Asymmetric synthesis using phase transfer catalysis

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Abstract

Asymmetric synthesis using chiral phase transfer catalysts with a brief introduction on principles of phase transfer catalysis is presented.

Key words: Asymmetric synthesis, phase transfer catalysis.

Section 1: Principles of phase transfer catalysis

1. Introduction

The two main goals in experimental organic chemistry have always been the generation of new compounds on the one hand and the development of new reactions on the other. The purpose of developing new reactions is usually simplification of existing methods of preparation. During the last two centuries of organic synthesis, new techniques for faster, simpler and cheaper methods of synthesis have been constantly emerging. One such technique which came into vogue about two decades ago is phase transfer catalysis.

In phase transfer catalysis (PTC), as the very name suggests, a substrate in an organic phase is reacted chemically with a reagent in another phase which is usually aqueous or solid. Since these phases are mutually insoluble, the concentrations of the two reactants in the same phase are too low for convenient reaction rates. One way to overcome this difficulty is to use a solvent that will dissolve both the species. If a hydroxylic solvent is used, the reaction may be slow because of extensive solvation of the anion. Solvolytic side reactions reduce the efficiency even further. Polar aprotic solvents are superior but they are expensive and difficult to remove after completion of the reaction. Therefore, an alternate method is needed to speed up the reaction between reactants in the two mutually insoluble phases. This can be achieved by means of a transfer agent—an agent or catalyst which is capable of solubulizing or extracting the reagent into the organic phase or conversely, the substrate into the aqueous phase. Such an agent, by its very function, is termed a phase transfer catalyst, and the whole process is referred to as phase transfer catalysis.

Thus, phase transfer catalysis can be defined as being concerned with accelerating or making possible reactions between chemical species residing in phases which are mutually insoluble.

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The technique of PTC has several advantages over conventional preparative methods:

(i) Anhydrous or aprotic solvents are no longer required.

(ii) The reaction rate is vastly improved. Reactions which have extremely slow rates or do not proceed at all are known to go to completion in a few hours by the addition of catalytic amounts of phase transfer agents.

(iii) Almost all PTC reactions are conducted at room temperature. The low reaction temperature prevents side reactions and thus increases yields.

(iv) The work up of the reaction is very easy.

(v) Aqueous alkali metal hydroxides can be used instead of expensive bases like alkoxides, sodamide, sodium hydride or metallic sodium.

Reactions involving phase transfer phenomena were known for a long time. In fact, patent references date back as far as 1913[1]. A considerable number of reactions were performed even after that and are found in the older literature. But these were performed only incidentally with no idea of exploring the mechanistic aspects or expanding the scope of this technique.

The first systematic exploration of reactions in two-phase systems was done by Makosza and co-workers in 1965[2]. Further, foundations from the physicochemical and analytical point of view were laid by Brandstrom *et al* in 1969 and 1970[3,4]. But the term 'phase transfer catalysis' was actually coined and first used by C. M. Starks in patents in 1968[5]. It was only since Starks' publication in 1971[6] that the scope of the method has been fully realized and extended beyond its original application of alkylation and carbene addition reactions. Since then the field has grown rapidly and the patent and journal references number more than 8000. There have been a number of reviews[7,8], monographs[9,10] and books[11,12] which aim to cover the methodology and its applications. PTC has also expanded into new fields such as solid–liquid PTC, polymer-bound 'triphase' catalysis[13,14], PTC in heterocyclic or metal organic chemistry[15], inverse catalysis[16] and stereoselective synthesis using chiral phase transfer catalysts[17,18].

2. Types of phase transfer catalysts

Two types of catalysts are currently in use: (i) Onium salts, and (ii) Crown ether group of catalysts.

2.1. Onium salts

Onium salts or 'quats' are quaternary ammonium, phosphonium, sulfonium or arsonium salts. They consist of ion pairs with a positively charged quaternary centre Q^+ and a counter ion X^-. Ion pairs are associations of oppositely charged ions to give neutral entities. In contrast to inorganic ions, the quats (R_4N^+, R_4P^+, R_4S^+ or R_4Ar^+) with sufficiently large R groups are poorly solvated in water and have more affinity to the organic solvents. The Q^+ cations can exchange their anions for the reagent anions Y^- to form an alternate ion pair Q^+Y^-. This ion pair being lipophilic can dissolve in the organic medium where Y^- participates in the reaction.

For PTC purposes, quaternary ammonium ions are of special interest because they are less

likely to interfere in reactions. Therefore, quaternary ammonium salts are the most widely used phase transfer catalysts.

2.2. Crown ether group of catalysts

Crowns are defined as macroheterocycles usually containing the basic unit $(-Y-CH_2-CH_2)_n$ where Y is O, S or N. Crown ethers in particular have met with immense interest in the last two decades, and various aspects of their preparation and chemistry have been reviewed[19,20]. Some examples are shown in Fig. 1. A large number of cryptates are also being used such as the compound **V** known as Kryptofix 222[21].
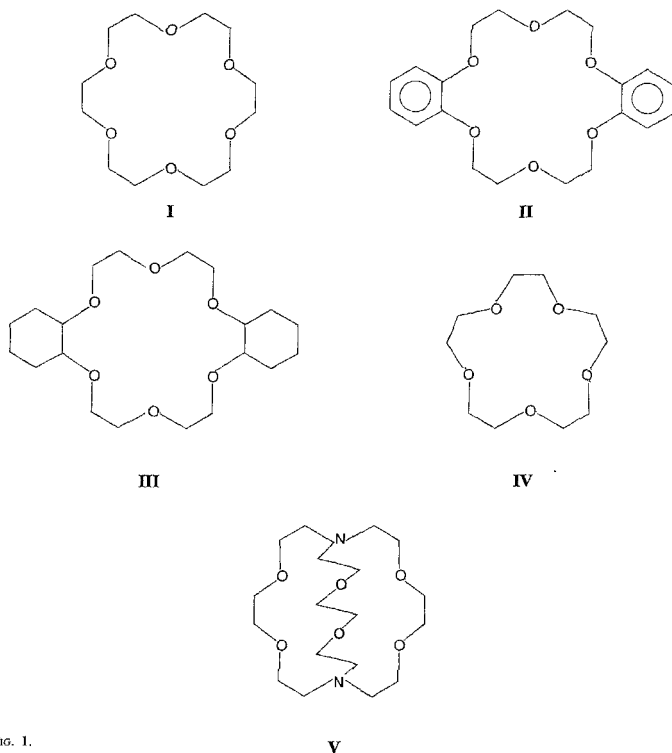

FIG. 1.

A common feature of all crowns and related substances is a central hole or cavity. By chelation within this hole, complexes of varying stability can be formed with other species depending upon the appropriate radii and electronic configurations. Cations, anions, neutral zerovalent metals, and some small neutral molecules such as nitrites are capable of complexation with crowns.

The cation complexes of general interest for PTC are those formed with potassium and sodium metal cations. Sodium is complexed by 15-member crowns while potassium needs 18-membered crowns. The complexation of the metal cation results in an ion pair. The cation–crown ether complex is comparable to a large onium ion and the anion is the accompanying counterion. This ion pair is similar in property to the onium salts. As the cation is masked by the crown ether, the anion is free, activated or 'naked' and thus is more reactive. But the chief drawback of these catalysts is their prohibitive cost. Also, these reactions should be conducted in anhydrous media as anion activation is suppressed by traces of water in the medium because of ion pair or anion solvation thus reducing the nucleophilicity. In addition, crowns tend to carry water into solvents as non-polar as chloroform[22].

2.3. Other catalysts

Apart from onium salts and crown ethers, other compounds to have been found useful are open chain polyethers of ethylene glycol and molecules which contain a number of such side chains bound to a central aromatic nucleus (the so-called poly-pod molecules). Their catalytic action is mechanistically similar to that of crown ethers.

3. Mechanism of PTC reactions

The mechanism of PTC reactions occurring in neutral or acidic media is different from those occurring in the presence of a highly concentrated inorganic base.

3.1. Mechanism under neutral conditions

The original PTC mechanism for displacement reactions proposed by Starks[23] is shown below:
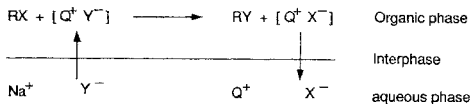
An ion pair, formed by the extraction of anion Y^- into the organic phase by the onium salt cation Q^+, undergoes a fast displacement with RX. The new salt (Q^+X^-) returns to the aqueous phase, where Q^+ picks up a new Y^- ion for the next cycle. The key step in this mechanism is the extraction of Y^- ion into the organic phase.

