Chapter I

Introduction
INTRODUCTION

The concept of “catalysis” is acclaimed as a method of controlling the rate and direction of a chemical reaction since it is introduced by Berzelius\(^1\) in 1835. It coordinated a number of disparate observations on chemical transformations by attributing them to a “catalytic force” and coined the term catalysis to refer to the ‘decomposition of bodies\(^3\) by this force. Now-a-days, “catalysts” are considered to be indispensable components for the majority of chemical reactions. As enzymes, they regulate an array of transformations within natural organisms from single cells to man. Researchers employed catalysts as supports for our daily lives starting with manufacture of fuels\(^2\), clothing\(^3\), plastic goods\(^4\), fertilizers\(^5\) and medicines\(^6\). Hence, “catalysis” is well described as the cornerstone of all chemical processes. Around 80% of all chemicals rely on catalysts of one kind or other during their synthesis.

In general, catalysts are conveniently divided into two groups, homogeneous and heterogeneous, according to whether or not the reactant and products share the same phase as the catalyst. Homogeneous catalysis provides mild and selective routes for the synthesis of valuable chemicals from simple organic precursors. But the catalysts are more sensitive to air and moisture. In addition, the catalysts are difficult to separate from the products. These problems are avoided by employing heterogeneous catalysts, and hence these catalysts have acquired more fascination among catalyst researchers. Although, numerous catalysts are available to accelerate various reactions, chemists find inconvenience to carry out immiscible substrate reaction. For example, the reaction between 1-chlorooctane with sodium cyanide\(^7\) could not proceed even after a long reaction time owing to the existence of two different immiscible aqueous/organic phases.
Normally for any type of organic reaction, it is a necessary condition to cause the perfect collision between the two reactants to get the desired product. The immiscible substrate reaction are normally very slow (due to some practical difficulties). This is particularly due to the sparingly soluble substrate in the biphasic media. There are variety of techniques available to circumvent this problem via., increasing the agitation rate, using cosolvents, such as alcohol or methanol etc. Increasing the agitation rates in any chemical reaction involves loss of mechanical/electrical energies. Similarly using cosolvents also decrease the rate of the reaction due to the hydrogen bonded with the substrates or catalyst. As a remedial measure, researchers have used aprotic solvents, such as dimethylsulfoxide, dimethyl formamide, hexamethylphosphoramide and acetonitrile, to carry those immiscible substrate reactions. It is observed that the use of cosolvents proceed the reaction without forming hydrogen bond and ultimately increased the rate of the reaction. Unfortunately, this polar aprotic solvent technique also has some disadvantages partially in industrial process; the solvents are expensive and difficult to remove by-products, are often accompanied by the generation of a desired product, requirement of high temperature, anhydrous solvent and are definitely an environmental hazard in large scale operations. In view of all these demerits, researchers/industrialist are not interested to use aprotic solvents also.

LI. PHASE TRANSFER CATALYSIS

Phase transfer catalysis came in to limelight in the mid-1960s and caught attention of many researchers for carrying out a wide class of otherwise slow heterogeneous reactions. Reactions of two substances located in different phases
are often inhibited because of the inability of the reactants to come together. For example, the reaction between 1-chlorooctane with sodium cyanide could not proceed even after allowing quite long time, hence for the first time Jerrouse used phase transfer technique; these immiscible reactions are brought about by the use of an agent which transfers one reactant across the interface into the other phase so that the reaction can proceed. The phase transfer agent is, however, not consumed during the course of the reaction but performs the transport duty repeatedly. The component that is responsible for transfer of reactant from aqueous to organic is called “Phase-transfer catalyst” and the whole process is said to be “Phase-transfer catalysis” (PTC).

In performing a phase-transfer reaction; the choice of a suitable catalyst plays a pivotal role. For any phase transfer catalyzed technique, the three factors are paramount importance; the ability of the catalyst to transfer one reagent from its phase into the phase of the second reagent; the reagent once transferred must be available in a highly reactive form and the recycling ability of the catalyst.

1.1.1. EXAMPLES OF PHASE TRANSFER CATALYSTS

Based on the structure of the molecule, the phase transfer catalysts are broadly classified as follows

1. Quaternary ammonium, phosphonium and arsonium ions

   \[ \text{R}_4\text{N}^+\text{X}, \text{R}_4\text{P}^+\text{X}, \text{R}_4\text{As}^+\text{X} \]

   Where R is usually alkyl or benzyl and X refers to the different anions in the catalyst.

2. Macrocyclic (Crown) and macrobicyclic (Cryptate) ethers.

3. Open chain polyether and single chain poly ethers

4. N-alkylphosphoramides

5. Methylene bridged phosphorous and sulfur oxides

Phase transfer catalysts are generally active depending upon the centralonium atoms. Quaternary onium salts are stable up to 150 C in the absence of
alkali and less stable around 70-80°C in the presence of alkali. Now variety of quaternary onium salts can be synthesized and are available commercially for various immiscible substrate reactions. Lower quaternary onium salts are easily recovered than with some higher salts due to its tendency to form stable emulsion. Phosphonium salts are thermally more stable than ammonium salts up to 150-170°C, where as ammonium salts loose their activity rather rapidly at temperature greater than about 110 -120°C.

12. GENERAL MECHANISM FOR THE PHASE TRANSFER CATALYZED REACTION

Liquid-Liquid PTC corresponds to a system made of two phases: an organic phase containing a liquid reagent with (or without) an organic solvent non-miscible in water and an aqueous phase containing in most cases a nucleophilic reagent M’Y’. Moreover a quaternary ammonium or phosphonium catalyst is partitioned between the two phases.

