PHASE TRANSFER CATALYSIS: A GREEN APPROACH IN ORGANIC SYNTHESIS

Jayashri R. Jagtap[a*], Pranali A. Jadhav[a], Meenakshi N. Deodhar[a], Rajshree S.Chavan[a]

a. *Department of Pharmaceutical Chemistry, Pune District Education Association's Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune, Maharashtra, India- 412301*

ABSTRACT:

Green chemistry, also called sustainable chemistry, is a new field that encourages the look and development of chemicals using principles that minimize the utilization and generation of toxic chemicals. Waste reduction by means of clever strategies and catalysis is the heart of green chemistry. In recent years, catalysts have taken an important role in solving a variety of problems, particularly associated with energy and environment. Catalysts are the primary nanomaterials with wide applications both in academic research and industry. Catalysis research features an incredible opportunity to improve the environment for the reason that the catalytic process can produce cleaner/greener technologies. In this review, the elementary concepts of phase-transfer catalysis (PTC), its classification, applications, and detailed aspects such as the most proficient and environment-friendly green method of organic synthesis, particularly for industrial purpose, have been reviewed.

Key words: Green chemistry, PTC, Applications, PT Catalyst, Greener, soluble PTC etc.

1. INTRODUCTION:

Over three decades, green chemistry has become a significant adoption by industry around the world and for all practitioners and learners in the research community as green chemistry accomplishes an economically beneficial ways for industry and helps to solve the scientific challenges of protecting human health and environment at the molecular level. Green chemistry, likewise known as sustainable chemistry, is defined as the design or synthesis of chemical products and processes which can eliminate or reduce the use or generation of hazardous substances[1].

The increasing use of catalytic process such as Phase- transfer catalysis (PTC) can substantially reduce waste formation at the source, resulting in primary pollution prevention. Phase transfer catalysts are heterogeneous and positive catalysts that facilitate reaction between two substances that have different immiscible phases. These catalysts accelerate the rate of reaction between chemicals and help in solubilizing salts in organic phases. PTC are used in the synthesis of organic chemical compounds *viz.* pharmaceuticals and agrochemicals. PTC are especially useful in green chemistry allowing the use of water so the need for organic solvents are reduced. Normally, the reaction with PTC can be carried out in mild conditions and easy workup procedure so highly used in industrial scale[2]. The objective of this review was to provide brief idea of Phase-transfer catalysis as one of the strategies of green chemistry.

1.1. History:

The term green chemistry was first established as in reaction to the Pollution Prevention Act 1990, which specified that U.S. national policy should minimize pollution by improved strategies such as cost-effective changes in processes, products, raw materials, and recycling as an alternative to treatment and disposal. For inspiring redesign of existing chemical products and processes with diminishing impacts on human health and the environment, in 1991, the U.S. Environmental

Protection Agency (EPA) Office of Pollution Prevention and Toxics had commenced a research grant program. The EPA, in partnership with the U.S. National Science Foundation (NSF), in the early 1990s continued to fund basic research study in green chemistry.

The attention towards academic and industrial green chemistry success stories was drawn by the introduction of the annual Presidential Green Chemistry Challenge Awards in 1996. The technology and the awards program are now a foundation stone of the green chemistry educational curriculum. In the mid-to-late 1990s the number of international meetings on green chemistry, such as the Gordon Research Conferences on Green Chemistry, and green chemistry networks established in the United States, the United Kingdom, Spain, and Italy.

In 1998, the twelve Principles of Green Chemistry were launched, providing a new theme with a clear set of guidelines for further development. The Royal Society of Chemistry launched its journal of Green Chemistry in 1999.

As national webs have grown-up, in the past 10 years, green chemistry associated issues have appeared in core journals, and green chemistry concepts have continued to gain alertness. A clear mark of this was provided by awarding Nobel Prize in 2005 for Chemistry to Chauvin, Grubbs, and Schrock, which clapped their work as “a great step forward for green chemistry”[3].

1.2. Trends in Green Chemistry:

The main goals of green chemistry are to design, development and utilization of chemical products and processes that lessen or abolish the use or formation of substances that are dangerous to the environment as well as human health. The main goals of green agenda are advanced through some of the following leading trends:

a. Research in the area of catalytic and biocatalytic reactions for obtaining highly specific, pure compounds free from toxic by-products.
b. Looking for new raw materials that are harmless and renewable, for example, biomass.
c. Planning for less toxic eco- friendly chemicals.
d. Discovering and testing a new alternative, safe and renewable reaction media such as water, ionic liquids, and supercritical fluids.
e. Finding and trying new alternative reaction conditions, such as microwave, ultrasound, and light catalysed reactions.
f. Exploration of alternative routes for the purification of contaminated air and water. [4]

1.3. Principles of Green Chemistry:

In the 1990s, John Warner and Paul Anastas proposed 12 principles of green chemistry that are still in use today. These principles, are based on the reduced or nonuse of hazardous solvents in chemical processes, moreover producing non- waste products. [5]

1. Waste prevention
2. Maximize atom economy
3. Less hazardous chemical synthesis
4. Designing safer chemicals and products
5. Safe solvents and auxiliaries
6. Design for energy efficiency
7. Use of renewable feedstock
8. Avoid chemical derivatives
9. Catalysis
10. Design for degradation
11. Real-time pollution prevention
12. Safer chemistry for accident prevention

1.4. Applications of Green Chemistry

1.4.1.Pharmaceutical applications:

Pharmaceutical companies have the ability to reduce the environmental pollution by using the knowledge related to green chemistry. Green chemistry is involved in developing innovative and safer drug delivery methods that are more efficient, effective and could help multitudes of patients[6].

Examples: -

1. Phosphoramidite: Solid-phase which is a blend of antisense oligonucleotides. It has been reformed to include the concepts of green chemistry by abandoning the usage and/or formation of toxic or hazardous materials and reutilizing the essential constituents like protecting groups amidites and solid support. Thus, improving the cost-efficiency and atom economy[7].
2. The use of chiral metal catalyst containing 2,2'-bis[diphenylphosphino]-1,1'-binaphthyl ligand for the formation of Naproxen with fine quantity of product and this was explained by Anastas *et al*[8].
3. The green chemistry used in the atorvastatin synthesis for production of a key intermediate and the processes take place in two steps: -
    i. Bio-catalytic reduction of ethyl-4-chloro-3-oxobutanoate is first step which occurs with the combination of keto-reductase and glucose for regeneration of the substance, essential for the enzyme activity, forming a desired product i.e., (S)-ethyl-4-chloro-3-hydroxybutyrate with high yield.
    ii. The next step is the substitution of chloro with cyano group. It was accelerated by halohydrin dehalogenase, and this reaction proceeds at neutral pH and atmospheric temperatures in presence of natural catalyst[9].
4. On the other hand, green chemistry doesn't give any waste product, and the reaction also occurs as a quick one-step process accelerated by little amount of catalyst. For example - Synthesis of Aspirin by microwave irradiation using catalysts such as $CaCO_3$, NaOAc, H_2SO_4, $MgBr_2.OEt_2$, $AlCl_3$, Et_3N as well as solvent free approach have been designed[10].

1.4.2.Green chemical reactions:

- Production of halide free aromatic amines:

Conventional synthesis of aromatic amines is finished by treating benzene with chlorine with the help of nitrogen and then displacing chlorine with a kind new group (nucleophilic substitution). This process has been illustrated in the synthesis of 4-amino-diphenylamine. Monsanto company has developed a new method for the synthesis of 4-aminodiphenylamine that avoids the use of halogenation intermediates (Fig.-1). In this process, nitrobenzene along with aniline is heated in the existence of tetramethyl ammonium hydroxide [TMA(OH)] to form tetramethyl ammonium salts. Hydrogenation of the latter gives the resulting 4-aminodiphenylamine[11].