Solvent extraction of ion pairs from aqueous into organic media is a thoroughly investigated field[24] and well known to analytical and industrial chemists. PTC reactions follow the same principles as ion pair extractions. Even the most simple two-phase substitution reaction involves a number of equilibria.
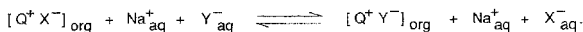
Overall reaction

$$Na_{aq}^+ \ Y_{aq}^- \quad + \quad RX_{org} \quad \xrightarrow[PTC]{Q^+ \ X^-} \quad Na_{aq}^+ \ X_{aq}^- \quad + \quad RY_{org}.$$
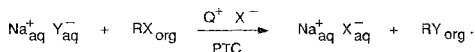
This can be broken down into two equilibria.

(a) Chemical reaction in the organic phase

$$RX_{org} \quad + \quad [Q^+ X^-]_{org} \quad \longrightarrow \quad RY_{org} \quad + \quad [Q^+ X^-]_{org}.$$

(b) Extraction equilibrium

$$[Q^+ X^-]_{org} \ + \ Na_{aq}^+ \ + \ Y_{aq}^- \quad \rightleftharpoons \quad [Q^+ Y^-]_{org} \ + \ Na_{aq}^+ \ + \ X_{aq}^-.$$

Experimental methods for the investigation of these extractions have been developed and the processes have been studied in detail.

Schill and Modin[25] define the stoichiometric extraction constant E_{QX} of equation (b) as

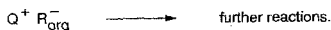$$E_{QX} \ = \ \frac{[Q^+ X^-]_{org}}{[Q^+]_{aq} \ [X^-]_{aq}}.$$

The magnitude of the stoichiometric extraction constant depends on various factors such as the organic solvent and the size and structure of anion and cation. It should be noted that a very large variety of extraction constants is possible through a judicious choice of ions. Even the most hydrophilic anion (such as OH⁻) can be extracted using very lipophilic cations and the most hydrophilic cations such as NMe₄⁺ are transported to the organic medium by using very lipophilic anions.

3.2. Mechanism in the presence of bases

Here the 'interfacial' mechanism first proposed by Makosza[26] is operative. In this mechanism, the substrate R–H is deprotonated at the interphase.

$$R - H_{org} + NaOH_{sol \ or \ aq} \ \rightleftharpoons \ R_{org}^- \ + \ Na_{sol \ or \ aq}^+ \ + \ H_2O.$$
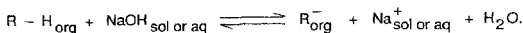
Anions R⁻ are dynamically anchored to the interphase and cannot react easily because no counter ion is available for them to enter the organic phase. The catalyst cation is able to liberate the R⁻ion and carry it, as an ion pair, to a reaction partner deep in the organic phase.

$$R_{org}^- \ + \ Q^+ X_{org}^- \quad \rightleftharpoons \quad [Q^+ R_{org}^-] \ + \ X_{sol \ or \ aq}^-$$

$$Q^+ R_{org}^- \quad \longrightarrow \quad \text{further reactions.}$$

In basic media also, as in neutral media, the same equation applies for the extraction coefficient and the ease of extraction of the ion pair $[Q^+ X^-]$ or $[Q^+ R^-]$ is governed by the same factors in both the cases. The various factors such as solvent, size and structure of anion and cation are considered in detail below.

4. Factors influencing PTC reactions

4.1. Influence of the solvent

Typical inorganic sodium and potassium salts do not dissolve in non-polar organic solvents. The same is true for inorganic anions with small organic cations, *e.g.*, tetramethylammonium. But if we use larger organic cations (*e.g.*, tetra-*n*-hexylammonium) the solubility of the salts in non-polar solvents increases and even small organophobic anions can be solubilized as non-polar solvents as hydrocarbons. The salts are present as ion pairs, held together by coulumbic forces. The ion pairs coexist in equilibrium with free ions in solution. In solvents of low dielectric constants (10–15) even at high dilution almost no free ions exist whereas in solvents of high dielectric constants the ion pairs dissociate to free ions. In fact, the formation of ion pairs as well as their physical and chemical properties are strongly influenced by interaction with the solvent. In this respect, solvents can be classed into three groups:

(a) Polar protic solvents readily solvate both anions and cations and therefore the anions are of low nucleophilicity and thus show low reactivity.

(b) Polar aprotic solvents (*e.g.*, DMSO, DMF) readily solvate cations. Anions, however, are poorly solvated, and the reaction rates are very high. Salts are highly dissociated in such solvents.

(c) Aprotic solvents of low polarity have dielectric constants ranging from 8.9 (methylene chloride) to 1.9 (hexane). Although typical inorganic salts are insoluble in these solvents, quats and crown ether-masked alkali metal salts are quite soluble especially in chlorinated solvents like dichloromethane and chloroform.

Aprotic solvents of low polarity are ideal for PTC work. They are immiscible with water and therefore the highly hydrated 'shielded' ion pairs of low reactivity are not formed. They are aprotic and therefore hydrogen bonding to the ion pair is avoided. Low-boiling chlorinated hydrocarbons (chloroform, methylene chloride, 1, 2-dichloroethane, etc.) are among the best solvents. Not only do they have high extraction capability, but also are inexpensive and easy to remove. Diethylether and ethyl acetate have low extraction capabilities and are thus not used. Alternately, one of the reagents may function as the solvent.

4.2. Influence of the onium cation

From various physicochemical and analytical studies it would appear that there is a relation between the catalyst cation size and the extraction constant. Lipophilicity of onium salts rises steeply with the number of C-atoms in the alkyl substituents. Gustavii[27] observed a linear relationship between log E_{QX} and n, the number of carbon atoms in the cation. As a first approximation and mostly independent of the anion, an average increase of 0.54 units for a carbon atom was found in a homologous series. That is, the extraction coefficient E_{QX} of the ammonium salts NR_4X increases by a factor of about 10 if the total number of carbon atoms

in the residues R is increased by 2. Almost all anions can be transferred by quaternary ammonium ions containing 14 to 25 carbon atoms. Even though the more lipophilic catalysts extract more efficiently, the optimal overall rate of a PTC conversion is generally not found with the most lipophilic catalyst, because other factors contribute in the rate-determining step, for example, solvation and intimacy of the ion pair.

4.3. Influence of the anion

Both the original catalyst counter ion and that liberated during the reaction should be as hydrophilic as possible. The catalyst anion should not be distributed in the organic phase to a much larger extent than the anion to be reacted as this may bring the conversion to a stand-still. This 'catalyst poisoning' is experienced if the nucleophile is rather difficult to extract (e.g., OOH⁻, OH⁻ or acetate) and iodide or tosylate are the leaving groups. Various authors[28-30] studied the extractability of various anions and arrived at a scale of lipophilicities. From this order, we can conclude that for medium-sized cations hydrogen sulfates are very useful as PTCs. Chloride is a second choice. Bromides, are sufficient in most cases. The more hydrophilic acetates, fluorides or hydroxides are the better it is but they are difficult to prepare as they are highly hygroscopic and/or unstable.

4.4. Stirring

Most laboratory preparations are performed using magnetic stirring. Reactions following extraction mechanism, i.e., for neutral PTC reactions, ~200 rpm is required in liquid/liquid systems whereas for solid/liquid systems, ~750–800 rpm is recommended. Reactions of the interfacial type, with viscous media like 50% NaOH, demand stirring rates >750, sometimes up to 1500 rpm for reproducible kinetic behaviour.

4.5. Amount of catalyst

Rates are proportional to the catalyst concentration if the reaction follows extractive mechanism. With interfacial mechanism, a more complex dependence is found. In literature, quantities varying from between a few mole per cent and several moles have been used. Low concentrations are desirable only for highly exothermic reactions or if the catalyst is expensive. In most reactions about 2–5 mol% catalyst concentration is generally used.

Section 2: Asymmetric synthesis using chiral phase transfer catalysts

1. Introduction

From the brief introduction to the principles of phase transfer catalysis in the foregoing section, it can be seen that the technique is very similar to enzyme catalysis. This, coupled with its simplicity, makes it a very advantageous technique. If conventional phase transfer catalysts are substituted with chiral catalysts, in principle, these should induce chirality in the products of prochiral reactants. Considering this, several authors have tried to perform enantioselective synthesis using chiral phase transfer catalysts derived mostly from natural products.

In the following pages a review of literature on this subject is presented to give an idea

of the state of art of the application of chiral phase transfer catalysts in asymmetric synthesis. The catalysts have been classified according to the natural compounds they have been derived from. An effort has been made, in this compilation, to give an impression of the diversity of both the structure of the chiral catalysts and of the reaction types where they are applied.

