UNIT 16

PRINCIPLE AND APPLICATIONS OF PHASE TRANSFER CATALYSIS

Structure

16.1 INTRODUCTION

In the previous unit you have learnt about chemistry of umpolung reactions. You have learnt about the important role of umpolung strategies in organic synthesis. These methods provide alternative approaches for the construction of new carbon-carbon C-C bonds. In this unit we will discuss another alternative approach to traditional chemical reactions which are generally conducted in a homogeneous medium. There are chemical agents which can facilitate the transport of reactants and reagents between two or more different immiscible phases. Such agents are referred as the phase transfer catalysts (PTC) or simply catalyst and the process or action by which a catalyst increases the reaction rate is called catalysis. Generally, this process involves the transport of ions between phases facilitated by the formation of a catalyst-reagent ion pair. After the intermediate ion-pair has crossed the phase boundary, this reactive ion-pair can participate in a number of different chemical reactions. Finally, the catalyst may be regenerated after the complete transportation of the reactant/reagent to complete the reaction.

Phase transfer acatalytic reactions are performed ain a combination of phases; the most common are liquid-liquid and liquid-solid phase reactions. In

the case of liquid-liquid phase transfer reactions, one phase is generally a non-polar organic solvent and the other phase is a polar solvent, typically an aqueous solution. Most often, a reagent is transferred from the aqueous phase

into the organic phase by the phase transfer catalyst. Solid-liquid phase transfer reactions are similar in most respects with the exception that one phase remains a solid and may be immobilized on any polymer support. The majority of phase transfer catalytic processes involve reactions of interest taking place in the organic phase. Although in certain cases this trend may be reversed and the desired reaction will proceed in the aqueous or solid phase. Phase transfer catalysts have wider application in the chemical industry as phase transfer catalysis processes offer the advantage of mild reactions conditions and acceleration of the reactions rates. They also provide high yield, solvent flexibility, and simplistic product isolation and minimize chemical waste. Therefore, phase transfer catalysis is an ideal tool for the adoption of green chemistry principles into organic synthesis.

Expected Learning Outcomes

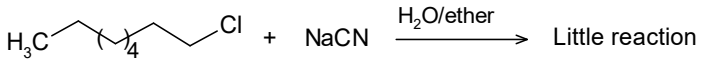
After studying this unit, you should be able to:

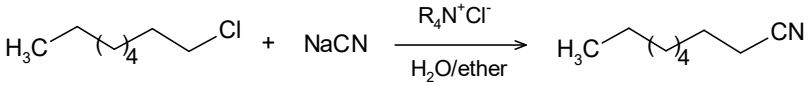
- define term phase transfer catalysis;
- explain mechanism of phase transfer catalytic processes;
- describe various reactions conducted in the presence of phase transfer catalyst; and
- describe applications of phase transfer catalysis reactions in organic synthesis.

16.2 TYPES OF PHASE TRANSFER CATALYSTS

The concept of phase transfer catalysis was first described by Starks in which various alkyl halides in an organic solvent underwent S_N2 displacement reactions by cyanide ions in aqueous solution catalyzed by a quaternary ammonium or phosphonium salt. These catalysts allowed for the transport of anion, normally insoluble in an organic solvent, to react with a suitable electrophile in the organic phase. This catalyst-reagent ion pair is sufficiently reactive to displace a halide from alkyl halide.

Let us start our discussion with some familiar examples to understand their role in organic synthesis. For example, consider S_N2 reaction of 1-chlorooctane with sodium cyanide. In this case, 1-chlorooctane is poorly soluble in the aqueous cyanide solution, and the sodium cyanide does not dissolve well in the organic solvent such as ether. Because of this, 1-chlorooctane and sodium cyanide solution form two separate layers. Heating of this two phase mixture under reflux and vigorous stirring for 1-2 days shows little reaction. But, when an appropriate quaternary ammonium salt such as tetrahexylammonium chloride is added, the substitution occurs rapidly in near 100% in 2-3h.

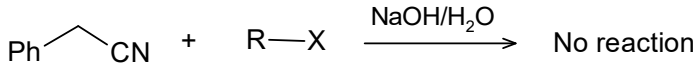




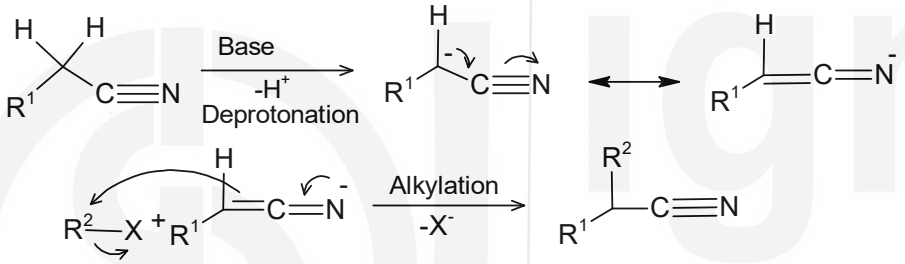
100 % yield in 2-3 Hr.

