters such as stirring speed, catalyst amount, substrate concentration, sodium hydroxide concentration and temperature on the reaction rate constant were studied individually using TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB catalysts. The observed results for each ACMPTCs are discussed under the following subsections.

5.1.6.1.1. Effect of varying stirring speeds

The effect of varying stirring speed on the rate of C-alkylation of α-pinene with epichlorohydrin was studied in the range 100-700 rpm in presence of four different ACMPTCs viz., TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB. The experiments were performed as described in experimental section.
From the plots of log(a-x) versus time, the pseudo-first order rate constants for each six-site ACMPTCs were evaluated and presented in Table 5 (Fig. 33). The observed rate constant shows that the rate of the reaction increases on increasing the stirring speed and becomes saturated at higher rpm. In the presence of insoluble PTBTEAPB, the rate constant increased from 100 to 200 rpm and suddenly increased with increasing stirring speed from 200 to 300 rpm. Further-increasing stirring speed, there is only smaller increment of rate constant observed. Similarly, in the presence of PTBTEAPMB, the rate of the reaction increased from 100-300 rpm and sharp increase in 300 to 400 rpm, further increasing agitation speed does not alter the reaction i.e. constant increase was observed from 400 to 700 rpm. At 200-300 rpm and 300 to 400 rpm, the substrates are in perfect collision with the catalytic surface of the PTBTEAPB and PTBTEAPMB catalyst respectively along with effective mass transfer. Further increase in agitation speed at above 200 rpm for PTBTEAPB and 400 rpm for PTBTEAPMB catalysts causes only slight (moderate) enhancement in rate constants and this implies a saturation higher encounter of substrates with the active sites. Therefore, the reaction is mass transfer controlled and the effect of varying the stirring speed is well documented in previous study.11-14

Starks et al.13 reported that similar behavior was displayed by reactions with a real ‘phase transfer’ (Stark’s extraction mechanism) and there is much smaller limit of stirring speed between physical and chemical control (100-400 rpm). Similar observation was reported by Landini et al.16 Starks et al.17, Herriott et al. and Freedman et al.19, which reflects kinetic control by mass transfer of the chemical reaction [Q’X’] at a steady state concentration. Similar trend was observed in Balakrishnan et al. studies by viz., dichlorocarbene addition to styrene' and C-
alkylation of phenyl acetone using ethyl iodide\textsuperscript{21}. Chiellini et al\textsuperscript{22} reported the continuous increase in the rate of ethylation of phenylacetone even up to stirring speed of 1950 rpm. It has also been reported that the rate of an interfacial reaction is proportional to the stirring speed in the range of 600 up to 1700 rpm. Generally the stirring speed affects the observed rate constants in triphase catalytic condition when the chemical reaction is fast. When the mass transfer is rate limiting, then the reaction rates are directly proportional to the catalytic surface area and inversely proportional to the radius of spherical catalyst particle.\textsuperscript{9} In the present study, the dependence of the reaction rate constants on the stirring speed above certain rpm level is indicative of hydroxide ion initiated mechanism (i.e. extraction mechanism).

Similarly, in the case of soluble ACMPTCs in TBTEAPMB, the rate is found to increase very slowly from 100-400 rpm and at 400-500 rpm a sharp increase was observed and with further increase of stirring speed the rate of the reaction does not increase. In the case of TBTEAPB, the rate constant are found to increase from 100-500 rpm and a sharp increase was noticed from 500 to 600 rpm and further increasing of rpm has no influence on reaction rate. From the observed results, the reaction kinetics is controlled by the chemical reaction in the organic phase for stirring rate greater than 500 rpm for TBTEAPMB and 600 rpm for TBTEAPB. In the two-phase reaction, mass transfer resistance is important in affecting the reaction rate. In general, either the organic or aqueous solution can disperse in smaller droplet size by agitation of the two phase solution. Hence the contact area of the interface between the continuous and dispersion phase increases with increase of the agitation speed. Further, the mass transfer coefficient is also highly dependent on the flow condition (e.g. agitation speed).
For agitation speed less than 500 rpm and 600 rpm under TBTEAPMB and TBTEAPB catalytic conditions respectively, both mass transfer and reaction resistance play an important role in determining the reaction rate. Further in present study, at stirring speed level of 500 rpm and 600 rpm anion exchange equilibrium is very fast relative to the organic displacement reaction and the substrate (a-pinene) consumption rate becomes independent of the stirring speed. Hence, the constancy of rate constant at above 500 rpm and 600 rpm is indicative evidence that the reaction may preceed via extraction mechanism. In order to follow the further physical parameters for the C-alkylation of a-pinene was studied by fixing the stirring speed at 500 rpm, this is the optimized agitation speed for all ACMPTCs. The saturation of substrate transfer rate from aqueous to organic at lower stirring speed irrespective of ACMPTCs (both soluble and insoluble catalysts) providing the strong evidence for the confirmation of multi catalytic active sites.

5.1.6.1.2. Effect of varying substrate concentration

Kinetic experiments were performed by varying the substrate concentration [4.71-20.42 mM] and keeping other parameters like [epichlorohydrin] [NaOH] and temperature (40 °C) as a non variant constant for all the four different six-site ACMPTCs individually. The pseudo-first order rate constants for each ACMPTCs were evaluated from their respective linear plots of log (a-x) versus time. The examination of observed rate constants in all the 4 types of six-site ACMPTCs reveals that the k_{obs} are gradually increased with increasing [substrate] (Table 6, Fig. 34) irrespective of the catalysts viz., TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB. The increase in the rate constant even at wide increase of concentrations of substrate may be attributed to more number of proper collisions.
between the catalytic active sites with the substrate in each ACMPTCs. Though the order of magnitude of concentration difference between substrate (4.41 to 17.28 mM) and catalyst (0.30 mM) is wide even then observed rate constant were not decreased remarkably with respect to low concentration of ACMPTCs, as reported in the early studies. This observations proved the presence and participation of multicyclitic site in each catalyzed reaction. Balakrishnan et al. reported that the rate of the reaction is inversely proportional to the substrate concentration for the study of C-alkylation of phenylacetone with n-bromobutane using triethylbenzylammonium chloride as a PTC. The efficiency of each six-site ACMPTCs were found to be more for insoluble ACMPTCs than their respective soluble analogues even on increasing the higher concentration of substrate. This is another evidence for the presence of multiactive site in each ACMPTC catalysts. Further we have also reported similar behavior of rate constant in the C-alkylation of phenylacetonitrile with 1-bromobutane under MPTC conditions. In view of these observations, we fixed 11.00 mM as a common concentration for other (variation) studies using selective six-site ACMPTCs.

5.1.6.1.3. Effect of varying catalyst concentration

The pseudo-first order constant for the akylation of a-pinene has been determined by varying the soluble ACMPTCs, i.e. TBTEAPMB and TBTEAPB concentration in the range from 2.0 x 10^-4 moles to 4.0 x 10^-4 moles (0.20 to 0.40 mM) and their insoluble analogues viz., PTBTEAPMB and PTBTEAPB were fixed in the range of 0.1g to 0.5g respectively, and keeping the other parameters as constant. The observed rate constants for each ACMPTCs irrespective of soluble/insoluble were found to be proportional to [catalyst]. The rate constant is found to increase with increasing concentration of each ACMPT Cs (Table 7, Fig.
The increase in rate constants should be due to the presence of a large number of active sites in each ACMPTCs; and it is also known from this observation that each catalyst contains multiactive-site per molecule; as a result the ratio of active site with respect to [substrate] is supposed to increase and thus reaction rate consistently increased irrespective of ACMPTCs. Molinari et al\textsuperscript{24} observed a similar dependence and reported that the pseudo first-order rate constant is directly proportional to catalyst using phosphonium ion as PTC for Br-I exchange reaction of 1-bromooctane. A bilogartmic plot of the rate constants versus the concentration of the catalyst gave a straight line with a slope value of 0.65 for TBTEAPMB, 0.52 for PTBTEAPMB, 0.34 for TBTEAPB and 0.77 for PTBTEAPB (Table 8, Fig. 36). Halpern et al\textsuperscript{25} reported a similar observation for dehydrobromination of phenethyl bromide in the presence of tetracytalammonium bromide as a PTC under zero order kinetics. The rapid increase in the rate of the reaction even at very low concentrations of each ACMPTCs may be due to their co-operative influence of the two-cationic (ammonium) active sites on the catalyst\textsuperscript{26} The overall observations in each of these catalysts variation study confirmed that the rates of the reaction were found to be linearly dependent on their respective catalyst concentration.

\textbf{5.1.6.1.4. Effect of sodium hydroxide}

In order to know the effect, of [NaOH] on C-alkylation of a-pinene in the presence of each of all the four six-site ACMPTCs individually, the kinetic experiments were performed by varying the concentration of NaOH in the range 2.78 -10.71 M irrespective of the catalyst, keeping the other experimental parameters constant. The observed rate constants for each ACMPTCs (irrespective of soluble/insoluble) were found to be proportional to concentration of aqueous
NaOH (Table 9, Fig. 37). A bilogarithmic plot of the reaction rate against sodium hydroxide concentration gives a straight line with a slope of 0.28 for TBTEAPMB, 0.35 for PTBTEAPMB, 0.21 for TBTEAPB and 0.39 for PTBTEAPB (Table 10, Fig. 38). This may be attributed to the large generation of Q⁺OH⁻ ion pair owing to high concentration of NaOH as well as the presence of multi-active site in each catalysts and also low solvation by water. The availability of large amount of Q⁺OH⁻ ion pair should facilitate to the effective abstraction of proton from α-pinene and subsequently producing carbanion; as a result this carbanion is attracted much by the nucleophile formed from alkylating agent (i.e. epichlorohydrin) and thus the reaction proceed faster and so large amount of product is formed in all the ACMPTCs. Further, the free OFF and H⁺ (abstracted from α-pinene) forms the water molecules which inturn easily hydrolyze the primary alkylated product (i.e. epoxide) and hence there is a secondary diol product observed. Therefore, the optimum [OH⁻] for C-alkylation of α-pinene with epichlorohydrin using each case of ACMPTC was fixed as 6.25 M, using (20% NaOH (w/w)). Furthermore, using lower [NaOH] in any PTC catalyzed reaction is advisable for industrial point of view as there is scope for easy reaction workup avoiding abuse of the reaction vessels and particularly this condition is absolutely harmless to the environment. The observed rate constant in the alkylation reaction is found to be more even at lower [NaOH] and is certainly an additional evidence for the presence of more active-sites in each ACMPTCs.

5.1.6.1.5. Thermodynamic parameters for the alkylation of α-pinene

The effect of varying the temperature on the rate of C-alkylation of α-pinene with epichlorohydrin using four different six-site ACMPTCs such as
TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB were studied individually in the temperature range between 30-50 °C maintaining other parameters constant. The observed pseudo first order rate constants for each catalyst were found to increase with increase in temperature (Table 11, Fig 39). The energy of activation ($E_a$) is calculated from Arrhenius plot and presented in Table 12. The other thermodynamic parameters viz., $AS^\#$, $AG^\#$ and $AH^\#$ were also evaluated and presented in Table 12 for all the four six-site ACMPTCs. Earlier studies report that the activation energy for the dehydrobromination of (2-bromoethyl)benzene using tetaoctylammonium bromide as PTC to be 8 k cal mol$^{-1}$; based on this $E_a$ value, they proposed an extraction mechanism for the reaction. 27 The lower values of activation energy and negative $AS^\#$ for the alkylation of a-pinene reaction indicate that the step (2) (i.e. chemical reaction) is not the rate-determining step. The results are characteristic of mild diffusion control till 100-200 rpm for PTBTEAPB, 100-300 rpm for PTBTEAPMB, 100-500 rpm for TBTEAPMB and 100-600 rpm for TBTEAPB; at a given temperature and stirring speed, there should be a definite effective mass transfer between the aqueous and organic phases. Lee et al. 28 reported a similar study, viz., the effect of temperature on the reaction rate for the formation of phenyl benzoate in the presence of tetrabutylammonium bisulfate (TBAHSO$_4$) as PTC and in the absence of PTC; the activation energies were reported as 3.6 kcal mol$^{-1}$ for tetrabutylammonium bisulfate phase transfer catalyst and 8.1 kcal mol$^{-1}$ without PTC and confirmed that the reaction proceeded via an extraction mechanism. A lower energy of activation (0-10 kcal mol$^{-1}$) was observed for the C-alkylation of a-pinene in presence of four different soluble and insoluble ACMPTCs. Since, the observed $E_a$ values are agrees well with the reported values.
and hence reaction should proceed through the hydroxide ion extraction mechanism irrespective of ACMPTCs.

S. 1.6.1.6. Mechanism

The C-alkylation of a-pinene appears to proceed by a two-step pathway. The mode of the addition of substrate into the reaction flask appears to have a significant role. Generally, in the alkylation of a-pinene, ACMPTCs react first with the base to form $Q^+\cdot OH^-$ which further reacts with the substrate and generated the anion of the substrate via abstraction of proton and later the addition of epichlorohydrin leads to dissociation into anions and cations and the cationic species react with the carbanion of a-pinene to form an alkylated epoxide product.

So far, in literature two types of mechanisms have been proposed frequently for phase transfer catalyzed reactions viz., extraction mechanism by Stark's and interfacial mechanism\textsuperscript{29} by Makosza. Increased rates with increased organophilicity or with larger symmetrical ammonium ions\textsuperscript{30,31} independence of reaction rate with respect to stirring speed (53,44,54) and linear dependence of reaction rate on [catalyst] confirm that the reaction should proceed via., extraction mechanism. Interfacial mechanism is strongly dependent on stirring speed (rpm), maximum reactivity with relatively hydrophilic triethylammonium ions\textsuperscript{32,34} and fractional order with respect to the catalyst are the parameters for confirmation of interfacial mechanism. In the present study, from the observed experimental results, i.e. dependence of the rate constant on the stirring speed beyond 500 rpm, dependence on [catalyst], [hydroxide ions], temperature and lower $E_a$ value, we conclude that the alkylation of a-pinene should proceed via., hydroxide ion extraction mechanism (Scheme 10) irrespective of four different ACMPTCs such as TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB.
5.1.6.2. DICHLOROCARBENE ADDITION TO (R)-LIMONENE

In the early years, synthesis of dichlorocarbene was a difficult task. In general, addition of dichlorocarbene to any olefins produced dihalocyclo derivatives, which are valuable compounds, on further treatment with sodium to give alkene, and thus reduced/converted into other valuable products. Dihalocyclopropanes are intermediate compounds for the synthesis of cyclopropane derivatives and other pharmaceutically valuable products. Since halocarbene undergoes hydrolysis in presence of water and hence, the reaction was carried out under vigorous anhydrous conditions. These difficulties are easily overcome by performing the reactions in biphasic medium using sodium hydroxide and quaternary ammonium salt as a phase transfer catalyst. For example, Doering and Hoffmann generated the dichlorocarbene from chloroform and tert-butoxide and
carried out addition reaction in cyclohexene to produce 7,7-dichlorobicyclo[4.1.0]heptane. However, this technique has got some limitations due to low conversion of reactant, even at extreme reaction conditions. Makosza and Wawrzyniewicz\textsuperscript{37} were the first to prepare dichlorocyclopropane under phase transfer condition successfully. There are numerous reports available for the dichlorocarbene addition to various olefins using single site PTCs\textsuperscript{38,42}.

In view of these important applications of dihaloderived products, we had decided to carry out the dichlorocarbene addition to (R)-limonene and also to investigate the kinetic aspects of this reaction using the same 4 types of six-site ACMPTCs such as TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB (Scheme 11).

5.1.6.2.1. Effect of stirring speed

The effect of varying stirring speed on the rate of the dichlorocarbene addition to (R)-limonene using four different soluble and insoluble ACMPTCs such as TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB was studied in the range of 100 to 700 rpm. The other parameters viz., [NaOH], [substrate], [Catalysts] and temperature are kept constant. The detailed experimental procedure
is described in experimental section (Page No. 77). From the plots \( \log(a-x) \) versus

time, the pseudo-first order rate constants were evaluated. A plot of \( k_{\text{obs}} \) versus

stirring speed is shown in table 13 (Fig. 40). The rate is found to increase rapidly

from 100-500 rpm and at 500-600 rpm a sharp increase was observed and further

increase of speed does not alter the reaction rates in presence of TBTEAPMB.

Similarly, the reaction rate increases steadily from 100-400 rpm, a sharp increase

was noticed up to 500 rpm and further increase of rpm has no influence of reaction

rate for soluble TBTEAPB. Further, in the presence of insoluble PTBTEAPMB, the

rate of reaction suddenly increases from 100-200 rpm and further increase in

stirring speed has no influence on rate of the reaction. Similarly, in presence of

insoluble PTBTEAPB, the rate slowly increases from 100-200 rpm and a sharp

increase was observed from 200-300 rpm and also on further increase in agitation

speed, the rate of the reaction is constant. From the observed results, it is clear that

the reaction Idnetics is controlled by the chemical reaction in the organic phase for

stirring rate greater than 600 rpm for TBTEAPMB and 500 rpm for TBTEAPB.

Further, stirring speed of 600 rpm and 500 rpm anion exchange equilibrium is very

fast relative to the organic displacement reaction and rate of the substrate ((R)-

limonene) consumption becomes independent of the stirring speed. Below 600 rpm

for TBTEAPMB and 500 rpm for TBTEAPB, the requirement for sufficient rapid

mass transfer of the reaction anion is not met and diffusion controlled kinetics is

observed. Hence, the constancy of the rate constant at above 600 rpm and 500 rpm

suggested that the reaction might proceed via an interfacial mechanism in the

presence of TBTEAPMB and TBTEAPB respectively.

Similarly, in the case of triphase catalysis, the insoluble ACMPTCs viz.,

PTBTEAPMB and PTBTEAPB shows sudden increase in rate from 100-200 rpm
and 200-300 rpm respectively, which indicates that the mass transfer of reactions from bulk liquid to surface of catalyst. Also, the substrate and the respective catalyst may undergo a more number of proper collisions in that particular rpm. Hence the rate of the reaction is more for both the catalyst even at lower stirring speed. Further increase in agitation speed at above 200 rpm for PTBTEAPMB and 300 rpm for PTBTEAPB catalysts shows only very low enhancement in rate constant and this implies saturation of encounter by substrates with the active sites. Therefore, the reaction is mass transfer, the controlled effect of varying the stirring speed is well documented in previous study. Starks et al reported similar behavior displayed by reactions with a real ‘phase transfer’ (Stark’s extraction mechanism), there is much smaller limit of stirring speed between physical and chemical control (100-400 rpm). Similar observation was reported by Landini et al., Starks et al., Herriott et al. and Freedman et al., which reflects kinetic control by mass transfer of the chemical reaction \([Q \cdot X]\) at a steady state concentration.

In a systematic kinetic study of dichlorocarbene addition under solid/liquid phase transfer catalysis in presence of tert-ButOK, a sharp increase in the rate constant between 400 to 500 rpm was observed. Similar trend was observed by Balakrishnan et al. studies viz., dichlorocarbene addition to styrene and C-alkylation of phenyl acetone using ethyl iodide. Chiellini et al reported a continuous increase in the rate of ethylation of phenylacetone even up to string speed of 1950 rpm. When the mass transfer is rate limiting, the reaction rates are directly proportional to the catalytic surface area of the polymeric catalyst and inversely proportional to the radius of spherical catalysts particle. Hence, the dependence of the reaction rate constants on the stirring speed above certain rpm in
the present study is indicative of an interfacial mechanism. Further, 500 rpm is an optimum stirring speed for all ACMPTCs for further study of various physical parameters.

5.1.6.2.2. Effect of substrate concentration

Kinetic experiments were performed by varying the substrate ((R)-limonene) concentration ranging from 4.71 to 20.42 mM and other reactants such as chloroform, [ACMPTCs] and [NaOH] and temperature are kept as constant. Pseudo-first order rate constants were evaluated from the linear plots of log (a-x) versus time. The observed reaction rate constant increases as the amount of substrate increases for all the ACMPTCs (Table 14, Fig. 41). The order of observed rate constant is as follows, PTBTEAPB > PTBTEAPMB > TBTEAPB > TBTEAPMB. The increase in the rate may be attributed to the proportionate increase in number of catalytic active sites available in each ACMPTCs. For low concentration of catalyst the probability of substrate reacting with the catalytic surface was increased and hence the rate of the reaction increases. At lower substrate concentrations, the probability of meeting the reactant molecule on the active sites of the ACMPTCs are low, even though active sites are available on the catalysts. But, on increasing the concentration of substrate, the concentration of substrate molecule in reaction solution is also correspondingly increased which subsequently enhances the probability of finding the substrate with the active site of the catalysts and thereby increase the reaction rate. This observation confirmed the presence of multi-active sites in all ACMPTCs and also the higher rate constant is due to the perfect collision between the substrate and active site of the ACMPlCs. Similar trend was observed by Balakrishnan et al.20 in the study of C-alkylation of phenylacetone with n-bromobutane and triethylbenzyl ammonium chloride as a
PTC. Recently, Balakrishnan et al\textsuperscript{21} reported the C-alkylation of phenylacetone with ethyl iodide in presence of disite PTC. In view of these observations, the optimum substrate concentration for the dichlorocarbene addition to limonene is fixed as 23.35 mM.