Since the appropriate key words were introduced only recently in the chemical abstract services, it was not easy to survey the literature in a systematic way. Much of the material of the present review is therefore based on the literature collections of Fluka group[31]. Additional references were found by searching citations in research papers and reviews. This overview is quite comprehensive but it is possible that some relevant citations have been missed.

1.1. Ephedrine alkaloid salts

The ephedrine group of alkaloids are open chain amino alcohols. d-Ephedrine is systematically named [S-(R*, S*)]-[1-(methylamino)ethyl] benzenemethanol. The other naturally occurring forms of ephedrine are (–)-N-methylephedrine, (+)-norephedrine, (–)-norpseudoephedrine, D-(+)-pseudoephedrine and L(–)-pseudoephedrine.
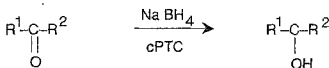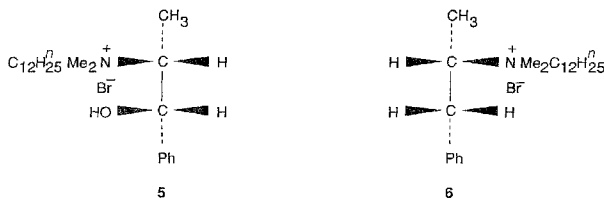
The earliest reference to ephedrine salts as phase transfer catalysts was in 1975. Hiyama et al[32] reported enantioselective oxirane synthesis by means of dimethylsulfonium methylide in the presence of quaternary ammonium salts of ephedrine. 2-Phenyloxirane was synthesized from benzaldehyde and achiral Corey's ylide in the presence of (–)-N,N-dimethylephedrinum bromide (1) with a reported enantiomeric excess of 67%. The use of (–)- ψ- ephedrine salts (2) resulted in oxiranes of opposite configuration. Chiral ammonium salts without the β-OH (3 and 4) did not induce any optical rotations. When catalyst:substrate ratio was increased, as much as 97% ee was reported. But these findings were later found to be incorrect[33].

1a R = Me
 b R = Et
 c R = n-Pr
 d R = n-Bu
 e R = n-C$_{16}$H$_{33}$

2a R = Me
 b R = Et

3 Y = H
4 Y = OMe
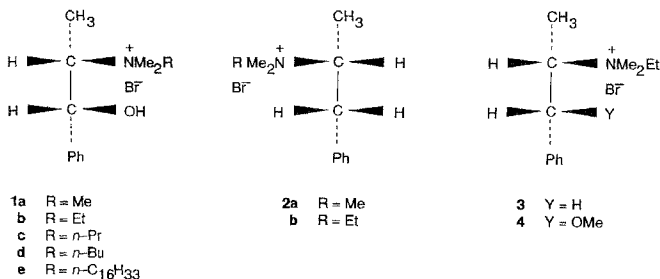
Colonna and Fornasier[34] used ephedrinium salts, (–)-N-dodecyl-N-methylephedrinium bromide (5) and N,N-dimethyl-N-dodecyl amphetaminium bromide (6) in the study of borohydride reduction of ketones. The use of these chiral catalysts could in principle lead to asymmetric induction with formation of optically active alcohols. But in the two phase reductions of 2-octanone, 1-phenyl-1-propanone and acetophenone no asymmetric induction

was found either at room temperature or at 0°C. The authors found that the presence of the OH group β to nitrogen enhances the rate of reduction. The explanation put forward was that the carbonyl group is activated towards borohydride attack through hydrogen bonding with the catalyst[34].

Balcells et al[35] investigated asymmetric reduction of hindered ketones A(a–e) using catalysts 1b, 1e, 5 and 6. Only catalyst 5 induced small rotations of up to 13% ee.
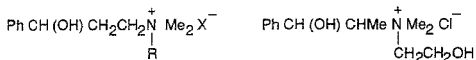
$$C_{12}H_{25}^n Me_2 \overset{+}{N} \blacktriangleright \text{-------} C \text{------} \blacktriangleleft H$$

5

6

A

	R^1	R^2
a	Ph	i-C_3H_7
b	Ph	t-C_4H_9
c	Mesityl	CH_3
d	α–Phenylethyl	CH_3
e	α–Phenylpropyl	CH_3

$$R^1\text{-}\underset{O}{\overset{\|}{C}}\text{-}R^2 \xrightarrow[cPTC]{Na\,BH_4} R^1\text{-}\underset{OH}{C}\text{-}R^2$$
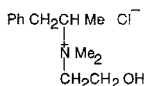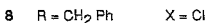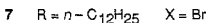
Again, slower reaction rates and racemic alcohols were obtained with **6** which does not contain an OH group. These authors also proposed that the interaction of the OH group of the catalyst with the carbonyl functionality in the substrate favours one of the two possible diastereomeric transition states.

In partial contradiction of these observations, Masse' et al[36] contend that even acetophenone and isobutyl methyl ketone give optically active alcohols in dichloromethane/ 2N NaOH / NaBH$_4$ systems with catalysts **5** and **1e**, but not with **1b**. The highest induction claimed is 39% ee with a 4:10 ratio of catalyst:substrate. The optical yields were found to be high at catalyst:substrate ratio 1:10. The stereoselectivity was found to be dependent on chainlength of the catalyst, with better selectivity using dodecyl rather than the hexadecyl substituent. In subsequent work, Masses' highest rotations could not be reproduced but some optical induction was still found.

A study to ascertain the influence of structural variations within the catalyst on asymmetric inductions[37] in borohydride reduction reactions was carried out in the presence of catalysts **5–10**. Optically active alcohols whose optical purities ranged from 1.1 to 13.7% were obtained. Catalysts without an OH group gave racemic alcohols. When the OH group was γ to N^+, the same induction which is quite low (1.1%) was observed. The induction was found to be the highest when the OH group is β to nitrogen.
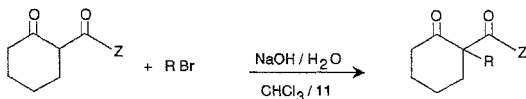
$$Ph\ CH\ (OH)\ CH_2CH_2\overset{+}{\underset{R}{N}}\ Me_2\ X^-\qquad Ph\ CH\ (OH)\ CHMe\ \overset{+}{\underset{CH_2CH_2OH}{N}}\ Me_2\ Cl^-$$

9

7   R = n–C$_{12}$H$_{25}$ X = Br

8   R = CH$_2$ Ph   X = Cl

$$Ph\ CH_2\underset{\underset{CH_2CH_2\ OH}{\overset{|}{\underset{|}{N}}Me_2}}{\overset{|}{C}}H\ Me\ \ Cl^-$$

10

When chiral PTC (–)-N-benzyl-N-methylephedrinium bromide(**11**) in chloroform solution was used, asymmetric alkylation of compound **B** has been claimed by Fiaud[38].

B

Z = OEt or OMe or Me
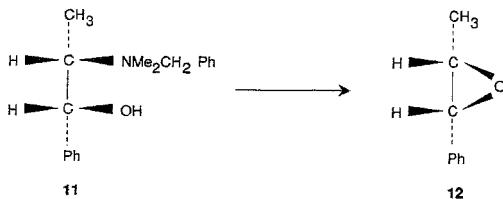
11   **12**

The maximum induction found was 6%. The reaction showed no optical inductions in hexane solution and gave lower optical yields with catalyst **1a**. This is the first asymmetric alkylation reported in literature. It should be noted that the ephedrinium salts decompose easily under phase transfer conditions to give chiral epoxides **12**[39].

These oxiranes have very high specific rotations ($[\alpha]_D = +117.6°$ neat). A small amount of impurity introduced by this oxirane, its reduction or ring opening products could, in fact, easily simulate a small optical yield of the main product. Indeed a reinvestigation of Fiaud's supposedly highest optical induction showed that at least 98%, perhaps all, of the rotation observed was due to impurities.

Asymmetric induction in Darzen's reaction was reported by Colonna et al[40]. The influence of structural variations and binding of the ephedrinium catalysts to a polymeric matrix on asymmetric induction has also been examined. Catalyst 5 gave an optical induction of 5%. The use of polymer-supported catalyst for the same substrate resulted in 23% ee. Optically inactive epoxides were obtained when catalysts without the β–OH were used.
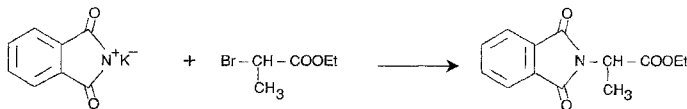
Colonna et al[41] found that asymmetric induction in the Michael addition of nitromethane to chalcone (Scheme 1) is greatly enhanced from 1% to ~20% ee by replacing, as catalyst, a chiral amine in methanol by its ammonium fluoride salt in an aprotic solvent. Thus (–)-N-dodecyl-N-methylephedrinium fluoride was shown to give 23% ee in the alkylation reaction. Similarly, N-benzyl-N-methylephedrinium flouride gave 26.4% ee but with a slightly lower chemical yield. Other Michael addition reactions, i.e., addition of sodium cyanide, diethylmalonate or α-methyl diethyl malonate to chalcone did not result in any optical induction. The addition of thiophenol to chalcone gave an optically active adduct with +32.9° specific rotation. Its optical purity was not determined.