In this process the ammonium salt acts as phase transfer catalyst, transfers the cyanide into the organic phase and activates the transferred cyanide for the reaction with the alkyl halide. It also transfers the displaced chloride anions back to the aqueous phase to start a new catalytic cycle

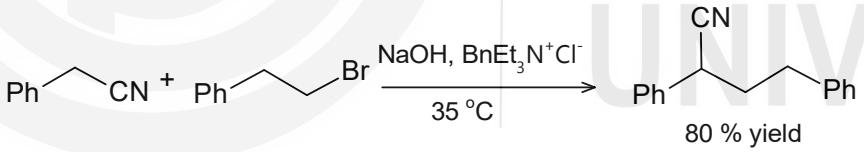
Consider another example of alkylation reaction of nitriles. No reaction occurs when a mixture of 2-phenylacetonitrile (benzyl cyanide), an alkyl halide and 50% aq. NaOH are vigorously stirred.



The nitrile group is similar to the carbonyl group increases acidic character of *α*-hydrogens, but the acidity of the *α*-hydrogen is much less (nitrogen is less electronegative than oxygen). Thus for deprotonation of nitriles, we require strong base such as $NaNH_2$ or metal alkyls such as BuLi. With sodium hydroxide, the nitrile does not get deprotonated completely for alkylation and only a small amount of anion is formed.

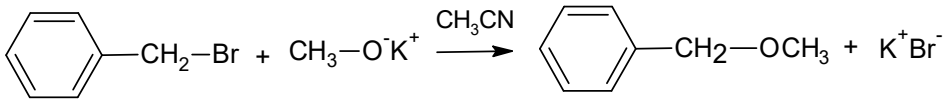


Upon addition of tetraalkylammonium chloride (benzyltriethylammonium chloride $BnEt_3N^+Cl^-$) in a catalytic amount, usually 1% molar, an exothermic reaction occurs and produces phenylalkylacetonitrile in high yield.



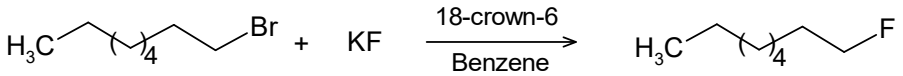
The above reaction is carried out in a two-phase mixture (water + an immiscible organic solvent) to prevent the hydroxide and 2-phenylethyl bromide reacting together to give 2-phenyl ethanol. The hydroxide stays in the aqueous layer, and the other reagents stay in the organic layer. A tetraalkylammonium chloride works as a phase transfer catalyst and allows sufficient hydroxide to enter the organic layer to deprotonate the nitrile.

Beside the quaternary ammonium and phosphonium salts (which together known as onium salts), crown ethers are also used as phase transfer catalysts. In the examples shown below, it illustrates how crown ether increases the rate of substitution reaction in the preparation of the benzyl methyl ether in acetonitrile (methyl cyanide) which does not dissolve the ionic compound. Here, the crown ether works as cation complexing agent, which surrounds and solvate the potassium ion and therefore enhances the reactivity of anionic nucleophile, cyanide ions.



5 % yield with no crown ether
100 % yield with 18-crown-6 ether

Similarly, in the presence of 18-crown-6, potassium fluoride is soluble in benzene and acts as a reactive nucleophile to give product in high yields.



The phase transfer catalyst used can be either soluble or insoluble in one of the two phases. Soluble catalysts include quaternary ammonium and phosphonium salts, polyethylene glycol and its derivatives, crown ethers and cryptands, and polymeric analogs. Insoluble catalysts include polymer-bound derivatives of soluble catalysts, or species which show negligible solubility in either phase and exists as a separate third phase. No one class of catalyst can be applied to all reactions amenable to phase transfer catalysis processes. In this unit our focus will be mainly on soluble phase transfer catalysts.

The various types of phase transfer catalysts are phosphonium and quaternary ammonium salts, crown ethers, cryptands, polyethylene glycols (PEG), etc. Table 16.1 summarizes some of the properties of frequently used phase transfer catalysts.

Table 16.1: Commonly used phase transfer catalysts

Catalyst	Stability and Activity	Use and Recovery
Ammonim salts	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	Thermally more stable than ammonium salts, although less stable under basic conditions.	Widely used. Recovery is relatively difficult.
Crown ethers	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	Stable and highly reactive, excluding the presence of strong acids.	Used sometimes despite high costs and toxicity, due to higher reactivity.
Polyethylene glycols	Lower activity but more stable than quaternary ammonium salts.	Often used and especially larger quantities of catalyst cause no problems. Reasonably easy to recover.

Let us discuss these catalysts in some detail.

Quaternary ammonium salts:

Quaternary ammonium cations have the ability to transfer the anionic reactants as non-solvated ion-pairs from aqueous media into organic media. The resultant effect is to increase the rate of the organic reaction by enhancing the reactivity of the anionic species and increasing the interaction rate with the organic substrate. Side reactions are frequently eliminated so that the overall yield of the desired product is increased. In the earlier examples we have shown how the quaternary ammonium salts increase the rate of reaction of a substitution reaction and also its yields. These catalysts are very cost effective and hence they are most widely used in the industry also.