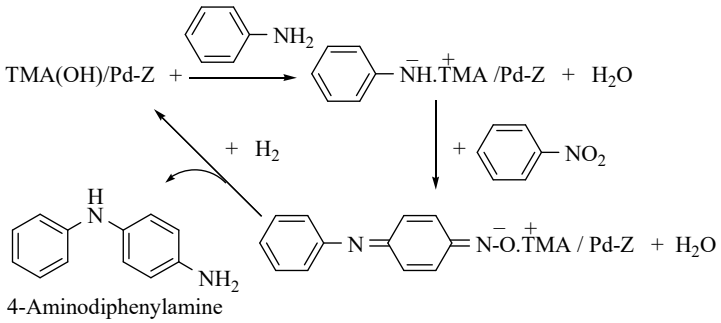


Fig. 1 – Synthesis of 4-Aminodiphenylamine.

- Homogeneous catalysis and atom economical system:

This system was developed by Trost. The objective of this work is to diminish the useless by-products of atoms created during process. An example of a reaction in which less or no by-products are formed is Aldol condensation[12].

1.4.3.As green reagents:

- Liquid oxidation reactor:

It permits harmless oxidation of organic chemicals by pure oxygen. The reaction occurs at low temperature and is quite useful. As a result, the amount of vent gas has been lessened.

- Non phosgene isocyanate synthesis:

Industrial production of isocyanates, or di-isocyanates in specific, has been entirely based on phosgene processes. Phosgene is a remarkably poisonous gas and large amounts of corrosive HCl are produced as a by-product. A new technique is developed as non-phosgene method for synthesis of isocyanates, which includes catalytic synthesis of N-substituted carbamates from nitro- or amino compounds with CO, dimethyl carbonate (DMC), urea and even CO_2 etc. as carbonyl sources, then thermal breaking of N-substituted carbamates to give corresponding isocyanates[13].

1.4.4.Reaction using green solvents:

Green solvents are substitutions of hazardous solvents resulting in more eco-friendly, biodegradable liquids such as vegetable oils, glycerol, and water. The use of supercritical fluid, i.e., CO_2 as an alternative to organic solvents already represents a means of waste reduction in the chemical industry. Asymmetric catalytic reactions, mostly hydrogenation and hydrogen transfer reactions, which can be carried out in supercritical carbon dioxide, provide selectivity superior to those performed in conventional solvents[14].

1.4.5.Manufacturing drugs:

Oligonucleotide drugs:

Synthetic oligonucleotide drugs are a growing class of drug molecules with widespread therapeutic value. Currently, they are produced by making use of HL-30™, (a polystyrene bead) at a dose of 90 mmol/g. It has plentiful restrictive characteristics: (1) Non-biodegradable, (2) Non-renewable, (3) It is a single-supply raw material. (4) It contributes ~40% of raw material fees. Hence, effective regeneration of consumed solid supports and their reuse is achieved in oligonucleotide synthesis.

1.4.6.In Agriculture:

- Soybean cyst nematode management:

Soybean cyst nematode pest remain to be a serious agricultural problem. As part of an interdisciplinary attempt to identify a biorational solution to the problem, analogs of glycinoeclepin A, which is a natural hatching stimulus of the nematode, were created and tested. Some of the analogs were found to inhibit the hatching of soybean cyst nematode eggs. The eggs are then so protected in the female such that it can survive for eleven to twelve days in soil[15].

1.4.7. Green chemistry in routine life:

1. Green Dry Cleaning of Clothes:

The most common solvent used for dry maintenance is Per-chloroethylene (PERC). It is also suspected as a source of cancer. To overcome this, Micell technology[16], practices liquid CO_2 and surfactant for dry cleaning clothes in place of PERC and CO_2 so that the necessity of halogenated solvent gets eradicated[17].

2. Bleaching Agents:

Green chemistry is also employed in day-to-day life for green dry cleaning of clothes. By employing green approaches, the use of perchloroethylene was replaced by liquid CO_2. Green bleaching agent such as hydrogen peroxide is used[18].

3. To Convert Turbid Water into Clear Green Solution:

In the existing times, the use of alum salt to treat municipal and industrial waste water is a routine practice. It has been found that alum is not ideal for this purpose because it is rising the hazardous ions in discharged water and may cause Alzheimer's disease. Thus, agriculture waste discharged such as kernel powder and tamarind seeds, act as the helpful agents to compose municipal and industrial waste water clears[19].

2. PHASE-TRANSFER CATALYSIS:

Some of the most important advances in chemistry, especially industrial chemistry, over the past decade have been in the area of catalysts. Catalysts play a major role in gaining the economic strength of the chemical industry. In 1971, for the first-time word "Phase Transfer Catalysis (PTC)" was coined by Starks which is a beneficial working concept. The technique of phase-transfer catalysis was introduced, developed, and understanding and application of this method for important organic reactions have prolonged exponentially. PTC is a synthetic organic method and manufacturing process technology that is applied effectively in a wide range of organic reactions. PTC is widely applied for simple organic reactions, in the synthesis of pharmaceuticals, agricultural chemicals, flavouring agents, perfumes, dyes and for polymerization reactions, monomer synthesis, and polymer modifications; for the analysis of trace organic and inorganic compounds; for environmental control processes and pollution and for many other applications. [20].

Nowadays, PTC is a predictable potential tool for enhancing efficiency, improving safety, and reducing environmental impact. The advances of the same in recent years have made a remarkable impact in organic synthesis and are being extremely employed to a multitude of organic transformations such as substitution, displacement, condensation, epoxidation, and polymerization reactions. Even though, various soluble single-site PTCs have extensively used for a number of organic reactions, but its usage is often limited, again because of its inseparability[21].

2.1. Basic Concepts in Phase-Transfer Catalysis:

PTC is the most powerful tool in many fields of chemistry. It is a widely applied technique for progressing reactions between two or more reagents in two or more immiscible phases, where the reaction is inhibited because the reactants cannot combine easily. A reagent called "phase-transfer agent" is added for transferring one of the reagents to a site where it can rapidly and conveniently react with another reagent. The basic requirement for PTC is that the transferred species must be in an extremely active state when transferred; if not, then large amounts of phase-transfer agents will be required. This activation function along with the transfer function, allows phase-transfer catalysis to happen with only a catalytic amount of phase-transfer agent[22].

2.2. Principle of Phase-Transfer Catalysis:

Reuben and Sjoberg explained the principle of PTC in 1981. The PTC reactions depend on the certain phase-transfer catalysts (PT catalysts) which permit the transport of one reagent from one phase into the second immiscible phase which contains the other reagent. Thus, the reaction occurs via combining the reagents which are originally in different phases. However, it is also important that the substance being transferred is in an active state for effective PT catalytic action, that is regenerated throughout the organic reaction[23].

2.3. Mechanisms of PTC:

The mechanism of PTC reaction was first proposed by Charles Starks, an industrial chemist, in 1971. Dr Starks called this mechanism as the "Extraction Mechanism"[24]. According to Starks work, a quaternary ammonium halide (Q^+X^-) present in the aqueous phase undergoes anion exchange with the anion (Y^-) of the reactant dissolved in the aqueous solution. The formed ion pair (Q^+Y^-) can pass through the liquid-liquid interface as a result of its lipophilic nature and goes from the interface into

the organic phase, this step indicates the phase transfer. In the organic phase, the anion of the ion pair undergoes a nucleophilic substitution reaction with the organic reagent making the desired product (RY). The cycle continues with subsequent return of catalyst to the aqueous phase.