5.1.6.2.3. Effect of catalyst concentration

The amount of catalyst was varied from \(2.0 \times 10^4\) to \(4.0 \times 10^4\) moles for soluble catalyst viz., TBTEAPMB and TBTEAPB and 0.1-0.5 g for insoluble catalysts viz., PTBTEAPMB and PTBTEAPB and other reactants are constant. The rate constants were plotted against the amount of the added catalyst (moles or g). The rate constants were linearly dependent on the amount of the each ACMPTCs used in each reaction. The observed order of rate constant for the ACMPTCs as follows, PTBTEAPMB > PTBTEAPB > TBTEAPB > TBTEAPMB. The increased rate constants are attributed to the increase in the number of catalytic active sites in each catalyst (Table 15, Fig. 42). In the case of insoluble catalyst, the rate constants are proportional to the amount of catalyst added to the reaction mixture, the rate-limiting step must take place at the active site present on the surface of the polymeric catalysts viz., PTBTEAPMB and PTBTEAPB. Regan\textsuperscript{*} studies the influence of the amount of catalyst on rate in the cyanide displacement reaction and showed that the rate of reaction was linearly dependent on the amount of catalyst. Balakrishnan et al\textsuperscript{20} also made a similar observation for the C-alkylation of phenylacetoniirile with 1-bromobutane. In the absence of the catalyst, no product was detected even after 5 hrs of reaction. The linear dependence of the rate constants irrespective of the catalyst concentration shows that the reaction should proceed through extraction mechanism.
Similar dependence of pseudo-first order rate constants on the amount of heterogenised phosphonium group from Br-I exchange reaction 1-bromo-octane was reported earlier and also they found that the limited interfacial area in the system, which becomes saturated with catalyst molecules. In the present study, a bi-logarithmic plot of the reaction rate constants versus the concentrations of the catalyst gave a straight line with slope values of 0.32 for TBTEAPMB, 0.22 for PTBTEAPMB, 0.14 for TBTEAPB and 0.20 for PTBTEAPB respectively (Table 16, Fig. 43). In the study of dehydrobromination of phenethylbromide\textsuperscript{21} using tetraoctylammonium bromide zero order kinetics with respect to the catalyst amount was observed. This suggests that the chemical reaction between the ion pair and the organic substrate is not the sole rate-determining step. The ACMPTC quaternary ammonium cations serve as a source of organic cation to form the organic phase soluble ion pairs with carbanions, hence transferring them into the organic phase for further transformation. The remarkable increase in yield of dichlorocarbene adducts reflects the ability of the quaternary ammonium salt to affect the :CCl\textsubscript{2} to be generated/ transferred to the organic phase, which was more reactive with the organic substrates than the water molecule. Starks reported a similar observation in the study of dichlorocarbene addition to cyclohexene using tridecyimethylammonium chloride.\textsuperscript{17}

5.1.6.2.4. Effect of sodium hydroxide concentration

In order to know the effect of [NaOH] on dichlorocarbene addition to limonene in presence of each six-site soluble and insoluble ACMPTCs viz., TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB was observed individually. Varying the concentration of NaOH in the range 2.78 - 7.05 M performed the kinetic experiments. The other experimental parameters such as
stirring speed, catalysts, temperature and substrate are kept constant. Pseudo-first order rate constants are evaluated from the plots of log (a-x) versus time. The reaction rate constants are strongly influenced by the concentrations of aqueous NaOH for all the ACMPTCs. The observed rate constants increased with increase in basicity of hydroxide ion concentration (Table 17, Fig. 44). A bilogarithmic plot of the reaction rate constants against sodium hydroxide concentration gives a straight line having a slope values of 0.37 for TBTEAPMB, 1.2 for PTBTEAPMB, 0.42 for TBTEAPB and 0.78 for PTBTEAPB respectively (Table 18, Fig. 45). This may be attributed to the fact that hydroxide ions are insufficiently solvated by water molecules and thereby the activity of hydroxide ions increases.

In the reaction of dichlorocarbene addition to limonene using each ACMPTCs, up to 30 % NaOH was employed whereas, 20 % NaOH is optimum concentration for the present study. This process is environmentally acceptable due to easy reaction workup and durability of the reaction vessels. In the case of LL-PTC conditions anions are transferred into the organic phase with certain number of molecules of water, which can noticeably reduce their reactivity. Highly concentrated alkaline solutions have low water activity and effectively act as desiccants for the organic phase. Further, the application of highly concentrated alkaline aqueous solutions were sometimes subjected to partial catalyst decomposition when quaternary onium salts are used as PTC agents, especially when heated. However onium salt degradation reactions mainly proceed in the organic phase viz., extraction of OH. The interfacial phenomenon is less important and they are strongly or completely inhibited if the extractability of OH is minimized. This can be avoided by reducing the water activity with high concentrated aqueous solutions of inorganic salts, in particular 30% aqueous NaOH.
Similar trend was observed in a kinetic study of the dichlorocarbene addition to hexene\textsuperscript{25} under phase transfer catalysed conditions. The application of highly concentrated alkaline aqueous solutions is sometimes subjected to partial catalyst decomposition when quaternary onium salts are used as PTC agents, especially when heated. However with onium salts degradation reactions mainly proceed in the organic phase via extraction mechanism of OH. The interfacial phenomenon is less important, and they are strongly or completely inhibited if the extractability of OH is minimized.

5.1.6.2.5. Effect of temperature variation

The effect of varying temperature on rate of dichlorocarbene addition to limonene was studied in the temperature range 30 to 42°C using all the four ACMPTCs. The other parameters are kept as constant. The kinetic profile of the reaction is obtained by plotting log (a-x) versus time. The rate constants increase with increase in temperature (Table 19, Fig. 46). The energy of activation (E\textsubscript{a}) is calculated from Arrhenius plot and presented in table 20. The other thermodynamic parameters viz., AS\textsuperscript{\theta}, AG\textsuperscript{\theta} and AH\textsuperscript{\theta} were also evaluated and presented in table 20. Many PTC/OH reactions have energy of activation upto 15 kcal mol\textsuperscript{-1} and these particular reactions may be carried out successfully without significant catalyst decomposition, if performed at low enough temperatures.

The activation energy for the ethylation of pyrroloidin-2-one under PTC condition was reported to be 12.4 kcal mol\textsuperscript{-1} and for this an interfacial mechanism was proposed.\textsuperscript{48} In a comprehensive study for the dichlorocarbene addition to isobutylene, it has been observed that the rate of formation of 1,1-dichloro-2,2-dimethyl cyclopropane increases with increase in temperature and the E\textsubscript{a} value was found to be 12.32 kcal mol\textsuperscript{-1}. Chou et al\textsuperscript{49} observed a favorable effect on the
extraction of tetrabutyl ammonium hypochlorite ion-pair from the aqueous phase into the organic phase on increasing the temperature in the study of the oxidation of benzyl alcohol by hypochlorite ion under PTC conditions. The activation energy for dehydrobromination of phenyl ethyl bromide that proceeds more rapidly in the presence of tetaoctyl ammonium, bromide was found to be 8 kcal mol\(^{-1}\) and they followed zero order kinetics in the presence of catalyst and also reported a hydroxide ion extraction mechanism governed by diffusion control. The \(E_a\) of intra-particle diffusion of anion exchange resins in aqueous solutions is in the order of 6-9 kcal mol\(^{-1}\). Shih et al. studied the effect of temperature on the rate of formation of phenyl benzoate in the presence of TBAHSO\(_4\) as PTC and without PTC. The activation energies calculated from corresponding Arrhenius plots are 7.89 kcal mol\(^{-1}\) with TBAHSO\(_4\) and 3.72 kcal mol\(^{-1}\) respectively, without PTC. In this case an extraction mechanism has been proposed.

A higher \(E_a\) value has been reported for the polystyrene bound triethyl ammonium ion catalyzed reaction, which was controlled by strict intrinsic reactivity under triphase reactions. The activation energy for the heterogeneous ethylation of phenylacetonitrile was reported to be 20 kcal mol\(^{-1}\) and it was proposed that this follows an interfacial mechanism. The activation energy of intra particle diffusion of anion exchange resins in aqueous solutions is of the order of 5-10 kcal mol\(^{-1}\). The present study, the observed energy of activation is higher for the dichlorocarbene addition to limonene, and hence we have proposed interfacial mechanism for all the ACMPTCs.

5.1.6.2. Kinetic model of the dichlorocarbene addition reaction

Chloroform was first reacted with the base to form trichloromethyl anion (\(\text{CCI}_3^-\)), which can be converted into dichlorocarbene (\(\text{CCI}_2\)). In organic
olefin does not react directly with the dichlorocarbene to form a
dichlorocyclopropane product due to easy hydrolysis of dichlorocarbene (Scheme
12).

\[
\begin{align*}
\text{CH} &= + \text{OH}^{-} \quad \rightarrow \quad \text{H}_2\text{O}^{-} + \text{CCl}_3^{-} \\
\text{CCl}_3^{-} &\rightarrow :\text{CCl}_2 + \text{Cl}^{-} \\
\text{H}_2\text{O} + :\text{CCl}_2 &\rightarrow \text{H}_2\text{O}^{-} :\text{CCl}_2^{-} \quad \rightarrow \quad \text{HOCI} + \text{OH}^{-} \quad \rightarrow \quad \text{CO} \\
\text{HCl} &\rightarrow \text{HCl}
\end{align*}
\]

Scheme 12

Hence the addition of phase transfer catalysts (quaternary ammonium salts,
QX) to the aqueous solution to generate dichlorocarbene in the organic solution is
essential. Then the intermediate (Q+CCl3) is formed from the reaction of
trichloromethyl anion and quaternary ammonium ion at the interface of two phases.
Further, the intermediate is transferred in to the organic phase, which reacts with
olefins to produce the product. The reaction mechanism is thus proposed as follows;

\[
\begin{align*}
6\text{CHCl}_3_{(org)} + 6\text{NaOH}_{(aq)} &\rightarrow 6\text{CCl}_3\text{Na}^{-}_{(aq)} + 6\text{H}_2\text{O}_{(aq)} \quad \rightarrow 1 \\
6\text{CCl}_3\text{Na}^{-}_{(aq)} + \text{Ph}(\text{CH}_2\text{OPhCH}=\text{C})_{(aq)} \rightarrow \text{Ph}(\text{CH}_2\text{OPhCH}=\text{C})_{(aq)} + \text{Cl}^{-}_{(aq)} \\
\text{Ph}(\text{CH}_2\text{OPhCH}=\text{C})_{(aq)} + 6\text{CCl}_3_{(aq)} &\rightarrow \text{Ph}(\text{CH}_2\text{OPhCH}=\text{C})_{(aq)} + 6\text{Cl}^{-}_{(aq)} \quad \rightarrow 2 \\
\text{C}_3\text{H}_7\text{H}^{-}_{(org)} + :\text{CO}_2_{(org)} &\rightarrow \text{C}_3\text{H}_7\text{H}^{-}\text{Cl}^{-}_{(org)} \quad \rightarrow 4 \\
\text{C}_1\text{H}_1\text{Cl}_2_{(org)} + :\text{CCl}_2_{(org)} &\rightarrow \text{C}_1\text{H}_1\text{Cl}_2_{(org)} \quad \rightarrow 5
\end{align*}
\]
where \( k_1 \) represents the intrinsic rate constant for the reaction of dichlorocarbene (\( \text{CCl}_2 \)) and (R)-limonene (C\text{10}H\text{16}) to produce the mono-dichlorocyclopropane (C\text{11}H\text{16}Cl\text{2}) in the organic solution, and \( k_2 \) the intrinsic rate constant for the reaction of mono-dichlorocyclopropane (C\text{11}H\text{16}Cl\text{2}) and dichlorocarbene (\( \text{CCl}_2 \)) to produce bis-dichlorocyclopropane (C\text{12}H\text{16}Cl\text{4}) in the organic phase. In this case, the change in rate of (R)-limonene due to reaction is expressed as

\[
- \frac{d[C_{10}H_{16}]_{\text{org}}}{dt} = k_1[C_{10}H_{16}]_{\text{org}}[\text{CCl}_2]_{\text{org}}
\]

Dichlorocarbene was not detectable during the experimental step. Hence, the concentration of dichlorocarbene was kept as a constant throughout the reaction. Thus the equation 6 can be written as

\[
- \frac{d[C_{10}H_{16}]_{\text{org}}}{dt} = k_{\text{obs,1}}[C_{10}H_{16}]_{\text{org}}
\]

where

\[
k_{\text{obs,1}} = k_1[\text{CCl}_2]_{\text{org}}
\]

Similarly the rate constant of bis-dichlorocyclopropane of the dichlorocarbene addition to (R)-limonene as follows

\[
k_{\text{obs,2}} = k_2[\text{CCl}_2]_{\text{org}}
\]

In this case the consecutive reaction of (R)-limonene and dichlorocarbene is irreversible and is expressed as,

\[
C_{10}H_{16} \xrightarrow{k_{\text{obs,1}}} C_{11}H_{16}Cl_2 \xrightarrow{k_{\text{obs,2}}} C_{12}H_{16}Cl_4
\]

From the equation 10, the change in rates of these three components is:

\[
\frac{d[C_{10}H_{16}]_{\text{org}}}{dt} = -k_{\text{obs,1}}[C_{10}H_{16}]_{\text{org}}
\]
\[
\frac{d[C_{11}H_{16}Cl_2]_{org}}{dt} = -k_{obs} \left[ C_{10}H_{16} \right]_{org} - k_{obs,2} \left[ C_{11}H_{16}Cl_2 \right]_{org} \quad - - - - (12)
\]

\[
\frac{d[C_{11}H_{16}Cl_2]_{org}}{dt} = k_{obs,2} \left[ C_{11}H_{16}Cl_2 \right]_{org} \quad - - - - (13)
\]

Equation 11 is integrated as

\[
\left[ C_{10}H_{16} \right]_{org} = \left[ C_{10}H_{16} \right]_{org, init} \cdot \exp \left( -k_{obs,1} t \right) \quad - - - - (14)
\]

where \([C_{10}H_{16}]_{org, init}\) is the initial concentration of (R)-limonene. Define the conversion of (R)-limonene \(X\) as

\[
X = \frac{a - \left[ C_{10}H_{16} \right]_{org}}{\left[ C_{10}H_{16} \right]_{org, init}} \quad - - - - (15)
\]

Thus the equation 15 can be expressed as,

\[-\ln(a-X) = k_{obs,1} t \quad - - - - (16)\]

The value of \(k_{obs,1}\) can be obtained by plotting the exponential data of \(-\ln(a-X)\) versus time. Substituting equation 14 into equation 12, we obtain the concentration of mono-dichlorocyclopropane, i.e.,

\[
\left[ C_{11}H_{16}Cl_2 \right]_{org} = \left[ C_{10}H_{16} \right]_{org, init} \cdot \frac{k_{obs,1}}{k_{obs,2} \cdot k_{obs,1}} \cdot \left( \exp(k_{obs,1} t) - \exp(k_{obs,2} t) \right) \quad - - - - (17)
\]

\[
\left[ C_{11}H_{16}Cl_2 \right]_{org} = K \left[ C_{10}H_{16} \right]_{org, init} \cdot \left( \exp(k_{obs,1} t) - \exp(k_{obs,2} t) \right) \quad - - - - (18)
\]

Where \(K = \frac{k_{obs,1}}{k_{obs,2} \cdot k_{obs,1}}\).

The value of \(k_{obs,3}\) can be estimated from the experimental data of mono-dichlorocyclopropane and from the knowledge of \(k_{obs,1}\) value given in equation 16 via parameter estimation.\(^{52}\)
5.6.2.7. Reaction mechanism

Dichlorocarbene addition reaction may occur in two steps, base
depronation of chloroform catalyzed by a phase transfer agent, followed by the
addition of electrophile. In the phase transfer system, two major mechanisms are
believed to be operative viz., Stark's extraction mechanism\(^\text{17}\) and Makosza's
interfacial mechanism\(^\text{53}\). From the observed experimental results, the dependency of
kinetic data on the stirring speed up to 200 rpm for PTBTEAPMB, 300 rpm for
PTBTEAPB, 400 rpm for TBTEAPB and 600 rpm for TBTEAPMB catalyst,
aqueous hydroxide ions, temperature, independence of stirring speed and higher \(E_a\)
values strongly prove that this reaction proceeded with interfacial mechanism
(Scheme 13).

In this interfacial mechanism, the hydroxide ion may be extracted from an
aqueous reservoir into an organic phase without the help of quaternary onium
cations. Then the ACMPTC/OH\(^-\) abstracted a proton from the chloroform in organic
phase to form an active intermediate ACMPTC/CCI\(_3^+\) which can be reacted with the
olefinic group containing limonene to give an mono dihalocyclopropanated product,
Further, the concentration of catalytic site per molecule is increased from single site
to multisite than the formation of Q\(^+\)CCI\(_3^-\) ion pair must be increased in multisite
than single site. As a result, the abstraction of proton from chloroform is more
effective than the single site PTC. Since there is a high concentration of Q\(^+\)CCI\(_3^-\)
ion pair in the medium, it has the tendency to add to another olefinic double bond to
form the mono addition product as a result of which there must be the formation of
bis-dihalocyclopropanated product.
5.1.6.3.1. MICHAEL ADDITION TO CYCLOPENTADIENE

Carbanions and other nucleophiles do not add to simple olefins easily, however they do so if the double bond is activated by conjugation to a group of \( \text{M} \) type. The addition of carbanion to an activated olefin is called Michael addition. Generally, Michael addition reaction is important, particularly for C-C bond
formations and stereoselective variants have been extensively investigated in recent years. Michael addition is one of the most useful reactions in the organic syntheses. The required basic catalysis for this reaction can be carried out by PTC methods. In the past twenty years, addition of acetamidomalonate,\textsuperscript{34,35} 2,4-pentandione,\textsuperscript{13} methyl acetoacetate,\textsuperscript{16} fluorne,\textsuperscript{16} substituted indanones,\textsuperscript{57} nitroalkenes,\textsuperscript{18} thiolates,\textsuperscript{18} cyanide,\textsuperscript{15} and methyl phenyl acetate\textsuperscript{9} anions to a large number of Michael acceptors, mainly \(\alpha,\beta\)-unsaturated ketones, under PTC conditions have been reported.

Michael addition of diethylmalonate to esters of 2-(1-hydroxyalkyl) propionate was studied and reported with a high stereoselectivity towards the syn-diastereomer using 18-Crown-6 as a PTC catalyst and catalytic amount of KF was used as the base in dimethyl sulfoxide or acetonitrile as solvent.\textsuperscript{60} Similarly, multiple Michael addition was achieved to form mostly tetra-, penta- and hexa ester’s and they were focused as potential lubricants.\textsuperscript{61} Two types of C-H bonds were deprotonated. Methylene (pKa=9) was first deprotonated and added to the double bond of methyl acrylate. The resulting methylene group, alpha to the ester (pKa= 19-20) were then deprotonated and added to other methylacrylate molecules. Michael addition of a deactivated methylene (sulfonic acid alpha to ester) to acrylate ester was performed and selectively yielded mono-addition products in 56-95\%.\textsuperscript{60} Reierson et al.\textsuperscript{62} reported the Michael addition of cyclopentadiene with methyl acrylate under PTC/high concentration of aqueous base (50\%) condition. There is no other report on the Michael addition of cyclopentadiene with methylmethacrylate under MPTC conditions.

Taking in to consideration of previous reports, we have decided to study the Michael addition to cyclopentadiene with methylmethacrylate using new soluble
and insoluble six-site ACMPTC’s viz., TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB. The kinetic experiments for the Michael addition to cyclopentadiene with methyl methacrylate were carried out under bi-phase/tri-phase medium with excess of aqueous sodium hydroxide (16% w/w) at lower temperature (36 °C) under pseudo-first order conditions (Scheme 14).

![Scheme 14](image)

The detailed kinetic study for the Michael addition to cyclopentadiene with methylmethacrylate by changing the different experimental variables is discussed as follows.