Depending upon the nature of the nucleophile two possibilities exist:

(i) M’Y’ is dissolved directly in water, e.g. Na’CN’, K’F’.

(ii) or M’Y’ is obtained by exchange between a neutral reagent and base,

\[
\text{YH} + \text{MOH} \rightarrow \text{M}^+\text{Y}^- + \text{H}_2\text{O}
\]

e.g. PhCH₂CN + NaOH \rightarrow Na⁺PhCHCN⁻ + H₂O

\[
\text{ROH} + \text{NaOH} \rightarrow \text{Na}^+\text{RO}^- + \text{H}_2\text{O}
\]
1.2.1. CLASSIFICATION OF PHASE TRANSFER CATALYSIS

Phase transfer catalysis can be classified into three different categories based on the physical states of the two phases. They are liquid/liquid, liquid/solid, and gas/solid PTC techniques.

1.2.1.1. Liquid-Liquid Phase transfer catalysis

Liquid-Liquid PTC (LL-PTC) composed of two phases; an organic phase containing a liquid reagent (RX) immiscible with water and an aqueous phase containing a nucleophilic reagent (Nu’) and the quaternary onium catalyst (Q+X’). Starks and Malcosaza reported two different mechanism with best illustration viz., extraction and interfacial mechanism. When sodium cyanide was mixed with octylchloride, no product was observed even after prolonged time, eventhough the former one is soluble in water. But on the introduction of catalytic amount of quaternary ammonium chloride, an exchange occurs in the aqueous phase between Na’CN’ and B114N’Cl’: The ion pair, BimN’Cl’, due to presence of 16 carbons of the quaternary ammonium ion, phase transfers into organic where the reaction take place. According to the interfacial mechanism, a molecule of an organic substrate say phenylacetonitrile (RH) in the organic phase located near the interface is deprotonated by the hydroxide ion which is also available near the interface but within the aqueous phase (step 1). An ion pair [Na+R’] is thus formed at the boundary and as such is insoluble in both the phases. The anchored [Na+R’] remains at the interface until the catalyst cation draws the organic anion deep into the bulk organic phase in the form of new ion pair [QR−]. The quaternary counter ion X’ is simultaneously liberated into the aqueous phase (step 2). Finally, [Q+R’] reacts with alkyl halide substrate R Y to produce the product R-R (step 3) and the [Q’Y−] thus formed may reenter a next catalytic cycle. The interfacial mechanism is shown below;
If a complexant is added, the solid $M^+Y^-$ is solubilized in the solvent and reacts under mild conditions. In a specific example, potassium permanganate is added to a solution of benzene containing an olefin. Under these conditions the crystals of KMn04 stand at the bottom of the flask, the solvent is colourless and no reaction occurs. If a small amount of 18 crown 6 is added, the solvent immediately turns purple (the permanganate dissolves) and the olefin is smoothly oxidized. The complexants first used were the crown ethers, prepared by Pedersen\textsuperscript{35}, which showed high complexing abilities of alkali and alkaline earth cations with the following properties.
a. extraction of cations owing to the selective complexation, which
depends upon the size and the substitution of the macrocyclic ethers\textsuperscript{45}.

b. activation of the anion paired to the complexed cation; the anion is said
to be “naked”\textsuperscript{46}

The chiral host molecules designed by Cram et al\textsuperscript{47} have achieved splendid
results in the separation of enantiomers and open new promises in asymmetric
induction.

Presently the majority of current syntheses are more likely to be carried
out with liquid-liquid transfer conditions, with quaternary ammonium and
phosphonium catalysts. Solid-liquid catalysis using complexants is still hampered
by the high price of catalysts like crown-ethers or cryptants. In some cases, when
water needs to be strictly avoided, reactions are conducted under solid-liquid
conditions, with a quaternary ammonium or phosphonium catalyst (not a
complexant). Moreover, in order to solve the problem of catalyst recovery a new
technique has been proposed.

1.2.1.3. Gas-liquid phase transfer catalysis

Another interesting variant of the two phase catalytic method with great
potential was reported and developed by Tund\textsuperscript{48} and co-workers. GL-PTC
provide a continuous-flow through the molten thermally stable PTCs such as
phosphonium salt crown ether and polyethylene glycol supported on a solid nucleophile without solvent. The GL-PTC technique is the analogy of gas-liquid chromatography. This can be chemically linked with inorganic support. Number of reactions had been carried out following GL-PTC technique, for instance, the synthesis of ethers and thioethers\textsuperscript{51,52}, interconversion of alkyl halides\textsuperscript{53,54}, esterification \textsuperscript{55} and trans-esterification\textsuperscript{56} are very important reactions.

1.2.1.4. Gas-Solid Phase Transfer catalysis (GS-PTC)

Yet another classification of PTC technique is a report of Gas-Solid phase transfer catalysis.\textsuperscript{57} It is indicated that by passing a gaseous alkyl halide over a catalytic column composed of a salt, a solid support and a phase transfer catalyst, a substitution product was obtained. The phase transfer catalyst was either free or immobilised on a silica matrix and thus the synthesis of alkyl iodides and esters were possible. \textsuperscript{58}
1.3. ADVANTAGES OF PHASE TRANSFER CATALYSTS$^{59}$

(i) **Increase** productivity

   (a) Higher the chemical yield
   
   (b) Reduced the cycle time
   
   (c) Reduce or consolidate unit operations
   
   (d) Increase reactor volume efficiency

(ii) Improve environmental performance

   (a) Eliminate, reduce or replace solvent
   
   (b) Reduce non-product output

(iii) Increase quality

   (a) Improve selectivity
   
   (b) Reduce variability

(iv) **Enhance** safety

   (a) Control exotherms
   
   (b) Use less hazardous raw materials

(v) Reduce other **manufacturing** cost

   (a) Eliminate workup unit operation
   
   (b) Use alternate less expensive or easier to handle raw materials

1.4. **TRIPHASE** CATALYSIS

Although, the soluble phase-transfer catalysts are so efficient and much familiar to carry out two-phase reactions particularly for synthesis of speciality chemicals with higher quantum yield, their usage is limited due to various reasons.