An outline of PTC reactions is given below (Fig.-2):

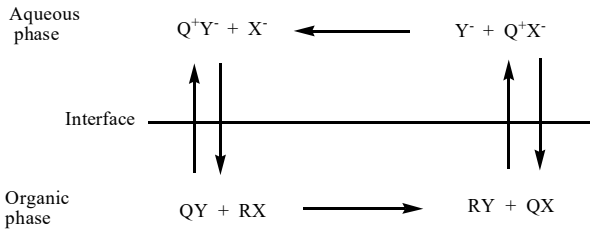


Fig. 2- Mechanism of PTC.

A requirement for a substance to function as a PT-Catalyst is to form ion pairs soluble in the organic phase and to remain transferred in a very active state[25].

An important issue which influences reactivity is the solvation. The amount of water that is co-extracted with the ion pair into the organic phase may affect the desired reaction. Reducing the hydration sphere of the anion or using solid-liquid PTC conditions can overcome this problem. As this mode supposes water-free reactions, it initiates limited followers in the field of analytical chemistry. Examples of such applications involved are the determination of carboxylic acids[26], the quantitation of acidic tryptophan metabolites[27], the determination of 5-fluorouracil in plasma[28] and uracil in DNA[29], the analysis of long chain fatty acids[30] and the simultaneous determination of haloacetic acids in trace amount in biological samples as their pentafluorobenzyl derivatives[31].

2.4. Classification of PTC reactions:

There are two main classes of PTC reactions: soluble PTC and insoluble PTC (Fig.- 3). Within each class, depending on the definite phases, the reactions are further classified as liquid-liquid PTC (LLPTC), gas-liquid PTC (GLPTC), and solid-liquid PTC (SLPTC). The PT catalyst form a separate liquid phase in some cases, and this different form of PTC can be grouped along with the traditional insoluble PTC, where the PT catalyst is immobilized on a solid support. Other nontypical variants of PTC include reverse PTC via a reverse transfer mechanism and inverse PTC (IPTC). In LLPTC, the nucleophile is dissolved in an aqueous phase, while in SLPTC it is a solid which is suspended in the organic phase[32].

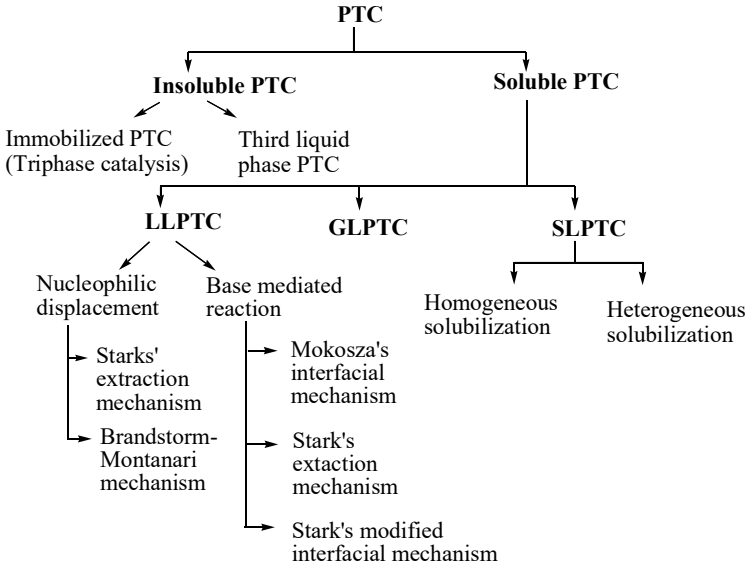


Fig. 3 – Classification of PTC reaction[33]**.**

2.4.1.LLPTC:

Traditionally, PTC has been widely applied in liquid-liquid systems. Phase-transfer catalysis in which chemical reactions occur in a two-phase liquid– liquid system is called LLPTC and it has been proved as an effective method for organic synthesis. The application of LLPTC in organic synthesis includes the synthesis of phenyl alkyl acetonitriles, transfer hydrogenation catalysis, alkyl oxidation, and sulfonation reactions (Fig.- 4), nitration, polymerizations, and condensation reactions[34].

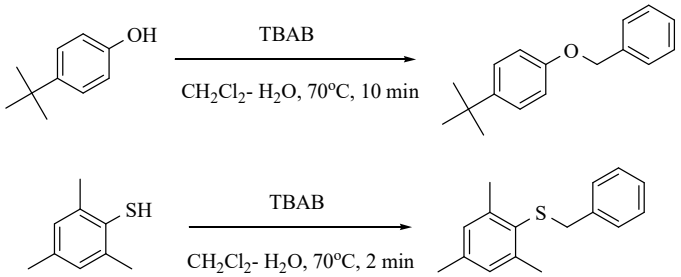


Fig. 4- Alkyl oxidation and sulfonation reactions in a liquid–liquid PTC system using a tetrabutyl ammonium bromide (TBAB) phase-transfer catalyst

2.4.2.SLPTC:

The main advantage of operating PTC in the solid-liquid mode in some reactions is that the degree of hydration of the ion pair can be lowered by the elimination of the aqueous phase, which results into an increase in its reactivity. Thus, higher selectivity and better yields are sometimes attained by working in the solid-liquid mode compared to process in the liquid-liquid (aqueous- organic) mode. For example, the reaction of benzyl bromide with phenylacetylene by using TDA-1 [Tris(3,6-dioxaheptyl)amine] as PT catalyst and a cobalt carbonyl complex as cocatalyst gives phenylacetic acid. The reaction occurs in presence of CO and NaOH and is operated as a liquid-liquid system due to fast hydrolysis of the acylcobaltcarbonyl intermediate, however the use of solid NaOH gives the equivalent lactone[35].

2.4.3.GLPTC:

In GLPTC, the use of PTC in gas-liquid-solid systems was involved. In GLPTC the organic substrate, present in a gaseous form is spread over a bed containing the inorganic reagent or certain additional solid reagent/cocatalyst (usually, solid potassium, carbon monoxide) in solid form[36], or an inert inorganic support[37,38], which are coated with a PT catalyst in its liquefied state. Although, even this is a gas-liquid-solid triphasic system, it has commonly been mentioned as GLPTC. Advantages of GLPTC involve ease of variation to continuous flow operation (together with the gaseous reagents running unceasingly over the solid bed), lack of organic solvent, facility of retrieval of the PT catalyst since it is clearly loaded onto the solid bed, and upgraded selectivity than LLPTC in certain cases.

A number of reactions can be performed under GLPTC conditions, counting a unique class of reactions using dialkyl carbonates[39,40]. In methylene activated compounds, DMC acts initial as a carboxymethyl agent that enables the protection of methylene active derivatives and permits nucleophilic displacement to occur with another molecule of DMC. This way of synthesis has been directed for the synthesis of anti-inflammatory drugs like ketoprofen in Belgium. In the similar mode, methylation of methyl-2- aroxyacetates and aroxylacetonitriles by using DMC offers up to 99% of the monomethylated derivatives, that are extensively utilized in the production of biologically active compounds and plant growth regulators[38]. Other reactions employing GLPTC contain halogen exchange, esterification, etherification, isomerization, alkylation, transhalogenation, Wittig and Horner reactions, and primary alkyl halides synthesis from primary alcohols. However, solid-liquid system and liquid-liquid systems are the major classes of reactions wherever PTC has maximum application, and upcoming discussion and investigation of PTC systems emphasize on SLPTC and LLPTC reactions.