Scheme 1.

Ephedrinium salts gave higher inductions in non-polar aprotic solvents (PhMe, CCl₄) than in solvents of higher dielectric constants (MeCN, MeOH and CH₂Cl₂). Temperature was also found to play a role in asymmetric induction. In the addition of nitromethane to chalcone with catalyst 5 and KF in toluene, the asymmetric induction decreased with increase in temperature.

N-alkylation of potassium phthalimide with ethyl 2-bromopropionate was carried out in the presence of ephedrinium salts[42]. These reactions were performed under solid–liquid phase transfer conditions. The optical purities were extremely low (0.85 to 2.5% ee). The reaction was found to proceed via a partial kinetic resolution of the substrate induced by the ion pair phthalimido–chiral ammonium cation (Scheme 2).

Scheme 2.

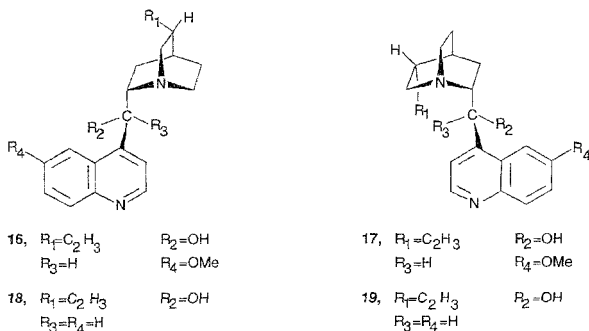A novel chiral PTC from ephedrine was prepared by Mazaleyrat[43]. By quaternerization with 2,2'-bis(bromomethyl)-1,1'-binaphthyl, axial chirality was introduced in the catalyst[43] (Scheme 3). When these catalysts were tested in sodium borohydride reduction of carbonyl

13a   **13b**

SCHEME 3.

compounds, modest enantiomeric excess (0-10.3% ee) were obtained, the highest being for phenyl *t*-butyl ketone with catalyst **13b**. Better results were obtained in the epoxidation of chalcone with 30% H_2O_2/ 12% NaOH in toluene. Catalyst **13a** induced 37.1% ee as compared to 1.7% with **13b**. The catalysts **13a** and **b** gave opposite enantiomers of the alcohol or epoxide, *i.e.*, (–) and (+), respectively.

Rate constants for acetophenone reductions with ephedrine catalysts have also been measured[44]. The synthesis of 1,2-dichloroalkalanes and acetylcyanohydrins was attempted using N-dodecyl-N-methyl ephedrinium bromide. Moderate chemical yields and very low optical yields were obtained[45].

Michael addition of diethylacetylamino malonate to chalcone by asymmetric phase transfer catalysis without solvent was carried out in the presence of ephedrinium salts **14** and **15**. Substituent effects on the benzyl moeity of the ammonium part of the catalyst was studied and a highest ee of 82% with the S(binaphthyl) catalyst was observed[46]. The high ee was attributed to the π–π attractive interactions between the catalyst and the electrophile (Scheme 4).
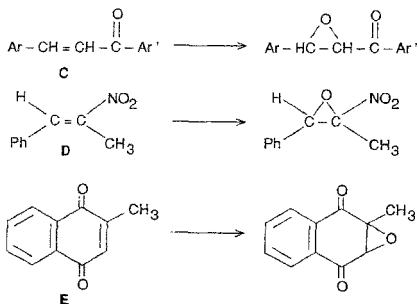
SCHEME 4.

1.2. Cinchona alkaloids

Quinine, quinidine, cinchonine and cinchonidine are the most important sources of chirality in the cinchona alkaloid family. They are important pharmaceutical drugs[47] and are also extremely useful in synthetic organic chemistry. Quinine is extensively used as a chiral-resolving agent[48]. Recently, chromatographic separation of chiral compounds has been achieved using quinine and quinidine-impregnated supports[49]. But the most interesting application of cinchona alkaloids resides in their ability to induce asymmetry when employed as chiral auxiliaries. Bredig and Fiske[50] made the first attempt to use these compounds to achieve optical induction in the preparation of cyanohydrins. They obtained an enantiomeric excess of 20%. Quinine acts as an asymmetric catalyst in a variety of synthetic transformations. The first case of a quinine-catalyzed Michael addition was reported in 1975[51]. In the [2+2] addition of chloral and ketene, optically active lactones with up to 98% ee were reported[52]. Cinchona alkaloid derivatives also act as excellent chiral ligands in asymmetric dihydroxylation of olefines[53].

From the point of view of phase transfer catalysis, cinchona alkaloid derivatives are the best known chiral PTCs to date. The quaternary salts prepared from the four important alkaloids, quinine(**16**), quinidine(**17**), cinchonine(**18**) and cinchonidine(**19**) are the most commonly used chiral phase transfer catalysts. Although quinine and quinidine are diastereomers, their opposite stereochemistry at the crucial carbons 8 and 9 is more characteristic of enantiomers. Thus, when these are used as chiral catalysts, if quinine gives one enantiomer in excess, the other enantiomer will predominate when quinidine is employed. Similar is the case with cinchonine and cinchonidine.

16, $R_1 = C_2H_3$ $R_2 = OH$
      $R_3 = H$ $R_4 = OMe$

18, $R_1 = C_2H_3$ $R_2 = OH$
      $R_3 = R_4 = H$

17, $R_1 = C_2H_3$ $R_2 = OH$
      $R_3 = H$ $R_4 = OMe$

19, $R_1 = C_2H_3$ $R_2 = OH$
      $R_3 = R_4 = H$

The first PTC reaction using cinchona alkaloids was reported by Wynberg *et al* [54,55]. Optically active epoxides were obtained in excellent chemical yields with ee up to 25% by a PTC process using benzylquininium chloride or benzylquinidinium chloride as chiral PTC. Epoxidations of compounds C, D and E (Scheme 5) were carried out in toluene in the presence of 30% H_2O_2/dilute sodium hydroxide and catalytic amounts of PTC. These represent the first clear cut examples of tangible asymmetric inductions in PTC processes. No mechanism was proposed. However, since the reaction is base catalyzed, it is possible that the enone picks up the OOH^- at the phase boundary, where the catalyst cation comes into play and exercises its chirality[11].
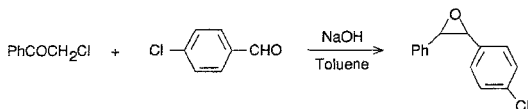

SCHEME 5.

Benzylquininium chloride (QUIBEC) was used to catalyze the sodium borohydride reduction of some aromatic ketones[37]. The highest optical yield was obtained in the case of phenyl *t*-butyl ketone(32%). The enantiomeric excess reported was 32% at 0°C and this

decreased to 25% at 25°C. The quinine salts were a little more selective than the ephedrine salts in the reduction of both simple and hindered ketones. The optical purities were however low (13 to 32% ee). Several other asymmetric epoxidations were carried out using QUIBEC[56]. Optically active epoxides were obtained from unsaturated ketones(chalcones) using 25% sodium hypochlorite as the epoxidizing agent. Racemic halohydrins, on kinetic resolution in the presence of QUIBEC, gave the epoxide in 6% enantiomeric excess.

A Darzen's condensation of chloroketones and aromatic aldehydes (Scheme 6) was attempted in the presence of QUIBEC. The epoxide was found to have an optical purity of 8%.
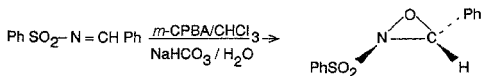

SCHEME 6.

In a number of 1,4-addition reactions catalysed by QUIBEC, the optical yield of products was found to be inversely proportional to the dielectric constant of the solvent[57]. Thus, nitrobenzene with the highest dielectric constant of 34.8 gave 10% ee whereas benzene with a dielectric constant of 2.28 showed an induction of 54% ee under the same conditions. The same is true in the epoxidation reaction of o-methoxychalcone.

Optically active 2-pthalimido esters were synthesized by means of phase transfer catalysis using cinchona alkaloid derivatives as the chiral catalysts[58]. Thus, when potassium phthalimide was reacted with ± 2-bromo alkanoates under solid–liquid phase transfer conditions in the presence of (–)-benzylcinchonidinium chloride (BCDC) or (–)-benzylcinchoninium chloride (BCNC), the esters obtained had optical purities of 9.5 and 19.1% ee, respectively.