The main challenge in designing liquid/liquid industrial PTC process has been the separation of the catalyst from the product. The chemical equilibrium separation of the process which are used in the purification of the product usually consume energy to get a product of a highly purity. In order to overcome this difficulty, Regen and his coworkers$^{60,64}$ proposed a so called "triphase catalysis", in which the catalyst is immobilized on a solid support (organic and inorganic
substances). From the industrial application point of view, this solid supported-catalyst can be easily separated from the final products simply by mechanical separation, such as centrifugation or filtration. In addition, either the plug flow reactor (PFR) or the continuous stirred tank reactor (CSTR) can be used to carry out the triphase catalytic reaction. Several reactions for hydrolysis and displacement were investigated with success. In general, both the organic solid polymer and inorganic solid silica$^{65,66}$ and aluminium oxide$^{67}$ can be used as the support of the triphase catalyst. However, the inorganic solid silica and aluminium oxide fracture easily during the agitation. Solid polymers are commonly used as the support of the triphase catalyst.

1.4.1. **REACTION MECHANISM**

As developed by Regen, the reaction of triphase catalysis is carried out in a three-phase liquid (organic)-solid (catalyst)-liquid (aqueous) system. The reaction process between two immiscible reactants by triphase catalysis in a porous solid pellet may involve as follows (a) mass transfer of reactants from bulk solution to the surface of the catalyst pellet; (b) diffusion of reactants to the interior of the catalyst pellet through pores; (c) surface or intrinsic reaction, of reactants with the active sites of the catalyst pellet; (d) diffusion of products outward to the exterior of the catalyst pellet through pores, and; (e) mass transfer of product to the bulk solution from the surface of the catalytic pellet.

![Diagram](image)

Probably the first pre-mediated and successful use of a polymer-supported phase transfer catalyst was that reported by Regen$^{60,64}$ using polymer-bound
benzyltrialkyl ammonium salts, although the results of investigations by Brown,\textsuperscript{68} using similar species and Montanari, \textsuperscript{70} using supported phosphonium salts, crown ethers and cryptands\textsuperscript{70} in addition, followed quickly afterwards. Regen has suggested the term “Triphase catalysis,” the cross linked polymer being regarded as a distinct third phase. Although this description may not be particularly accurate in the light of emerging experimental results, it does provide a useful qualitative picture and the expression is gaining continued popularly.

If a similar mechanism to the one proposed for unbound catalysts operates in supported system, then it is necessary to imagine the phase boundary existing at the catalytic sites as depicted below,

![Diagram of phase boundary](image)

The process of transporting anions back and forth across the boundary can then occur via local backbone and side chain motion of the catalyst support. This model would predict the efficiency of the catalysis to be improved by increasing the length and hence the flexibility of the linkage between the catalyst and the polymeric backbone by introducing a ‘spacer arm’ and this seems to be so in practice. Number of applications of polymer-supported PTC’s in organic reactions have been reported.\textsuperscript{90,101} This technique has the advantage of homogeneous catalysis owing to the selection of a catalyst having an appropriate molecular structure and heterogeneous catalysis since the catalyst is easily filtered off and recovered after the reaction. However, the rates were often less than most of analogous soluble phase transfer catalysis because of diffusional limitations.\textsuperscript{1,88}
1.5. DIFFERENT TYPES OF MECHANISMS IN PHASE TRANSFER CATALYSIS

Two major mechanisms have been proposed so far to explain the behavior of most phase transfer catalyzed reactions initiated by the hydroxide ion, (PTC/OH- systems) the Stark’s Extraction mechanism and the Makosza’s interfacial mechanism.102

1.5.1. STARK’S EXTRACTION MECHANISM

This mechanism describes liquid-liquid PTC in which an ion-pair, formed by extraction of anion Y' into the organic phase by the onium salt cation Q1, undergoes a rapid displacement with RX. The new salt [Q+X'] then returns to the aqueous phase, where Q+ picks up a new Y' ion for the next cycle (Scheme 1).

\[
\text{Organic Phase} \\
R-Y + Q^+X^- \rightarrow R-X + Q^+Y^- \\
\text{Interfacial Region} \\
NaY + Q^+X^- \leftrightarrow NaX + Q^+Y^- \\
\text{Aqueous Phase}
\]

Scheme 1

1.5.2. INTERFACIAL MECHANISM

In the case of interfacial mechanism, the ‘quat’ frequently employed in PTC/OH- reactions are tetrabutylammonium hydroxide and it does not exhibit a measurable ability to extract the hydroxide ion. This would suggest that the classical triethyl benzyl ammonium ion (TEBA) that is more hydrophilic would extract the OH- to an even lesser extent. TEBA induces enhanced reactivity in hundreds of PTC/OH- reactions, whereas nucleophilic substitutions proceed very
slowly. Since these nucleophilic substitutions have been characterized under extraction mechanism, it was assumed that another mechanism must be involved in PTC/OH" reactions. Maicosza\textsuperscript{102} thus proposed an alternative mechanism called the “interfacial mechanism”.