5.1.6.3.2. Effect of stirring speed

The effect of varying stirring speed on the rate of the Michael addition to cyclopentadiene with methylmethacrylate using ACMPTCs such as TBTEAPMB, PTBTEAPMB, TBTEAPB and PTBTEAPB were studied individually by varying the stirring speed in the range of 100 to 700 rpm. The other parameters viz., [NaOH], [substrate], [Catalysts] and temperature were kept as constant. The detailed experimental procedure is described in experimental section (Page No. 81). From the plots of log(a-x) versus time, the pseudo-first order rate constants were evaluated. A plot of $k_{obs}$ versus stirring speed is shown in table 21 (Fig. 47). The rate is found to increase very slowly from 100-500 rpm and a sharp increase was observed upto 600 rpm and further increasing of agitation speed does not alter the
reaction rates in presence of TBTEAPMB and TBTEAPB. In the case of insoluble catalysts viz., PTBTEAPMB, the rate of reaction is suddenly increased from 100-300 rpm and a sharp increase was observed at 300-400 rpm, further increase in stirring speed does not alter the reaction rate. Similarly, under PTBTEAPB catalyst, the rate is slowly increased from 100-400 rpm and a sharp increase was observed from 400-500 rpm and further increase in agitation speed, the rate of the reaction is constantly maintained. From the observed results, the reaction kinetics is controlled by the chemical reaction in the organic phase for stirring rate greater than 600 rpm for TBTEAPMB and TBTEAPB. Further, the stirring speed level of 600 rpm anion exchange equilibrium is very fast relative to the organic displacement reaction and the substrate (cyclopentadiene) consumption rate becomes independent of the stirring speed. Below 600 rpm for TBTEAPMB and TBTEAPB, the requirement for sufficient rapid mass transfer of the reaction anion is not met and diffusion controlled kinetics is observed. Hence, the constancy of reaction rate constant at above 600 rpm is an indicative evidence that the reaction is proceed via interfacial mechanism.

Similarly, in the case of triphase catalyst viz., PTBTEAPMB and PTBTEAPB has shown sudden increase from 300-400 rpm and 400-500 rpm respectively. This indicates the effective mass transfer of reactions from bulk liquid to surface of the respective solid ACMPTCs and also existence of more number of perfect collisions due to presence of multiactive sites in each ACMPTCs. Hence the rate of the reaction is higher at lower stirring speed. Further increase in agitation speed at above 400 rpm for PTBTEAPMB and 500 rpm for PTBTEAPB shows enhancement in the rate constant and this indicates the saturation of perfect collision with the active site of the catalysts. Therefore, the reaction is mass
transfer, the effect of varying the stirring speed is well documented in previous study. Starks et al reported similar behavior displayed by reactions with a real ‘phase transfer’ (Stark’s extraction mechanism), there is much smaller limit of stirring speed between physical and chemical control (100-400 rpm). Similar observation was reported by Landini et al., Starks et al., Herriott et al. and Freedman et al., which reflects kinetic control by mass transfer of $[Q^+ X^-]$ at a steady state concentration. In a systematic kinetic study of dichlorocarbene addition under solid/liquid phase transfer catalysis in presence of Z-BuOK a sharp increase in the rate constant between 400 to 500 rpm was observed. Similar trend was also observed by Balakrishnan et al. in studies viz., dichlorocarbene addition to styrene and C-alkylation of phenylacetone using ethyl iodide. Chiellini et al. reported similar stirring speed dependency reaction and suggested the interfacial mechanism. Generally the stirring speed affects the observed rate constants in triphase catalytic condition, when the chemical reaction is very fast. When the mass transfer is rate limiting, the reaction rates are directly proportional to the catalytic surface of the polymeric catalyst (surface area) and inversely proportional to the radius of spherical catalysts particle. Hence, the dependence of the reaction rate constants on the stirring speed above certain rpm observed in the present study is indicative of an interfacial mechanism. Therefore, stirring speed is 500 rpm for studying all other physical parameters.

5.1.6.3.2. Effect of substrate concentration

Kinetic experiments were performed individually using all the four ACMPTCs and by varying the amount of cyclopentadiene from 14.86 to 32.68 mM and keeping other reagents like [methylmethacrylate], [ACMPTCs], [NaOH] and temperature as constant. Pseudo first order rate constants are evaluated from the
linear plots of log(a-x) versus time. The observed reaction rate constants are
directly proportional to the [substrate] irrespective of ACMPTCs (Table 22,
Fig. 48). The increase in the rate may be attributed to the proportionate increase in
the number of catalytic active sites available in the each ACMPTCs. Hence the
molar ratio of the cyclopentadiene (irrespective of lower/higher concentration) to
catalyst increases the rate constant considerably due to the more probability of
cyclopentadiene reaching the catalytic surface/active-site. This observation
confirms that ACMPTCs have multiactive sites per molecules. Hence, we fixed
23.77 mM as a common substrate concentration for other variation studies.

5.1.6.3.3. Effect of varying catalyst concentration

The pseudo-first order rate constant for the Michael addition to
cyclopentadiene with methyl methacrylate has been determined by varying the
concentration of each soluble ACMPTCs, (i.e TBTEAPMB and TBTEAPB) in the
range of 0.20 mM to 0.40 mM and their corresponding insoluble ACMPTCs viz.,
PTBTEAPMB and PTBTEAPB in the range of 0.1g to 0.5g respectively. Keeping
with the other parameters are kept constant. The observed rate constants for each
ACMPTCs were found to be proportional to [catalyst]. The rate constants are
calculated from the plots of log(a-x) vs time. The rate constants are dependent on
the increase in the number of active sites per molecule of the ACMPTCs (Table 23,
Fig. 49). The order of rate constant for the ACMPTCs are as follows,
PTBTEAPMB > PTBTEAPB > TBTEAPB > TBTEAPMB. Control experiments
were performed; there is no product to detect even after five hours of the reaction.
Molinary et al.63 have observed a similar dependence of pseudo-first order late
constants on the amount of heterogenised phosphonium groups for Br-I exchange
reactions of 1-bromo octane. A bilogarthmic plot of the reaction rate constant
versus the concentration of catalyst gave a straight line having a slope values 0.20 for TBTEAPMB, 0.59 for PTBTEAPMB, 0.40 for TBTEAPB and 0.47 for PTBTEAPB (Table 24, Fig. 50). From the observed slope values, we found that the order of catalytic efficiencies is followed as PTBTEAPMB > PTBTEAPB > TBTEAPB > TBTEAPMB. These results reveals that polymer-supported ACMPTCs are more reactive than the corresponding soluble ACMPTCs, the reasons are discussed in the preceding sections. Similar results are reported by Halpern et al.\textsuperscript{32} for the study of dehydrobromination of phenethyl bromide in the presence of tetra octylammonium bromide as a PTC under zero order kinetics with respect to the catalyst concentration.

5.1.6.3.4. Effect of varying sodium hydroxide concentration

Kinetic experiments were conducted by varying the concentration of aqueous NaOH from 2.5 M to 7.5 M irrespective of the catalyst and other parameters are kept constant. The rate of the reaction strongly depends on the strength of sodium hydroxide. Pseudo-first order rate constants are evaluated from the plots of log(a-x) vs. time (Table 25, Fig. 51). The reaction rate constant is strongly influenced by the concentration of aqueous NaOH for all the ACMPTCs. The observed rate constants are continuously increased with increase in the concentration of hydroxide ion. The orders of rate constant obtained are as follows, PTBTEAPMB > PTBTEAPB > TBTEAPB > TBTEAPMB. This may be due to the fact that it is not only the presence of higher amount of OH\textsuperscript{-} ions but also insufficient solvation of OH\textsuperscript{-} ions in water molecules as a result of that the activity of hydroxide ion increases. A bilogarthmic plot of the reaction rate against NaOH concentration gives a straight line having slope values 0.47 for TBTEAPMB, 1.02
for PTBTEAPMB, 0.54 for TBTEAPB and 0.79 for PTBTEAPB (Table 26, Fig. 52).

5.1.6.3.5. Effect of temperature

The effect of varying temperature on the rate of Michael addition to cyclopentadiene with methylmethacrylate were studied in the temperature range 30 to 42 °C using all the four ACMPTCs individually. The other parameters were kept as constant. The kinetic profile of the reaction is obtained by plotting log(\(a-x\)) vs. time. The observed rate constants are directly proportional to the temperature (Table 27, Fig. 53). The energy of activation (E_a) is calculated from Arrhenius plot and it is found to be 18.32 for TBTEAPMB, 19.90 for PTBTEAPMB, 22.37 for TBTEAPB, and 22.65 kcal mol\(^{-1}\) for PTBTEAPB catalyst. The other thermodynamic parameters viz., \(\Delta S^0\), \(\Delta G^0\) and \(\Delta H^0\) were also evaluated and presented in table 28 for all the four six-site ACMPTCs. The observed enthalpy of activation is negative value hence the Michael addition is an exothermic reaction.

At higher temperature the cyclopentadiene was reacted with the intermolecular Diels–Alder reaction to give the dimeric product (Scheme 15). So the optimum temperature required to conduct the kinetic study of Michael addition reaction is fixed as 36 °C.
The reaction of dehydrobromination of phenethyl bromide proceeds more rapidly in the presence of tetraoctylammonium bromide as a PTC and $E_a$ was 8 kcal mol$^{-1}$ and for this an extraction mechanism was proposed. The activation energy of intra particle diffusion of an anion exchange resins in aqueous solutions is of the order of 5-10 kcal mol$^{-1}$. The contribution of intrinsic reactivity limitations is more than that of the intraparticle diffusion limitations as is evident from higher $E_a$ value and less negative $\Delta S^\circ$. A higher $E_a$ value has been reported for the polystyrene bound triethylammonium ion catalysed reaction, which was controlled by strict intrinsic reactivity under triphase conditions. The activation energy for the heterogeneous ethylation of phenylacetonitrile was reported to be 20 kcal mol$^{-1}$ and an interfacial mechanism was reported. The $E_a$ value for the alkylation of pyrrolidin-2-one under solid/liquid PTC in the presence of potassium carbonate was reported to be 12.4 kcal mol$^{-1}$. A higher $E_a$ value and dependency of stirring speed on the reaction rate even above sudden 100 rpm, led the authors to propose an interfacial mechanism. Wang et al also reported a higher $E_a$ value (40.19 and 32.63 kJ/mole) for the study of dibromo-o-xylene and 1-butanol to synthesize diether compound under two phase PTC conditions. The present study, based on the observed higher activation energy $E_a$ (18-22 kcal mol$^{-1}$) and dependency of stirring speed for Michael addition of cyclopentadiene with methylmethacrylate, we concluded that this reaction proceeded via interfacial mechanism.

5.1.6.3.6. Reaction mechanism

Michael addition reaction may occur in two steps, base deprotonation of methylmethacrylate catalyzed by a phase transfer agent, followed by the addition of electrophile. In the phase transfer system, two major mechanism are believed to be operative viz., Stark's extraction mechanism and Makosza's interfacial
mechanism. The characterization of each mechanism are already described in the previous section. From the observed experimental results, the dependency of kinetic data on the stirring speed, [catalyst], [hydroxide ions], temperature and higher $E_a$ value strongly suggest an interfacial mechanism (Scheme 16).

In this interfacial mechanism, the hydroxide ion may be extracted from an aqueous reservoir into an organic phase without the help of quaternary onium cations. The OH may abstract a proton from the cyclopentadiene to form an active intermediate of cyclopentadienyl anion, which can be form an ion-pair with ACMPTC to ACMPTC/cyclopentadienyl anion. Further, the α, (3-unsaturated carbonyl compound containing olefin reacted with the cyclopentadienyl anion to give mono addition product. Since there is a high concentration of ACMPTC/cyclopentadienyl anion ion pair in the medium, it has the tendency to add to another olefinic double bond containing cyclopentadiene to form dimer product.

When one considers the base catalyzed addition of cyclopentadiene to methylmethacrylate (Scheme 16), it is found that the electrophiles add to the double bond so as to form the more stable carbocations. Since the addition of the electrophile is the rate-determining step, other states that the more stable carbocations intermediate forms via the energetically more favorable transition state. This forms the modern statement of the Markovnikov rule, which states that, in addition to unsymmetrical alkenes, the positive part of the reagent adds to that unsaturated carbon that already has the greatest number of hydrogens. This statement suggests that the nucleophile attacks via S$_\text{N}_1$ rather than the S$_\text{N}_2$ mechanism. However, the overall stereo specific anti addition in the process clearly
indicates that nucleophilic substitution step occurs with inversion of configuration, i.e., $S_N2$ reaction.

Scheme 16
Reference


42. I. V. Chau, M. Schlosser *Synthesis* 112 (1973).
PART II
PART II

Cinchona alkaloid derived catalysts are suitable to many catalytic asymmetric reactions due to their greater functionality, commercial availability and low cost. A wide array of catalysts has been synthesised so far. However, an extensive study especially, a chiral resolution study in particular, is needed under these catalysts. Catalytic asymmetric synthesis is an extremely important technique owing to its role in producing the life-saving drugs. Based on their track record, cinchona alkaloids have continued to play a pivotal role in this area exclusively for the synthesis of various a-amino acids. It is also very clear that amino acids are very important biomolecules since they serve as primary building blocks of proteins as well as the launchpad for many synthetic endeavors and as a result they play a central role in chemistry, biology and medicine. The availability of coded and uncoded a-amino acids is thus a vital subject for a wide range of research interest. One of the most direct routes to synthesise a-amino acids is the α-alkylation of glycine and their analogues. For organic chemists who want to apply a specific transformation, the substrate and the nature of a catalyst system are the most important information in synthetic design and planning.

The part II of the thesis describes the characterization of 28 types of chiral multi-site phase transfer catalyst (CMPTC) in section A and their applications to various enantioselective syntheses of a-amino acids and N-aryl aziridine derivatives in section B. In detail, section B explains the study of catalytic efficiency of these 28 CMPTCs individually in catalyzing the enantioselective synthesis of mono and dialkylation of ketimine and aldimine respectively. It also explains the reasoning for the selection of efficient CMPTCs from the 28 different CMPTCs based on their chemical yield and ee’s of mono and dialkylation
reactions. Further, these sections also discuss the preparation of various enantioselective N-arylziridines using relatively superior CMPTCs assessed from the early alkylation reactions.

Section A of the discussion pertains to the synthesis and characterization of 28 types of CMPTCs derived from two pseudo enantiometric compounds viz., cinchonine (14 types) and cinchonidine (14 types) respectively as a chiral precursor. In order to understand clearly the classification of these 28 types of CMPTCs, the following table is presented here considering the presence of number of active site in each molecule (catalyst) from each enantiomer viz., cinchonine/cinchonidine; their structural variation i.e whether CMPTCs containing C₉ free -OH or C₉ protected through either by tosylation or allylation.

<table>
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<th>S.No</th>
<th>Number of active sites present in per molecule of CMPTCs</th>
<th>Number of different types of CMPTCs</th>
<th>Cinchonine based CMPTCs</th>
<th>Cinchonidine based CMPTCs</th>
<th>Total No. of the CMPTCs</th>
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<td>Cy free -OH</td>
<td>C₉(0) protected</td>
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<tr>
<td></td>
<td>Total</td>
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<td>7</td>
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</tbody>
</table>
SECTION A

5.2.1. CHARACTERIZATION OF DIFFERENT TYPE OF CMPTCs

5.2.1.1. Single site chiral phase transfer catalyst

5-Methydsalicylaldehyde was reacted with the paraformaldehyde in presence of hydrochloric acid to obtain the product viz., 3-chloromethyl-5-methyl-2-hydroxybenzaldehyde. The structure of the product was confirmed by the appearance of C-Cl stretching frequency at $716.15 \text{ cm}^{-1}$ in FT-IR spectrum. In proton NMR spectrum, the two methylene protons showed a singlet at $3.2 \text{ ppm}$ and in $^{13}C$-NMR the methylene carbon was noticed at $40.6 \text{ ppm}$ showing the formation of 43. The compound 43 was quaternised with the cinchonine giving compound 45. The structure of 45 was confirmed by the disappearance of the C-Cl stretching frequency at 700-730 cm$^{-1}$ and appearance of C-N stretching frequency at $1105 \text{ cm}^{-1}$ in FT-IR and in $^1H$-NMR (Fig. 54), the N-quaternised adjacent two methylene protons appeared as a multiplet at 4.50-4.51 ppm and carbon also appeared at 61.2 ppm in $^{13}C$-NMR indicating the formation of 45.

Further, with a view to prepare a C9 (O) protected CMPTC, the C9 free -OH present in compound 45 was tosylated and produced compound 46. The tosylation of the compound was confirmed by FT-IR spectrum, the formation of C-O stretching frequency at 1149.5 cm$^{-1}$ (Fig. 55). Further, the compound 46 was confirmed by the $^1H$ and $^{13}C$-NMR analyses; six methyl protons appeared as a singlet at 1.3 ppm in $^1H$-NMR (Fig. 56) and its methyl carbon shows peak at 20.71 ppm in $^{13}C$-NMR indicating evidences for the formation of compound 46. Finally, compound 46 was further confirmed by HRMS spectrum, where, in the parent ion viz., $[\text{C}_3\text{H}_2\text{N}_2\text{O}_2\text{S}]^{+}$ had showed an experimental value as 599.2 and the corresponding calculated value has found to be 599.3. The similar pattern of
spectral results were also observed for the cinchonidine derived CMPTCs such as 48 (catalyst with C9 free -OH) and 49 (catalyst with C9 (O) protection by tosylation).

5.2.1.2. Different types of di-site chiral phase transfer catalysts

Two sets (cinchonine and cinchonidine) containing 12 different types of di-site CMPTCs were synthesised by following the different experimental conditions/procedure. Among these 2 sets of pseudo enantiomer CMPTCs, 6 types are derived from cinchonine and other 6 types are derived from cinchonidine components. In each set of CMPTCs, 3 contain C9 free -OH and other 3 types are C9 (O) protected through allylation. However, these 2 sets of enantiomeric CMPTCs were prepared individually from 3 different structurally varied organic compounds such as 4,4'-bipyridyl, m-xylene and p-xylene respectively as core components for the synthesis of respective di-site CMPTCs. The synthesis and characterization of each set of the CMPTCs are described as follows.

5.2.1.2.1. Biperidinyl based chiral di-site PTCs

4,4'-Bipyridine was treated with 1 equivalent of 1-chloroethanol to get the compound of 1-(2-hydroxy-ethyl)-[4,4']bipyridinyl-l-ium 51. The structure of the 51 was confirmed by FT-IR i.e the presence -OH are known through the appearance of broad band at 3485 cm⁻¹, compound 51 was then hydrogenated using platinum dioxide to get 52, the hydrogenation of 52 was established from the disappearance of C=N stretching frequency (1100-1300 cm⁻¹) and appearance of C-N stretching (1127 cm⁻¹); the appearance of broad band for -OH (3423 cm⁻¹) and N-H (3567 cm⁻¹) in the FT-IR spectrum shows an indicative evidence for the formation of the compound. In the 'H-NMR, the N-H proton exhibit a broad singlet at 6.70 ppm and the disappearance of aromatic protons around 6.5-9.0 ppm lending additional evidence for the formation of 52. Furthermore, the compound 52 was
reacted with the 1 equivalent of 1-chloroethanol to get dihydroxy compound 53 and subsequently this compound was converted into dichloride using PCl\textsubscript{3} giving compound 54. The dichlorination of the compound 54 was confirmed from the disappearance of -OH stretching frequency (around 3400-3600 cm\textsuperscript{-1}) and appearance of C-Cl stretching frequency at 720.2 cm\textsuperscript{-1} in FT-IR spectrum. Similarly, the 'H-NMR spectrum of compound 54 shows the peak for chloromethylene proton as a triplet at 3.82-3.86 ppm giving another evidence for the formation of 54. The compound \textit{l,l'-bis-(2-chloro ethyl)}-[4,4'] bipiperidinyll 54 was quaternised using cinchonine to produce the di-site chiral PTC 55a, the quaternisation of 55a was varied from FT-IR spectrum (Fig. 57) i.e the disappearance of C-Cl stretching frequency around 700-730 cm\textsuperscript{-1} and appearance of C-N stretching frequency at 1265 cm\textsuperscript{-1} providing evidence for the formation of 55a. In the case of 'H-NMR (Fig. 58), methylene proton showed as a triplet at 2.88-2.95 ppm and its methylene carbon was also noticed at 52.13 ppm in \textsuperscript{13}C-NMR (Fig. 59) confirming the structure of 55a. The compound 55a was further confirmed through HRMS (ESI) analysis, wherein the [C\textsubscript{53}H\textsubscript{74}Ne\textsubscript{0}2\textsuperscript{2+}] ion shows the experimental value of 810.80 and the corresponding calculated value has 811.15.

With a view to prepare a Csi(O) protected CMPTC, the 55a was allylated using allyl bromide and in turn the allylation of the compound 55b was established through FT-IR, i.e disappearance of -OH stretching frequency around 3400-3600 cm\textsuperscript{-1} and formation of C-O stretching frequency at 1245 cm\textsuperscript{-1}. Furthermore, in \textit{'H-NMR} (Fig. 60, 61), the allyl methylene proton shows a doublet peak at 5.67-5.70 ppm and its corresponding methylene carbon gives a peak at 69.79 ppm in C-NMR (Fig. 62). In the case of LC-MS analysis, the [C\textsubscript{58}H\textsubscript{78}N\textsubscript{6}O\textsubscript{2}\textsuperscript{2+}] ion (Fig. 63) gives the experimental value as 893.00 and the calculated value has 892.63. Similar spectral studies were also performed for the same di-site CMPTCs synthesised from
cinchonidine for both free C9-OH and its corresponding allylated derivative (protected). All the observed spectral results for 56a and 56b are the resemblance of the cinchonine based CMPTCs (55a, 55b) except the chirality result. Therefore, two di-site CMPTCs derived from cinchonidine containing viz., free C9-OH (56a) and allylated group (56b) were structurally confirmed.