2.5. Types of Phase Transfer Catalysts:

The various types of phase transfer catalysts are phosphonium and quaternary ammonium salts, PEG (polyethylene glycols), crown ethers, cryptands, etc. Table 1 summarizes some of the properties of frequently used PT catalysts[41].

Catalyst	Cost	Stability and Activity	Use and Recovery
Ammonium salts	Cheap	Moderately stable in basic conditions and up to 100°C. Decomposition by Hofmann elimination under basic conditions. Moderately active.	Widely used. Recovery is relatively difficult.
Phosphonium salts	Expensive than ammonium salts	Thermally more stable than ammonium salts, although less stable under basic conditions.	Widely used. Recovery is relatively difficult.
Crown ethers	Expensive	Stable and very active catalysts both under basic conditions and at higher temperatures up to even 150-200°C.	Often used. Recovery is difficult and causes environmental issues due to their toxicity.
Cryptands	Expensive	Stable and highly reactive, excluding the presence of strong acids.	Used sometimes despite high costs and toxicity, due to higher reactivity.
PEG	Very cheap	Lower activity but more stable than quaternary ammonium salts.	Often used and especially larger quantities of catalyst cause no problems. Reasonably easy to recover.

Table 1 – Commonly used PT catalysts

2.5.1. Quaternary ammonium salts:

Among all types, the quaternary ammonium salts (commonly called as quats) are the cheapest and hence the most widely used in the industry. They are chemical compounds having nitrogen in their skeleton and forming a salt with different groups. Fig. 5 shows the commonly used ammonium salts as PT catalysts[42].

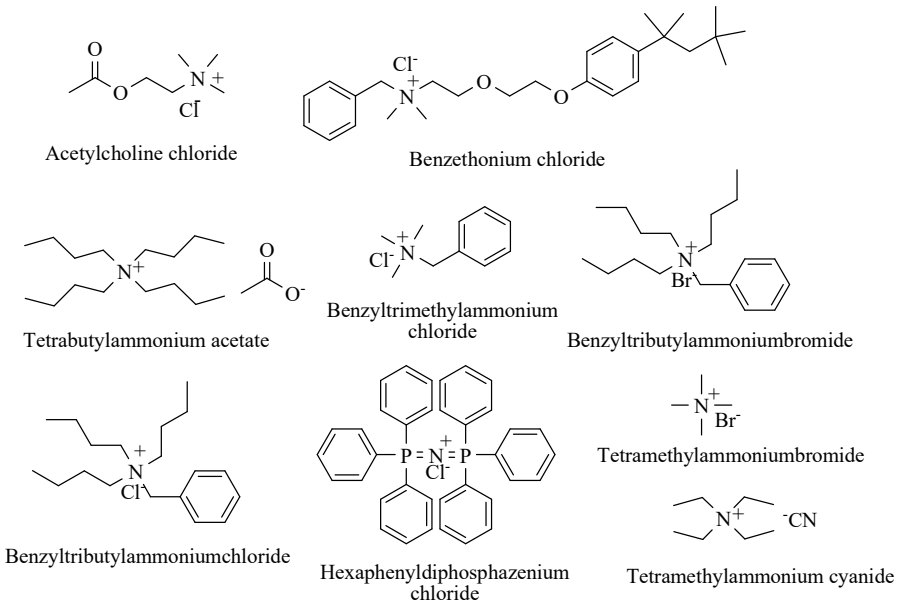


Fig. 5- Commonly used ammonium salts as PT catalysts

2.5.2. Phosphonium Salts:

These are also analogous to the ammonium salt. The only difference is that instead of nitrogen, it contains phosphorous. Some commonly used phosphonium salts as PT catalysts are shown in Fig. 6[43–45].

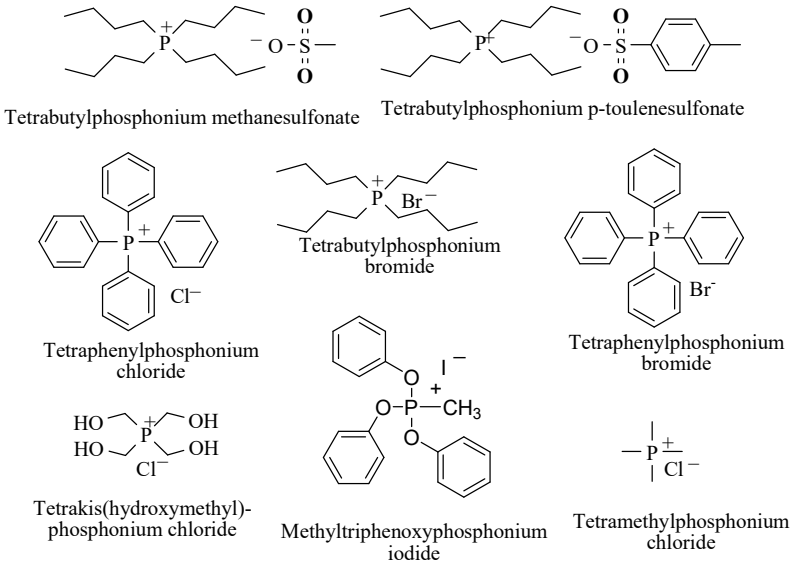
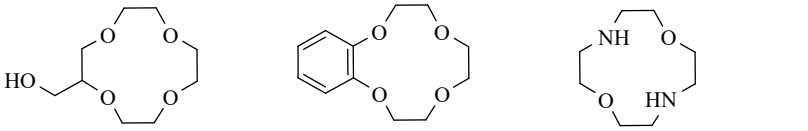


Fig. 6- Phosphonium salts used as PT catalysts

2.5.3. Crown ethers and Cryptands:

Macrocyclic and macrobicyclic polydentate ligands as crown ethers and cryptands are commonly applied as PT catalysts, precisely in solid-liquid systems, owing to their capacity to complex and solubilize metal cations, with the corresponding anion to retain charge balance. Although, regardless of their great activity as successful PT catalysts, crown ethers (Fig.- 7) and cryptands are not practicable for maximum industrial purposes due to their superior costs and toxicity[46–48].



2-(Hydroxymethyl)-12-crown 4-Ether Benzo-12-crown 4-Ether 4,10-Diaza-12-crown 4-Ether

Fig. 7- Crown ether used as PT catalyst

2.5.4. Polyethylene glycols:

Polyethylene glycols (PEGs) and their derivatives are also extensively utilized as PT catalysts. Although they are less active than quaternary ammonium salts and crown ethers, they are comparatively inexpensive and environmentally harmless. PEGs are nontoxic, stable, easy to regain and easily biodegradable, and are available without difficulty. For reactions with hydroxide transfer step in solid-liquid systems in inconspicuously polar solvents, PEGs acts as a great PT catalyst with occasionally better activities than crown ethers. Water solubility renders them unfortunate catalysts meant for liquid-liquid systems, even though in certain instances the PEG can produce a third catalyst-rich phase and became active PT catalyst[49].