Quaternary ammonium salts are chemical compounds having nitrogen in their skeleton and large hydrocarbon groups enough to convey good solubility in nonpolar solvents. In other words, the cations are highly lipophilic. Quaternary ammonium salts form ion pair with different anions. When these phase transfer catalysts are added, the lipophilic cations are transferred to the nonpolar phase and anions are attracted from the water to the organic phase to maintain electrical neutrality. The anions are weakly solvated in the organic phase and therefore exhibit enhanced nucleophilicity. Fig. 16.1 shows the commonly used ammonium salts as phase transfer catalysts.

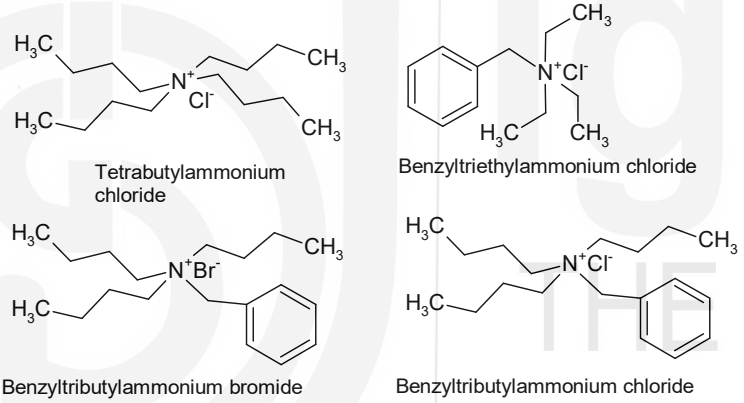


Fig. 16.1: Commonly used ammonium salts as phase transfer catalysts.

Phosphonium Salts:

These are analogous to the ammonium salts. The only difference is that instead of nitrogen, it contains phosphorous. Some commonly used phosphonium salts as phase transfer catalysts are shown in Fig. 16.2.

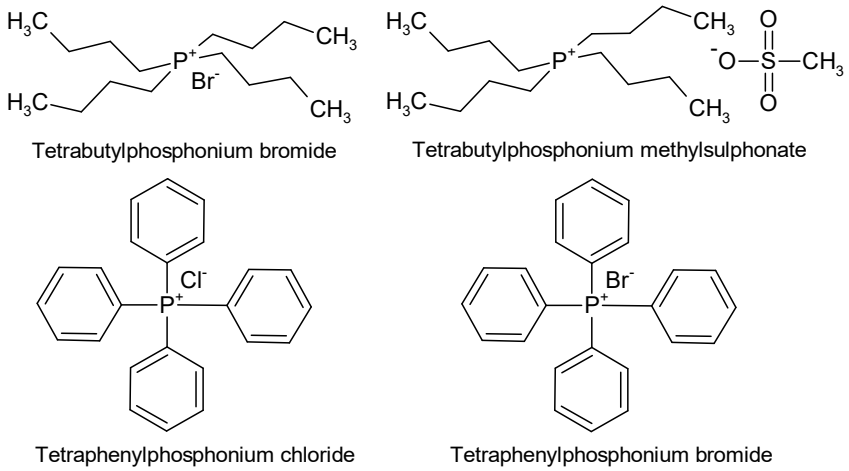


Fig. 16.2 Phosphonium salts used as phase transfer catalysts.

Crown ethers and Cryptands:

Macrocyclic and macrobicyclic polydentate ligands as crown ethers and cryptands are commonly used as phase transfer catalysts. The crown ethers and cryptands are a family of cyclic polyethers (Fig.16.3). These compounds can solubilize salts in nonpolar solvents by complexing with the cation in the cavity of the crown ether. In solution, the anions become more reactive as nucleophiles because they are weakly solvated. Regardless of their great activity as successful phase transfer catalysts, crown ethers and cryptands are not practicable for most industrial purposes due to their high costs and toxicity.

Crown ethers are specific for the cation they bind, and this is related to the size of the cavity. As show above, 18-crown-6 binds K^+ preferentially, but smaller crown ethers can bind Li^+ or Na^+

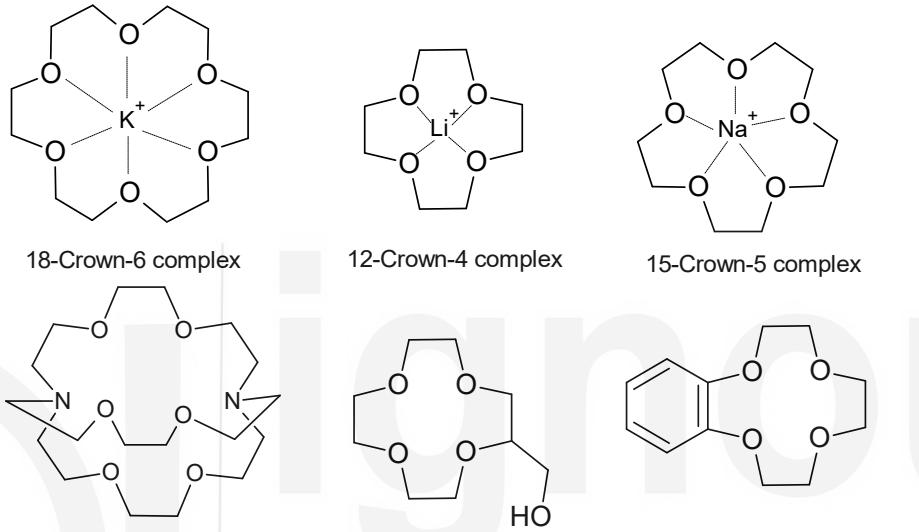
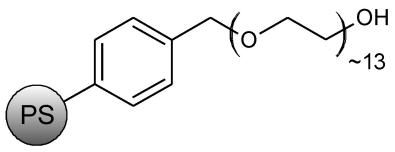