5.2.1.2.2. m-p-Xylene based chiral di-site phase transfer catalysts

Both w-xylene and />xylene were used individually to prepare soluble di-site chiral phase transfer catalysts, m-Xylene was treated with N-bromosuccinimide and produced the 1,3-dibromoxylene 57. Then the compound 57 was reacted with the triethoxysphosphine to get the compound 58 and further condensed with the p-tolualdehyde to give 1,3-(bis-(4-methyl styryl) benzene 59. The formation of compound 59 has been established by spectra viz., the appearance of olefinic (C=C) stretching frequency at 1665 cm\(^{-1}\) in FT-IR, the appearance of two vinylic proton as a doublet of doublet at 7.09-7.35 ppm in \(^1H\)-NMR (Fig. 64) and its mass value found at 310.80 (Fig. 65). Further, the styryl compound 59 has been chlorinated using N-chlorosuccinimide and produced the 1,3-bis(4-chloromethyl styryl)benzene compound 60 and it was confirmed from the appearances of C-Cl stretching frequency at 718 cm\(^{-1}\) in FT-IR and singlet for four methylene proton at 4.38 ppm in \(^1H\)-NMR (Fig. 66). Then, compound 60 was quaternised with the cinchonine to get the quaternised CMPTC 61a. The quaternisation of 61a was confirmed from the disappearance of C-Cl stretching frequency (around 700-730 cm\(^{-1}\)) and appearance of C-N stretching (1129 cm\(^{-1}\)) in FT-IR (Fig. 67), the appearance of singlet at 1.60 ppm for four \(N^+\)-benzyl methylene proton in \(^1H\)-NMR (Fig. 68) and its corresponding methylene carbon noticed at 65.72 ppm in \(^{13}C\)-NMR (Fig. 69). The compound 61a was further confirmed from its LC-MS analysis (Fig. 69).
i.e. the parent ion peak \([C_{62}H_{64}N_{2}O_{2}]^{2+}\) gives value as 897.00 and the corresponding calculated value has found to be 897.20.

Then, in order to synthesise the corresponding C9 (O) protected CMPTC, the compound 61a was allylated by following the earlier procedure to give 61b. The allylation of 61b was confirmed from the disappearance of -OH stretching frequency (in the range from 3400-3600 cm\(^{-1}\)) and the formation of C-O stretching frequency (at 1245 cm\(^{-1}\)) in FT-IR spectra (Fig. 71) and appearances of triplet for four allylic methylene at 6.82-6.84 ppm in \(^1\)H-NMR (Fig. 72 & 73) and its corresponding carbon as a singlet at 72.17 ppm in C-NMR (Fig. 74) shows the supporting evidence for the allylation of 61b. Similarly, in the case of MALDI-TOF mass spectrum, the parent ion (Fig. 75) viz., \([C_{68}H_{72}N_{4}O_{2}]^{+}\) gives the value of 977.24 and its calculated value is 976.56, the close agreement of these two values confirms the allylation of 61b. Similarly, we also prepared the corresponding enantiomer i.e. cinchonidine based di-site CMPTCs containing C9 free -OH 62a and its C9 (O) protected (allylated) 62b from m-xylene. The structure of the 62a (confirmed by LC-MS (Fig. 76)) and 62b were analysed and confirmed based on the various spectral results, here too, the observed results are similar to 61b and 61b except for the change of chirality.

In the case of p-xylene related di-site CMPTCs, the experimental procedure adopted in each steps is exactly the same as that we followed in m-xylene based cinchonine/cinchonidine CMPTC’s. The structure of the compound obtained in each steps are confirmed with the different spectral techniques. The CMPTCs derived from cinchonine/cinchonidine using p-xylene as a core component such as (67a, Fig. 77-79) C₉ free -OH, (67b, Fig. 80) C₉ (O) protected i.e. allylated and C₉ free -OH (68a) and C₉ (O) protected (68b) respectively were found to show spectra
similar to those of m-xylene based CMPTCs and hence the each CMPTC structure is confirmed.

5.2.1.3. N,N-bis(2-chloroethyl)-p-toluidine based tri-site CPTCs

Two set containing four different types of tri-site CMPTCs were prepared by following different experimental procedure using N,N-bis(2-hydroxy ethyl)-p-toluidine as a core compound. Wherein, two derived from cinchonine and two from cinchonidine. As usual, in each set of CMPTCs both C9 free -OH and C9 (0) allylated functionality (protected) are present. As a first step of the catalyst preparation, N,N-bis(2-chloroethyl)-p-toluidine was synthesised by chlorination of NN-bis(2-hydroxy ethyl)-p-toluidine using PCI3. The chlorination of 69 was known from the disappearance of -OH stretching frequency (around 3400-3600 cm⁻¹) and appearance of C-Cl stretching frequency (at 715 cm⁻¹) in FT-IR spectrum. Similarly, the chloromethylene proton has been observed as a triplet at 4.01-4.05 ppm in 1H-NMR spectrum is an additional evidence for chlorination. Then, this chlorinated compound 69 was further chlorinated with sulfuryl chloride to get the trichloro compound of bis-(2-chloro-ethyl)-(4-chloromethylphenyl)amine 70. The trichlororination of 70 was known from 1H-NMR spectrum, wherein the two benzyl methylene proton appeared as a singlet at 4.25 ppm. Further, compound 70 was quaternised with cinchonine (3.5 equivalent) to give the tri-site chiral PTC’s 71a. The structure of 71a was established with FT-IR, i.e the disappearance of C-Cl stretching frequency around 700-730 cm⁻¹ and appearance of C-N stretching frequency at 1226 cm⁻¹ lends the evidence for quaternisation reaction (Fig. 81). In the case of 1H-NMR (Fig, 82), the two benzyl methylene proton and four N-methylene proton gives a peak as singlet at 3.65 ppm and multiplet at 2.17-2.30 ppm respectively. The methylene carbon appeared as three spectral lines at 65.4, 61.3 and 50.1 respectively in 13C-NMR spectrum showing evidence for the
quaternisation reaction. Finally, the structure of 71a was confirmed by its MALDI-TOF spectrum (Fig. 83) results, i.e. for $[C_{68}H_{80}N_{7}O_{3}]^{3+}$ ion, the calculated value (1043.41) and the obtained value (1043.35) are in good agreement, hence proves the structure and also the presence of tri-sites per molecule in 71a.

Further, in order to synthesise Cg (O) protected tri-site CMPTC, the compound 71a was allylated to give the product 71b. The allylation of compound 71b was known from FT-IR, i.e the disappearance of OH stretching frequency (around 3400-3600 cm$^{-1}$) and formation of C-O stretching frequency (at 1236 cm$^{-1}$). The six allylmethylene proton was noticed as a multiplet at 3.35-3.50 ppm in $^1$H-NMR and its methylene carbon has appeared as a singlet at 78.6 ppm in $^{13}$C-NMR providing the further confirmation for allylation of 71b. In HRMS (ESI) analysis, the parent ion $[C_{77}H_{92}N_{7}O_{3}]^{34}$ gives the calculated value as 1163.60; the experimentally found value is 1163.54. Similarly, we also synthesised two types of tri-site CMPTCs containing Cg free -OH (72a) and Cg (O) allylated (72b) respectively using cinchonidine as a precursor.

5.2.1.4. Tetra-site chiral phase transfer catalysts

Two set containing 8 different categories of tetra-site CMPTCs were synthesised by following the different experimental procedure, wherein, 4 types are derived from cinchonine (set 1) and other 4 types are prepared from cinchonidine (set 2). In each set, 2 CMPTCs contains Cg free -OH and other 2 CMPTCs are C9 (O) protected by allylation. Among the 8 CMPTCs, the first 4 are obtained from tetrabromopentaerythritol as a source material using both cinchonine/cinchonidine. The second 4 CMPTCs are prepared using extended tetrabromopentaerythritol (spacer chain) as a source material.
5.2.1.4.1. Tetra-site chiral phase transfer catalysts without spacer chain

Tetrabromopenterythritol 75 was directly quaternised with cinchonine (4.5 equivalent) and obtained the tetra-site CMPTC 76a, the structure of the quaternised compound was established from the FT-IR results (Fig. 84), i.e. the disappearance of C-Br stretching in the range of 500-600 cm\(^{-1}\) and appearance of C-N stretching frequency at 1055 cm\(^{-1}\) shows an evidence for the quaternisation of 76a. Further, four hydroxyl proton and eight N'-methylene proton produced prominent broad singlet at 5.36 ppm and 4.20-4.35 ppm respectively in \(^1H\)-NMR (Fig. 85) and its corresponding N'-methylene carbon has been observed at 68.7 ppm in \(^13C\)-NMR. The structure of 76a was further ensured from HRMS analysis, wherein the parent molecular ion \([M+H]^{+}\) peak of the compound appeared at 1243.90, calculated value being 1245.68. All these spectral results prove the formation of 76a.

Then, the C\(_3\) -O(O) protected CMPTC has been prepared by allylation of 76a using allyl bromide and obtained the 76b. The allylation of 76b has been known from the disappearance of hydroxyl group (around 3400-3600 cm\(^{-1}\)) and the formation of C-O stretching frequency at 1280 cm\(^{-1}\) in FT-IR (Fig. 86). Similarly, the appearances of triplet at 4.54-4.59 ppm for eight allylic methylene protons in \(^1H\)-NMR and its corresponding methylene carbon at 68.8 ppm as a singlet (Fig. 87) in \(^13C\)-NMR; the vinylic methylene & methyne (CH=CH\(_2\)) peaks observed as a doublet at 5.81-5.87 ppm and pentet at 5.70-5.75 ppm respectively in \(^1H\)-NMR; and its corresponding carbons observed as a singlet at 82.7 (methylene) and 113.8 (methyne) respectively in \(^13C\)-NMR proved the evidence for the formation of 76b. Finally, the HRMS analysis for molecular ion \([M+H]^{+}\) gives the concordant values for both experimental (1402.98) and calculated (1404.88) showing strong evidence for the structure of 76b. Similar spectral results were also
obtained for the cinchonidine based tetra-site CMPTCs such as 77a (C9 free -OH) and 77b (C9 -(O) protected) confirming of the catalyst structure.

5.2.1.4.2. Pentaerythritol based tetra-site chiral PTCs with spacer chain

In general, introduction of additional organic moiety in terms of linear chain or aromatic ring as a spacer to any catalyst molecule has always found to be a greater impact in the efficiency. With a view to examine such a fact in the new CMPTCs exclusively in tetra-site CMPTCs, we substituted an aromatic form of spacer chain to the tetrabromopentaerythritol 75 by condensation reaction. That is, tetrabromopentaerythritol 75 has been treated with the methyl-p-hydroxy benzoate to yield compound 78. The structure of compound 78 was established using FT-IR analysis. The disappearance of C-Br stretching frequency (around 650-700 cm\(^{-1}\)), appearance of C-O stretching frequency (at 1274 cm\(^{-1}\)); peak at 1704 cm\(^{-1}\) for carbonyl group shows the evidence for the formation of compound 78. Compound 78 was allowed for reduction to yield 79 containing alcohol functionality. The formation of product 79 was known from the disappearance of C=0 stretching frequency (at 1704 cm\(^{-1}\)) and appearance of OH stretching frequency (broad peak at 3440 cm\(^{-1}\)) in FT-IR and its appearance of corresponding -OH proton as a broad singlet at 5.75 ppm in \(^1\)H-NMR (Fig. 88) indicating presence of alcholonic group in 79. Similarly, the eight benzyl methylene proton noticed as a singlet at 4.78 ppm in \(^1\)H-NMR and its corresponding methylene carbon found at 68.52 ppm in \(^13\)C-NMR suggested the formation of 79. Further, the alcoholic compound was converted in to bromide compound 80, the bromination of 80 has been known from the disappearance of OH stretching around 3400-3600 cm\(^{-1}\) and formation of C-Br stretching frequency at 586 cm\(^{-1}\) in FT-IR and the methylene proton appeared as singlet at 4.56 ppm in \(^1\)H-NMR and its corresponding methylene carbon exhibit at 38.2 ppm in \(^13\)C-NMR proved the structure of 80.
Furthermore, the bromide compound 80 was quaternised with the cinchonine and produced the tetra-site CMPTCs with extended spacer chain 81a. The formation of C-N stretching frequency noticed at 1060 cm\(^{-1}\) in FT-IR (Fig. 89) and the eight benzylic methylene proton appeared as a singlet at 5.39 ppm in \(^1\)H-NMR (Fig. 90) and its corresponding methylene carbon gives the singlet at 63.1 ppm in \(^13\)C-NMR (Fig. 91) providing the evidence for quaternisation of 81a. Finally, in HRMS analysis the parent molecular ion [C\(_{368}\)H\(_{720}\)N\(_4\)O\(_4\)]\(^{+}\) gives the value as 1668.91, calculated value 1669.92. Furthermore, the free C\(_9\) -OH present in 81a was protected by allylation and obtained the C\(_9\) (O) protected 81b; the allylation has been confirmed from FT-IR analysis (Fig. 92). The disappearance of C\(_9\) -OH stretching frequency around 3400-3600 cm\(^{-1}\) and formation of C-O stretching frequency at 1267 cm\(^{-1}\) indicates the allylation of 81b. Similarly, the eight allylic methylene protons are noticed as a doublet at 4.63-4.67 ppm and its corresponding methylene carbon are found as a singlet at 72.3 ppm in \(^1\)H-NMR (Fig. 93) and \(^13\)C-NMR (Fig. 94) respectively lending the support for allylation. This tetra-site CMPTC 81b with spacer chain was further confirmed by HRMS (ESI) analysis (Fig. 95). The molecular ion of [C\(_{368}\)H\(_{720}\)N\(_4\)O\(_4\)]\(^{+}\) has showed the experimental value as 1828.57 and its corresponding calculated value as 1829.05. The close agreements of these two values provide strong evidence for the formation of 81b. Similar, spectral results were also observed for the cinchonidine based CMPTCs with spacer chain such as 82a (C\(_9\) free –OH) and 82b (C\(_9\) (O) protected) except the change of chirality, hence the observed results proves the structure of respective CMPTCs.
The structure of the various CMPTCs derived from cinchonine/cinchonidine as a chiral precursor

Figure 1
5.2.2. Enantioselective synthesis of a-amino acids using various CMPTCs

Although, we have prepared and characterized 28 types of CMPTCs (Figure I) using pseudo enantiomer viz., cinchonine (14 types) cinchonidine (14 types) respectively as a chiral precursor, the catalytic activity and chiral efficiency of each catalyst in both the types may sometimes behave differently in the reaction medium. To examine this fact and also to know the efficiency of these CMPTCs, we conducted the enantioselective synthesis of a-amino acids and aziridination reactions. It is clear that, in each type of CMPTCs the number of active site present in a molecule is varied from single-site to tetra-site. Hence, the efficiency of the CMPTCs always depends on the total number of active-site in a molecule (catalyst), structure of the catalyst, whether CMPTCs containing free C9 -(OH) or C9 (O) protected either by tosylation or allylation and presence of bulky spacer chain (aromatic ring) to the CMPTCs. Otherwise, in general the enantioselectivity in terms of R and S form of product has been observed with respect to nature of the chiral center of CMPTCs and found in general with enhanced selectivity. The 28 types of cinchonine/cinchonidine derived CMPTCs including Cg free -OH and C9 (O) protected were consists of single-site (4 No), di-site (12 No), tri-site (4 No) and tetra-sites (8 No) and were obtained with quantity of 70-95% yield. Then the catalytic amount of each of these CMPTC’s were employed individually and studied for the effect of alkylation of N-diphenyl methylene glycine fer-butyl ester (ketimine) 1 and N-(p-chlorophenyl) methylene glycine tert-butyl ester (aldimine) 2 respectively using various alkyl halides under identical reaction condition (Figure II).
The first reaction viz., the reaction between highly crystalline ketimine 1 with different alkyl halide in the presence of each of these 28 types of CMPTCs were able to produce only the monoalkylated product 4 with different range of yield and ee’s (Scheme 1) although catalysts containing more than one active-site per molecule ranging from single-site to tetra-site.

![Figure II](image)

**Scheme 1**

Similarly, in the second reaction viz., the reaction between aldimine 2 with different alkylhalide using the same 28 CMPTCs individually gives only the \(a, a'\)-dialkylated product with different amount of yield and ee’s. The reason for the formation of mono and dialkylated products using the ketimine and aldimine respectively in the presence of the same 28 types of CMPTCs individually were explained in the following section. Also, the amount of increased/decreased chemical yield/ee for each CMPTCs containing C9 free -OH or C9 (O) protected were discussed in the subsequent discussion. However, finally the different amount of alkylated products such as mono alkylated 4 (Scheme 1) and dialkylated 6
(Scheme 2) obtained from ketimine and aldime respectively were undergoes hydrolysis and produced the respective racemic mixture of amino acid derivatives.

5.2.2.1. Comparative study focusing the efficiency of different CMPTCs derived from cinchona alkaloids using alkylation of Schiff base as model reactions

It is observed that, the induction of chirality in achiral substance using different CMPTCs is an effective process, because of its simplicity, economy and easy work-up procedure. However, its success always depends on the amount of chemical yield and the degree of enantioselection. Keeping in view of these points, we prepared new 28 types of CMPTCs and the catalytic efficiency of each of these CMPTCs in terms of quantum of yield and ee’s were studied in detail. It was found that they depend on various factors, such as (i) structure of the CMPTCs; (ii) the
influence of the electrophiles (steric and electronic) of substrate; (iii) the structure of the nucleophile of the alkylating agent; (iv) the polarity of the solvents; (v) the formation of ion-pair between the inorganic base with the cation of the respective CMPTCs (R₂N⁺) and also the concentration of the base. We examined the influences of each of these factors in the alkylation of ketimine 1 and aldimine 2 (Schiff bases) respectively.

The chemical yield and enantioselective efficiency of all the CMPTCs in alkylation of ketimine were evaluated individually under identical reaction conditions taking 10 mM of each of these catalysts along with ketimine 1 (N-(diphenylmethylene)glycine tert-butyl ester), allyl halides and 20% aqueous NaOH (5 ml w/v) in toluene/CH₂Cl₂ (8:2 ml) medium at −10 °C for 5hrs. The enantioselectivities of the alkylated imines 4 were determined by chiral HPLC analysis. The amount of chemical yield and the nature of alkylation (whether it is mono or dialkylation) are known from weighing method and spectral techniques such as FT-IR, ¹H-NMR, ¹³C-NMR and mass analysis respectively. The observed result shows that the chemical yield strongly depends on the number of active sites of the each CMPTC’s (Table 1). Further, irrespective of CMPTCs, CMPTC with Cs free –OH or Cs (O) protected (either by tosylation/allylation) or the CMPTC contain single-active-site or multi-active-site per molecule were all in a position to produce only the mono alkylated product. Where as in the case of aldimine we observed dialkylated product irrespective of CMPTCs.

That is, in the case of ketimine 1 the hydrogens on the achiral methylene are more acidic than the aldimine methylene hydrogens 2. However, the ketimine undergoes only mono alkylation even in the presence of ten equivalents of alkyl
halides. But the aldimine 2 undergoes two consecutive alkylations in 99% chemical yield and 99% ee without any problem. This reflects the enormous steric crowding on the carbanion from the 1' (Scheme 3) which is responsible for the failure in the second alkylation even though the methane hydrogen in 1' should be much more acidic than the corresponding one in 2' due to the -I effect of two phenyl rings. Anyhow the steric factor determines the course of the reaction over the reactivity (kinetic) factor of the substrates.

Therefore, irrespective of the structure of CMPTCs and their number of active site present in each molecule, we observed only the mono alkylated product.
in ketimine and dialkylated product in aldriaine respectively with different range of yield and ee’s (Table 1, 5).