Various other innovative PT catalysts have been formed which have definite applications in specified types of reactions. For example:

- Kondo *et al*. [43,50,51] have established polymeric equivalents of dipolar aprotic solvents such as N-N-dimethylformamide, dimethyl sulfoxide, tetramethylurea, N-methyl-2-pyrrolidone, and so on, in both immobilized and soluble forms. Similarly, chiral PT catalysts are widely used based on optically active amines for example, chinine, ephedrine, or other cinchona alkaloids[52].
- Rhone-Poulenc synthesized TDA-1 (tris(3,6-dioxahelptyl) amine), which is an effective PT catalyst for solid-liquid reactions, stable under strongly basic situations, and at elevated temperatures[53].
- Balakrishnan and Jayachandran[54] stated the application of a new multisite diammonium dichloride as a PT catalyst for deposit of diochlorocarbene to styrene. Advantages of a multisite catalyst includes higher catalytic activity for every gram of catalyst used and a lesser amount of contamination of products.
- The use of a new high-temperature PT catalyst, i.e., EtHexDMAP (N-alkyl salt of 4-dialkylamino- pyridine) for polymer and monomer synthesis was specified by Brunelle in 1987 [55] . In 1987 Idoux and Gupton[56] reported the practice of polymer bound PT catalysts through one PTC site on the polymer. Similarly, multisite PT catalysts may also be produced from simple polyhalo substrates by their soluble non-polymeric methods.
- Shaffer and Kramer[57] reported a different grouping of PTC with inverse PTC (Section on PTC in the Industry) for polymerization reactions named bimechanistic PTC, wherever an ammonium salt was employed to enable transfer from the aqueous phase to the organic phase.

2.6. Choice of PT Catalyst:

There are two main necessities of a PT catalyst[58]:

The PT agent should be cationic and must contain an adequate chemical structure to be capable for splitting the nucleophilic anion in the organic phase. The cation-anion bonding must be low for superior anionic reactivity.

Relevant factors in employing a PT catalyst are:

- Stability beneath reaction conditions
- Ease of formation or availability of catalyst
- Ease of separation or recovery
- Activity and
- Toxicity

Although no definite guidelines are provided for the selection of Nobel catalysts for a given reaction system, analysis depending on some of the above-mentioned factors can suggest an appropriate method to screen PT catalysts for a given system. We can compare at this various PT catalysts: crown ethers and cryptands, quaternary onium salts, and PEGs in terms of cost, toxicity, and stability regarding temperature and basic conditions.

2.7. APPLICATIONS OF PHASE TRANSFER CATALYSIS:

The applications of PTC are found in a variety of reactions as follows:

- Usually, it shows a phenomenal role in green chemistry to lessen waste, use of less solvent, faster and expedient approach.
- In organic synthesis, generally the reagents form a heterogeneous nature in a reaction medium and such reactions are catalyzed by PTC. Therefore, the PTC is broadly used industrially.
- The varied application of PTC in aqueous system allows more boosted environment-friendly green synthesis. Solvent free synthesis is also feasible via PTC[59].
- One more advanced application of PTC is the asymmetric alkylation where the chiral quaternary ammonium salt, which are derived from cinchona alkaloids are employed[60].
- Similarly, the polyester polymer is prepared from bisphenol-A and acid chloride, the PTC catalyzed pesticide production is popular typically through alkylation of phosphothioates. Bisphenol A has been reacted under PTC conditions with a variety of electrophiles to prepare polycarbonate, polyester, polyether, epoxyresin, polyethersulfone, and the polyetherimide monomer (Fig.- 8)[61]. These reactions are good examples of nucleophilic displacement (nucleophilic aromatic substitution, nucleophilic aliphatic substitution, and acylation) and represent the largest volume of commercial PTC applications.

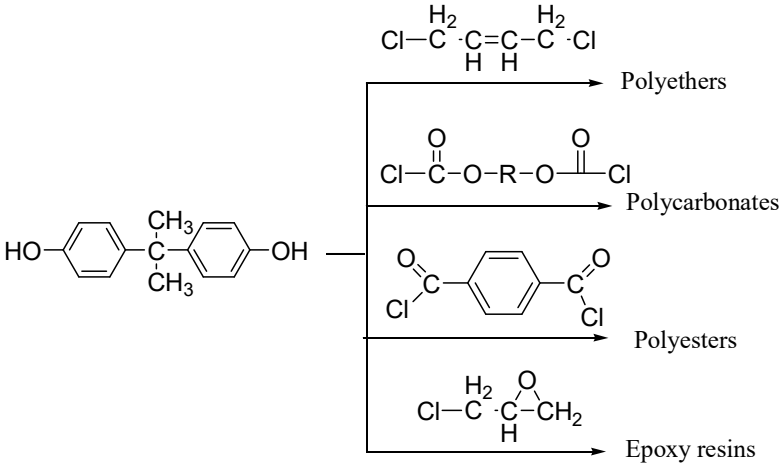


Fig. 8- Examples of polymerization catalysed by PTC

- Polymers can be modified under PTC conditions. For example, glycidylazide polymer (solid rocket fuel) can be made from polyepichlorohydrin and azide. Tributylamine serves as an in-situ phase-transfer catalyst for the preparation of a poly (vinyl chloride) plasticizer.
- **N-alkylation of nitrogen heterocycles:** PTC is also the system of choice for N-alkylation of nitrogen heterocycles such as pyrrole, indole, benzothiazine, imidazole, etc. Base-promoted N-alkylation (Fig.- 9) is a significant step in the production of a wide variety of drugs. Also N-Alkylation of pyrazoles with 4,6-dichloropyrimidines in the SLPTC mode using KOH as base and Bu4NBr as the PT catalyst, a solvent is a key step in the preparation of antiulcer agents[62].

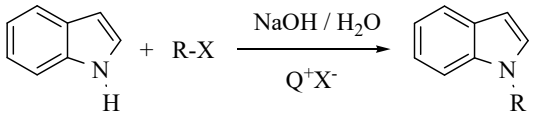


Fig. 9- N-alkylation of Nitrogen heterocycles

- Applications including the usage of a co-catalyst involving co-catalysis via surfactants, alcohols, and further weak acids in hydroxide transfer reactions, the use of iodide, or reactions brought out with dual PT catalysts have been also stated[63].
- **Oxidation of toluene and its derivatives:** PTC can also be useful in oxidizing toluene and chlorotoluenes with oxygen (Fig.- 10). Substituted/unsubstituted toluene on oxidation with cobalt chloride ($CoCl_2$) and didecyldimethylammonium bromide at 135-160°C and 12-15 atm in air gives substituted/unsubstituted benzoic acids[64].

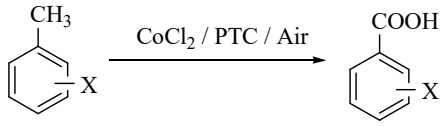


Fig. 10 – Oxidation of Toluene

- In nucleophilic substitution reactions and in reactions in the existence of bases including the deprotonation of moderately and weakly acidic organic compounds[65].
- **Halogen exchange reaction:** *p*-Nitrophenetole is prepared by using *p*-nitrochlorobenzene via the aromatic nucleophilic substitution reaction (Fig.- 11). In this reaction, a dimethyldialkylammonium salt was employed as PT catalyst, in which the alkyl groups contained a C_{12}-C_{18} moiety[66].