2,3-Epoxycyclohexanone has been obtained in an optically active form for the first time by epoxidation of cyclohexenone catalyzed by QUIBEC[59]. The epoxidation was performed using t-buOOH in toluene in the presence of solid sodium hydroxide and 20% ee was observed. Substitution on the cyclohexanone ring was found to lower induction.

Further examples of asymmetric epoxidations in the presence of cinchona salts have been reported. The epoxidation of substituted 1,4-naphthoquinones was performed in the presence of QUIBEC[60]. The highest ee was obtained in the case of 2-phenylnaphthoquinone (~45% ee). In the other cases, the ee's range from 5 to 39% ee for 2-methylnaphthoquinone and 2-cyclohexylnaphthoquinone, respectively. A possible mechanism of these epoxidations was discussed.

When the oxidation of N-benzylidene-2-benzene sulfonamide was carried out in the presence of MCPBA using (–)-QUIBEC or (+)-BCNC as a chiral PTC, optically active 2-benzenesulfonyl-3-phenyl oxaziridine was obtained[61] in 1.4 to 10.6% ee (Scheme 7).


SCHEME 7.

Cinchona alkaloid salts were used in a number of Michael addition reactions such as the addition of nitroalkanes[41] and other nucleophiles to *trans*-chalcone, cyclohexenone, α, β-unsaturated sulfones and sulphoxides with KF as the base. Optical yields up to 35% ee have been obtained in these reactions[62, 53, 64]. Furthermore, the effect of a number of variables such as: (i) structural variations within the catalyst, (ii) temperature of reaction, (iii) the polarity of solvent, and (iv) the nature of the inorganic base on optical yields was studied in detail. A comparative study of optical yields obtained using salts derived from cinchona and ephedra alkaloids was also made[65]. Various derivatives of cinchona alkaloids were used for this purpose. It was found that cinchona alkaloid 'onium salts gave higher asymmetric induction than the ephedra salts in most reactions. The authors found that the presence of the hydroxyl group β to the onium function is essential to achieve substantial induction. The absolute configuration at the C-8 and C-9 carbons of the cinchona alkaloid was found to determine the stereochemical course of the reaction. The authors proposed that while conformationally free ephedrine salts are more efficient with the conformationally mobile chalcone, the opposite is true with the more rigid cyclohex-2-enone where cinchona 'onium salts are the more efficient catalysts.

Further experiments were conducted to determine the importance of the β hydroxy functionality. When acylated catalysts were used in the synthesis of optically active ethyl-2-phthalimido propionates (solid–liquid PTC) and asymmetric borohydride reduction of aromatic ketones (liquid–liquid PTC) no optically active product was obtained. This confirms the experimental evidence previously given, that the β-hydroxy functionality plays an important role in optical induction and the stereochemical course of reactions. Additional support for this observation was obtained from other experimental results—(i) the reduction of acetophenone using benzylbrucinium chloride, a conformationally rigid catalyst without an OH substituent afforded racemic alcohol under liquid–liquid conditions; (ii) the kinetic resolution of ethyl-2-bromopropionate and the borohydride reductions was repeated in the presence of N-benzyldeoxyquininium chloride. In N-alkylation, no reaction occurred while the reduction of phenyl *t*-butyl ketone with NaBH₄ afforded a racemic alcohol.

In contradiction to the above results, Verbicky and O'Neal [66] claimed that optically active ethers were obtained with chiral catalysts which were neither sterically demanding nor containing any hydroxy functionality. The catalyst they used was 2-methylbutyltriethylammonium bromide (20). These results could not be reproduced by other authors[67]. Moreover, even a sterically more demanding catalyst 21 could not induce asymmetry in the above reaction. This reiterates the fact that a multipoint interaction between catalyst and the substrate is essential for optical induction.
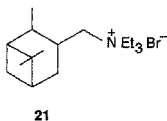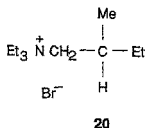
A perusal of the literature so far has shown that the selectivity in PTC reactions is dependent on various factors like: (i) the structure of the phase transfer catalyst, (ii) reaction

conditions such as temperature, polarity of the solvent, catalyst concentration, etc., and (iii) the structure of the substrate. Of these, the most important factor was recognized to be the structure of the catalyst. Several groups tried to modify the structure of the cinchona salts so as to obtain higher enantioselectivities.
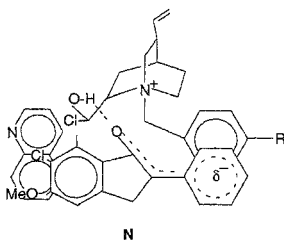
Baba *et al*[68-70] prepared novel phase transfer catalysts **22**, **23** and **24** which were so designed as to have a C_2 symmetry in the first two catalysts and a rigid framework with a fluorenyl group in the third catalyst.

24
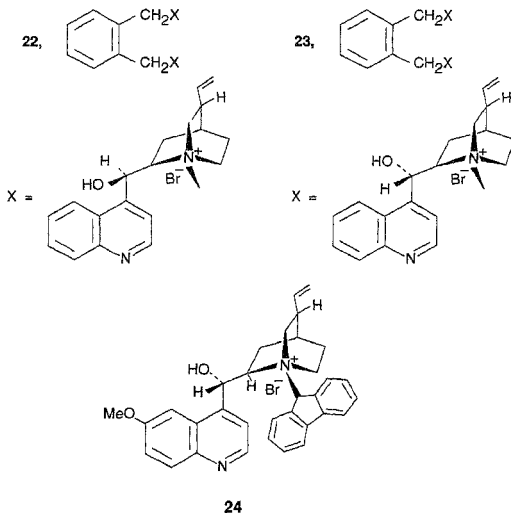
Conformationally free epoxidizing agents **F** and **G** as well as rigid epoxides **H**, **I** and **J** were used in the epoxidation of cyclohexenones and 2-methylnaphthoquinone. The fluorenyl group, either when introduced into the PTC or used as the oxidizing agent, remarkably improved optical yields.

Epoxidation of cyclohexenone with **F** in the presence of catalyst **22** gave the corresponding oxirane in 33% ee whereas with peroxides **H–J**, selectivity improved to 63% ee (61, 63 and 38% ee, respectively). Similarly, with catalyst **24**, the oxidising agent **F** yielded 61% ee.

But the real breakthrough was made by Dolling *et al*[18,71,72] in alkylation reactions. N--p-Trifluoromethylbenzyl cinchoninium bromide (**25**) was used to catalyze the alkylation of indanones. Thus, compound **K** was methylated with·MeI in the presence of the above PTC and NaOH to give a ratio of products (+)/(−) = 95.3 : 4.7 (Scheme 8). Alkylation of the

F

G

H

I

J

2-propyl compound **L** by ClCH$_2$CH = CClMe in toluene/aq.NaOH containing the catalyst **25** gave the S-(chlorobutenyl)propyl indanone (Scheme 9) in 99% yield and 92% ee. Analogous alkenylation in the presence of N-(p-trifluoromethylbenzyl)cinchonidinium bromide gave the R enantiomer.

K

SCHEME 8.

SCHEME 9.

The high stereoselectivity of the alkenylations was explained to be the result of a tight ion pair formation between the PTC and the indanone enolate[73]. It was proposed that the indanone anion (**M**) and the N-benzylcinchoninium halide (**25**) fit naturally on top of each other to form a complex (**N**) which is held by the interaction between the benzyl group of the catalyst and the 2-phenyl group of **M** on the one side and between the quinoline and methoxydichlorobenzene moieties on the other. The C-9 hydroxyl provides a directional handle for the ionic attraction *via* hydrogen bonding to the indanone anion.

25   R = CF$_3$ X = Br

M

N

Lee and Wong[74] used the above catalyst in the alkylation of oxindoles. Enantiomers of alkylated oxindoles, useful intermediates for the preparation of physostigmines, were prepared by the reaction of racemic oxindoles ± **O** (R = Me, Et, CH₂Ph) with 1 eq. of XCH₂CN (X=Cl, Br, I) in a two-phase aqueous–organic mixture containing a strong inorganic base and a cinchoninium or quininium catalyst. The best catalyst was found to be N-(4-trifluoromethylbenzyl)-cinchoninium bromide (**25**) which gave 72% ee in the alkylation of **O** (R = Me) with ClCH₂CN (Scheme 10).


Scheme 10.

The first practical asymmetric synthesis of α-amino acids was reported by O'Donnell *et al*[75] using cinchona alkaloid 'onium salts. The structure of the substrate plays a role in the enantioselectivity, with the sterically more demanding amino acids such as *t*-butyl (diphenylmethylene) glycinate giving the highest ee of 56%. The notable point here is that the catalysts with or without the *p*-CF₃ group on the N-benzyl ring showed the same inductions. Increasing the concentration of base increased optical yields with the best result of 66% ee obtained with 50% NaOH solutions.