The quantitative product analysis results in terms of percentage of yield and ee’s catalysed by 28 CMPTCs along with literature reported CMPTCs (83 and 84) are presented in Table 1. The ketimine alkylation reaction results reveals that the percentage of product yield and enantiomeric excess for the CMPTCs contains Cg free -OH irrespective of cinchonine derived CMPTCs (Table 1, entries 2-8) and cinchonidine derived CMPTCs (Table 1, entries 18-24) were almost similar and were observed to be in the range of 65 to 94% (yield) and 47 to 89% (ee’s) respectively. Similarly, in the case of C9 (O)-protected CMPTCs derived from both cinchonine (entries 10-16, Table 1) and cinchonidine (entries 26-32, Table 1) catalysed the reaction with same efficiency and ee but better than their respective C9 free -OH CMPTCs. That is, CMPTCs contains C9 (O) protected irrespective of cinchonine/cinchonidine derived, the catalytic efficiency were found in the order of w-xylene based di-site (61b, 62b) > tetra-site (with spacer chain) (81b, 82b) > p-xylene derived di-site (67b, 68b) > tri-site (71b, 72b) > 4,4’-bipyridyl based di-site (55b, 56b) > tetra-site with out spacer (77b, 78b) > single site (46, 49). That is, both cinchonine and cinchonidine derived CMPTCs produced the higher chemical yield in the range of 62 to 99% and higher enantiomeric excess found in the range of 48 to 99%. The comparative results shows that invariably in each CMPTCs, the C9 (O)-protected CMPTC’s produced an enhanced yield and ee’s than their corresponding CMPTCs containing C9 free -OH. The reaction for the formation of higher amount of chemical yield and ee depends on the molecular assembly and orientation between catalyst and substrate.
Table 1. Comparative study for the alkylation of ketimine using different CMPTCs under identical reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>CMPTCs</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Absolute Configuration</th>
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</tr>
<tr>
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<td>66</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>61a</td>
<td>94</td>
<td>85</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>67a</td>
<td>91</td>
<td>78</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>71a</td>
<td>87</td>
<td>89</td>
<td>R</td>
</tr>
<tr>
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<td>77a</td>
<td>65</td>
<td>57</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>81a</td>
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<td>83</td>
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<td>32</td>
<td>82b</td>
<td>97</td>
<td>95</td>
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*To sylated single-site chiral phase transfer catalysts

* Reported single-site chiral phase transfer catalysts
S.2.2.2. The piofoable molecular assembly responsible for improved chemical yield and enantioselection

The higher amount of alkylated glycineimine 4 yield and ee’s in the presence of Cg (O) protected CMPTC’s such as cinchonine derived 46, 55b, 61b, 67b, 71b, 771> and 81b (entries 10-16, Table 1) and cinchonidine derived 49, 56b, 62b, 68b, 72b, 78b and 82b (entries 26-32, Table 1) is purely based on the stereochemistry/molecular assembly of CMPTC’s with substrates. That is, in general irrespective of Cg free OH or C9 (0) protected CMPTC’s, there should be three factors which influence chemical yield and ee’s: (i) effective contacts of ion-pair formed between R4N+ of CMPTC’s with anion of a-carbon of the glycineimine (ii) with the same ion-pair interaction of the enolate of the glycineimine with R4N of CMPTC’s (iii) intermolecular hydrogen bonding between C9 free -OH of CMPTC’s with anions of a-carbon of glycineimine. We strongly believed that the above three possible electrostatic processes are responsible for deciding the yield 4 and ee’s.6

In the reaction, on deprotonation of the a-carbon of the ketimine 1 by the Off the a-carbon anion of the glycineimine is generated which in turn forms an ion pair with the of the CMPTCs and a subsequently negative charge is developed on the enolate of the substrate leading to an ion-pair with the R4N+ of the CMPTCs. These ion-pair formation brings the substrates closer by reducing the bondin,
distance of $R_N^+$ of CMPTC’s. Subsequently, there is the possibility for hydrogen bonding through the same electrostatic attraction between the anion of a-carbon of glycineimine with C9 free -OH of the CMPTC’s in turn prevents the movements of anionic substrate species towards $R_N^+$ of the CMPTC’s. Whereas, in C9 (0) protected CMPTCs catalysed reaction irrespective of cinchonine (entries 9-16, Table 1) and cinchonidine (entries 25-32, Table 1), the possibility for formation of hydrogen bond between the C9 free-OH with a-carbon anion of glycineimine is completely unobserved since the free -OH at C9 position is protected through tosylation in single-site CPTCs and by allylation with other CMPTCs. As a result, the first two electrostatic processes (i) and (ii) may be more dominant and thus anionic substrate (ketimine) are moved fastly closer to $R_N^+$ active site of CMPTC’s without any constraint and followed by further attraction of anion of a-carbon of glycineimine with the carbocation of the alkyl halide facilitating higher order of chemical yield and enantioselectivity parallely.

In contrast, in the case of CMPTC’s containing C9 free OH irrespective of cinchonine (entries 2-8, Table 1) and cinchonidine (entries 18-24, Table 1), the catalyst produced only low yield and ee’s than their corresponding C9 (0) protected one. This is because, in the reaction process though the first two processes (i) and (ii) are operative, the third process viz., the formation of intermolecular hydrogen bonding between C9 free OH with anions of a-carbon of glycineimine prevents the
movements of substrate anions closer toward $R_4N^+$ of the CMPTCs, thus the amount of formation of ion-pair between of CMPTCs with anions of $\alpha$-carbon of glycineimine (Figure Ilia, a) is considerably less and subsequently the contact of carbocation towards anions of $\alpha$-carbon is also less (Figure IV). Hence, there has been a relatively lower yield and ee’s were obtained in the presence of C9 free -OH CMPTC’s (Figure Ilia, b).

Otherwise, in a precise way, C9 (0) protected CMPTC’s such as 46 and 49 by tosylation and other CMPTC’s by allylation leads to facilitate the reaction more effectively without any hydrogen bond with substrate. Whereas C9 free OH of the CMPTC’s forming hydrogen bond with substrate hence, C9 (0) protected CMPTC’s are superior catalysts then their corresponding C9 free -OH CMPTCs since they have produced the enhanced yield (Figure III, c,d). Further, the ee were also found to improve based on their chiral action and position of the chiral center.

It was observed that the “R” enantiomers were more predominant than the “S” ones with cinchonine as a catalyst; whereas “S” enantiomer were more predominant in the case of cinchonidine based CMPTCs. Similar studies are also reported in literature. With a view to visualize a mechanism, a two-dimensional diagram of the molecular is presented (Figure III).
Figure IIIa. Formation of various intermediates/molecular assemblies during enantioselective C-alkylation of ketimine using $\text{C}_9$ free $-\text{OH}$ CMPTCs

Figure IIIb. Formation of various intermediates/molecular assemblies during enantioselective C-alkylation of ketimine using $\text{C}_9$ (O) protected CMPTCs (hydrogen bonding completely ruled out)
5.2.2.3. Order of catalytic efficiency among the similar number of active-site present in CMPTCs

5.2.2.3.1. Among the single-site C₉(O) protected CPTC’s

A comparative study between CMPTC’s carrying similar number of active sites in catalysing the alkylation of ketimine shows that the yield and ee’s using new single site CPTC such as 46 and 49 gives the same yield « 67% and ee’s « 49% (entries 2, 10, 18 and 26, Table 1). In the literature, similar C₉(O) protected single-site PTC such as 83b and 84b derived from the same cinchonine and cinchonidine respectively gives the maximum yield as 62% and ee as 35% (entries 1, 9, 17 and 25, Table 1). These comparative yield and ee’s results proves that our CPTC of C₉(O) protected through tosylation functionality is slightly superior to the CPTC of C₉(O) protected by allylation reported in literature. This is because, C₉(O) tosylated CPTC more effectively facilitates the reaction as well as chiral transfer than the C₉(O) allylated CPTC. Similarly, the other possibility of intermolecular hydrogen bonding between the free -OH present in the phenol moiety
(spacer) of all the SPTCs and carbanion of the a-carbon of the glycine imine or enolate of the glycine imine may also be ignored due to intramolecular hydrogen bonding with the adjacent formyl group (Figure IV) of the newly synthesized single-site CPTCs (46 and 49).

Figure IV. Intermolecular hydrogen bonding between the phenolic -OH of the spacer chain with the adjacent aldehyde group of the spacer chain in all the SPTCs.

5.2.2.3. 2. Among the di-site Cy (O) protected CPTCs

Similarly, among the C9 (O) protected di-site CMPTC’s irrespective of cinchonine/cinchonidine, the order of catalytic efficiency in terms of yield and ee’s were found to be 100 and 99% for w-xylene derived CMPTCs (61b, 62b) > 99 and 81% for p-xylene derived CMPTCs (67b, 68b) > 97 and 90% for bipyridyl derived CMPTCs (55b, 56b). The higher yield and enantioselection found in w-xylene derived di-site CMPTC (entries 12 and 28, Table 1) is due to the fact that initially the substrate deprotonation occurs by the base (OH ) and then the anions of oc-carbon of glycineimine is appropriately fixed between the asymmetric environment of two R,N’ site of CMPTC’s by an effective dipole dipole interaction (ion-pair interaction), as a result of which, two cationic moieties are simultaneously activated and co-operatively influence the reaction (Figure V). Similar observation is already
reported by the Shibasaki et al. for the alkylation of ketimine in presence of two-centre PTC derived from L or D-tartaric acid.

Figure V. A schematic representation for the two cationic moieties of CMPTCs 61b or 62b are simultaneously activated and co-operatively influenced the reaction due to dipole-dipole interaction (ion-pair)

The CPTC derived from β-xylene (67b, 68b) and bipyridyl CMPTC’s (55b, 56b) in both cases, although they possess two R₄N⁺ cationic site, but the relative special position of these two cationic sites are just opposite or they are positioned away with each other. As a result, α-carbon anion of glycineimine are not appropriately fixed between the two R₄N⁺ catalytic sites favourably as in w-xylene derived CMPTC’s. That is, instead of co-operative influences/attraction of R₄N⁺
site on the anions of the a-carbon glycineimine, there is only a linear or individual ion-pair attraction in both p-xylene (Figure VI) and bipyridyl CMPTC’s based reaction.

Similarly, the formation of low yield and ee’s for bipyridyl based CMPTCs (55b, 56b) as compared with p-xylene based CMPTCs (67b, 68b) is due to the formation of no bond resonance. That is, during the alkylation reaction using 4,4'-bipyridyl based CMPTCs, the lone pair present in piperidine ring nitrogen can be easily transferred to electron deficient nitrogen (quaternary nitrogen) and thus formed a no bond resonance. This is in turn detached/deactivate the catalytic site of the CMPTCs 55b and 56b (Figure VII). This type of no bond resonance is not observed either in m-xylene or p-xylene derived CPTC’s. However, in all the three categories of CMPTC’s there is a C₂-symmetry exists which always promotes the reaction and obtained the higher chemical yield and ee. Similar observation was
reported already by Maruoka et al.\textsuperscript{19} for the reaction of C-alkylation of glycine imine using C\textsubscript{2}-symmetry oriented binaphthol based quaternary ammonium salt as as chiral phase transfer catalyst.

Figure VH Detachment/Deactivation of bipyridyl based CMPTC due to no bond resonance formation

5.2.2.3. Among the tetra-site C\textsubscript{9} (O) protected CPTCs

The C\textsubscript{9} (O) protected tetra-site CMPTC’s containing spacer chain viz., 81b and 82b had shown a higher chemical yield ((yield 99% and ee’s as 95%) (entries 16, 32, Table 1)) than the corresponding tetra-site CMPTC’s having no spacer chain such as 77b and 78b ((76% and ee’s as 59%) (entries 15, 31, Table 1)). It is well known that even in the normal reactions, substitution of linear or aromatic spacer chain (benzyl) in cinchonine/cinchonidine functionality might always accelerate the reaction. This could be due to increase in the hydrophobic effect and also the absence of steric hindrance in 81b and 82b. That is, the induction of spacer molecule to the core component pushed the active site apart and hence free from hindrance and thus facilitate linearly the free contact of ion-pair interaction between
R₂N⁻ with anion of α-carbon of glycine imine; and followed by attraction of carbocation accelerate the reaction which in turn leads to proceed with improved yield and ee than with their corresponding CMPTC’s containing no spacer chain. Further, the tetra-site catalyst with no spacer chain CMPTC’s 77b and 78b had a severe steric hindrance due to close spatial arrangement of quinoline ring of cinchona alkaloids present immediately to the each corner of pentaerythritol (Figure VIII). Thus the formation of poor ion-pair interaction hence, low yield and ee were noticed in 77b and 78b.

Figure IX CMPTCs with no spacer molecules having severe steric hindrance between the neighbouring groups of the quinoline part of the alkaloid moiety

Similar observations reported by O’Donell¹¹ who developed a CMPTC of benzyl ammonium salt derived from versatile cinchona alkaloids containing N-benzyl substituent for the asymmetric alkylation of glycineimine, wherein, they found low yield and ee’s. In contrast, the results obtained with these catalyst were improved by Lygo et al¹² and Corey et al⁸ synthesized catalyst who substituted a bulkier 9-methylnaphthacenyl group in SPTC (84a and 84b) and achieved the good
increase in yield and enantioselectivity for the same reaction. Similarly, the newly synthesized CMPTC’s containing spacer chain (81b and 82b) is found to be good. Hence, it is desirable to synthesise CMPTC’s with effective and moderate spacer chain like 81b and 82b to accelerate the reaction more effectively with high yield and ee’s.

5.2.2.4. Selection of superior CMPTC from all the 14 CMPTCs

The overall catalytic efficiencies of all the 14 C9 (0) protected CMPTC’s in terms of the chemical yield and ee’s were found in the order of w-xylene based di-site (61b and 62b) > tetra-site with spacer chain (81b and 82b) > /7-xylene based CMPTCs (67b and 68b) > tri-site (71b and 72b) > 4,4'-bipyridyl based di-site (55b and 56b) > tetra-site with out spacer (77b and 78b) > single-site (46 and 49). Although the tetra-site CMPTCs with spacer chain and tri-site CMPTCs contain 4 and 3 active sites respectively in a molecule, the yield and ee’s were found to be lower compared with /w-xylene di-site CMPTCs (61b and 62b). The reasons for this trend of observations are obviously known and in fact we have already highlighted in detail in the previous discussion. That is, the higher yield and ee’s for /w-xylene derived C9 (O) protected CMPTCs (61b and 62b) is due to presence of C2-symmetry and the effective formation of contact ion-pair between the of CMPTCs with anion of the substrate via co-operative influenced due to close spatial arrangement of two active-site (Figure V). Hence, a higher yield and ee than the tetra-site (81b and 82b) and tri-site CMPTCs (71b and 72b).

Further, the tetra-site CMPTCs with spacer chain 81b and 82b contain lone-pair of electrons on the oxygen atoms (present in each corner of pentaerythritol) shift the electron density to the electron deficient terminal R4N+ site of the CMPTCs via aromatic ring spacer chain, as a result no bond resonance is formed (Figure IX). This leads to detachment/deactivation of catalytic site, thus lose their attracting power (electrophile attracting power) towards the anions of a-carbon of the of the glycine imine. As a result, the formation of degree of ion-pair between R4N+ of tetra-site CMPTCs (81b and 82b) with anions of a-carbon of the glycine
inline is relatively lower. Thus produced a lower yield and ee than their o-xylene
derived di-site CMPTCs though the tetra-site CMPTCs (with spacer chain) contains
four active sites in a molecule.

Figure IX. Detachment/deactivation of CMPTC due to no bond resonance
formation

Similarly, the low yield and ee obtained using tri-site CMPTCs (71b and
72b) than with the m-xylene derived CMPTCs (61b and 62b) is also due to the
same electronic effect. That is, as we observed in tetra-site based CMPTCs (81b
and 82b), tri-site CMPTCs also contain a lone pair of electrons on the nitrogen
atom of aniline moiety (or Mustared gas analogs) and thus electron density is transferred to electron deficient R₄N⁺ of CMPTCs via benzene ring of aniline and thus leads to formation of no bond resonance. The formation of no bond resonance leads to detachment of catalytic site or the partial neutralization of R₄N⁺ charge. This in turn reduced the attracting power of these electrophiles resulting the lower degree of ion-pair contact between R₄N⁺ of CMPTCs with anions of α-carbon of glycine imine (Figure Xa, 71b and 72b).

Figure Xa. Detachment/deactivation of CMPTC due to no bond resonance formation

The other possibility of no bond resonance formation is also detached/deactivate the catalytic site of 71b and 72b. That is, the lone pair of the nitrogen is transferred to electron deficient R₄N⁺ of the CMPTCs and produced the aziridinium ion (Figure Xb). Hence, 71b and 72b produced lower yield and ee’s
than with m-xylene derived CMPTCs (61b and 62b) although they contains 3 active-site in a molecule. In contrast, this type of electronic effect viz., the no bond resonance and reducing the cationic charge of \( R_4N^+ \) of CMPTCs are not found in w-xylene derived CMPTCs (61b and 62b). This is an additional factor in favor of efficiency of m-xylene based CMPTCs.

![Diagram](image)

Figure Xb. Detachment/deactivation of tri-site CMPTC due to no bond resonance formation (to form an aziridinium ion)

In fact, similar analogy of study viz., the influence of electronic effect have already been reported by Dolling et al., but in the sense opposite to that observed in this work. That is, they observed a higher ee (60-80%) by introducing the
electron withdrawing functionality in para N-benzyl moiety of the cinchona alkaloid catalysts. In a true sense, electron withdrawing group like (F, Cl) are in a position to pull the electrons via N-benzyl ring which in turn increase the electron deficiency of R₄N⁺ of the reported CMPTCs thus facilitating stronger ion pairing and hence they produced higher chemical yield and ee’s. In the new tetra-site and tri-site CMPTCs, instead of electron withdrawing, electron donating functionality is present in the benzene ring, i.e. the hetero atom like ‘O’ in tetra-site (with spacer chain) and ‘N’ in tri-site are donating the electron to the R₄N⁺ site via benzyl moiety and thus formation of no bond resonance or partial neutralization of R₄N⁺ site of CMPTCs. This in turns afforded the detachment of catalytic site or deactivation of CMPTCs.

Furthermore, the tetra-site CMPTCs without spacer chain (77b and 78b) had produced relatively lower yield with maximum of 76% and ee with maximum of 59% (entries 15, 31, Table 1) than with bipyridyl based di-site CMPTCs such as 55b and 56b; i.e. the obtained maximum yield is 97% and ee is 90% (entries 11 and 27, Table 1). This is obviously due to severe steric hindrance owing to close spatial arrangements of cinchona alkaloid ring and high rigidity of tetra-site CMPTCs 77b & 78b and that tends to restrict the free entry of the anion of α-carbon of the glycine imine towards R₄N⁺ site of the CMPTCs. This may probably lower the ion-pair interaction than with the bipyridyl di-site CMPTCs resulting the lower yield and ee although 77b and 78b contain four active-site per molecule of catalyst (refer the catalyst structure in page No. 215).
5.2.3. Optimization of reaction variables for the effective alkylation of ketimine using superior CMPTC’s

In order to carry out the alkylation of ketimine with various alkyl halides more effectively using superior CMPTCs, we have optimized the reaction conditions by adjusting the reaction variables such as nucleophiles, electrophiles, solvents and its concentration, aqueous base and their concentration and temperature. The preceding section of the discussion strongly suggested that although we have synthesized 28 types of CMPTCs starting from single-active site to tetra-site the C9 (O) protected di-site CPTCs derived from w-xylene. (61b and 62b) are found to be superior to any other CMPTCs in terms of chemical yield and ee’s. Hence, among the two superior CMPTCs we have chosen m-xylene based di-site CMPTC derived from cinchonine (61b) as a model catalyst for conducting and optimizing the reaction variables for the effective improvement of chemical yield and ee’s.

5.2.3.1 The influence of substitutional group present in ketimine (electrophiles) on reaction

The alkylation of ketimine was carried out with various substituted benzyl halides in the presence of superior di-site CMPTC viz., 61b using 20% aqueous NaOH (5 ml) and mixture of solvent such as toluene and CH₂Cl₂ (8:2 v/v) at lower temperature (-10 °C). From the obtained results (Table 2), we observed that the chemical yield and ee’s of the reaction are found to increase with increasing bulkiness of the substituting groups in benzyl moiety of the alkyl halides. That is, the yield and ee were found to decrease in the order of i-Bu > -OCH₃ > CF₃ > CH₃ > -NO₂ > -CN > -Br > -H. This trend of yield and ee results shows that the presence
of bulkiness and electron donating substituents in the alkyl halide like t-butyl and 
-OCH₃ had improved the chemical yield and ee's dramatically. In fact, the total
disappearance of substrate has been noticed than with alkyl halide contains electron
withdrawing functionality like -CF₃, -NO₂, -CN, -Br and -H. The magnitude of
chemical yield and asymmetric induction normally depends on several factors. That
is, the presence of functionality in the alkyl halide had also played one among the
role in promoting the yield and ee. The t-butyl and -OCH₃ present in alkyl halide
normally donate the electron to the benzene ring of the substrate, hence the
delocalisation of π-electron occurred and that leads to decrease the π-π stacking
interaction with the π-orbital present in the benzene ring of the catalyst (Figure XI).
Since the π-π stacking interaction is reduced or prevented, the electrophiles of
the carbocation formed from the alkyl halide, would easily get attracted towards R₃N⁺
site of the CMPTC's which inturn provide the effective ion-pair interaction and
hence the maximum yield and ee are observed.