Organic Phase

\[
\begin{align*}
R-Y + Q^+X^- & \rightarrow R-X + Q^+Y^- \\
\text{Interfacial Region} & \quad M^+Y^- + Q^+X^- \rightarrow M^+X^- + Q^+Y^- \\
\text{Aqueous Phase} & \quad M^+Y^- \quad M^+X^-
\end{align*}
\]

1.6. APPLICATIONS OF PHASE TRANSFER CATALYSIS

The applications of single-site phase transfer catalysts (SPTC) have been well documented because of its high reaction rate, high selectivity, lower energy requirements and moderate operating temperature. Owing to these positive advantages, the soluble SPTC have been applied in several areas of chemistry viz., heterocyclic chemistry,\textsuperscript{103} macromolecular chemistry,\textsuperscript{104} industrial chemistry,\textsuperscript{105} dye chemistry\textsuperscript{105}, and medicinal chemistry.\textsuperscript{106,107} The SPTC’s have been used more specifically to the synthesis of various life saving dings or pharmaceutical intermediates. It has also been used for general purpose reactions of varied categories depending upon the strong base reactions such as alkylation (C-, N-, O-, S-alkylation),\textsuperscript{108} chiral alkylations,\textsuperscript{109} oxidation,\textsuperscript{110} (permanganate, hypochlorite/hypobromite, hydrogen peroxide, oxygen/air, persulfate, transition metal co-catalysis (carbonylation, reduction and hydrogenation, coupling reaction),\textsuperscript{110} condensation (Aldol,\textsuperscript{110} Michael,\textsuperscript{111} Witting,\textsuperscript{112,113} Darzens\textsuperscript{114}),
elimination, addition, polymerization, dehydrohalogenation, nucleophilic aromatic substitution, nucleophilic aliphatic substitution reactions viz., esterification, various displacement reactions such as (cyanide, halide, azide, sulfide, thiocyanate, sulfite, nitrite, hydroxide, carbonate, cyanate) and also for the preparation of organometalic compounds. The following discussion describes some of the important/selective application of different SPTC’s in various reactions exclusively in organic chemistry.

1.6.1. C-ALKYLATION

C-alkylation is one of the most fundamental organic reactions for building the carbon skeleton of organic compounds. The Carbon-hydrogen bond of typical hydrocarbons does not easily lend itself to dissociation into a proton and a carbanion. Either an extremely strong base is needed to deprotonate the C-H bond of an inactivated hydrocarbon or the C-H bond must be activated by strong electron withdrawing groups to stabilize the carbanion to be formed. It is known that PTC technique is a simple and less expensive method for performing alkylation reactions. Most of the alkylation studies reported in literature are involved an organic phase in contact with 50% aq. NaOH solution and a quaternary ammonium salt or a stoichiometric amount of a quaternary ammonium ion-pair. Phenyl acetonitrile was the first compound reported to undergo phase transfer C-alkylations in the presence of ethyl bromide, concentrated aqueous sodium hydroxide/1mol-% TEBA, the reaction is mildly exothermic and requires 3-5 hour at 28-35°C. Another interesting prospect arises when dihalides are used to alkylate ketones. Apparently 4-membered ring formation is disfavored to such an extent in the acenaphthene case that 1,3-dibromopropane C-alkylates and then O-alkylates after a second enolization. The product is the tetracyclicenol ether as shown in the following scheme.
In general, alkyl bromides are better C-alkylating agents than chlorides provided concentrated sodium hydroxide is used in considerable excess. Iodides and to some extent bromides (with a lower excess of NaOH) have an adverse effect on alkylation, because iodide is extracted into the organic phase is preference to the phenyl acetonitrile anion. Recently, alkylations were carried out in the presence of solid K$_2$CO$_3$/dibenzo-18-crown-6 in benzene solution.\textsuperscript{123} The C-alkylation of P-lcto esters is effected with 1-halopropane in the presence of N-Bu$_4$Br and NaOH.\textsuperscript{113}

A convenient synthesis of a-mercapto alkanoic acids involves PTC alkylation\textsuperscript{8} of dithiocarbamates and subsequent hydrolysis. Similarly, a-Substituted phenyl acetaldehydes are C-alkylated in the presence of aqueous NaOH/NBu$_4$I. It has also been reported that free arylacetic acids can be a-alkylated in a one-pot solid/liquid (powdered KOH/CTI2Cl2/TEBA)\textsuperscript{119} procedure as mentioned in the following scheme.

Methyl 2-phenyl sulfmyl acetates can be converted into cinnamic esters by a one-pot alkylation. The C-alkylation of chloromethane sulfonamides gives 55-88\% yield when a small amount of TIMPT is present in addition to NBu$_4$Br/50\%NaOH.\textsuperscript{120} Aryl acetylenes was also synthesized from alkyl iodides in
the presence of powdered KOH/18-crown-6 in fair yields without catalyst poisoning. In contrast, 1,3,3-triphenyl propane and phenyl acetylene (NaOH/PTC) gave unpleasant mixtures of products on reaction with ethyl iodide or benzyl and allyl halides respectively.\textsuperscript{121,123}

The cyclopentadiene was alkylated with tert-butyl bromide, 5(3%NaOH and Aliquat-336 as a PTC which gives 44% of yield.\textsuperscript{124,125}

![Diagram of cyclopentadiene alkylated with tert-butyl bromide](image)

Des Abbayes et al.\textsuperscript{131} reported the alkylation of aryl acetic esters and was greatly improved by complexation of aiyl group with chromium tricarbonyl.