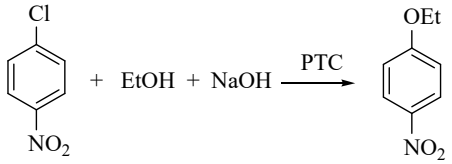


Fig. 11 – Synthesis of *p*-Nitrophenetole

- For some kinds of chemical reactions which are carried out in the presence of a PT catalyst in biphasic systems; simple, cheap, and mild bases like NaOH and K_2CO_3 can be used as an alternative to toxic alkali metal alkoxides, amides, and hydrides[67].
- It is also applicable in perfumery and fragrance industry like the synthesis of phenylacetic acid, an intermediate in the perfumery industry[68].
- **Production of dyes:** An electrochemical two-phase process using a graphite electrode with tetrabutylammonium salt as catalyst and dichromate as a regenerable oxidant has been developed for the oxidation of anthracene to anthraquinone (Fig.- 12)[66].

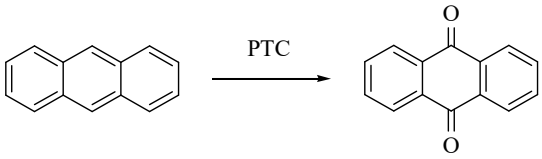


Fig. 12- PTC for oxidation of anthracene to anthraquinone

PTC is also employed for the aromatic displacement reaction[69] of chlorine by sulfite in 1,4-diamino-2,3-dichloroanthraquinone (Fig.-13) to give the corresponding disulfonic acid, which is used as an important dye intermediate[70].

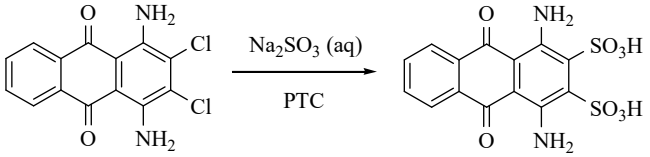


Fig. 13- PTC catalysed sulfite displacement reaction

- **Production of agrochemicals:** There are some reactions where PEGs as catalysts are more advantageous to conventional quaternary ammonium salts, e.g., in Butachlor (herbicide) synthesis (Fig.- 14) PEG has been reported to be superior to $TEBACI^-$[53].

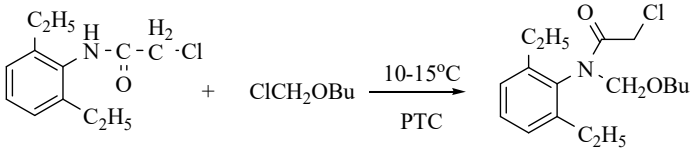


Fig. 14- Butachlor synthesis by using PTC

Another herbicide, Trichlopyr were prepared by the solid-liquid PTC reaction of the sodium salt of trichloropyridinol with methyl chloroacetate (Fig.- 15)[66].

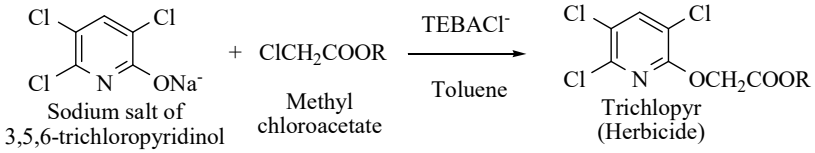


Fig. 15- Synthesis of Trichlopyr

- **Aerobic oxidations in asymmetric synthesis:** The chiral PTC represents the most frequently exploited approach among the organocatalytic aerobic oxidation methods. Also as organocatalytic methods are tolerant to both air and water, making them especially attractive for various practical applications. Work of Sano group represent a recent example of asymmetric hydroxylation of oxindoles in the immiscible solvent system (toluene/water) mediated by chiral cinchonidine-derived PTC, furnished the corresponding 3- hydroxylated oxindole product in upto quantitative yields and 67-93% enantioselctivities (Fig.- 16) [71].

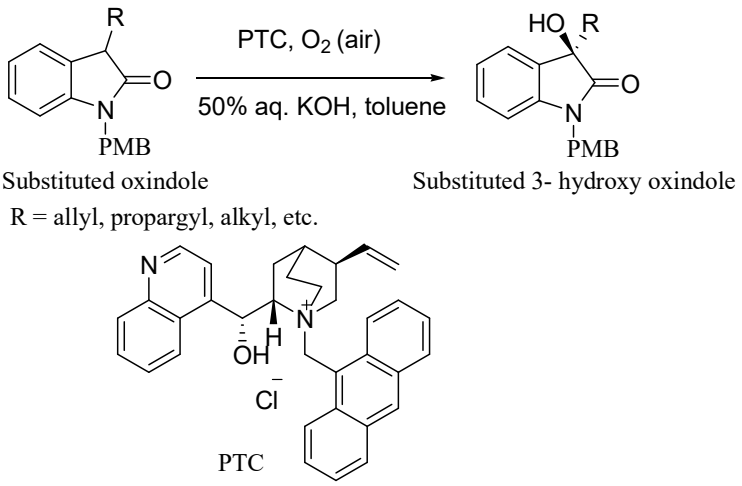


Fig. 16- Asymmetric hydroxylation of oxindoles under PTC

3. CONCLUSION:

Waste minimization is the basis of green chemistry and PTC is one of the strategies to achieve the goal of green chemistry. Since the past four decades, the popularity of PTC has been growing and many significant reactions are executed as desired by employing PTC. Currently, more expanded chemical compositions with ammonium, phosphonium, crown and non-ionic PTC are advanced and available commercially that allows us to pick the specificity to the particular reaction nature. Therefore, we expect that this concise review will disseminate information regarding PTC with the most frequently used/ available PTC reagents in one place.

LIST OF ABBREVIATIONS:

EPA: Environmental Protection Agency

[TMA(OH)]: Tetramethyl ammonium hydroxide

HCl: Hydrochloric acid

DMC: Dimethyl carbonate

PERC: Per-chloroethylene

PTC: Phase Transfer Catalysis

PT Catalyst: Phase Transfer Catalysts

LLPTC: Liquid-liquid phase transfer catalysis

GLPTC: Gas-liquid phase transfer catalysis

SLPTC: Solid-liquid phase transfer catalysis

TDA-1: Tris(3,6-dioxaheptyl) amine

CO: Carbon monoxide

NaOH: Sodium hydroxide

PEG: Polyethylene glycol

EtHexDMAP: N-alkyl salt of 4-dialkylamino- pyridine

KOH: Potassium hydroxide

K_2CO_3: Potassium carbonate

$CoCl_2$: Cobalt chloride

TEBACl: Tri ethyl benzyl ammonium chloride

CONSENT FOR PUBLICATION

None

CONFLICT OF INTEREST

None

ACKNOWLEDGEMENT:

The authors acknowledge the support from Pune District Education Association's Seth Govind Raghunath Sable College of Pharmacy, Saswad (Maharashtra) 412301.

REFERENCE:

1. Anastas PT, Heine LG, Williamson TC, editors. Green Chemical Syntheses and Processes. Washington, DC: American Chemical Society; 2000.

2. Jeffrey SB, Anont T, Tristan HL. Phase-Transfer and Other Types of Catalysis with Cyclopropenium Ions. Chemistry. 2015 May 11; 21(20): 7365-7368.

3. de Marco BA, Rechelo BS, Tótoli EG, Kogawa AC, Salgado HRN. Evolution of green chemistry and its multidimensional impacts: A review. Saudi Pharm J. 2019 Jan;27(1):1–8.

4. Ahluwalia VK, Kidwai M. New Trends in Green Chemistry. Dordrecht: Springer Netherlands; 2004.

5. Ivanković A. Review of 12 Principles of Green Chemistry in Practice. Int J Sustain Green Energy. 2017;6(3):39.

6. Kirchhoff MM, Ryan MA. Greener approaches to undergraduate chemistry experiments. Washington, D.C.: American Chemical Society; 2002.