In contrast, the other electron withdrawing functionality such as -CF₃, -NO₂,
-CN and -Br are available in para position, as a result there is an effective π-π
stacking interaction¹¹b between the π-bond present in aromatic ring of alkyl halide
with the π-bond present in the aromatic ring of the CMPTC's (Figure XI); this in
turn strongly prevents the movement of electrophiles (carbocation of the alkyl
halides) towards R₃N⁺ of the CMPTC's and thus decrease the chemical yield and ee
(entries 3, 6, 7 and 8, Table 2). That is, the alkyl halide containing t-butyl and
-OCH₃ functionality favorably facilitate the reaction as a result there is a good
number of proper molecular spatial orientation of CMPTC's with substrate (α-
carbon of glycine imine & carbocation) and such orientation leads to provide the enhanced chemical yield and ee.

\[
\begin{align*}
\text{Where } X &= \text{-Bu, -OMe, -NO}_2, \\
&\quad \text{-CF}_3, \text{-CH}_3, \text{-H etc.}
\end{align*}
\]

**Figure XI.** The possible molecular orientation for the formation of \(\pi-\pi\) stacking interaction between the CMPTCs and carbocation of the substrate

In fact, similar studies have been reported by Lygo et al.\(^{12}\) but wherein, they have mentioned that the simple alkyl halide like \(\text{CH}_3I, \text{CH}_3(\text{CH}_2)I\) would tend to produce low yield, whereas as the high molecular weight alkyl halide like benzyl bromide, allyl bromide and tert butyl iodoacetate had produced higher chemical yield and mild enantioselectivity in the synthesis of aspartic acid derivatives. Similarly, Park et al.\(^{14}\) have synthesised not only the higher enantioselectivity but also the chemical yield in the enantioselective alkylation of \(N\)-(diphenylmethylene)glycine tert butyl ester. Arai et al.\(^{15}\) made a similar observation for the alkylation of \(\alpha\)-Fluorotetralone in presence of *Cinchona* based chiral
Entry Alkylhalides (Electrophiles) Yield (%) e.e (%) Abs. config.
1 -H 52 87 R
2 4-CH₃ 93 91 R
3 4-OMe 94 96 R
4 4-CF₃ 89 85 R
5 4-/-Bu 99 98 R
6 4-NO₂ 82 90 R
7 4-CN 78 89 R
8 4-Br 65 88 R

5.2.3.2. The influence of nucleophile in the alkylation of ketimine

We have also carried out the C-alkylation of ketimine 1 containing different functionalities (nucleophiles) such as N-(diphenylmethylene)glycine tert-butyl ester and A-(diphenylmethylene)glycine wo-propyl ester in presence of 61b and 20% aq. NaOH. The presence of tert-butyl and isopropyl functionality in glycine imine is studied individually with a view to know their effect on the yield and ee. The tert-
butylglycinate benzophenone (Schiff base 1) has been employed as a nucleophile for the alkylation reaction. Here too, we observed a higher chemical yield (99%) and ee (98%) since the substrate containing bulky substituents in the ketimine 1 remarkably influenced the chemical reaction (equation 1, scheme 4). In contrast, the isopropyl glycinate benzophenone Schiff base 6 produced lower yield (63%) and ee (72%) (equation 2, scheme 4). A similar observation was reported by O’Donnell et al. for the synthesis of α-amino acids using Cinchona alkaloid derived CPTC.

Scheme 4

5.2.3.3. The effect of solvent and base on the enantioselective alkylation of ketimine

The effect of solvent and its concentration, the effect of different base and their concentration were studied in detail in the alkylation of ketimine using the superior CMPTCs viz., 61b. The obtained result (Table 3) show that there is no alkylated product was found in presence of CH₂Cl₂ as solvent. This is because, the solvent easily interact with CMPTCs due to its high polar nature and also hydrophobic attraction that leads to disturb the skeleton structure of CMPTCs. In contrast, the presence of toluene alone leads to lower amount of chemical yield (39%) and ee (36%) owing to its partial solubility of the CMPTCs. Similarly,
neither CH₂Cl₂ nor toluene is a suitable solvent to carry out the reaction effectively owing to its higher/lower solubility of CMPTCs. Hence, we have decided to carry out the alkylation reaction using mixture of solvents like toluene and CH₂Cl₂ by varying different ratios in volume. The mixture of solvents would certainly improve the solubility of the CMPTCs, hence a gradual enhancement in the yield and ee is noticed. Exclusively, the volume ratio 8:2 of toluene/CH₂Cl₂ gives a remarkable improvement in the yield and ee; a further increase/decrease the concentration of the toluene/CH₂Cl₂ would alter the chemical yield and ee. Hence, 8:2 volume ratios of toluene/CH₂Cl₂ are found to be an optimum concentration for the effective improvement of yield and ee (entry 6, Table 3).

Similarly, under strong base like NaOH with high concentration (more than 20% w/v) all the CMPTCs are decomposed, as a result there is no product formed (Table 3). Hence we have decided to carry out all the reaction by fixing a moderate NaOH concentration (20% w/v). The change of NaOH to KOH with or without K₂CO₃ and the mixture of NaOH/K₂CO₃ by keeping the proper volume ratio of toluene/CH₂Cl₂ as constant (8:2 v/v) does not improve the reaction yield and ee (entries 8, 9 and 10, Table 3). In contrast, they are drastically reduced the yield and ee exclusively in NaOH/K₂CO₃ base mixture (entry 9, Table 3). Otherwise, other studies reveal that it is essential to maintain the volume ratio of solvent and relevant base and its concentration for the effective improvement of alkylation yield and ee. The percentage of chemical yield and ee’s are gradually increased by decreasing the addition of dichloromethane to toluene (entries 3-6, Table 3). Similar studies have been reported by Mazon et al.¹⁶ for the alkylation of ketimine in the presence of dendritic based cinchona alkaloid as a CPTCs.
### Table 3. Influences of different bases and solvent in C-alkylation of ketimine

```
\[ \text{Ph} = \text{N} - \text{O} \quad \text{t-Bu} = \text{PhCH}_2\text{Br}, \text{solvent,aq base, -10°C} \]
```

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents (10 mL)</th>
<th>Aq base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>NaOH</td>
<td>99</td>
<td>98 (R)</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>NaOH</td>
<td>59</td>
<td>36 (R)</td>
</tr>
<tr>
<td>3</td>
<td>PhMe/CH$_2$Cl$_2$ (3:7)</td>
<td>NaOH</td>
<td>17</td>
<td>19 (R)</td>
</tr>
<tr>
<td>4</td>
<td>PhMe/CH$_2$Cl$_2$ (5:5)</td>
<td>NaOH</td>
<td>77</td>
<td>79 (R)</td>
</tr>
<tr>
<td>5</td>
<td>PhMe/CH$_2$Cl$_2$ (7:3)</td>
<td>NaOH</td>
<td>86</td>
<td>88 (R)</td>
</tr>
<tr>
<td>6</td>
<td>PhMe/CH$_2$Cl$_2$ (8:2)</td>
<td>NaOH</td>
<td>99</td>
<td>98 (R)</td>
</tr>
<tr>
<td>7</td>
<td>PhMe/CH$_2$Cl$_2$ (9:1)</td>
<td>NaOH</td>
<td>95</td>
<td>86 (R)</td>
</tr>
<tr>
<td>8</td>
<td>PhMe/CH$_2$Cl$_2$ (9:1)</td>
<td>KOH</td>
<td>87</td>
<td>61 (R)</td>
</tr>
<tr>
<td>9</td>
<td>PhMe/CH$_2$Cl$_2$ (8:2)</td>
<td>NaOH/K$_2$CO$_3$ (1:1)</td>
<td>42</td>
<td>73 (R)</td>
</tr>
<tr>
<td>10</td>
<td>PhMe/CH$_2$Cl$_2$ (8:2)</td>
<td>K$_2$CO$_3$ (1:1)</td>
<td>82</td>
<td>91 (R)</td>
</tr>
</tbody>
</table>

### 5.2.3.4. Effect of temperature on alkylation of ketimine under CMPTC conditions

The results on chemical yield and ee for the alkylation of ketimine under CMPTC condition reveals that the variation of the reaction temperature also affects the chemical yield and level of the asymmetric induction. That is, at fixed concentrations of solvents, NaOH, catalyst, and substrate, we conduct the reaction by varying the temperature from 40 °C to -25 °C. The obtained result shows that when the temperature was decreased from 40 °C to -10 °C, the yield and ee were
found to improve gradually. Particularly, at −10 °C, the chemical yield (99%) and ee (98%) are drastically improved. A further decrease of temperature from −10 °C does not improve the chemical yield and ee (entries 8 and 9, Table 4). Hence, the optimum temperature for effective alkylation reaction is determined as −10 °C (entry 7, Table 4). However, the enantioselectivity were not either improved or decreased periodically with respect to decreasing the temperature. This random change in enantioselectivity is something unusual. Similar observations are also made by Mazon et al16 for the alkylation of glycine imine in the presence of dimeric anthracenyl derived cinchona alkaloid quaternary ammonium salts as phase transfer catalysts. Park et al14 also reported a similar trend of results in yield for the synthesis of α-amino acids at lower temperature (−20 °C) using ortho-fluoro dimeric-cinchona derived phase transfer catalyst.

Table 4. Effect of temperature on enantioselective alkylation of glycine-imine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>58</td>
<td>36 (R)</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>76</td>
<td>71 (R)</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>80</td>
<td>60 (R)</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>75</td>
<td>67 (R)</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>87</td>
<td>83 (R)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>89</td>
<td>91 (R)</td>
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<tr>
<td>7</td>
<td>-10</td>
<td>99</td>
<td>98 (R)</td>
</tr>
<tr>
<td>8</td>
<td>-20</td>
<td>81</td>
<td>76 (R)</td>
</tr>
<tr>
<td>9</td>
<td>-25</td>
<td>78</td>
<td>70 (R)</td>
</tr>
</tbody>
</table>
5.2.3.S. DsaSkylation of aWimine using selected CMPTC

We also conducted a study for the dialkylation of aldimine 2 using few selected CMPTCs containing both C₉ free -OH and C₉ (0) protected CMPTCs derived from cinchonine. That is, the cinchonine based di-site CMPTCs derived from bipyridyl (55a and 55b), m-xylene (61a and 61b), tri-site (71a and 71b) and tetra-site with spacer chain (81a and 81b) were employed individually to carry out the above reaction using different alkyl halides under identical reaction conditions. Irrespective of the CMPTCs and number of active-sites in a molecule, we observed only the dialkylated product with different range of chemical yield and ee (entries 1-19, Table 5). The obtained results in terms of yield and ee shows that in the alkylation of aldimine also C₉ (O) protected (by allylation) CMPTCs were found to dominate in producing the high yield and ee than their corresponding C₉ free -OH CMPTCs due to the elimination of hydrogen bonding. That is, the C₉ free -OH of the CMPTCs should form a hydrogen bond with the α-carbanion of the glycine imine, whereas, protected C₉ (0) should not. The reasons for the formation of dialkylated product are discussed elaborately in preceding discussion (refer page No. 223).

Further, the temperature is found to influence the chemical yield and ee. That is, at optimum temperature (-20 °C) the yield and ee are observed to be higher irrespective of CMPTCs; whereas at higher temperatures (25 °C) the ee was observed to decrease drastically (entries 1,11, Table 5) and the yield were found to decrease mildly. If the temperature is decreased to -30 °C, no reaction was observed. Even, when the best CMPTCs 61b and 71b were used as catalysts (entries 4, 18, Table 5) at -30 °C and -20 °C no yield and ee were observed.
Table 5. Dialkylation of aldimine in presence of different types of CMPTCs.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>CMPTCs</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Absolute Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₂Br</td>
<td>55a</td>
<td>25</td>
<td>86</td>
<td>57</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>PhCH₂Br</td>
<td>55b</td>
<td>-20</td>
<td>95</td>
<td>97</td>
<td>R</td>
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<td>PhCH₂Br</td>
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<td>-20</td>
<td>83</td>
<td>79</td>
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<td>71b</td>
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<td>71a</td>
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<td>81b</td>
<td>-20</td>
<td>97</td>
<td>99</td>
<td>R</td>
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<td>15</td>
<td>CH=CHCH₂Br</td>
<td>71a</td>
<td>-20</td>
<td>89</td>
<td>74</td>
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<td>16</td>
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<td>61b</td>
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<td>99</td>
<td>96</td>
<td>R</td>
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<td>81a</td>
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<td>86</td>
<td>65</td>
<td>R</td>
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<td>71b</td>
<td>-20</td>
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<tr>
<td>19</td>
<td>(CH₃)₃CHBr</td>
<td>81b</td>
<td>-20</td>
<td>65</td>
<td>72</td>
<td>R</td>
</tr>
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</table>
Similarly, the change of alkyl halide does not influence much on neither a chemical yield and nor a ee except the benzylic 2-naphthyl bromide and propargylic bromide as a nucleophile which reduced substantially the enantioselectivity (entries 11, 17, Table 5). Among the catalytic efficiency of different CMPTCs, here too the m-xylene derived di-site CMPTCs was observed to be more effective than other CMPTCs; the reasons are already described (refer page No. 228). Lygo et al\textsuperscript{12}, Belokon et al\textsuperscript{17} and Ooi et al\textsuperscript{18} had also reported the dialkylation of aldimine in presence of 50% aqueous KOH under various Cinchona derived chiral phase transfer catalysts.

S.2.3.6. Stability of the CMPTCs

Generally the most important factor to be considered for any catalyst synthesis of achiral and chiral molecules is the stability of the catalyst. In the present study, with a view to examine the stability of chinchona alkaloid based CMPTCs, we have performed a study taling bipyridyl based di-site CMPTCs containing both C9 free -OH (55a) and C9 (O) protected (55b) as test catalysts 10 mM of these test CMPTCs viz., 55a and 55b were taken individually in various beakers in presence 5 ml of NaOH at various concentrations such as 10%, 20% and 30% w/v solution respectively. Each of these mixtures was dissolved in toluene/CH\textsubscript{3}Cl (8:2 v/v) and stirred for about 1 hr at room temperature. The progress of the reaction was monitored individually through TLC. After completion of 1 hr, each reaction mixture was washed with water and the respective product was isolated through column chromatography using benzene:ethylacetate mixture.
(70:30) as an eluent. The oxirane product $55a_3$ and olefinic compound $55b_2$ from $55b$ were obtained and characterized by various spectral techniques such as FT-IR, $^1$H-NMR and mass. The decomposition of $55a$ and $55b$ at higher concentration of NaOH (30%) is explained in the following paragraph. The formation of oxirane in $55a$ and olefinic product $55b$ is evidence for the decomposition of CMPTCs at high concentration of base.

The enantioselective alkylation of Schiff base at higher concentration of base irrespective of CMPTCs gave disparate results, which can be explained by invoking a catalyst-degradation mechanism (Scheme 5). At high concentrations of base, initially, the deprotonation of the catalyst $55a_1$ (Cg free -OH) occurs leading to the formation of zwitterionic alkoxide $55a_2$, this in turn undergoes a slow fragmentation to epoxide $55a_3$. In the case of Cg (0) allylated CMPTC ($55b_1$) at high concentration of base (30%), Hofmann elimination occurs and giving compound of $55b_2$ viz., olefinic compound. The formation of $55b_2$ (Scheme 5) was confirmed by various spectral techniques such as FT-IR, $^1$H-NMR and mass. Based on these observations, the base concentration was fixed at 20% and to maintain the structural stability of CMPTCs without decomposition. Similar studies have been reported by Paramzit Singh et al.$^{19}$, Siva et al.$^{20}$ Maruoka at al$^{10}$ and O Donnell et al$^{11d}$ for cinchona alkaloid derived CPTCs in the alkylation of glycine imine at higher concentration of base.
Scheme 5. A schematic representation for the catalyst decomposition studies

S.2.3.7. Interfacial mechanism for the mono/di alkylation of ketimine under CMPTC condition

A general mechanistic scheme (Scheme 6) for the mono and dialkylation of active methylene compounds such as ketimines 1 and aldimes 1 using various alkyl halides in the presence of CMPTCs is illustrated in the following section. The mechanistic pathways for both ketimine and aldime are similar. Three main steps have been proposed in these reaction process: (i) deprotonation of the active methylene compound using base, which generally occurs at the interface of the two layers liquid-liquid (LL) (aqueous/organic) PTC; (ii) extraction of anion (anion of
the α-carbon of the glycine imine substrate) into the bulk organic phase by ion exchange with the cation of the chiral quaternary ammonium salt to form a lipophilic ion-pair (Q\textsuperscript{+}RC=\text{CHCO}_{2}\text{Bu}), and (iii) the attraction of carbocation of the respective alkyl halide towards anions of the α-carbon of the glycine imine which already formed an ion-pair with the chiral center of R\text{+}N\textsuperscript{-} of CMPTCs. In the case of R and S isomer formation of alkylated imine derivatives would solely depend on the nature of CMPTCs. Similar mechanism has been proposed by O’Donnel et al\textsuperscript{15} and Maruoka et al\textsuperscript{16} for the alkylation of Schiff base in the presence of cinchona alkaloid derived CPTCs.

\[ \text{Scheme 6. Interfacial mechanism for the mono/di alkylation of ketamine under CMPTC condition} \]
5.2.3.8. CHARACTERIZATION OF ALKYLATED PRODUCTS

**tert-Butyl-2-diphenylmethyleneaminohexanoate (R, Entry 1, Table 2)**

FT-IR (KBr) cm\(^{-1}\): 3025 (C-H), 2979 (C-H), 2921 (C=C), 2868 (C-C), 1729 (C=O), 1664 (C=O); \(^1\)H-NMR (300 MHz) \(\delta\): 0.8-1.02 (t, 3H, J=6.0 Hz, methyl), 1.21 (s, 9H, methyl), 1.25-1.30 (m, 4H, methylene), 2.02-2.09 (q, 2H, methyne), 3.98-4.03 (t, 1H, J=7.52 Hz, methyne), 7.17 (m, 1H, aromatic), 7.48-7.29 (m, 5H, aromatic), 7.66-7.51 (m, 3H, aromatic), 7.81-7.83 (m, 1H, aromatic); \(^13\)C-NMR (75 MHz, DMSO d\(_6\)) \(\delta\): 14.7, 22.3, 27.5, 29.6, 51.5, 59.2, 72.6, 128.6, 129.2, 130.5, 137.6, 167.9, 187.3; m/z: [M]\(^+\) 351.23; HRMS calcd. for C\(_{25}\)H\(_{27}\)NO\(_2\) : 351.2301 Found 351.2298.

**tert-Butyl-3-(4-methylphenyl)-2-diphenylmethyleneaminopropanoate (R, Entry 2, Table 2)**

FT-IR (KBr): 3021 (C-H), 2876 (C-H), 1710 (C=O), 1595 (C=N), 1227 (C-O); \(^1\)H-NMR (200 MHz, DMSO d\(_6\)) : 1.37 (s, 9H, methyl), 2.22 (s, 3H, methyl), 3.01-3.05 (d, 2H, J=8.0 Hz, methylene), 4.38-4.44 (t, 1H, J=6.0 Hz, methylene), 7.07-7.10 (d, 2H, J=6.0 Hz, \(p\)-methylbenzyl aromatic), 7.24-7.28 (d, 2H, J=8.0 Hz, \(p\)-methylbenzyl aromatic), 7.51-7.77 (m, 10H, aromatic); \(^13\)C-NMR (50 MHz, DMSO d\(_6\)) : 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/z: [M]\(^+\) = 399.17; HRMS calcd. for C\(_{27}\)H\(_{30}\)NO\(_2\) : 399.2198 Found 399.2101.
*tert*-Butyl-3-(4-methoxyphenyl)-2-diphenylmethyleaminopropanoate  \((R, \text{Entry 3, Table 2})\)

FT-IR (KBr): 3042 (C-H), 2965 (C-H), 1698 (C=O), 1555 (C=N), 1236 (C-O), 786 (C-Br); \(^1\)H-NMR (200 MHz, DMSO\(d_6\)): 1.26 (s, 9H, methyl), 3.07 (s, 3H, methoxy proton), 3.21-3.26 (d, 2H, \(J=10.0\) Hz, methylene), 4.45-4.49 (t, 1H, \(J=4.0\) Hz, methylene), 7.02-7.05 (d, 2H, \(J=6.0\) Hz, benzyl aromatic), 7.38-7.40 (d, 2H, \(J=4.0\) Hz, benzyl aromatic), 7.41-7.55 (m, 10H, aromatic); \(^13\)C-NMR (50 MHz, DMSO \(d_6\)): 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; m/z : \(M^+ = 415.18\); HRMS calcd. for \(C_{27}H_{26}NO_6\) : 415.2397; Found 415.2186.