Fig. 16.3: Crown ethers and Cryptand used as phase transfer catalyst.

Polyethylene glycols:

Polyethylene glycols (PEGs) and their derivatives are also extensively utilized as phase transfer catalysts. Although they are less active than quaternary ammonium salts and crown ethers, they are comparatively inexpensive and environmentally friendly. Polyethylene glycols are nontoxic, stable, easy to regain and easily biodegradable, and are available without difficulty. They are generally used as immobilized phace transfer catalyst on insoluble polymer backbones.

For reactions with hydroxide transfer step in solid-liquid systems in polar solvents, polyethylene glycols acts as a highly efficient phase transfer catalyst with occasionally better activities than crown ethers. Water solubility makes them poor catalysts meant for liquid-liquid systems, even though in certain instances the polyethylene glycols can produce a third catalyst-rich phase and become active phase transfer catalyst. For example polymer-support poly ethylene glycol is shown below which is extensively used in organic synthesis.



Polymer-Supported Poly(Ethylene Glycol) 600

SAQ 1

In what way phase transfer catalyst are different from homogenous catalysts?

SAQ 2

What are the different types of phase transfer catalysts?

16.3 MECHANISMS OF PHASE TRANSFER CATALYSIS

Two competing mechanisms are thought to exist for PTC processes:

1. Extraction Mechanism
2. Interfacial Mechanism

1. Extraction Mechanism

The extraction mechanism, first proposed by Starks in the early 1970's, postulates that the phase-transfer catalyst can transport counter ions between the aqueous and organic phases. For example, the chloride displacement of 1-chlorooctane with cyanide ion in presence of tetraalkylammnonium (R_4N^+) and/or phosphonium salts (R_4P^+), Q^+ (Fig. 16.4). First, the phase-transfer catalyst exchanges its native counter ion for a cyanide anion in the aqueous phase. Second, the newly formed ion pair, Q^+CN^-, must then be extracted into the organic phase by crossing the interface where the equilibrium of this transfer is determined by the properties of the ion pair. The Q^+CN^- ion pair is then poised to react with 1-chlorooctane in the organic phase, and this step is referred to as the intrinsic reaction. In this case, the intrinsic reaction regenerates the catalyst, but the original ion pair, Q^+Cl^-, must be extracted back into the aqueous phase to complete the catalytic cycle. The sequences of steps that transport cyanide into the organic phase are referred to as transfer steps.

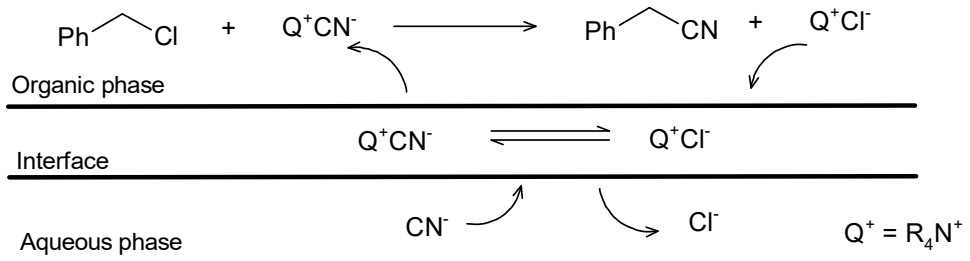


Fig. 16.4: Starks extraction mechanism.

Interfacial Mechanism

The second mechanism is referred to as the Makosza interfacial mechanism. This mechanism is postulated from the observation that highly lipophilic tetraalkylammonium salts showed limited or no aqueous solubility yet still remained highly active catalysts. As an example, the PTC alkylation of

phenylacetonitrile with benzyl bromide and aqueous hydroxide base illustrates the Makosza interfacial mechanism (Fig. 16.5). **Unlike the Starks extraction mechanism, Q^+, does not enter the aqueous phase.** First, phenylacetonitrile migrates to the interfacial layer where it undergoes deprotonation by a hydroxide anion, which is also present in the interface. The resulting nitrile anion is formed in the interface layer. This intermediate is too polar to be extracted into the organic phase and too basic to persist in the aqueous phase. Concurrently, Q^+Br^- will exist in equilibrium between the organic phase and interfacial layer. Once at the interface, Q^+Br^- can undergo an ion exchange with the nitrile anion. The resulting ion pair is now sufficiently lipophilic to be extracted into the organic phase and participate in the intrinsic reaction, in this case an alkylation with benzyl bromide.