7. Sanghvi YS, Ravikumar VT, Scozzari AN, Cole DL. Applications of green chemistry in the manufacture of oligonucleotide drugs. Pure Appl Chem. 2001 Jan 1;73(1):175–80.

8. Anastas PT, Bartlett LB, Kirchhoff MM, Williamson TC. The role of catalysis in the design, development, and implementation of green chemistry. Catal Today. 2000 Jan;55(1–2):11–22.

9. Ma SK, Gruber J, Davis C, Newman L, Gray D, Wang A, et al. A green-by-design biocatalytic process for atorvastatin intermediate. Green Chem. 2010;12(1):81–6.

10. Montes I, Sanabria D, García M, Castro J, Fajardo J. A Greener Approach to Aspirin Synthesis Using Microwave Irradiation. J Chem Educ. 2006 Apr;83(4):628.

11. Bochkarev VV, Soroka LS, Bashkin JK. Resource-efficient technology to produce 4-aminodiphenylamine. Resour-Effic Technol. 2016 Dec;2(4):215–24.

12. Wardencki, Waldemar & Curyło, J. & Namieśnik, Jacek. Green chemistry - Current and future issues. Pol J Environ Stud. 2005 Jan;14(4):389–95.

13. Wang P, Liu S, Deng Y. Important Green Chemistry and Catalysis: Non-phosgene Syntheses of Isocyanates - Thermal Cracking Way. Chin J Chem. 2017 Jun;35(6):821–35.

14. Dhage SD, Shisodiya KK. Applications of Green Chemistry in Sustainable Development. Int Res J Pharm. 2013 Aug 10;4(7):1–4.

15. Laird T. Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition VCH: Weinheim, Germany. 1996/1997. Section A, 28 vols. Section B, 8 vols. DM 19 400. Org Process Res Dev. 1997 Sep;1(5):391–2.

16. Blaser H-U, Malan C, Pugin B, Spindler F, Steiner H, Studer M. Selective Hydrogenation for Fine Chemicals: Recent Trends and New Developments. Adv Synth Catal. 2003 Jan;345(12):103–51.

17. Sauer NN. Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes Edited by Paul T. Anastas and Tracy C. Williamson (U. S. Environmental Protection Agency). Oxford University Press: New York, NY. 1999. 360 pp. $115.00. ISBN 0-19-850170-6. J Am Chem Soc. 2000 Jun;122(22):5419–20.

18. Tundo P, Anastas PT, editors. Green chemistry: challenging perspectives. Oxford; New York: Oxford University Press; 2000. 269 p. (Green chemistry series).

19. Jessop PG, Leitner W, editors. Chemical Synthesis Using Supercritical Fluids. 1st ed. Wiley; 1999.

20. Ahluwalia VK, Kidwai M. Green Catalysts. In: New Trends in Green Chemistry. Dordrecht: Springer Netherlands; 2004. p. 27–38.

21. Murugan E, Tamizharasu G. New soluble multi-site phase transfer catalysts and their catalysis for dichlorocarbene addition to citronellal assisted by ultrasound—A kinetic study. J Mol Catal Chem. 2012 Nov;363–364:81–9.

22. C.M. Starks, M. Halper. Basic Concepts in Phase Transfer Catalysis. In: Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives. Springer Science & Business Media; 1994. p. 1–22.

23. Brändström A. Principles of Phase-Transfer Catalysis by Quaternary Ammonium Salts. In: Advances in Physical Organic Chemistry. Elsevier; 1977. p. 267–330.

24. Starks CM. Phase-transfer catalysis. I. Heterogeneous reactions involving anion transfer by quaternary ammonium and phosphonium salts. J Am Chem Soc. 1971 Jan;93(1):195–9.

25. Starks CM, Liotta CL, Halpern M. Phase-transfer catalysis: fundamentals, applications, and industrial perspectives. New York: Chapman & Hall; 1994. 668 p.

26. Arbin A, Brink H, Vessman J. Alkylation of carboxylic acids by solid-liquid phase-transfer catalysis for determination by gas chromatography. II. J Chromatogr A. 1980 Aug;196(2):255–63.

27. Naritsin DB, Boni RL, Markey SP. Pentafluorobenzylation Method for Quantification of Acidic Tryptophan Metabolites Using Electron Capture Negative Ion Mass Spectrometry. Anal Chem. 1995 Mar 1;67(5):863–70.

28. Wang K, Nano M, Mulligan T, Bush ED, Edom RW. Derivatization of 5-fluorouracil with 4-bromomethyl-7-methoxycoumarin for determination by liquid chromatography-mass spectrometry. J Am Soc Mass Spectrom. 1998 Sep; 9(9): 970–6.

29. Ren J, Ulvik A, Refsum H, Ueland PM. Uracil in Human DNA from Subjects with Normal and Impaired Folate Status as Determined by High-Performance Liquid Chromatography−Tandem Mass Spectrometry. Anal Chem. 2002 Jan;74(1): 295–9.

30. Lu C-Y, Wu H-L, Chen S-H, Kou H-S. A fluorimetric liquid chromatography for highly sensitive analysis of very long chain fatty acids as naphthoxyethyl derivatives. Chromatographia. 2000 Mar; 51(5–6): 315–21.

31. Jia M, Wu WW, Yost RA, Chadik PA, Stacpoole PW, Henderson GN. Simultaneous Determination of Trace Levels of Nine Haloacetic Acids in Biological Samples as Their Pentafluorobenzyl Derivatives by Gas Chromatography/Tandem Mass Spectrometry in Electron Capture Negative Ion Chemical Ionization Mode. Anal Chem. 2003 Aug; 75(16): 4065–80.

32. Marc Halpern, Hayder A. Zahalka, Yoel Sasson, and Mordecai Rabinovitz. Hydroxide Ion lnitiated Reactions Under Phase Transfer Catalysis Conditions: 9. Dehydrohalogenation of (haloethyl)benzenes by Quaternary Ammonium Salts. J, Org Chem. 1985 May 28; 50(25): 5088–92.

33. Naik SD, Doraiswamy LK. Phase transfer catalysis: Chemistry and engineering. AIChE J. 1998 Mar;44(3):612–46.

34. Weatherley LR. Intensification of Liquid–Liquid Processes. 1st ed. Cambridge University Press; 2020.

35. Arzoumanian H, Petrignani J-F. Solid—liquid phase transfer and cobalt catalyzed synthesis of but-2-enolide. Tetrahedron Lett. 1986 Jan; 27(49): 5979–80.

36. Tundo P, Venturello P. Synthesis, catalytic activity, and behavior of phase-transfer catalysts supported on silica gel. Strong influence of substrate adsorption on the polar polymeric matrix on the efficiency of the immobilized phosphonium salts. J Am Chem Soc. 1979; 101(22): 6606–13.

37. Tundo P, and M. Badiali. High Activity in Displacement Reactions Catalyzed by Quaternary Onium Salts Immobilized on Inorganic Matrices. Reactive Poly. 1989; 10: 55.

38. Tundo P, and M. Selva. Simplify Gas-Liquid Phase-Transfer Catalysis. Chemfech. 1995;25(5):31.

39. Trotta F, Tundo P, Moraglio G. Selective mono-N-alkylation of aromatic amines by dialkyl carbonate under gas-liquid phase-transfer catalysis (GL-PTC) conditions. J Org Chem. 1987 Apr;52(7):1300–4.