![](image)

1.6.2. **CARBENE REACTIONS**

Phase transfer catalyst was little more than a curiosity in the late 1960's when Makosza first published his two-phase method for the generation of dichlorocarbene. Using a reservoir of 50% aqueous sodium hydroxide, a cosolvent of chloroform with olefin, and a catalytic amount of benzyltriethyl ammonium chloride, Makosza was able to achieve high yields of cyclopropanation products. Dichlorocyclopropanation had previously been a difficult reaction to conduct and the ease and economy of the new method attracted broad interest in the organic chemical community. Dichlorocarbene could be generated in a two phase aqueous-organic system in which NaOH was used as base and that first captured the attention of the organic chemical community.
community. Apart from several methods reported in literature for generation of dihalocarbenes,\textsuperscript{132-136} the phase transfer catalytic method in aqueous conditions seemed more facile in view of its easy handling, cost effectiveness, high yields and purity of products etc., Makosza\textsuperscript{133} reported the following dichlorocyclopropanation of cyclohexene.

They have also formulated the mechanism for the reaction leads to formation of dichlorocyclopropanation product under phase transfer conditions. Initially, reaction of CHCl\textsubscript{3} with OH\textsuperscript{−} gave the CCl\textsubscript{3} \textsuperscript{−} anion intermediate at the aqueous-organic phase boundary, where it was transferred into the organic phase by the quaternary cation and from where the dichlorocarbene is generated.

\[
\text{CHCl}_3 + \text{NaOH} \quad \overset{(\text{Org})}{\overset{(\text{aq})}{\rightleftharpoons}} \quad \overset{(\text{int})}{\text{CCl}_3\text{Na}^+ + \text{H}_2\text{O}} \\
\text{CCl}_3\text{Na}^+ + \text{Q}^+\text{Cl}^- \quad \overset{(\text{int})}{\overset{(\text{org})}{\rightleftharpoons}} \quad \overset{(\text{org})}{\text{CCl}_3\text{Q}^+ + \text{NaCl}} \\
\text{CCl}_3\text{Q}^+ \quad \overset{(\text{org})}{\rightleftharpoons} \quad \overset{(\text{org})}{\text{CCl}_2 + \text{Q}^+\text{Cl}^-}
\]

Dihalocarbenes are very useful compounds that can be reduced to cyclopropane derivatives treated with sodium to give allenes and can be converted to a number of other products. Literature reports of the generation and reaction of dichlorocarbene [CCl2] stress the importance of operating under strictly anhydrous conditions because of the ready and rapid hydrolysis of dichlorocarbene. Cinquini and Coworkers\textsuperscript{137} reported the reaction of styrene with
dichlorocarbene produced from the reaction of aqueous CHCl₃ with NaOH in the presence of phase transfer catalyst to yield 1,1-dichloro-2-phenyl cyclopropane.

\[
\begin{align*}
\text{C} & \quad \text{CHCl}_3 \\
\text{O} & \quad \text{Q}^+\text{Cl}^- \\
\end{align*}
\]

It should be noted that this reaction, sometimes called the Makosza reaction was simultaneously discovered by Starks, and examples are reported in a patent, which is contemporaneous with Makosza's paper.

In some cases, the dichlorocyclopropanation product is not isolated but undergoes secondary reactions and rearrangement. For example, the dichlorocarbene adducts of norbornene¹³⁸ and 3-methylindole¹³⁹ are examples. In both cases, the intermediate adduct loses chloride by ionization and simultaneous opening of the cyclopropane ring to an allylic carbonium ion leads to ring expanded products as illustrated in eqns. (1) and (2).

**Equation 1**

```
\begin{align*}
\text{C} & \quad [\text{C}] \\
\text{Cl} & \quad [\text{C}] \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

**Equation 2**

```

\[
\begin{align*}
\text{C} & \quad \text{CHCl}_3 \\
\text{O} & \quad \text{Q}^+\text{Cl}^- \\
\end{align*}
\]
In addition to dichlorocarbene, dibromo-,\textsuperscript{140-142} chlorofluoro-,\textsuperscript{143} bromofluoro-,\textsuperscript{144} fluoroiodo-,\textsuperscript{145} chloroiodo-,\textsuperscript{146} and diiodocarbenes\textsuperscript{146} have all been generated under phase transfer catalytic conditions. Attempts to generate difluorocarbene have been unsuccessful. Of these dihalocarbenes, only dibromocarbene has been extensively studied. It has been found that good yields of dibromocarbene from the relatively expensive bromoform can be obtained when a small amount of alcohol (preferably n-butanol) is added to the reaction mixture\textsuperscript{141} and the best catalyst for the reaction is not a quaternary salt, but tributylamine.\textsuperscript{142}

1.6.3. OTHER ORGANIC REACTIONS

There are several organic reactions reported in literature such as N-alkylation,\textsuperscript{147} 0-alkylation,\textsuperscript{148} S-alkylation,\textsuperscript{149} Aldol condensation,\textsuperscript{150} Witting reactions,\textsuperscript{151} dehydrohalogenation,\textsuperscript{152} oxidation,\textsuperscript{153} reduction,\textsuperscript{154} etc., under PTC conditions. All these products are more useful in pharmaceuticals, agricultural chemicals and other purposes than the other products.

1.6.4. CONDENSATION REACTIONS

1.6.4.1. MICHAEL ADDITION

Michael reaction is important particularly for C-C bond formations, and steroioselective variants have been extensively investigated in recent years. Michael addition\textsuperscript{157} of diethylmalonate to esters of 2-(I-hydroxyalkyl) propionate was studied and reported with a high stereoselectivity towards the syn-diastereomer (4:1 to 20:1) using 18-Crown-6 as a catalyst and catalytic amount of KF was used as the base in dimethyl sulfoxide or acetonitrile as solvent. Similarly, multiple Michael addition was achieved\textsuperscript{155} to form mostly tetra-, penta- and hexa ester’s and they were focused as potential lubricants. 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 groups, 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 esters was performed and selectively yielded mono-addition products in 56-95% yield.\(^{157}\)

Reierson et al.\(^{158}\) reported the Michael addition of cyclopentadiene with methyl acrylate under PTC/high concentration of aqueous base (50%) condition.

\[
\begin{array}{c}
\text{C} & \text{H} & \text{C} \\
\text{H}_2 & \text{C} & \text{CH}_3 \\
\text{CH}_2\text{CH}_2\text{COOCH}_3 \\
\end{array}
\]

![Michael Addition Reaction](image)

Toke et al.\(^{159}\) also reported chiral phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone reaction using asymmetric PTC.