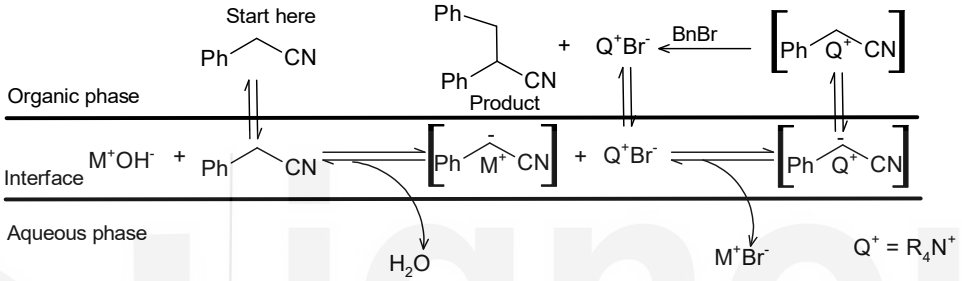


Fig.16.5: Makosza interfacial mechanism for phenylacetonitrile alkylation.

Given the several phase equilibria which transverse the interfacial layer, the rate determining step of a particular interfacial PTC process often involves an intermediate at the interphase. Therefore, an interfacial PTC mechanism is strongly dependent on the interfacial surface area between the bulk phases. For this reason, efficient agitation methods (e.g. stirring speed) are necessary for a PTC reaction operating under an interfacial mechanism.

Both these mechanisms are probably correct depending on the quaternary catalyst, with the first being more likely with small to medium sized quaternary cations, while the second is more correct for medium and large quaternary cations. For asymmetric PTC, most catalyst employed remains in the organic phase with transfer occurring at the interface (2nd mechanism).

16.4 APPLICATIONS OF PHASE TRANSFER CATALYSIS

Phase-transfer catalysis (PTC) is a powerful tool to carry out many organic reactions in a practical fashion, both in the laboratory and on the industrial scale. Significant cost savings and major process improvements can be achieved in reactions performed in water–organic solvent mixtures. Particularly striking is the possibility of replacing expensive solvents and dangerous bases that require strictly anhydrous conditions with aqueous bases and apolar, environmentally friendly, easily recyclable solvents. During the last decade notable results, both in terms of yields and stereoselectivity, were obtained in various reactions performed in the presence of chiral, nonracemic quaternary ammonium salts.

PTC is particularly useful for reactions of organic anions with nonpolar organic reactants. They are also applicable for numerous reactions in which anions

are intermediates for generating other active species such as carbenes, nitrenes and organometallic reagents.

Reactions have been reported in the following areas:

i) Nucleophilic Substitutions

ii) Alkylations

iii) Carbene reactions

iv) Oxidations and reductions

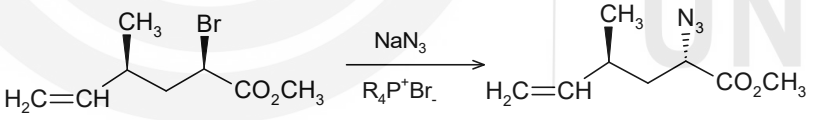
v) Aldol and related condensations

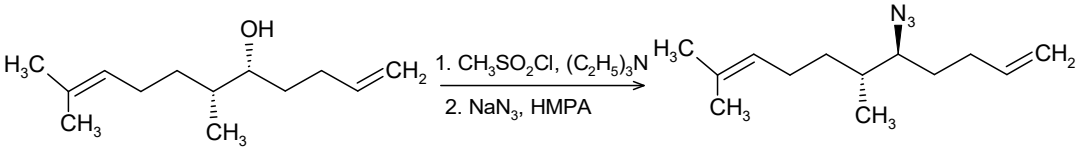
Here we are reporting some representative examples from the literature.

Nuclophilic substitutions

The objective in selecting the reaction conditions for a preparative nucleophilic substitution is to enhance the mutual reactivity of the leaving group and nucleophile so that the desired substitution occurs at a convenient rate and with minimal competition from other possible reactions. Phase transfer catalysis provides an alternative approach of achieving this objective. In earlier example of nucleophilic substitution of cyano group, you have seen how it was difficult to replace halogen group by cyano group in normal reaction conditions. But this transformation can be completed in very less time under phase transfer conditions. Phase transfer catalyst such as crown ethers, quaternary ammonium and phosphonim salts surround and solvate the cation and therefore enhance the reactivity of anion nucleophile. Now consider few more examples of nucleophilic substitution reactions under phase transfer condition:

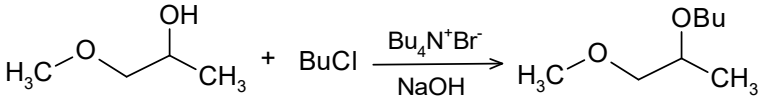
1. Phase transfer conditions can used for the preparation of azides