In an extension of the above work, synthesis of *p*-hydroxy-α-amino acids by aldol condensation between *t*-butyl(diphenylmethylene) glycinate and aldehydes under phase transfer catalytic conditions in the presence of chiral N-benzyl cinchoninium chloride was attempted[76]. A maximum enantioselectivity of 12% was reported with heptanal.

Molecular recognition techniques were used to examine complexes formed between chiral phase transfer catalysts derived from quinine and enolates that were known to be alkylated in high enantioselectivity[77]. The results support the alkylation mechanism put forward by Dolling *et al*[73].

1.3. Sparteine and brucine alkaloids

Derivatives of brucine, **26a**, **26b** and **26c** and (–)-16-methyl sparteinium iodide (**27**) have been used as chiral phase transfer catalysts in some typical reactions such as sodium borohydride reductions of pivalophenone, in the oxidation of 2-ethyl-1-tetralone, in the Michael addition of cyanide ion to pivalacetophenone and in the epoxidation of chalcone. The autooxidation of 2-ethyl-1-tetralone in the presence of catalysts **26a** and **26b** led to moderate optical yields (26 and 25%). But in all the other cases the optical purities were low. The low selectivities were attributed to the absence of an OH group β to the nitrogen and also to the insufficient rigidity and face specificity in these systems[78].
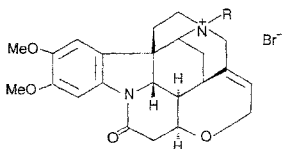
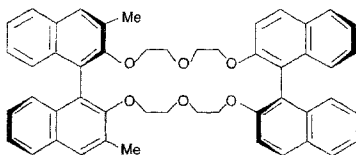**26a**, R = CH₂Ph
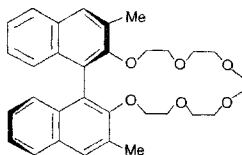**26b**, R = CH₂C₆H₄CF₃
26c, R = CH₂COOEt
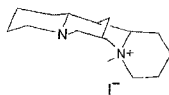
27

1.4. Chiral crown ethers

In the recent years, a large number of crown ethers have been synthesized and their chemistry studied. A few authors have tried to synthesize chiral crowns for asymmetric synthesis. Bis(dimethyl)naphthocrowns (**28, 29**) were synthesized by Cram *et al*[17]. Carbon acids **P**, **R**,


28

29

and **T** (Scheme 11) when added to methyl vinyl ketone or methyl acrylate in toluene in the presence of the above catalysts gave the corresponding Michael adducts **Q**, **S** or **U** (Scheme 11). The chemical and optical yields were excellent. The enantiomeric excesses reported were 99, 83 and 65% ee for compounds **Q**, **S** and **U**, respectively.

Optically active crowns such as **30** were also used as PTCs in benzoin condensations, a C-alkylation, a base-catalysed autoxidation and a hypochlorite epoxidation[79, 80]. Catalyst **30** gave a maximum ee of 71% in Michael addition reactions. Important observations include a
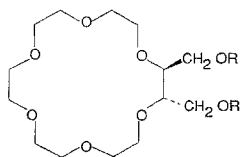
30   R = Benzyl

possible inversion of configuration when changing potassium for sodium ions and when increasing the side groups at the crown. Additional stereogenic centres in the side chains and OH groups were not found to be advantageous, at least in the studied cases.

1.5. L(+)-Methionine derivatives

Chiral salts **31** and **32** were prepared starting from L-(+)-methionine and their behaviour investigated[81] in 1,4 addition reactions, *i.e.*, the addition of nitromethane to chalcone, of
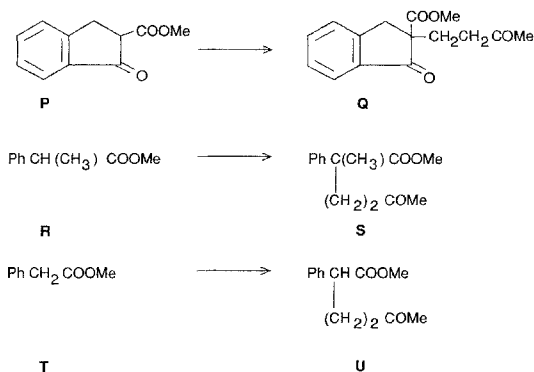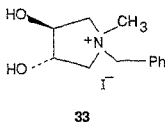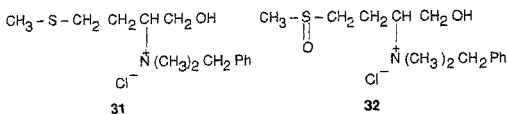

SCHEME 11.

thiophenol to cyclohexenone and methyl vinyl ketone to methyl-1-oxoindan-2-carboxylate. Though the chemical yields were quite high, no optical inductions were observed.

1.6. Tartaric acid derivatives

A chiral catalyst (3S,4S)-1-benzyl-3,4-pyrrolidin-diol onium iodide (**33**) was synthesized from D(+)-tartaric acid[82]. Alkylation of active methylene compounds using this catalyst under solid–liquid phase transfer conditions was reported.

The catalyst was found to be more active than conventional tetra-alkyl ammonium salts,

$CH_3 - S - CH_2$ $CH_2 CH CH_2 OH$

$\overset{+}{N} (CH_3)_2 CH_2 Ph$

Cl^-

31

$CH_3 - \overset{O}{\underset{||}{S}} - CH_2 CH_2 CH CH_2 OH$

$\overset{+}{N} (CH_3)_2 CH_2 Ph$

Cl^-

32

HO,,,,

HO····

$\overset{+}{N}$—CH_3

—Ph

I^-

33

giving high chemical yields. But the optical rotation of the product reported is quite low (0.92°—no % ee reported).

2. Other catalysts

2.1. Benzyl[cis,2(hydroxymethyl)cyclohexyl] dimethyl ammonium bromide (34)

Both enantiomers, (+) and (−) of the title compound, were prepared[83] in 30–40% overall yield from commercially available *cis* 1,2-cyclohexanedicarboxylic anhydride in six steps. Enantioselective alkylation of active methylene compounds using this catalyst gave values

$CH_2 OH$

cis

$\overset{+}{N}$—$CH_2 Ph$

$\overset{|}{Br^-}$

CH_3 CH_3

34
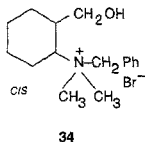
comparable to those obtained with ephedrinium catalysts. The highest specific rotation (+18.2°) was obtained for the addition of allyl bromide to 2-acetylcyclohexenone (−23.5° reported by Fiaud[38]).

2.2. (2R, 3R)- 2, 3- Dihydroxytetramethylene-bis (diphenylbenzylphosphonium) dibromide(35)

Optically active phosphonium salts were used as catalysts in borohydride reductions[84]. The catalyst **35** showed optical induction in the reduction of acetonaphthone giving 22.2% ee of the optically active (−) alcohol. Catalyst **36** gave the racemic alcohol. The extent of asymmetric induction in the reduction of bulky trityl phenyl ketone with **35** reached a maximal value of 41.5% ee. Catalysts **37** and **38** gave very low optical purities of 5%.

2.3. Triphase catalysts

Colonna *et al* [40] reported in 1978 that in Darzen's reaction optical purities improved from
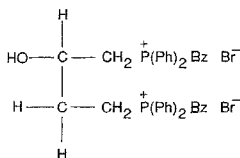
2.5% in the case of ephedrine catalysts to 20–25% when these catalysts were attached to a polystyrene support. In general, this early optimism has not been followed by any significant success. Low optical purities of 2.5% were reported in ester synthesis from acid salts,
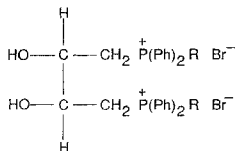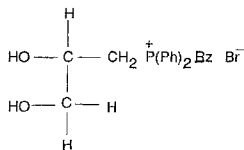

35   R = Benzyl
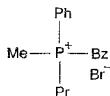
36

37

38

chloride and an anhydride, using optically active polyamines[85] under solid–liquid phase transfer conditions. There have been other reports of small levels of induction[86, 87]. The significance of these results is not clear. Further, no improvement in the enantioselectivity was observed when methionine salts were attached to polymer supports[81].

Optically active adducts were obtained in Michael additions when cinchona and ephedra alkaloid salts bonded to polymers were used as triphase catalysts[88]. While the polymer-supported ephedrine catalysts did not induce any optical activity the cinchona salts bonded to polymers showed a selectivity of up to 27% ee in the Michael addition of ester to methyl vinyl ketone. The corresponding results for the unsupported catalysts is not available for comparison.