![Michael Addition Reaction](image)

1.6.4.2. **Barzen’s condensation**

Makosza et al.\(^{116}\) first reported Darzens reactions in presence of PTC. Chloroacetonitrile was allowed to react with the cyclohexanone in the presence of NaOH (50%) and triethylbenzyl ammonium chloride for about 30 min. at 15-20 °C and the product viz., glycidic nitrile was obtained \(\approx 79\%\).

![Barzen's Condensation Reaction](image)

Similarly, a-Chlorophenylacetonitrile was also condensed with benzaldehyde in the presence of 50% NaOH, TEBAC \(^{160}\) as a PTC using benzene.
Recently Balakrishnan et al.\textsuperscript{161} also reported the Darzen’s condensation between the cyclohexanone with n-bromobutane under di-site phase transfer catalyst.

1.7. CHIRAL PHASE TRANSFER CATALYSIS

It is well known that the application of achiral phase transfer catalyst has been frequently applied in various fields of chemistry, particularly in the organic synthesis.\textsuperscript{162,163} However, asymmetric synthesis reactions using chiral phase transfer catalyst have not been extensively studied as compared to general asymmetric synthesis reactions.\textsuperscript{163,164} The field of catalytic asymmetric synthesis is providing synthetic chemists with a new and powerful tool for the potential asymmetric synthesis of complex organic molecules. The most notable catalysts are transition metals to promote the reactions in the presence of a chiral ligands.

It is true that most of the popular catalytic synthesis are inorganic in nature; one must not forgot the use of purely organic catalysts like (S)-proline\textsuperscript{166} simple peptide and particularly the best popular choice of viz., “cinchona alkaloids”. Normally, the asymmetric organic chemists used to select their asymmetric catalysts based on the factors like (i) the variety of reactions that the catalyst can promote (ii) the availability of both enantiomeric catalyst at a reasonable cost (iii) the foremost factor is the stability of that catalyst. The updated literature survey reveals that the “cinchona alkaloids” are popular chiral source, since it meets all these criteria and making them one of the most adoring asymmetric catalysts to date. The constituents of cinchona alkaloids consist of two pseudo enantiomeric pairs such as cinchonine and cinchonidine, quinine and quinidine. These constituents are extracted from the Bark of the cinchona tree; at a native of
tropical region. Due to the presence of various functional groups and hence its structure cinchona alkaloids, emerged as versatile chiral basic catalysts.\textsuperscript{167} The earliest uses of cinchona alkaloids in asymmetric catalysts were demonstrated by Pracejus in 1960’s to catalyze the symmetric alkaholysis of ketenes\textsuperscript{178} and subsequently Morrison and Mosher\textsuperscript{169} and Wynberg\textsuperscript{167} have employed the same for different prochiral synthesis. The asymmetric version of chiral phase transfer catalyst (CPTC) derived from the cinchona alkaloids have been developed and successfully employed to different types of useful organic reactions.\textsuperscript{170a,b} \textsuperscript{171} The first pioneering work for the development of cinchona alkaloids-type phase transfer catalysts was introduced by O’Donnell et al.\textsuperscript{171-176} and showed that benzylammonium salts derived from one of the versatile cinchona alkaloids viz., “Cinchonidine” and were used for the asymmetric alkylation of the glycinate imines. The synthetic methodology has been developed for carbon-carbon bond constructions by either anionic or cationic amino acid equivalents as well as the process, which establish carbon-nitrogen\textsuperscript{176} and carbon oxygen bonds.

\[
\begin{align*}
\text{N-Alkylation Chemistry} & \quad \text{ or } \quad \text{\alpha--Anionic Chemistry} \\
\alpha--\text{Cationic Chemistry} & \quad \text{(Phase Transfer Catalysis)} \\
\text{Carbon Chemistry}
\end{align*}
\]
The asymmetric synthesis of α-amino acids remains a major challenge in organic chemistry. The very first attractive method for the synthesis of α-amino acids was introduced by O’Donnell in 1989; used the liquid/liquid phase transfer catalyzed asymmetric alkylation of N,N-diphenylmethyleneglycine tert-butyl ester (scheme 1) with the aid of N-benzyl cinchona alkaloid salts as phase transfer catalysts and it is considered as a first generation catalyst (Fig la).

![Scheme 1. Alkylation of glycine imine (Schiff base)](image)

Figure 1. The different generations of chiral phase transfer catalysts derived from cinchona alkaloids in different periods.

The second generations of CPCT’s (Fig.lb) derived from cinchona alkaloids were subsequently developed and reported by the same O’Donnell and co-workers on 1994 i.e the N-alkyl O-alkyl cinchona alkaloid salts. Then the third generation of CPCTC’s was described independently by Lygo and Corey in 1997 in which 9-anthracenylmethylcinchonidinium bromide (Fig. 1 c) was introduced as an effective unit making the nitrogen face, leading to
substantially improved enantiomeric excess (figure 1). Recently, Maaioka et al. developed very efficient non-cinchona alkaloid catalysts, C2-symmetric chiral quaternary ammonium salts prepared from (S)-binaphthol.