40. Tundo P, Venturello P. Catalysis mechanism of phosphonium salts supported on silica gel in organic-aqueous two-phase systems. J Am Chem Soc. 1981 Feb;103(4):856–61.

41. Sanjeev D. Naik and L. K. Doraiswamy. Phase Transfer Catalysis: Chemistry and Engineering, Reactors, Kinetics, and Catalysis. AIChE Journal. 1998 Mar;44(3):612–46.

42. Petrova GP, Li H-B, Maruoka K, Morokuma K. Asymmetric Phase-Transfer Catalysis with Homo- and Heterochiral Quaternary Ammonium Salts: A Theoretical Study. J Phys Chem B. 2014 May 15;118(19):5154–67.

43. Molinari H, Montanari F, Quici S, Tundo P. Polymer-supported phase-transfer catalysts. High catalytic activity of ammonium and phosphonium quaternary salts bonded to a polystyrene matrix. J Am Chem Soc. 1979 Jul;101(14):3920–7.

44. Cao D, Chai Z, Zhang J, Ye Z, Xiao H, Wang H, et al. Thiourea-phosphonium salts from amino acids: cooperative phase-transfer catalysts in the enantioselective aza-Henry reaction. Chem Commun. 2013;49(53):5972.

45. Tomoi M, Ogawa E, Hosokama Y, Kakiuchi H. Phase-transfer reactions catalyzed by phosphonium salts attached to polystyrene resins by spacer chains. J Polym Sci Polym Chem Ed. 1982 Dec;20(12):3421–9.

46. Landini D, Maia A, Montanari F, Pirisi FM. Crown ethers as phase-transfer catalysts. A comparison of anionic activation in aqueous–organic two-phase systems and in low polarity anhydrous solutions by perhydrodibenzo-18-crown-6, lipophilic quaternary salts, and cryptands. J Chem Soc Perkin Trans 2. 1980;(1):46–51.

47. Landini D, Montanari F, Pirisi FM. Crown ethers as phase-transfer catalysts in two-phase reactions. J Chem Soc Chem Commun. 1974;(21):879.

48. Mathias LJ, Carraher CE. Crown Ethers and Phase Transfer Catalysis in Polymer Science.

49. Totten GE, Clinton NA. Poly[Ethylene Glycol] Derivatives as Phase Transfer Catalysts and Solvents for Organic Reactions. J Macromol Sci Part C Polym Rev. 1988 Jan;28(2):293–337.

50. Kunihiro Ohta, Yasuhito Inagaki, Makoto Minafuji, Haruhiko, Yasui, Nobuo Nakashima, Masaki Iwasaki, Keizo Furukawa and Kazuichi Tsuda, Shuji Kondo. Polymeric analogues of dipolar aprotic solvents as phase transfer catalysts. Pure & Appl Chem. 1988;60(3):387–94.

51. Kondo S, Yasui H, Tsuda K. Insoluble Polymeric Sulfoxides as Liquid-Solid-Liquid and Solid-Solid-Liquid Triphase Catalysts. Makromol Chem. 1989 Sep;190(9):2079–89.

52. Bhattacharya A, Dolling U-H, Grabowski EJJ, Karady S, Ryan KM, Weinstock LM. Enantioselective Robinson Annelations via Phase-Transfer Catalysis. Angew Chem Int Ed Engl. 1986 May;25(5):476–7.

53. Lavelle P. Phase Transfer Catalysts. Spec Chem. 1986;6(16):18–20.

54. Balakrishnan T, Jayachandran JP. New 'multi-site' phase transfer catalyst for the addition of dichlorocarbene to styrene. J Chem Soc Perkin Trans 2. 1995;(11):2081–5.

55. Starks CM, editor. Phase-Transfer Catalysis: New Chemistry, Catalysts, and Applications. Washington, DC: American Chemical Society; 1987.

56. Idoux, J. P., and J. T. Gupton. Multisite Phase Transfer Catalysts. In: Phase- Transfer Catalysis: New Chemistly, Catalysts, and Applications. Amer. Chem. Soc. Symp.; 1987. p. 38.

57. Shaffer, T. D., and M. C. Kramer. Bimechanistic Phase Transfer Catalyzed Polythioetherfication. Malcromol Chem. 1990; 191: 3157.

58. Varughese P. Phase Transfer Catalysts - Principles and Techniques (Starks, Charles M.; Liotta, Charles). J Chem Educ. 1979 Jul;56(7): A242.

59. Solvent Free Synthesis of Pyrimidine, Quinazolinone and Diazatricyclo Derivatives via Phase-Transfer Catalysis Method. Chem Sci Trans. 2015.

60. Ooi T, Maruoka K. Recent Advances in Asymmetric Phase-Transfer Catalysis. Angew Chem Int Ed. 2007 Jun 4;46(23):4222–66.

61. Brunelle DJ, Singleton DA. N-alkyl-4-(N′,N′-dialkylamino)pyridinium salts: thermally stable phase transfer catalysts for nucleophilic aromatic displacement. Tetrahedron Lett. 1984 Jan;25(32):3383–6.

62. Gallo RJ, Makosza M, Dou HJ-M, Hassanaly P. Applications of Phase Transfer Catalysis in Heterocyclic Chemistry. In: Advances in Heterocyclic Chemistry. Elsevier; 1984. p. 175–234.

63. Urata K, Takaishi N. Applications of phase-transfer catalytic reactions to fatty acids and their derivatives: Present state and future potential. J Am Oil Chem Soc. 1996 Jul;73(7):831–9.

64. Hronec M. Phase transfer catalysis in oxidation processes. In: Sasson Y, Neumann R, editors. Handbook of Phase Transfer Catalysis. Dordrecht: Springer Netherlands; 1997. p. 317–35.

65. Albanese D, Landini D, Maia A, Penso M. Key Role of Water for Nucleophilic Substitutions in Phase-Transfer-Catalyzed Processes: A Mini-Review. Ind Eng Chem Res. 2001 May 1;40(11):2396–401.

66. Sharma M. Application of phase transfer catalysis in the chemical industry. In: Sasson Y, Neumann R, editors. Handbook of Phase Transfer Catalysis. Dordrecht: Springer Netherlands; 1997 [cited 2021 Jul 11]. p. 168–99.

67. Jászay ZM, Petneházy I, Tőke L. Reaction of chlorides of phosphoric, sulfonic, and carboxylic acids on solid potassium carbonate surface under PTC circumstances: Reaction of Chlorides of Phosphoric, Sulfonic, and Carboxylic Acids on Solid Potassium Carbonate Surface. Heteroat Chem. 2004;15(6):447–50.

68. Mujahid Alam M, Adapa SR. A Facile Synthesis of Phenylacetic Acids via Willgerodt-Kindler Reaction Under PTC Condition. Synth Commun. 2003 Mar;33(1):59–63.

69. Starks CM, Liotta CL, Halpern ME. Phase-Transfer Catalysis Displacement Reactions with Simple Anions. In: Phase-Transfer Catalysis. Dordrecht: Springer Netherlands; 1994. p. 339–82.

70. Wang F, Huang J, Xu J. Continuous-flow synthesis of azo dyes in a microreactor system. Chem Eng Process - Process Intensif. 2018 May;127: 43–9.

71. Sano D, Nagara K, Itoh T. Catalytic asymmetric hydroxylation of oxindoles by molecular oxygen using a phase-transfer catalyst. Org. Lett. 2008; 10(8): 1593-1595.