*tert*-Butyl-3-(4-trifluoromethylphenyl)-2-diphenylmethyleaminopropanoate  \((R, \text{Entry 4, Table 2})\)

FT-IR (KBr): 3076 (C-H), 2904 (C-H), 1732 (C=O), 1610 (C=N), 1230 (C-O); \(^1\)H-NMR (300 MHz, DMSO\(d_6\)): 1.32 (s, 9H, methyl), 3.25-3.29 (d, 2H, \(J=12.0\) Hz, methylene), 4.32-4.38 (t, 1H, \(J=9.0\) Hz, methylene), 7.05-7.09 (d, 2H, \(J=12.0\) Hz, aromatic), 7.41-7.44 (d, 2H, \(J=9.0\) Hz, aromatic), 7.47-7.76 (m, 10H, aromatic); \(^13\)C-NMR (75 MHz, DMSO \(d_6\)): 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 \([M^+] = 453.18\).
**tert-Butyl-3-(4-nitrophenyl)-2-diphenylmethyleneaminopropanoate (R, Entry 6, Table 2)**

FT-IR (KBr): 3056 (C-H), 2903 (C-H), 1723 (C=O), 1567 (C=N), 1467 (N-O), 1223 (C-O), 1074 (C-N), $^1$H-NMR (200 MHz, DMSO d$_6$): 1.10 (s, 9H, methyl), 3.12-3.15 (d, 2H, $J$=6.0 Hz, methylene), 4.28-4.33 (t, 1H, $J$=5.0 Hz, methylene), 7.23-7.66 (m, 14H, aromatic) m/z M$^+$ = 430.18.

**tert-Butyl 3-(4-cyclophenyl)-2-diphenylmethyleneaminopropionate (R, Entry 7, Table 2)**

Mp. 164 °C, FT-IR (KBr) cm$^{-1}$: 3067 (C-H), 2989 (C-H), 2210 (C=N), 1735 (C=O), 1644 (C=C), 1136 (C-O), $^1$H-NMR (300 MHz, DMSO d$_6$) $\delta$: 1.22 (s, 9H, methyl), 3.32 (2dd, 2H, $J$=13.3 Hz, methylene), 4.20-4.25 (t, 1H, $J$=7.5 Hz), 7.18 (d, 2H, $J$=8.3 Hz, aromatic), 7.26-7.62 (m, 10H, aromatic), 7.67-7.70 (d, 1H, $J$= 9.0 Hz, aromatic), 7.80-7.83 (d, 1H, $J$=9.0 Hz, aromatic), $^{13}$C-NMR (75 MHz, DMSO d$_6$): 21.7, 39.5, 64.6, 68.5, 110.2, 119.6, 127.2, 127.8, 127.9, 128.7, 128.9, 129.1, 129.3, 130.3, 130.5, 131.8, 132.3, 132.7, 135.9, 139.5, 144.2, 170.1, 177.4; m/z [M$^+$] 410.15; HRMS calcd. for C$_{27}$H$_{28}$N$_2$O$_2$: 410.19 Found 410.17
**tert-Butyl-3-(4-bromophenyl)-2-diphenylmethylenecaminopropanoate (R, Entry 8, Table 2)**

FT-IR (KBr): 3024 (C-H), 2888 (C-H), 1698 (C=O), 1555 (C=N), 1236 (C-O), 786 (C-Br); ¹H-NMR (200 MHz, DMSO-d₆): 1.26 (s, 9H, methyl), 3.21-3.26 (d, 2H, J=10.0 Hz, methylene), 4.45-4.49 (t, 1H, J=4.0 Hz, methyne), 7.02-7.05 (d, 2H, J=6.0 Hz, benzyl aromatic), 7.38-7.40 (d, 2H, J=4.0 Hz, benzyl aromatic), 7.41-7.56 (m, 10H, aromatic); ¹³C-NMR (50 MHz, DMSO-d₆): 24.2, 37.7, 61.4, 73.4, 120.2, 129.4, 130.4, 131.9, 132.5, 133.7, 137.5, 141.6, 166.2, 178.1; m/z: M⁺ = 464.10.

**tert-Butyl-3-(2-naphthyl)-2-diphenylmethylenecamo-propionate (R, Entry 10, Table 5)**

FT-IR (KBr) cm⁻¹: 3026 (C-H), 2888 (C-H), 1727 (C=O), 1087 (C-O); ¹H-NMR (300 MHz, DMSO-d₆): 0.85 (s, 3H, methyl), 3.36 (2dd, 2H, J=13.4 Hz, methylene), 7.12-7.87 (m, 12H aromatic); ¹³C-NMR (75 MHz, DMSO-d₆): 17.3, 24.6, 37.3, 61.7, 73.5, 124.8, 125.7, 126.7, 127.2, 127.4, 127.5, 127.9, 128.6, 129.0, 130.8, 133.5, 137.3, 164.5, 176.3.

**tert-Butyl-3-(vinyl)-2-(4-bromophenylmethylenecaminopropanoate (R, Entry 14, Table 5)**

FT-IR (KBr): 3044 (C-H), 2965 (C-H), 1726 (C=O), 1676 (C=N), 1258 (C-O); ¹H-NMR (300 MHz,
DMSO\textsubscript{d6} $\delta$: 1.41 (s, 9H, methyl), 3.21-3.25 (d, 2H, $J$=12.0 Hz, allylic methylene), 4.05-4.11 (t, 1H, $J$= 9.33 Hz), 4.97 (dd, 2H, $J$=7.74, 7.40 Hz, vinyl), 5.23-5.27 (t, 1H, $J$=6.18 Hz, vinylic methyne), 7.11-7.63 (m, 4H, aromatic), 9.12 (s, 1H, benzylidene methyne), \textsuperscript{13}C-NMR (75 MHz, DMSO d\textsubscript{6}) $\delta$: 15.2, 27.3, 40.4, 54.3, 110.6, 126.4, 130.4, 133.1, 136.4, 138.2, 159.3, 184.5, m/z (M$^+$1): 309.76

tert-Butyl-2[(4-chlorobenzylidene)-amino]-2-methyl-3-phenylpropionate  (R, Entry 6, Table 5)

FT-IR (KBr) cm\textsuperscript{-1}: 1686 (C=O), 1667 (C=NN), 1230 (C-O), 1145 (C-N), \textsuperscript{1}H-NMR (200 MHz, DMSO d\textsubscript{6}) $\delta$: 1.42 (s, 9H, -CH\textsubscript{3}), 1.86 (s, 3H, methyl), 2.67 (s, 2H, methylene), 7.04-7.09 (s, 1H, benzylidene methyne), 7.12-7.15 (m, 9H, aromatic), \textsuperscript{13}C-NMR (50 MHz, DMSO d\textsubscript{6}) $\delta$: 18.4, 27.2, 28.6, 36.8, 68.7, 72.9, 109.2, 114.5, 124.3, 132, 135.6, 143.2, 157.2, 167.3.

tert-Butyl-3-(4-bromo-phenyl)-2-[4-chlorobenzylidene]-amino]-2-methyl propionate  (R, Entry 12, Table 5)

FT-IR (KBr) cm\textsuperscript{-1}: 1722 (C=O), 1660 (C=NN), 1225 (C-O), 1145 (C-N), \textsuperscript{1}H-NMR (200 MHz, DMSO d\textsubscript{6}) $\delta$: 1.40 (s, 9H, methyl), 1.55 (s, 3H, methyl), 3.42 (s, 2H, methylene), 7.08 (d, 2H, $J$=8.64 Hz, benzyl aromatic), 7.37 (d, 2H, $J$= 7.9 Hz, benzyl aromatic), 7.44 (d, 2H, $J$= 6.7 Hz, 4-Cl-aromatic) 7.72 (d, 2H, $J$= 6.4 Hz, 4-Cl- aromatic), 8.12 (s, 1H, methyne), \textsuperscript{13}C-NMR (50 MHz, DMSO d\textsubscript{6}) $\delta$: 20.2, 28.9, 42.5, 67.4, 73.6, 120.2, 129.0, 130.4, 130.8,
131.9, 135.4, 136.8, 137.1, 163.7, 175.8; m/z [M+]=438.27; Element. Analysis for
C₇H₅NO₂BrCl Calc. C, 57.75; H, 5.31; N, 3.21; Found C, 56.97; H, 5.15; N, 3.10.

tert-Butyl-2-[(4-chlorobenzylidene)-amino]-2-methyl-pent-4-ynoic acid (R,
Entry 16, Table 5)

FT-IR (KBr) cm⁻¹: 1723 (C=O), 1650 (C=N), 1230 (C=O), 1125 (C=N); ¹H-NMR
(200 MHz, DMSO d⁶) δ: 1.42 (s, 9H, -CH₂), 1.88 (s, 3H, methyl), 2.25 (s, 1H, methyne), 7.15-7.24 (m, 4H, aromatic), 8.40 (s, 1H, benzylidene methyne) ¹³C-NMR (50 MHz, DMSO d⁶) δ: 14.2, 27.2, 47.3, 63.2, 127.4, 129.4, 130.4, 165.6, 182.1.

tert-Butyl-2[(4-chloro-benzylidene)-amino]-2,3-diethyl-butyric acid (R, Entry
19, Table 5)

FT-IR (KBr) cm⁻¹: 1725 (C=O), 1650 (C=N), 1225 (C=O), 1160 (C=N); ¹H-NMR (200 MHz, DMSO d⁶) δ: 1.22 (s, 9H, methyl), 1.44 (d, 6H, J=8.0 Hz), 1.65 (s, 3H, methyl), 2.25 (s, 1H, methyne), 3.40 (m, 2H, methylene), 7.10-7.32 (m, 4H, aromatic), 8.56 (s, 1H, benzylidene methyne) ¹³C-NMR (50 MHz, DMSO d⁶) δ: 12.5, 17.3, 27.9, 32.4, 72.4, 76.5, 129.5, 132.4, 136.8, 138.9, 163.2, 185.2; m/z (M⁺): 310.5; C₁₂H₁₄ClNO₂: Calc. value: C, 65.90; H, 7.79; N, 4.55; Found: C, 65.44; H, 8.12; N, 4.17.
5.2.4. ENANTIOSELECTIVE SYNTHESIS OF N-ARYLAZIRIDINES USING CMPTCs

The induction of chirality in achiral aziridines using chiral multi-site phase transfer catalysts (CMPTC) is an attractive field due to its simplicity, high yield, enantioselectivity, economy and environmentally benign nature. This section of the discussion describes the synthesis of enantioselective N-arylaaziridines with improved yield and ee using the cinchonine/cinchonidine derived best 20 different CMPTCs observed from the preceding studies such as single-site (45, 46, 48 and 49), di-site obtained from m-xylene (61a, 61b, 62a, 62b) and p-xylene (67a, 67b, 68a, 68b), tri-site (71a, 71b, 72a, 72b) and tetra-site with spacer chain (81a, 81b, 82a, 82b). Further, again it is our interest to examine the efficiency among these chosen CMPTCs containing both C9 free -OH and C9 (O) protected in catalyzing the synthesis of aziridination reactions and also compare the catalytic efficiency in terms of yield/ee with existing methods reported in literature.

In order to examine the catalytic efficiency of these chosen 20 different CMPTCs, they were studied individually to effect the aziridination of different hydroxamic acids 1 with several olefins 2 in a biphasic system using various solvents in the presence of 10-30% aqueous base Scheme 1. The formation of aziridine derivatives 3 obtained in each CMPTCs under identical conditions were confirmed by ^1H-NMR, ^13C-NMR and mass spectra. The absolute configurations of the N-aryl aziridine derivatives were measured by chiral HPLC and ^1H-NMR (using (tris[3-(heptafluoropropyl)-hydroxymethylene]-d-camphorato]europium(III) as a chiral shift reagent) analyses. Eventhough, its success was known based on the chemical yield and the degree of enantioselection one should consider a variety of
parameters such as (i) the structure of the CMPTC; (ii) the nature of the electrophiles (steric and electronic); (iii) the structure of the nucleophile; (iv) ion-pair interaction formed between the catalysts and with anions of substrate (v) the inorganic base and its metal cation and the concentration used to accelerate the CPTCs. We examined all these factors in our study and also deduced an optimized reaction condition for the maximum production of aziridination yield and ee’s by adjusting the reaction variables using different commercially available hydroxamic acids with various acrylate olefins as substrates.

![Scheme 1](image)

5.2.4.L The proposed mechanism for the enantioselective aziridination of hydroxamic acids with various olefins under CMPTC conditions

In order to explain the detailed aspects of the obtained results specifically on increased/decreased aziridination yield/ee with respect to different CMPTCs, the reaction mechanism is first examined, to understand the formation of chiral aziridination products from hydroxamic acids and acrylate olefins. It is possible that the formation of aziridine products proceed via an interfacial mechanism. The various steps involved in the reaction may be as follows: (i) initially, the hydroxamic acid is deprotonated by the base to form an active intermediate of acyloxy anion (4), at the aqueous or organic interface (ii) the intermediate undergoes
rearrangement to produce two active intermediates viz., amide anion (5) and N-acyloxy anion (6); (iii) the active amide anion undergoes further rearrangement to a more stable intermediate of N-acyloxy anion (6) (iv) the movement of this anion (N-acyloxy anion) from the interface to the bulk organic phase followed by ion-pairing with the active-site viz., cation (R4N+) of the respective CMPTC (v) finally, there is also an electrostatic attraction between the acrylate olefin with the existing ion-pair of R4N+ with N-acyloxy anion and that leads to the production of aziridine; (vi) though, there is a formation of intermediate an epoxide, but that possibility is not that much favoured, hence we are not considered that intermediate for the aziridination reaction.

![Scheme 2](image-url)
A similar mechanism was proposed by Pereira et al.\textsuperscript{22} and Boche et al.\textsuperscript{23} for the synthesis of oxyaziridines; wherein the isomerization of O-acyl derivative 4 was proposed on heating with triethylamine followed by the formation of various thermodynamically favorable intermediates from the hydroxamic acid viz., N-acyloxy, O-acyloxy, epoxide and amide, and oxaziridine which in turn undergoes electrostatic attraction with R,N\textsuperscript{+} of the respective catalyst followed by attraction of olefins and formed the aziridine derivatives.

5.2.4.2. Comparative study focusing the efficiencies among the selected CMPTCs in the aziridination reaction

In order to assess the catalytic efficiency of these selected (superior) CMPTCs in aziridination reactions, they were studied individually under identical reaction conditions taking 5 mM of each of these selected CMPTCs using different substituted hydroxamic acids 1 with different acrylate olefins 2 and 10% aqueous NaOH (5 ml w/v) in toluene (10 ml) medium at -10°C for 5 hrs. The formation of aziridine yields is quantitatively measured by normal weighing method. The enantioselectivities was determined by chiral HPLC analysis of the aziridine derivatives 3. The formation of aziridine derivatives is confirmed by various spectral techniques such as FT-IR, \textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR and mass analysis respectively. The obtained product results are presented in table 1. The consolidated
product analysis result reveals that the yield and ee strongly depend on number of catalytic-sites in each of the CMPTC’s (Table 1). Further, here too irrespective of CMPTCs, i.e whether it is cinchonine/cinchonidine derived one or CMPTC with C9 free -OH or C9 (0) protected either by tosylation/allylation were all found to influence directly the chemical yield and ee. Furthermore, the results (entries 1-20, Table 1) also suggest that the percentage of product yield and ee for the CMPTCs containing C9 free -OH CMPTCs (entries 1-5 and 11-15, Table 1) were found almost similar and were observed in the range of = 75 to 91% (yield) and 75 to 90% (ee’s) respectively. Similarly, in the case of C9 (0) protected CMPTCs derived from both cinchonine and cinchonidine (entries 6-10 and 16-20, Table 1), the reactions were found to proceed more effectively than their corresponding C9 free -OH CMPTCs. That is, irrespective of cinchonine/cinchonidine the C9 (O) protected CMPTCs produced a higher chemical yield in the range of 89 to 97% and higher enantiomeric excess in the range of 90 to 99%. The formation of yield and ee depends on the stereochemistry/molecular assembly between the CMPTCs and substrates.
Table 1. The comparative results of aziridination obtained using selected CMPTC’s

<table>
<thead>
<tr>
<th>Entry</th>
<th>SPTC/CMPTC</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Absolute Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C9 free -OH cinchonine derived CMPTCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>82</td>
<td>75</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>61a</td>
<td>89</td>
<td>92</td>
<td>R</td>
</tr>
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<td>3</td>
<td>67a</td>
<td>81</td>
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<td>R</td>
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<tr>
<td>5</td>
<td>81a</td>
<td>75</td>
<td>83</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C9(0) protected cinchonine derived CMPTCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>46*</td>
<td>84</td>
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<td>R</td>
</tr>
<tr>
<td>7</td>
<td>61b</td>
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<td>89</td>
<td>94</td>
<td>R</td>
</tr>
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<td></td>
<td></td>
<td>C9 free -OH cinchonidine derived CMPTCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>79</td>
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<td>83</td>
<td>S</td>
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<td>14</td>
<td>72a</td>
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<td>90</td>
<td>S</td>
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<tr>
<td>15</td>
<td>82a</td>
<td>82</td>
<td>85</td>
<td>S</td>
</tr>
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<td></td>
<td></td>
<td>C9(0) protected cinchonidine derived CMPTCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>49*</td>
<td>79</td>
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<td>17</td>
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<tr>
<td>19</td>
<td>72b</td>
<td>93</td>
<td>96</td>
<td>S</td>
</tr>
<tr>
<td>20</td>
<td>82b</td>
<td>90</td>
<td>96</td>
<td>S</td>
</tr>
</tbody>
</table>

*Tosylated CPTCs
5.2.4.2.1. The role of Stereochemistry /Molecular assembly for the formation of higher/lower yield and ee of chiral aziridine derivatives

The obtained results indicated that the stereochemical course of the aziridination mainly depends on the stereochemistry/molecular assembly between the substrates such as N-phenyl-N-hydroxamic acid derivatives 1 and different electron deficient olefins 2 and with selected CMPTC’s. The formation of higher aziridination yield (entries 6-10, 16-20, Table 1) and its ee’s of each reaction catalyzed by C9 (O) protected CMPTCs would be mainly attributed to an effective contact of ion-pair formed between the positive quaternary onium ions (R4N+) of the respective CMPTC’s with N-acyloxy anion due to electrostatic attraction and also the same attraction between the R4N+ of the respective CMPTC’s with n bond present in a (3-carbons of the acrylate olefin 2 (Figure I-III). The results also suggested that apart from the ionic interaction between the catalyst and substrates, there is also a stacking interaction between the benzyl group of the respective C9 (O) protected CMPTC with aryl group of the hydroxamic acid which would further facilitate the binding of the two species (Figure III, e). This in turn shows to facilitate effective ion-pair interaction and thus effect for parallel increasing of yield and ee then their corresponding CMPTCs containing C9 free -OH. While the decreased aziridination product yield and ee’s noticed in C9 free -OH irrespective of cinchonine/cinchonidine CMPTCs (entries 1-5, 11-15, Table 1) are due to the formation of the hydrogen bond between the reactants (6 and 2) and the free hydroxyl group present at C9 free -OH position of the CMPTCs (Figure I, a & b)). Because of this hydrogen bond formation the yield and ee are found to be less. A similar observation is reported on O-acryloyl derivative wherein the C9 (O) is protected (Figure II, c & d). Here also the mechanistic considerations are the same namely the prevention of hydrogen bonding at C9(O) position of the catalysts.
Figure I. Formation of various intermediates/molecular assemblies during enantioselective aziridinating reaction using C₄ free –OH CMPTCs

Figure II. Formation of various intermediates/molecular assemblies during enantioselective aziridinating reaction using C₄ (O) protected CMPTCs
Figure III. Formation of $\pi$-$\pi$ interaction between the spacer chain (aromatic) of all the CMPTCs with aromatic ring of the N-acyloxy anion of the hydroxamic acid

5.2.42.2. ASSESSMENT OF SUPERIORITY OF THE CMPTCS

CONTAINING $C_9$ FREE - Oil AND $C_9$(O) PROTECTED

S.2.4.2.2.1. Among the single-site CPTCs

Further, to the best of our knowledge there is no report available for $C_9$(O) tosylated and N-substitution of 3-formyl-5-methyl-2-hydroxybenzyl cinchona derived compound as a single-site CPTC’s. The reaction yield and ee’s for the reaction catalysed by single-site viz., tosylated CPTCs such as 46 and 49 were proved to be more effective for all the aziridination reactions and thus produced higher amount of yield and ee (entries 6 and 16, Table 1) than with their $C_9$ free - OH catalysts 45 and 48 (entries 1, 16, Table 1). This is because, since the free -OH
pient in C9 position of catalyst (45 and 48) has been derivatized as a tosylate and as a result, it facilitates the formation of N-arylated aziridine and its ee’s. Particularly, the tosylation leads to prevent the formation of hydrogen bond between the catalysts and anions of olefins and N-acyloxy derivatives. Further, the other possibility of hydrogen bonding between the free -OH present in the phenol moiety of the catalyst and N-acyloxy anion or carbonyl oxygen (olefin) may also be ignored due to intramolecular hydrogen bonding with the adjacent formyl group (Figure IV). Therefore, the a and (3-carbons of the olefinic double bond and N-acyloxy anion are freely brought closer towards (in bonding distance) R,N’ site of catalyst 46 and 49 through electrostatic attraction of t-bond and ion-pair formation respectively and also the n-% stacking between the spacer chain of the aromatic moiety of the CMPTCs and aromatic ring of the hydroxamic acid. The formation of R and S isomers of aziridine derivatives would solely depend on chiral taster between substrate and nature of the catalysts.