In connection with the development of Sharpless asymmetric dihydroxylation, the discovery of ligands with two independent Cinchona alkaloid units attached to heterocyclic spacers led to considerable increases in both the enantioselectivity and the scope of the substrate. Recently, dimeric (Figure 2) 2a, 2b and trimeric 2c quaternary cinchona catalysts derived from o-, m- or p-xylene dibromide (2a), 9,10-dibromo anthracenyl (2b) and mesitylene tribromide respectively have been employed as chiral PTC’s achieving good enantioselectivities.

Figure 2. Various types of dimeric and trimeric CPTC’s
1.8. APPLICATIONS OF CMPTC’S FOR THE VARIOUS ASYMMETRIC REACTIONS

1.8.1. Alkylation of Schiff bases: Synthesis of α-amino acids

Alkylation of glycine Schiff bases is a well known and straightforward procedure for the synthesis of α-amino acids in the racemic or optically active form. Depending on the reaction sequence used, either mono- or disubstituted-amino acids are available.

Further studies on this process by O’Donnel and co-workers showed that the active species involved in the reactions were not N-benzylammonium salts of the alkaloid, but O-alkyl-N-benzylammonium salts such as lb which are formed in situ from the alkaloid and alkylating agents. An O-allyl group was found to be preferred over an O-benzyl substituent. Enantioselectivities of the alkylation reactions catalyzed by second generation catalysts were slightly better compared to those of the first, generation catalysts.

Scheme 2. Mono alkylation of Schiff base under CPTC’s conditions

Mono alkylation of schiff base was a key step for several asymmetric syntheses of unnatural amino acids; metal-binding 2-amino-ο-(2,2'-bipyridinyl)propanoic acid, pyridinoxamino acid derivatives, as well as
dityrosine and isodityrosine.188 O’Donnell189 reported the enantioselective catalytic alkylation of L-alanine-derived Schiff base (Scheme 3), leading to chiral α,α-methylalkyl amino acids using N-benzylammonium chloride as a CPTC’s up to 50% ee’s. Recently Lygo improved the enantioselectivity of this process by using third generation catalysts up to 87% ee.190

\[
\begin{align*}
&\text{RX, } \text{K}_2\text{CO}_3/\text{KOH} \\
&\text{Cl} \quad \text{N} \quad \text{COO}t-\text{Bu} \\
&\text{N} \quad \text{Me} \\
&\text{Cl} \quad \text{N} \quad \text{COO}t-\text{Bu} \\
&\text{R} = \text{Bu}, \text{-xC}_6\text{H}_4\text{CH}_2, 2\text{-naphthyl, allyl} \\
&\quad \text{t-BuOOCCH}_2, \text{n-Bu}
\end{align*}
\]

Scheme 3. Dialkylation of L-alanine-derived Schiff base under CPTC’s

There are several enantioselective organic reactions reported in presence of chiral phase transfer catalysts viz., addition of carbonyl compounds (Aldol condensations,191-195 indium promoted additions,196-198 Darzens reactions,199-203 Baylis-Hilman reactions,204,205 diethyl zinc additions,206-208 Michael additions,209-213 other addition reactions214), cycloadditions215-217 (synthesis of β-lactones, synthesis of β-lactams, Diel-Alder reaction),218 Claisen rearrangement,219 carbon-oxygen bond formation (epoxidation of enones and cis olefins, asymmetric dihydroxylation, asymmetric aminohydroxylation, α-hydroxylation of ketones),218 hydrogenations and reductions (heterogeneous hydrogenation of activated ketones, heterogeneous hydrogenation of other substrates, homogeneous reductions),218 carbon heteroatoms (N,P,S,F) bond formations,218 miscellaneous reactions etc.218

1.8.2. SYNTHESIS OF ENANTIOSELECTIVE N-ARYL AZIRIDINE

Aziridine are saturated three-membered heterocycles containing one nitrogen atom. This class of compounds dates back to 1988, when Gabriel (unwittingly) synthesized the parent member.219 Like other three membered rings
such as cyclopropane and epoxides. Aziridines are highly strained. Ring strain renders aziridines susceptible to the ring-opening reactions that dominate their chemistry as shown below, makes them useful synthetic intermediates that folly deserve a prominent place in the arsenal of the organic chemist.

In view of the long history of aziridine chemistry, it is not surprising that the literature on the subject is very extensive. For the interested reader requiring a general introduction, several excellent discussions are available. The ability of aziridines to undergo highly regio-and stereo selective ring-opening reactions makes them very valuable in organic synthesis. This ability has not gone unnoticed in nature, where a number of molecules possessing an aziridine ring have been shown to exhibit potent biological activity, which is intimately associated with the reactivity of the strained heterocycle.

Structure-activity relationships have identified the aziridine ring as being essential for antitumour activity and a vast amount of work has been concentrated on synthesizing derivatives of these natural products with increased potency. There are several reports for the synthesis of Chiral aziridines (Figure 3) from various substrates via, nitrenes, azirines, aminoalcohols, imines, etc.

\[
\begin{align*}
\text{Ph} & \quad \text{OH} & \quad \text{N} & \quad \text{COR} & \quad + & \quad \text{EWG} & \quad \rightarrow & \quad \text{GWE} & \quad + & \quad \text{RCO}_2\text{Na} \quad \quad \text{eq. 1} \\
\text{Ph} & \quad \text{OH} & \quad \text{N} & \quad \text{COR} & \quad + & \quad \text{EWG} & \quad \stackrel{\text{CPTC}}{\rightarrow} & \quad \text{GWE} & \quad + & \quad \text{RCO}_2\text{Na} \quad \quad \text{eq. 2}
\end{align*}
\]
Chiral aziridines are very important substances in asymmetric synthesis since they have been shown to be useful chiral auxiliaries, chiral ligands for transition metals and chiral substrates in the preparation of biologically active species such as amino acids, beta-lactams and alkaloids. Although many methodologies are available for chiral aziridines, only a very few are catalytic in nature. An efficient catalytic synthesis of chiral N-tosylaziridines has been developed by Jacobsen and Evans. Recently, Jacobsen has reported a catalytic asymmetric method for N-arylaziridines with enantiomeric excesses up to 67% but in poor yields.