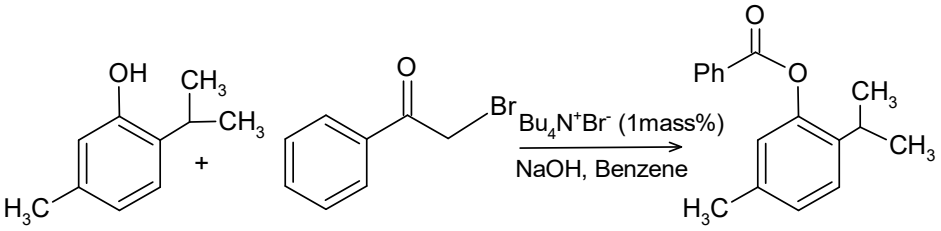
Alkylations

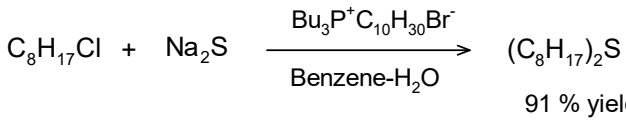
Alkylations are the most common application of phase transfer catalysts. We have already discussed alkylation of nitriles. Alcohols can also alkylated using quaternary ammonium salts to give dialkyl ethers.



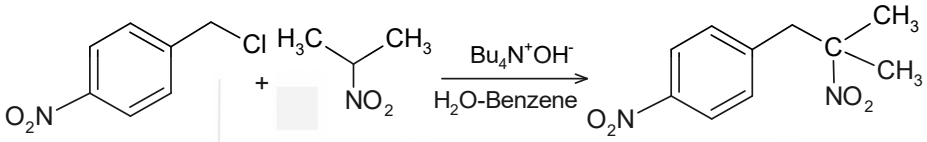
97 % Yield

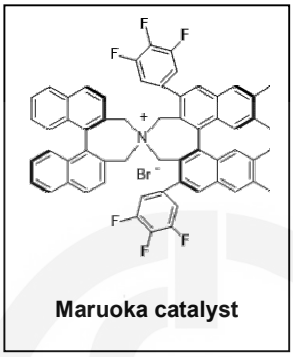
Similarly phenols can also alkylated using phase transfer catalyst.





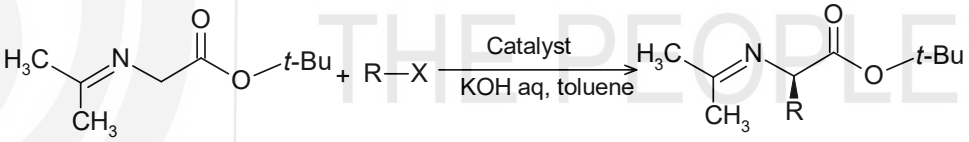
Nitroalkanes can be alkylated in a single step with hydroxide as a base in phase transfer conditions. This keeps the HO^- and the electrophile apart, preventing alcohol formation.





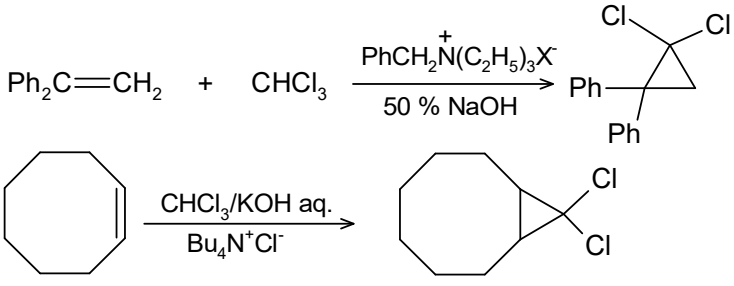
Maruoka catalyst

Phase transfer catalyzed processes can also give enantioenriched products by the action of chiral, nonracemic catalyst. Such processes are referred to as asymmetric phase-transfer catalysis (APTC) reactions. For example consider the asymmetric phase-transfer catalysis by the Maruoka catalyst. In this case protected glycine can be alkylated enantioselectively using very small amounts of the chiral quaternary ammounium salt.



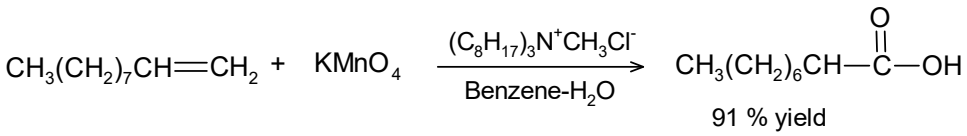
Carbene reactions

Phase transfer catalysis has proved to be effective in generation of cabenes by *α*-elimination of haloalkanes. Both tetraalkylammonium salts and crown ethers can be used to promote *α*-elimination reactions of chloroform and other haloalkanes. The carbenes can be trapped by alkenes to form dichlorocyclopropanes.