**Figure IV.** Intramolecular hydrogen bonding between the phenolic -OH of the benzyl moiety of the spacer chain and adjacent group of aldehyde in SCPTC (45-49).
5.2.4.2.2=2. Among the other CMPTCs

The comparative efficiencies among the selected C₉ (O) protected CMPTCs were found in the order of di-site (m-xylene based) > tetra-site > tri-site > single-site > di-site (y-xylene based) i.e., Among these C₉ (O) protected CMPTCs, the di-site derived from m-xylene irrespective of cinchonine/cinchonidine (61b and 62b) as a chiral precursor are observed to be superior to any other C₉ (O) protected CMPTCs. The reasons are already described in the discussion on alkylation of ketimine (page No. 223). That is, AW-xylene derived di-site CMPTCs, the R₄N⁺ groups present in the catalysts simultaneously influence the reaction since they are spatially positioned effectively interact with the substrate and thus facilitate strong ion-pairing formation between the R₄N⁺ of the catalysts and substrates. Generally, as per as aziridination reaction is concerned, there are three possible ways for the ion-pair formation and one possibility for π-π stacking interaction. That is, R₄N⁺ of the CMPTCs forms ion-pair with (i) N-acyloxy anion; (ii) with γ-bond of α and P carbon of the acrylate olefins; (iii) with enolate of the olefinic substrate. Additionally, the π-π stacking interaction is also possible between the styryl ring of the CMPTC with aromatic ring of the N-acyloxy anion which in turn facilitate to bring the substrate closer to CMPTCs. All these processes i.e, the electrostatic process (i, ii and iii) as well as π-π stacking interaction (hydrophobic attraction) should co-operatively favor in the reaction and a higher yield and ee for 61b and 62b (figure V, a & b)) than with any other CMPTCs.
Figure Va. Effective ion-pair contact between the R, N⁺ of the CMPTCs (61b & 62b) with anion of the substrate by co-operative influence due to close spatial fixing arrangement of two cationic moieties.

Figure Vb. π-π Stacking interaction (hydrophobic attraction) between the aromatic ring of the N-acyloxy anion with styryl aromatic ring of the CMPTCs (61b & 62b).

The lower yield and ee in presence of other CMPTCs such as p-xylene derived di-site, tri-site and tetra-site with spacer chain is due to the following...
reasons. The product yield and ee results reveals that even though the ionic forces of attraction between these CMPTCs with substrate (i & ii) and \( \gamma \)-\( \eta \) interactions\(^5\) between the spacer group of the respective catalysts with aromatic ring of the N-acyloxy anions are facilitating the binding of the CMPTCs with substrates, but because of poor molecular orientation we have found lower yield and ee than with the \( \beta / \beta \)-xylene derived CMPTCs. Especially, in \( p \)-xylene derived di-site CMPTCs, the positions of the two active sites are just opposite to each other as we mentioned earlier (refer page No. 230); hence these two active-sites are not involved in the reaction cooperatively. Similarly, although the tetra-site CMPTC with spacer chain and tri-site CMPTC contains 4 and 3 active-sites respectively in a molecule, but the yield and ee's were found to be low when compared with \( m \)-xylene di-site CMPTCs irrespective of cinchonine/cinchonidine. For this too, we have already highlighted the reasons in the previous (enantioselective synthesis of amino acid) discussions under the title of “No bond resonance”.

5.2.4.2.3. Optimization of N-aryl aziridination reaction

In order to establish a conducive reaction condition for the effective synthesis of aziridination reaction, we have decided to conduct the reaction under biphase condition using the superior CMPTCs viz., \( m \)-xylene based di-site CMPTC derived from cinchonine 61b as a test catalyst. The other experimental parameters such as base, solvent, temperature have been suitably varied and determined by conducting the elaborate studies on these variables. Similarly, we have also carried
out the aziridination reaction by changing the different olefins with the purpose to selecting the efficient olefins for effective reaction and better yield. Similarly, it is also our interest to examine the substitutional effect of both hydroxamic acid as well as acrylate olefins to know their individual influence on the chemical yield and ee.

5.2A2.3.1. The effect of different olefins on the aziridination reaction

The aziridination reaction was carried out in the presence of different olefins with hydroxamic acids under identical and biphasic experimental conditions keeping the other variables as constant. This study gives interesting results (Table 2) and observations. In fact, we observed that both enantioselectivity as well as yields were found to be sensitive for changing the functionality of olefins. Among the four different olefins, the /-butyl acrylate 2a was found to undergo the aziridination reaction more rapidly than the other olefins in the presence of 61b, giving a the higher yield (79%) and ee (94%). The order of chemical yield and optical induction were found to increase with increasing bulkiness of the ester group\textsuperscript{20} i.e Me < Et < i-Pr < t-Bu (entries 1-4, Table 2). Hence, it is decided to carry out all the aziridination reactions using /-butylacrylate olefin. The olefins containing -CO<sub>2</sub>Me (entry 2a, table 2) do not not effectively undergoes the aziridination reaction. In contrast, there is a drastic reduction in chemical yield (35%) and ee (43%).
Table 2. Enantioselective aziridination of various olefins 2 with hydroxamic acid 1

![Diagram of aziridination reaction]

<table>
<thead>
<tr>
<th>Entry</th>
<th>EWG</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
<th>Abs.</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>-CO₂ Me</td>
<td>35</td>
<td>43</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>-CO₂ Et</td>
<td>52</td>
<td>67</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>-CO₂ i-Pr</td>
<td>64</td>
<td>79</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>-CO₂ t-Bu</td>
<td>79</td>
<td>94</td>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

5.2.4.2.3.2. Effect of base and its concentration on aziridination reaction

We have conducted the aziridination reaction using different inorganic bases viz., NaOH, KOH, LiOH, K₂CO₃ and Ca(OH)₂ individually at different concentrations ranging from 10%-30% (w/v) keeping the other parameters as constant in toluene medium to examine the effect of chemical yield and ee’s. The obtained results reveal that the change of bases and their corresponding concentration had been remarkably influenced in the aziridination reactions (entries 1-12, Table 3). For example, the aziridine yield and ee’s obtained in the presence of NaOH are found to be higher than the other bases like KOH, K₂CO₃ and Ca(OH)₂ irrespective of the concentration. The formation of higher chemical yield and ee’s are strongly dependent on the concentration of aqueous base also. Particularly, irrespective of base, the low concentration (10%) gives the higher yield and ee. Especially, among the 10% (w/v) solution of various bases, the NaOH solution is high molar concentration than the other bases such as KOH, K₂CO₃ and Ca(OH)₂. Hence, NaOH facilitate the reaction with higher yield and ee due to relatively
higher availability of OH. In the case of high concentration (30 %) irrespective of base the yield and ee's were found to be less. Even for a strong base like NaOH at high concentration we observed a drastic reduction in the chemical yield and ee. This may probably be due to the decomposition of CMPTC. Similar results have been reported for C- and O-alkylations of C-benzyl and benzyl ethers respectively using tetrabutylammonium hydrogen sulfate as a soluble phase transfer catalyst.

Table 3. Effect of base and its concentration on the aziridination reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aqueous Base (%) (w/v)</th>
<th>Conc. (%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH</td>
<td>10</td>
<td>84</td>
<td>95</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>NaOH</td>
<td>20</td>
<td>75</td>
<td>85</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>NaOH</td>
<td>30</td>
<td>46</td>
<td>73</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>KOH</td>
<td>10</td>
<td>38</td>
<td>28</td>
<td>R</td>
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<tr>
<td>5</td>
<td>KOH</td>
<td>20</td>
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<td>18</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>KOH</td>
<td>30</td>
<td>24</td>
<td>15</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃</td>
<td>10</td>
<td>41</td>
<td>31</td>
<td>R</td>
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<tr>
<td>8</td>
<td>K₂CO₃</td>
<td>20</td>
<td>32</td>
<td>25</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>K₂CO₃</td>
<td>30</td>
<td>25</td>
<td>22</td>
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<tr>
<td>12</td>
<td>Ca(OH)₂</td>
<td>30</td>
<td>08</td>
<td>09</td>
<td>R</td>
</tr>
</tbody>
</table>
S.2.4.2.3.3. Effect of solvents on aziridination reaction under CMPTC condition

Enantioselective aziridination reaction was carried out in different non-aqueous solvents using test CMPTC 61b under biphasic condition keeping the other variables as constant. From the obtained results (Table 4), it is seen that the change of solvent is found to be an important influential factor in the aziridination reaction owing to solvent polarity. The chemical yield and ee’s have been found to increase gradually in the order DMF < acetonitrile < methanol < ethanol < dichloromethane < diethylether < toluene-dichloromethane < benzene < toluene. The results obtained with various solvents have been related to their dielectric constants. The decreased product yield/ee’s in high polar solvents like DMF, acetonitrile, ethanol, methanol, diethylether, CH₂Cl₂ etc. and non polar solvent like benzene may be due to the higher degree of solvation of CMPTC’s, which in turn decreases the efficiency of the catalyst. That is, most probably the high polar solvents should reduce the ionic interaction between the catalyst and the anionic aziridinating agents reducing the yield and ee. In the case of toluene, which is a low polar solvent, the degree of solvation of CMPTC’s is considerably less. Hence, the degree of decay due to solvation of CMPTC’s of the catalyst is almost minimized/ignored. Otherwise, the interaction between R₄N⁺ of the catalyst and anion of the aziridinating agent is more. This in turn improves the potential of the catalyst as well as effective attraction of the substrate and catalyst and hence the reaction yield and ee’s were
found to be higher in toluene medium. Similar observation was already reported by Sundaresan Prabhakar et al, Hughes et al, and O’Donnell et al for the synthesis of enantioselective N-arylaziridines in toluene medium under Camphor-based chiral catalysts.

Table 4. The effect of solvents on chemical yield and ee’s in aziridination reactions in presence of CMPTC 61b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>( \varepsilon ) (Dielectric constant)</th>
<th>Yield (%)</th>
<th>E.e (%)</th>
<th>Abs.config</th>
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<tr>
<td>1</td>
<td>Toluene</td>
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<td>94</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>Benzene</td>
<td>4.20</td>
<td>56</td>
<td>58</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>Diethyl ether</td>
<td>4.30</td>
<td>47</td>
<td>42</td>
<td>R</td>
</tr>
<tr>
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<td>Dichloromethane</td>
<td>10.40</td>
<td>37</td>
<td>53</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>Methanol</td>
<td>32.70</td>
<td>34</td>
<td>51</td>
<td>R</td>
</tr>
<tr>
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<td>Ethanol</td>
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<td>36</td>
<td>58</td>
<td>R</td>
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<td>Acetonitrile</td>
<td>37.50</td>
<td>29</td>
<td>19</td>
<td>R</td>
</tr>
<tr>
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<td>DMF</td>
<td>42.00</td>
<td>22</td>
<td>14</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>Toluene-CH2Cl2 (4:1, v/v)</td>
<td>-</td>
<td>56</td>
<td>52</td>
<td>R</td>
</tr>
</tbody>
</table>
5.2.4.2.3.4. Effect of temperature

In order to study the effect of temperature, we have carried out the aziridination reaction at various temperatures ranging from 30 °C to -25 °C. The observed results indicate that the optimum temperature for effective aziridination yield and ee is -10 °C, (entries 1-8, Table 5). When the temperature is increased, there is no influence in the chemical yield and ee’s (entries 1-3, Table 5) and on further decrease of temperature i.e below -10 °C, the yield of azidine and ee does not improve (entries 6-8, Table 5). It is known that if any reaction proceeds effectively at higher temperature meaning that the reaction is normally thermodynamically favourable. Whereas, in this case, the aziridination reaction is found to proceed even at low temperature shows that the reaction is not thermodynamically controlled.

Table 4. The effect of temperature on chemical yield and ee’s in aziridination reactions in presence of CMPTC 61b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<tbody>
<tr>
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<td>5</td>
<td>76</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
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<td>74</td>
<td>44</td>
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<tr>
<td>3</td>
<td>10</td>
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<td>74</td>
<td>45</td>
</tr>
<tr>
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<td>0</td>
<td>5</td>
<td>82</td>
<td>85</td>
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<tr>
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<td>-10</td>
<td>2</td>
<td>96</td>
<td>97</td>
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<td>6</td>
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<td>76</td>
</tr>
<tr>
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<td>-25</td>
<td>5</td>
<td>60</td>
<td>59</td>
</tr>
</tbody>
</table>
5.2.4.2a. The influence of substitutional group present in hydroxamic acid on aziridination reaction under CMPTC condition

The increased/decreased chemical yields/ee’s of the reactions are mainly due to the presence of electron donating/withdrawing group on the JVN-aromatic moiety of the hydroxamic acid 1. We have carried out the reaction by taking different substitutional hydroxamic acids under identical reaction conditions maintaining other parameters as constant. It is clear from the results (Table 6) that the aziridines yield and ee’s are found to be more in the case of substrates having electron-donating group present in the aromatic ring (entries 6,7, Table 6). This is probably may due to a greater tendency for the formation of N-acyloxy anion. In contrast, when electron-withdrawing groups are present in A-f-aromatic moiety (entries 2-5, Table 6), the yield and ee’s are found to be lower except for the 4-chloro benzyl derivatives (entry 2, Table 6).
Table 6. The effect of substitution on chemical yield and ee’s in aziridination reactions in presence of CPTC 61b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxamic acid</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>3-Br</td>
<td>82</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>4-Br</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>4-N0₂</td>
<td>68</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>4-OMe</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>4-OEt</td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>4-Me</td>
<td>83</td>
<td>95</td>
</tr>
</tbody>
</table>

\[
\text{HO}_{2}\text{C}-\text{Bu} + \text{CO}_2\text{f-Bu} \xrightarrow{\text{61b (10 mM) NaOH/}\text{Tollene} \cdot \text{HCl}} \text{COO}^-\text{Bu}
\]
5.2.4.2.3.6. CHARACTERIZATION OF N-ARYLAZIRIDINE DERIVATIVES

tert-Butyl-1-phenyl-aziridine-2-carboxylate (Table 6, Entry 1)

The product was purified by silica gel column chromatography using hexane/EtOAc (90:10) as an eluent; yield: 80%; mp 125.5-126.5°C; FT-IR (KBr) cm⁻¹: 1178, 1460, 1720, 3100; ¹H NMR δ: 1.40 (s, 9H), 1.96 (d, 2H, J=7.2 Hz), 2.42 (t, 1H), 6.58-7.08 (m, 5H); ¹³C NMR δ: 29.1, 29.8, 43.2, 73.4, 113.3, 118.6, 129.4, 144.2, 172.4; m/z = 220.10; Anal. calc'd for C₁₃H₁₇NO: C, 71.14; H, 7.76; N, 6.38; found: C, 71.13; H, 7.76; N, 6.36.

tert-Butyl-1-(4-chlorophenyl)aziridine-2-carboxylate (Table 6, Entry 2)

The product was purified by column chromatography on silica gel using hexane/EtOAc (90:10) as eluent; yield: 87%; yellow oil; [α]D²⁰ +20 (c=0.87, CH₂Cl₂); FT-IR (KBr) cm⁻¹: 1174, 1470, 1710, 3090; ¹H NMR δ: 1.40 (s, 9H), 1.92-2.95 (m, 2H), 2.42-2.44 (m, 1H), 6.53-6.56 (m, 2H), 7.05-7.13 (m, 2H); ¹³C NMR δ: 28.4, 29.6, 43.7, 73.6, 112.4, 114.5, 129.9, 142.6, 175.3; m/z = 253.09; Anal. calc'd for C₁₃H₁₅ClNO₂: C, 61.49; H, 6.31; N 5.52; found: C, 61.47; H, 6.31; N, 5.50.

tert-Butyl-1-(3-bromophenyl)aziridine-2-carboxylate (Table 5, Entry 3)

The product was purified by column chromatography on silica gel using hexane/EtOAc (90:10) as eluent; yield: 82%; yellow oil; [α]D²⁰ +20 (c=0.80, CH₂Cl₂); ¹H NMR δ: 1.41 (s, 9H), 2.4 (t, 1H, J=5.2 Hz), 1.96 (d, 2H, J=7.3 Hz), 6.53-6.56 (m, 1H), 6.76-6.79 (m, 2H),
6.96-6.99 (m, 1H), 13C NMR δ: 29.1, 29.8, 43.2, 73.3, 112.2, 116.4, 121.3, 124.1, 131.7, 146.7, 172.0; m/z = 297.04; Anal. calc'd for C13H14BrNO2: C, 52.36; H, 5.41; N, 4.70; found: C, 52.35; H, 5.39; N, 4.70.

tert-Butyl-1-(4-bromophenyl)aziridine-2-carboxylate (Table 6, Entry 4)

The product was purified by column chromatography on silica gel using hexane/EtOAc (90:10) as eluent; yield: 70%; yellow oil; [α]20 ^2 = 0.87, (CH2Cl2); FT-IR (KBr) cm⁻¹: 1175, 1474, 1720, 3095; 1H NMR δ: 1.42 (s, 9H), 1.92-1.95 (m, 2H), 2.42-2.45 (m, 1H), 6.53-6.59 (m, 2H), 7.15-7.22 (m, 2H); 13C NMR δ: 26.5, 27.5, 43.8, 73.5, 112.2, 114.5, 129.9, 141.6, 175.3; m/z = 296.87; Anal. calc'd for C13H14BrNO2: C, 52.36; H, 5.41; N, 4.70; found: C, 52.30; H, 5.28; N, 4.66.

tert-Butyl-1-(4-nitrophenyl)aziridine-2-carboxylate (Table 6, Entry 5)

The product was purified by column chromatography on silica gel using hexane/EtOAc (90:10) as eluent; yield: 90%; [α]20 ^20 = 20 (c=0.86, CH2Cl2); 1H NMR δ: 1.38 (s, 9H), 1.89-1.93 (m, 2H), 2.42-2.50 (m, 1H), 6.85 (dd, 2H, J=4.8 Hz), 8.00-8.11 (dd, J=4.8 Hz); 13C NMR δ: 28.7, 29.6, 44.1, 73.7, 114.0, 124.5, 137.2, 151.5, 175.7; m/z = 265.07; Anal. calc'd for C13H14N2O4: C, 59.08; H, 6.10; N, 10.60; found: C, 59.10; H, 6.08; N, 10.58.
tert-Butyl-1-(4-methoxyphenyl)aziridine-2-carboxylate (Table 6, Entry 6)

The product was purified by column chromatography on silica gel using hexane/EtOAc (90:10) as eluent; yield: 86%; [α]D + 20 (c=0.84, CH2Cl2); yellowish oil. FT-IR (KBr) cm⁻¹: 1170, 1465, 1715, 3080; ¹H NMR δ: 1.38 (s, 9H), 1.93-1.95 (m, 2H), 2.44 (t, 1H), 3.74 (s, 3H), 6.47-6.50 (m, 2H), 6.57-6.60 (m, 2H); ¹³C NMR δ: 28.7, 29.9, 43.6, 56.0, 73.8, 114.3, 115.1, 136.8, 151.6, 172.6; m/z = 251.15; Anal. calcd for C₉H₁₂O₃N: C, 67.46; H, 7.64; N, 5.62; found: C, 67.45; H, 7.63; N, 5.61.

tert-Butyl-1-(4-ethoxyphenyl)aziridine-2-carboxylate (Table 6, Entry 7)

The product was purified by column chromatography on silica gel using hexane/EtOAc (90:10) as eluent; yield: 86%; [α]D + 26 (c=0.84, CH2Cl2); yellowish oil. FT-IR (KBr) cm⁻¹: 1170, 1467, 1718, 3082; ¹H NMR δ: 1.39 (s, 9H), 1.93-1.97 (m, 2H), 2.42 (t, 1H), 2.85 (q, 2H), 3.75 (t, 3H), 6.47-6.50 (m, 2H), 6.57-6.60 (m, 2H); ¹³C NMR δ: 22.7, 26.6, 42.5, 55.2, 59.3, 73.8, 113.3, 112.4, 136.8, 152.6, 172.6; m/z = 263.15; Anal. calcd for C₁₀H₁₃O₃N: C, 68.42; H, 8.04; N, 5.32; found: C, 68.10; H, 7.85; N, 5.27.

tert-butyl-1-(p-tolyl)aziridine-2-carboxylate (Table 6, Entry 8)

The product was purified by column chromatography on silica gel using hexane/EtOAc (90:10) as eluent; yield: 83%; yellow oil; ¹H NMR δ: 1.94-1.99 (m, 9H), 2.36 (s, 2H), 2.45 (m, 1H), 3.65 (s, 3H), 6.50-6.57 (m,
$^2$H), 6.86-8.92 (m, 2H); $^{13}$C NMR $\delta$: 20.2, 29.5, 42.5, 51.2, 112.4, 127.2, 131.3, 142.6, 172.4; m/z = 233.31; Anal calcd for C$_{14}$H$_{18}$NO$_3$: C, 72.02; H, 8.21; N, 6.00; found: C, 71.85; H, 8.01; N, 5.79.
References


18. (a) T. Ooi, E. Tayama, K. Doda, M. Takeuchi, K. Maruoka, *Synlett* 1500 (2000);