Lobo et al. also reported a new catalytic enantioselective method for N-arylaziridines based on the quaternary salts of Cinchona alkaloids as phase-transfer catalysts. Further they also have previously reported that N-acyl-N-arylhydroxylamines and O-acyl-N-arylhydroxylainines are efficient aziridinating agents for electron deficient olefins. But they are obtaining aziridines in moderate to good yields and enantiomeric excesses up to 62% (Scheme 4) under chiral phase transfer catalyst conditions.
Recently Jacobsen et al.\textsuperscript{223} have studied the synthesis of N-arylaziridines using bisoxazolines Copper (I) complex and reported an enantiomeric excess up to 67% with a modest chemical yield (< 50%). Joao Aires-de-sousa et al\textsuperscript{226} have also reported a new catalytic enantio selective method for the preparation of N-aryl aziridines in the presence of quaternary salts of cinchona alkaloids as a soluble phase transfer catalysts. They have also studied that the N-arylhydroxylamines and O-acyl-N-arylhydroxylamines as an efficient aziridinating agents for electron deficient olefins and reported different chiral aziridines using cinchona alkaloid derived chiral phase transfer catalyst, but here the chemical yield is 80% with yield up to only 38%.

In this context, we envisaged that good results could be obtained with this type of cinchona derived ammonium salts if a builder group containing starting materials were employed as a bridge between the alkaloid moieties, in analogy to Lygo's,\textsuperscript{179} Park,\textsuperscript{183} Jew\textsuperscript{182} and Corey's\textsuperscript{180} improvements relative to the monomeric catalysts. In order to improve the catalytic efficiencies and ee's, the catalysts were examined by newly synthesized single, dimeric, trimeric and tetrameric catalysts derived from inexpensive starting materials with cinchona alkaloids as a chiral moieties. The catalytic efficiencies were studied by the syntheses of a-amino acids and N-aryl aziridines.

Scheme 4. Enantioselective aziridination of hydroxamic acids
1.9. THE ORIGIN OF MULTI-SITE PHASE TRANSFER CATALYST

Phase transfer catalysis has become, in recent years, a widely used, well-established synthetic technique, applied with advantage to multitude of organic transformations. In addition to steadily increasing number of reports in the primary literature, there are several reviews, comprehensive monographs and an ACS audio course which describes the phase transfer process and which provide extensive compilation of phase transfer agents and reaction type. While the lists of applications and in many cases the synthetic results are impressive, phase transfer catalysts (PTCs) suffer some of the same disadvantages as more conventional homo- and heterogeneous catalysts, i.e., separation and recovery. A catalyst which contains only one reactive site is known as single site phase transfer catalyst viz., tetraethyl ammonium chloride (TEAC), tetrabutyl phosphonium chloride (TEPC), tetrabutyl phosphonium bromide (TBPB) etc. If the PTC has more than one active site, they are called as "Multi site phase transfer catalyst" (MPTC). The soluble single site phase transfer catalyst such as TEAC, TEPC, TBPB, viz are immensively popular due to their availability and easy reaction work up. Even though, the vast number of the single site catalysts are available for research, the selection of catalyst mainly depends on the scale of economy. The efficacy of the catalytic activity of these multisite PTCs towards simple Sn2 reactions was reported. In general multisite PTCs offer the potential of providing greater PTC activity and to effect a particular synthetic transformation under mild conditions.

Systematic survey of the literature reveals that the studies of Idoux et al as a first report dealing with multi-site-phase transfer catalysts containing only three active site (phosphonium ion) type of soluble and insoluble polymei-bound catalyst. Balakrishnan et al had also reported the soluble MPTC containing two and three active site (triethyl ammonium ion) type of catalysts which are used for the
Balakrishnan et al. and Wang et al. have also reported soluble ammonium quaternary onium ions having two active sites and the efficiency of the di-site PTC were also examined through simple S-n2 reactions and some weak nucleophilic SnAr reactions. Recently, dimeric and trimeric chiral quaternary ammonium catalysts were synthesized from o-, m- or p-xylene dibromide, bis(bromomethyl)naphthalenes and mesitylene tribromide respectively. These CPTC’s have been employed for C-alkylation of N-(diphenylmethylene)glycine tert-butyl ester and have been found to be good in terms of chemical yield and ee’s. In the recent past our research group also developed multi active centres of achiral and chiral catalysts. Recently we reported the alkylation of phenylacetonitrile and α-pinene under MPTC condition containing six-site catalysts.

There is no other report on the MPTC containing more than four active site either in soluble or insoluble form. No doubt that the number of catalytic site can decide the efficiency of reaction which in turn control the economy of the reaction process. Taking in to consideration the above mentioned aspects, we have decided to synthesise novel soluble, as well as, insoluble achiral and chiral multisite PTC containing maximum possible active sites (two to thirty two sites) catalysts from inexpensive starting materials and studying their efficiency in C-alkylation of α-pinene, dichlorocarbene addition to (R)-limonene, Darzen’s condensation to 4-nonanolide with 1,6-dibromohexan-2-one, Michael addition to cyclopentadiene with methylmethacrylate and enantio selective synthesis of α-amino acids & N-aryl aziridines respectively.
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