Oxidation

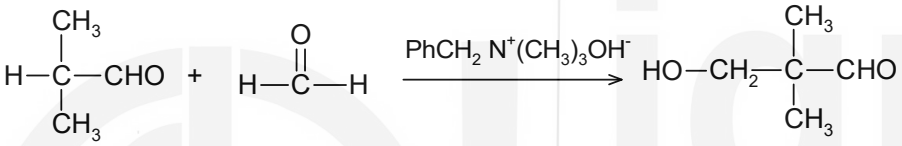
Phase-transfer catalysis is particularly useful in oxidation reactions because the oxidizing agents are insoluble in most organic solvents, while the substrates are generally insoluble in water.



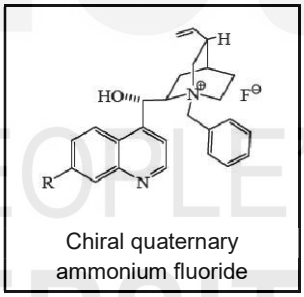
Benzylic and allylic alcohols have been selectively oxidized to the aldehydes in presence of saturated alcohols by the use of potassium manganate ($KMnO_4$) under phase-transfer conditions.

Aldol and related condensations

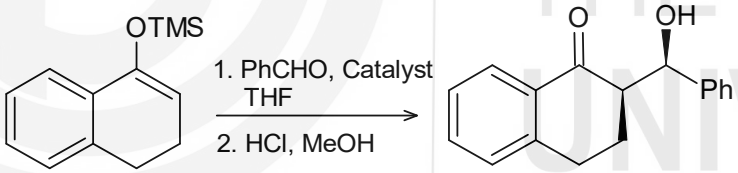
Aldol product can be obtained in high yields using phase transfer catalyst. For example 3-Hydroxy-2,2-dimethylpropanal (hydroxypivaldehyde) (HPA) is a precursor intermediate for the synthesis of neopentyl glycol (NPG) can be prepared by aldol condensation of isobutyraldehyde and formaldehyde at 20 °C using benzyltrimethylammonium hydroxide, a basic phase transfer catalyst in almost quantitative yield with ~100% selectivity.



The asymmetric aldol products can be prepared using chiral phase transfer catalysts. In this reaction given below, silyl enol ether reacts with benzaldehyde using chiral quaternary ammonium fluoride as a catalyst and the silylated aldol is hydrolyzed with hydrochloric acid to give the aldol product.

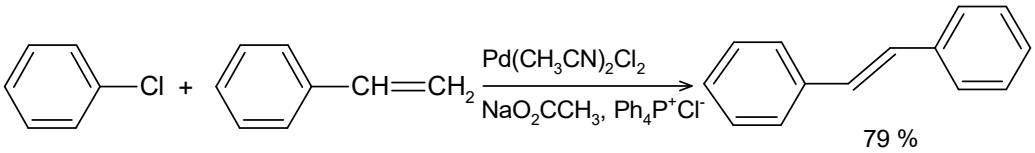


Chiral quaternary ammonium fluoride

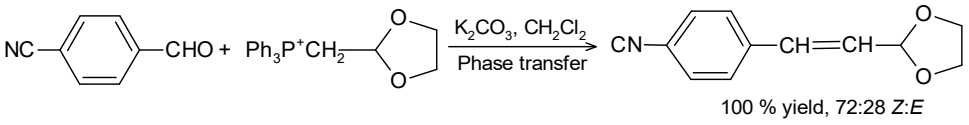


Heck reaction

Aryl chlorides are not very reactive under normal Heck reaction conditions but reaction can be achieved by addition of phase transfer catalyst, tetraphenylphosphonium salts with $Pd(OAc)_2$ or $PdCl_2$ as the catalysts.



Wittig Reaction



100 % yield, 72:28 *Z*:*E*

SAQ 3

Complete following reactions:

a) $CH_3OCH_2CH(OH)CH_3 + BuCl \xrightarrow[NaOH]{Bu_4NBr}$

b) $PhCH_2CN + CH_3CH_2CH_2Br \xrightarrow[35\ ^oC]{NaOH,\ BnEt_3N^+Cl^-}$

c) $C_8H_{17}Cl + Na_2S \xrightarrow[Benzene\text{-}H_2O]{Bu_3P^+C_{10}H_{30}Br^-}$

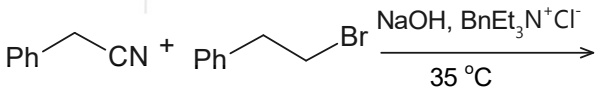
16.5 SUMMARY

In this unit we have discussed chemistry of phase transfer catalysis. These reactions provide an alternate approach for the synthesis of organic molecules in two or more phases. There are number of advantages that phase transfer catalysis offers over homogeneous alternatives:

- Usually the reactions under phase transfer conditions require mild reaction conditions thus involves inexpensive reagents (NaOH, KOH, K_2CO_3 etc. instead of NaH, KHMDS *t*-BuOK, etc.).
- The reactions are relatively easy to perform and are highly scalable.
- Phase transfer catalytic processes are consistent with the principles of green chemistry, for this reason industrial applications are growing.