In partial contradiction to the above results, Kelly et al [89] reported <1% ee with polymer-supported cinchona catalysts. These catalysts were used in a range of two-phase reactions which included a number of displacement reactions, sodium borohydride reductions of prochiral ketones, epoxidation of chalcone, addition of nitromethane to chalcone and the addition of thiophenol to cyclohexenone. Some of the reactions were performed under solid–liquid conditions and others under liquid–liquid conditions. Despite the wide range of chiral catalysts employed in a variety of phase transfer reactions, no significant optical inductions were observed. In general, the chemical yields reported were high but the accompanying optical rotations were very low—corresponding to <1% enantiomeric excess.

Triphase catalysis with poly-amino acids was tried by Julia et al [90]. These catalysts are very specific to chalcone epoxidations. Excellent optical yields of 96% ee were reported with poly-S-alanine. But the modification of the amine to its quaternary salt, which is the catalyst of interest in the context of phase transfer catalysis, not only reduced chemical yields but also affected the asymmetric induction, lowering it to 20% ee.

Sarkar and Rao[91] described the use of montmorillonite-supported (−)-N-dodecyl-N-methylephedrenium borohydride in the reduction of ketones under phase transfer conditions. The reductions of the ketones were quite facile but the accompanying asymmetric inductions were quite low ranging from 1.92% to 9.07% ee.

2.4. Transition metal complexes

Complexes derived from (S)-2-(aminomethyl) pyrrolidine or its N'-benzyl derivative, benzaldehyde or benzophenone derivatives and $Cu(NO_3)_2$, $Ni(NO_3)_2$ or Na_2PdCl_4 catalyze the alkylation of amino acid Schiff base complexes. Benzylation of these complexes under phase transfer conditions and acidolytic decomposition of the complexes afforded phenylalanine and α-methylphenylalanine in 33–87% yield and 3–21% optical purity[92,93].

3. Outlook

The present status on asymmetric synthesis using chiral phase transfer catalysts thus reveals that only moderate success has so far been achieved. The recent papers however demonstrate that very high enantiomeric purities are obtained in specific systems using some of the chiral PTCs. Regarding the nature of a chiral PTC while some essential requirements such as a β-OH are known it is still not clearly understood about the interactions between the substrate and the catalyst. This aspect is also receiving attention as evidenced by a very recent publication[46]. In our laboratory, we have synthesised several chiral PTCs from readily available and naturally occurring (+)-camphor and interesting results are obtained regarding the structural requirements of them (unpublished work)[94]. From these studies and others it is believed that the new and novel chiral PTCs of general utility will be developed in the near future.

References

1.		Ger. Offen. 1913, 268621; *Chem. Zentrabl.*, 1914, 310.
2.	MAKOSZA, M AND SERAFIN, B.	*Roc. Chem.*, 1965, **39**, 1223–1230, and subsequent papers.
3.	BRANDSTROM, A. AND GUSTAVII, K.	*Acta Chem. Scand.*, 1969, **23**, 1215–1218.
4.	BRANDSTROM, A.	*Kem. Tidskr.*, 1970, **82**, 32–37.
5.	STARKS,C. M. AND NAPIER, D. R.	Catalysis of heterogeneous reactions, Ital.Pat., 1968, 832,967, Brit. Pat., 1971, 1,227,144, French Pat., 1969, 1,573,164, and further concordances, *Chem. Abstr.*, 1970, **72**, 115271t.
6.	STARKS, C. M.	*J. Am. Chem. Soc.*, 1971, **93**, 195–199.
7.	DEHMLOW, E. V.	*Tetrahedron*, 1971, **27**, 4071–4075.
8.	DEHMLOW, E. V.	Recent progress in performing and understanding phase transfer catalysis, *Proc. IUPAC 6th Symposium, Organic Synthesis, Modern Trends*, 1986, 179–189.
9.	WEBER, W. P. AND GOKEL, G.W.	*Phase transfer catalysis in organic synthesis*, 1977, Springer-Verlag.

10. BRANDSTROM, A. — *Preparative ion pair extraction An introduction to theory and practice*, 1974, Apotekarsocieteten/Hassle Lakemdel, Stockholm

11. DEHMLOW, E. V. AND DEHMLOW, S. S. — *Phase transfer catalysis*, 2nd enlarged edn. 1983, Verlag Chemie, Weinheim.

12. STARKS, C M AND LIOTTA, C. — *Phase transfer catalysis, Principles and techniques*, 1978, Academic Press.

13. FORD, W. T. AND TOMOI, M. — *Adv Polym. Sci*, 1984, **55**, 49-104.

14. SHERRINGTON, D. C. AND KELLY, J. — *Polym Sci Technol.*, 1984, **24**, 249–261.

15. CASSAR, L. — *Ann. N Y Acad. Sci*, 1980, **333**, 208–224.

16. HARADA, A. — *Yuki Gosei Kagaku Kyokaishi*, 1990, **48**, 517–521.

17. CRAM, D. J. AND SOGAH, G. D Y — *J Chem Soc , Chem Commun*, 1981, 625–628.

18. BHATTACHARYA, A., DOLLING, U. H, GARBOWSKI, E. J. J, KARADY, S, RYAN, K. M. AND WEINSTOCK, I. M. — *Angew Chem*, 1986, **98**, 442–443; *Angew Chem. Int. Edn Engl*, 1986, **25**, 476–477.

19. GOKEL, G.W. AND DURST, H. D. — *Synthesis.* 1976, 168–184.

20. CRAM, D.J. AND GRAM, J M. — *Science*, 1974, **183**, 803–809.

21. DIETRICH, B., HOSSEINI, M. W., LEHN, J. M. AND SESSIONS, R. B. — *J. Am. Chem. Soc*, 1981, **103**, 1282–1283.

22. DE JONG, F., REINHOUDT, D. N., AND SMITH, C. J. — *Tetrahedron Lett.*, 1976, 1375–1378.

23. STARKS, C. M. AND OWENS, R. M. — *J. Am. Chem. Soc.*, 1973, **95**, 3613–3617.

24. DYRRSSEN, D., LILJENZIN, J. O. AND RYDBERG, J. — *Solvent extraction chemistry*, 1967, North–Holland

25. MODIN, R. AND SCHILL, G. — *Acta Pharm Suec*, 1967, **4**, 301–326

26. MAKOSZA, M. — *Pure Appl. Chem.*, 1975, **43**, 439–462.

27. GUSTAVII, K. — *Acta Pharm Suec.*, 1967, **4**, 233–246.

28. CLIFFORD, W. E. AND IRVING, H. — *Anal. Chim. Acta*, 1964, **34**, 1–10.

29. MAKOSZA, M. AND BIALECKA, E. — *Synth Commun.*, 1976, **6**, 313–318.

30. IVANOV, I. M., GINDIN, L. M. AND CHICHAGOVA, G.N. — Anion exchange extraction series–*Izv. Sib. otd Akad Nauk SSR, Ser. Khim. Nauk*, 1967, 100–104; *Chem Abstr*, 1968, **69**, 13377c. Anion exchange extraction principles, *Khim Protsessov Ekstr., Mater Konf. Khim. Ekstr.*, 3rd edn, 1969, (Pub. 1972), 207–210; *Chem Abstr.*, 1973, **78**, 8481.

31. KELLER, W.E. — *Phase transfer reactions*, Vols I and II, 1986 and 1987, Fluka–Compendium.

32. HIYAMA, T., MISHIMA, T., SAWADA, H. AND NOZAKI, N. — *J. Am Chem. Soc.*, 1975, **97**, 1626–1627.

33. HIYAMA, T., SAWADA, H., TSUKANAKA, H. AND NOZAKI, H. — *Tetrahedron Lett.*, 1975, 3013–3016.

34. COLONNA, S. AND FORNASIER, R. — *Synthesis*, 1975, 531-532.

35. BALCELLS, J., COLONNA, S. AND FORNASIER, R. — *Synthesis*, 1976, 266–267.

36   MASSE, J. P. AND PARAYRE, E. R.   *J Chem. Soc., Chem. Commun*, 1976, 438–439.

37. COLONNA, S. AND FORNASIER, R.   *J. Chem. Soc., Perkin Trans 1*, 1978, 371–373.

38. FIAUD. J.-C.   *Tetrahedron Lett.*, 1975, 3495–3496.

39   DEHMLOW, E. V., SINGH, P.   *J. Chem. Res. (S)*, 1981, 292–293.
     AND HEIDER, J.

40. COLONNA, S., FORNASIER, R.   *J Chem. Soc., Perkin Trans. 1*, 1978, 8–11.
     AND PFEIFFER, U.

41. COLONNA, S., HIEMSTRA, H.   *J Chem. Soc , Chem Commun*, 1978, 238–239.
     AND WYNBERG, H.

42. ANNUZIATA, R., CINQUINI, M.   *J. Chem. Soc , Perkin Trans. 1*, 1980, 2422–2424.
     AND COLONNA, S.

43. MAZALEYRAT, J. P.   *Tetrahedron Lett.*, 1983, **24**, 1243–1246.

44. MASSE, J. P. AND PARAYRE, E. R.   *Bull Soc. Chim. II*, 1978, 395–400.

45. JULIA, S. AND GINEBREDA, A.   *Tetrahedron Lett.*, 1979, 2171–2174.

46. LOUPY, A. AND ZAPARUCHA, A.   *Tetrahedron Lett*, 1993, **34**, 473–476.

47. GOODMAN, L. S. AND GILMAN, A. G.   *The pharmaceutical basis of therapeutics*, 7th edn, 1985,
                                             pp.756 &1041, McMillan.