16.6 TERMINAL QUESTIONS

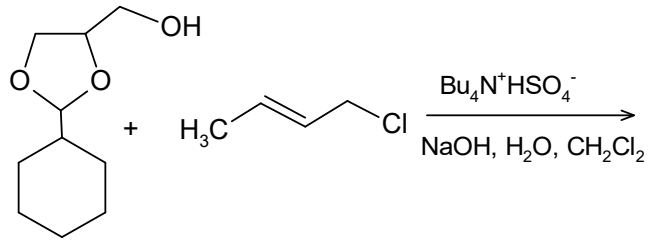
1. Complete the following reaction and write its mechanism.



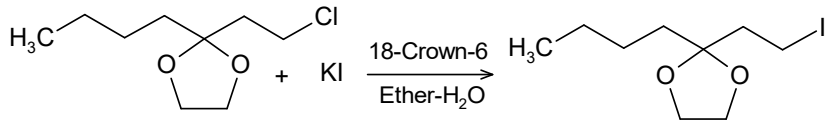
2. Discuss the role of crown ethers in the phase transfer reactions.

3. Complete following reactions:

a)



b)



c) $Cl(CH_2)_3Cl + KCN \xrightarrow[CH_3CN]{}$

d) $Cl(CH_2)_3Cl + KCN \xrightarrow[CH_3CN]{\text{18-Crown-6}}$

16.7 ANSWERS

Self Assessment Questions

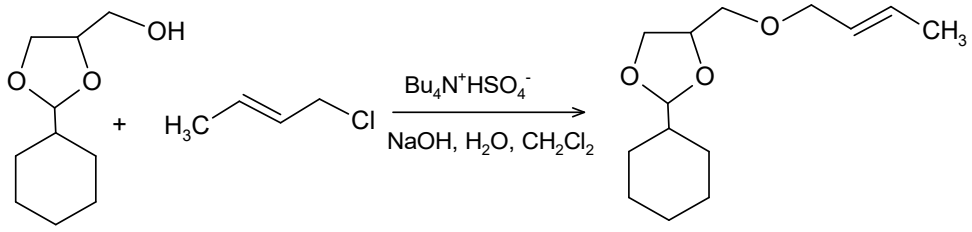
1. Homogeneous catalysts are those which exist in the same phase (gas or liquid) as the reactants, while phase transfer catalyst may be soluble in one or two phases and facilitates the migration of a reactant from one phase into another phase where reaction occurs. Typically, phase transfer catalysis involves the use of phase transfer catalyst such as onium salts and crown ethers placed in a two-phase liquid–liquid system.
2. Common phase transfer catalysts are onium salts (ammonium and phosphonium salts), crown ethers (macrocyclic polyethers), cryptands (aza-macrobicyclic ethers), and polyethylene glycols (PEG), etc..
3. a) $CH_3OCH_2CH(OH)CH_3 + BuCl \xrightarrow[NaOH]{Bu_4NBr} CH_3OCH_2CH(OBu)CH_3$

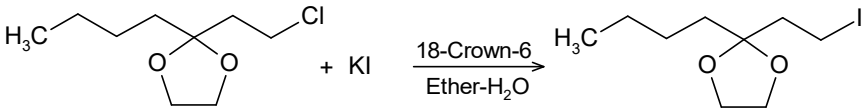
   b) $PhCH_2CN + CH_3CH_2CH_2Br \xrightarrow[35\ ^oC]{NaOH,\ BnEt_3N^+Cl^-} PhCHCN$ (with $CH_2CH_2\ CH_3$)

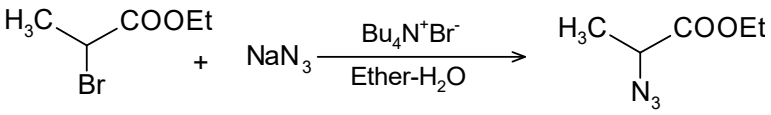
   c) $C_8H_{17}Cl + Na_2S \xrightarrow[Benzene\text{-}H_2O]{Bu_3P^+C_{10}H_{30}Br^-} (C_8H_{17})_2S$, 91 % yield

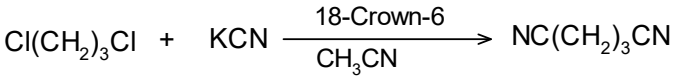
Terminal Questions

1. Ph–CN + Ph–Br $\xrightarrow[35\ ^oC]{NaOH,\ BnEt_3N^+Cl^-}$ Ph–CH(CN)–CH$_2$–CH$_2$–Ph, 80 % yield

   Its mechanism is similar to Interfacial Mechanism.
2. Crown ethers can solubilize salts in nonpolar solvents by complexing the cation in the cavity of the crown ether. In solution, the anions become more reactive as nucleophiles because they are weakly solvated.
3. a) 

b) 
H3C
Cl
O
O
+ KI
18-Crown-6
Ether-H2O
H3C
I
O
O

c) 
H3C
COOEt
Br
+
NaN3
Bu4N+Br-
Ether-H2O
H3C
COOEt
N3

d) 
Cl(CH2)3Cl + KCN
18-Crown-6
CH3CN
NC(CH2)3CN