48. JOCQUES, J . COLLET, A. AND WILEN, S. H. *Enantiomers: racemates and resolution*, 1981, pp. 254 & 257,
                                             Wiley.

49. SALVADORI, P., ROSINI, C.,   *Tetrahedron*, 1987, **43**, 4969–4978.
     PINI, D., BERTUCCI, C., ALTEMURA, P.,
     BARRETTA, U. G. AND RAFFAELLI, A.

50. BREDIG. G. AND FISKE, P. S.   *Biochem. Z*, 1912, **46**, 7–23.

51. WYNBERG, H. AND HELDER, R.   *Tetrahedron Lett*, 1975, 4057–4060.

52. WYNBERG, H. AND STARING, E. G. J.   *J Am. Chem. Soc*, 1982, **104**, 166–168.

53. WAI, J. S. M., MARKO, I.,   *J Am. Chem Soc.*, 1989, **111**, 1123–1125.
     SVENDSEN, J. S., FINN, M. G.,
     JACOBSEN, E. N. AND SHARPLESS, K. B.

54. WYNBERG, H.   *Chimia*, 1976, **30**, 445–451.

55. HELDER, R., HUMMELEN, J. C.,   *Tetrahedron Lett.*, 1976, 1831–1834.
     LAANE, R. W. P. M., WIERING, J. S.
     AND WYNBERG, H.

56. HUMMELEN, J. C. AND WYNBERG, H.   *Tetrahedron Lett.*, 1978, 1089–1092.

57. WYNBERG, H. AND GREUDANUS, B.   *J. Chem Soc., Chem. Commun.*, 1978, 427–428.

58. JULIA, S., GINEBREDA, A. AND GUIXER, J. *J. Chem. Soc., Chem. Commun.*, 1978, 742–743.

59. WYNBERG, H. AND MARSMAN, B.   *J. Org. Chem.*, 1980, **45**, 158–161.

60. PLUIM, H. AND WYNBERG, H.   *J. Org. Chem.*, 1980, **45**, 2498–2502.

61. DAVIS, F. A. AND STRINGER, O. D.   *J. Org. Chem.*, 1982, **47**, 1774–1775.

62. ANNUNZIATA, R., CINQUINI, M. AND   *Chem. Ind.*, 1980, 238.
     COLONNA, S.

63. WYNBERG, H.   *Top. Stereochem.*, 1986, **16**, 87–129.

64. COLONNA, S., RE, A. AND WYNBERG, H.   *J. Chem. Soc., Perkin Trans. 1*, 1981, 547–552.

65. JULIA, S., GINEBREDA, A., GUIXER, J., MASANA, J., TOMAS, A. AND COLONNA, S. *J Chem. Soc., Perkin Trans 1*, 1981, 574–577.

66. VERBICKY, J. W. JR. AND O'NEIL, E. A. *J. Org. Chem*, 1985, **50**, 1786–1787.

67. DEHMLOW, E. V. AND SLEEGERS, A. *J. Org Chem.*, 1988, **53**, 3875–3877.

68. BABA, N., ODA, J. AND KAWAGUCHI, M *Agric Biol. Chem*, 1986, **50**, 3113–3117.

69. BABA, N., KAWAHARA, S., HAMADA, M. AND ODA, J. *Bull Inst Chem Res, Kyoto Univ.*, 1987, **65**, 144–146

70. BABA, N., ODA, J., KAWAHARA, S. AND HAMADA, M. *Bull. Inst. Chem. Res, Kyoto Univ.*, 1989, **67**, 121–127.

71. DOLLING, U. H., DAVIS, P. AND GABROWSKI, J. J. *J. Am. Chem Soc.*, 1984, **106**, 446–447.

72. DOLLING, U. H., GABROWSKI, E. J AND PINES, S. H. A manipulated enantiomer mixture by asymmetric chiral phase transfer catalysis, Eur. Pat. Appl. EP 121,872, 17th Oct. 1984, *Chem. Abstr*, 1984, **102**, 113080u.

73. HUGHES, D. L., DOLLING, U. H., RYAN, K. M., SCHOENEWALDT, E. F. AND GABROWSKI, E. J. *J Org. Chem*, 1987, **52**, 4745–4752.

74. LEE, T. B. K. AND WONG, G. S. K. Process for the enantioselective synthesis of alkylated oxindoles used as intermediates in the preparation of physostigmine, Eur. Pat. Appl. EP 438,796, 31 July, 1991, *Chem Abstr.*, 1991, **115**, 183092s.

75. O' DONNEL, M. J., BENNETT, W. D. AND WU, S. *J. Am. Chem. Soc.*, 1989, **111**, 2353–2355.

76. GASPARSKI, C. M. AND MILLER, M. J. *Tetrahedron*, 1991, **47**, 5367–5378.

77. LIPKOWITZ, K.B., CAVANAUGH, M. W., BAKER, B. AND O'DONNELL. *J. Org. Chem.*, 1991, **56**, 5181–5192.

78. DEHMLOW, E. V. AND ROMERO, M. S *J. Chem. Res. (S)*, 1992, 400–401.

79. DEHMLOW, E. V. AND ENUFINKE, V. *Liebigs Ann Chem.*, 1992, 283–285.

80. DEHMLOW, E. V. AND COLONNA, S. *Liebigs Ann Chem.*, 1992, 1091–1094.

81. BANFI, S., CINQUINI, M. AND COLONNA, S. *Bull Chem. Soc. Jap*, 1981, **54**, 1841–1843.

82. VALLI, V. L. K., SARMA, G. V. M. AND CHOUDARY, B. M. *Indian J. Chem B*, 1990, **29**, 481–482.

83. SAIGO, K., KODA, H. AND NOHRA, H. *Bull Chem. Soc. Jap.*, 1979, **52**, 3119–3120.

84. KINISHI, R., UCHIDA, N., YAMAMOTO, Y., ODA, J. AND INOUYE, Y. *Agric. Biol. Chem*, 1980, **44**, 643–648.

85. BERGMANN, E. D. AND CORETT, R. *J. Org. Chem.*, 1956, **21**, 107–110.

86. KOBAYASHI, N. AND IWAI, K. *Makromol. Chem., Rapid Commun.*, 1981, **2**, 105–108.

87. KAWAKAMI, Y., SUGIURA, T., MIZUTANI, Y. AND YAMASHITA, Y. *J. Polym Sci.*, 1980, **18**, 3009–3020.

88. HODGE, P., KOSHDELL, E. AND WATERHOUSE, J. *J. Chem. Soc, Perkin Trans. 1*, 1983, 2205–2209.

89. KELLY, J and SHERRINGTON, D. C.   *Polymer*, 1984, **25**, 1499–1504.

90   JULIA, S., GUIXER, J., MASANA, J.,   *J Chem Soc , Perkin Trans. 1*, 1982, 1317–1323.
     ROCAS, J., COLONNA, S.,
     ANNUNZIATA, R. AND MOLINARI, H.

91. SARKAR, A. AND RAO, B. R.   *Tetrahedron Lett.*, 1991, **32**, 1247–1250.

92. ESIKOVA, I. A. AND SEREBRYAKOV, E.P.   *Izv Akad. Nauk. SSSR, Ser. Khim ,* 1989, 1836–1843.

93. BELOKON, Y. N., VIDENSKAYA, S. O.,   *Izv. Akad Nauk SSSR, Ser Khim ,* 1991, 126–134.
     SOPOROVSKAYA, M. B., TYRYAAPKIN, V. A.
     AND BELIKOV, V. M.

94   BHARATI RAO, T.   *Asymmetric synthesis using phase transfer catalysis,*
                                                 Ph.D. Thesis, University of Kerala, Trivandrum, June 1993.