
1 PHASE TRANSFER REACTIONS

Chemical reactions involving two or more molecules usually proceed at higher rates in one phase. However, it is not always feasible or expedient to render some reactions under homogeneous conditions. In such cases the phase transfer technique should be considered.

Improvement of reactions by phase transfer catalysis (PTC) represents a breakthrough in chemical technology. Although sporadic reports appeared before the 1960s, consolidation of the concept through a series of publications on the theme of extractive alkylation [Markosza, 1965], a patent describing catalysis of heterogeneous reactions [Starks, 1968], and the observations concerning reactions of quaternary ammonium salts in nonpolar media [Brandström, 1969, 1972] initiated an avalanche of research in the methodology.

While the most common phase transfer technique deals with reactants in two immiscible liquids, its scope encompasses gas-liquid, gas-solid, liquid-solid, and presumably solid-solid systems. In comparison with conventional methods, PTC holds considerable advantages in terms of cost (which avoids expensive anhydrous dipolar aprotic solvents), time, mildness, and simplicity. It is often observed that reactivities and selectivities are enhanced under such conditions.

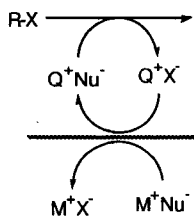
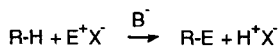
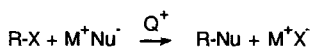
From an electrochemical study [Tan, 1994] of the Williamson ether synthesis under phase transfer catalysis, it is concluded that the role of the catalyst is to establish a Galvani distribution potential difference between the two phases which acts as the driving force for transferring the reactive ions from the aqueous medium to the organic layer.

The general features of a typical PTC substitution reaction carried out in a system of organic and aqueous phases specifies reaction taking place in the organic layer. The phase transfer agent is present in catalytic amount and capable of moving one reactant in its resident solvent into that of the other reactant or the interfacial region. Only then the two species can react with reasonable speed. Needless to say that strong agitation is a most crucial to maximize reaction rates.

Actually there are two mechanistic models for the PTC reaction. In the Starks extraction mechanism the catalyst is biphilic, thus well qualified by a quaternary ammonium or phosphonium salt, either of which having finite solubility in both phases on account of its charge and organophilicity, capable of ferrying the counter anion from the aqueous phase to the organic layer by the partition phenomenon. The

2 Distinctive Techniques for Organic Synthesis

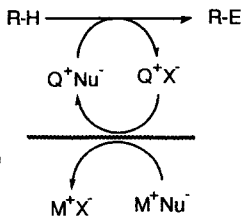
anion generated from reaction will pair with the quaternary onium species and enter the aqueous phase and a second catalytic cycle starts at this point. The interfacial mechanism (proposed by Makosza and modified by Brandström and Montanari) describes cases in which the catalyst is highly organophilic and it functions by anion exchange in the interfacial region. In other words, the cation of such a catalyst virtually never stays in the aqueous phase.



org. phase

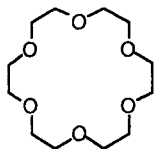
aq. (solid) phase

cation-catalyzed
phase transfer reaction

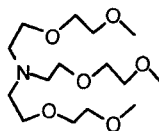


anion-catalyzed
phase transfer reaction

It should be recognized that a PTC reaction consists of anion transfer and intrinsic reaction steps and the determining factors for each may be different, and high rates of both steps of the process are necessary. It is also important that the transferred anion be highly reactive, and likely be when pairing with a quaternary ammonium or phosphonium ion. The greater distance separating the cation and the anion in comparison with the that in the corresponding alkali metal salts increases the nucleophilicity of the anion. Actually the same principle applies when a crown ether with proper cavity to accommodate the cation is added to complex the metal ion in the alternative PTC system. Interestingly, tris(3,6-dioxahexyl)amine is an excellent solid-liquid PTC [Soula, 1985] because it is inexpensive, relatively nontoxic and capable solubilizing alkali metal ions as well as transition metal ions by virtue of molecular flexibility., although the anion activation power is lower than cryptands.



18-crown-6



tris(2-(2-methoxyethoxy)ethyl)amine

A recently developed method for expedient preparation of cyclophosphazenic polyiododands [Gobbi, 1994], which have high catalytic activities, should render these very competitive in future utility.

Micelles and PTC have similarities and differences. Micelles are formed by addition of surfactants to aqueous-organic biphasic systems, but PTC are not necessarily surfactants and vice versa. Generally micelle systems have limited synthetic value owing to problems associated with emulsions.

Common anions are hydrophilic, their transfer into an organic phase must overcome the energy of hydration, which is particularly important for the smaller ions and those having a greater charge. The association of the anion to quaternary onium ions has a positive effect. Divalent anions have practically no affinity for cations in nonpolar organic solvents and therefore do not function at all. On the other hand, overly strong association renders ion pairs highly lipophilic and the catalyst regeneration becomes difficult. Thus quaternary iodide salts are rather poor catalysts and reactions that generate iodide ion are usually shut down at relatively low conversions.

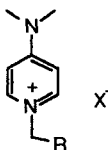
It should be reiterated that a useful PTC should be soluble in the organic solvent because typical catalyst regeneration rate in the aqueous phase is 5-10 orders of magnitude greater than reaction rate in the organic layer. Quaternary salts having 10-30 carbon atoms are usually suitable, but the cation structure is also critical. Thus a cation containing one long alkyl chain and three methyl or ethyl groups are poor catalysts, for they tend to form micelles and stay in the aqueous phase. A general conclusion is that quaternary onium ions possessing all butyl or larger groups have superior anion transfer capability. Aryl and secondary alkyl group substituents present, the latter tend to undergo elimination.

While both quaternary ammonium and phosphonium salts have been successfully used as phase transfer catalysts, different situations may demand the choice of one or the other. Phosphonium salts are thermally more stable than ammonium analogues (which are prone to undergo internal displacement at elevated temperatures), but both are attacked by hydroxide ion to give phosphine oxides and Hofmann elimination products, respectively.

Other conditions that affect a phase transfer reaction include pertinent ion-pairing and the polarity of the organic solvent. Generally, saturation of the aqueous phase with an inorganic salt improves phase transfer by salting out (reducing the degree of hydration) the phase transfer agent (anion). Sometimes the presence of a solvating compound such as an alcohol in small quantities to modify the structure of the anion can have dramatic benefit. Regarding organic solvent polarity, nonpolar

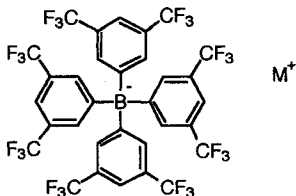
solvents tend to magnify the partition differences of the anions while polar solvents such as CH_2Cl_2 have a leveling effect.

The choice of PTC is also based on criteria such as selectivity, stability under reaction conditions, availability and cost, and ease of removal or recovery. For example, a series of pyridinium salts [Dehmlow, 1989] are excellent catalysts for anhydrous alkylation of sodium phenoxides, but they are useless in the presence of aqueous bases because of their susceptibility to under decomposition to pyridones (and thiopyridines in the presence of Na_2S).



The diverse demands provide a constant stimulus to the development of new catalysts. For example, triphenylsulfonium and -selenonium salts [Kondo, 1989, 1992] meet the criteria of effective PTC, and the simple admixture of an acyl chloride with a tertiary amine furnishes acyltrialkylammonium chloride [Bhalerao, 1992] which serves well in solid-liquid phase transfer reactions. Chiral quaternary ammonium salts have shown great promise in promoting asymmetric reactions.

While most catalysts serve to transfer anions to the organic phase in which reactions take place, a few others can ferry cationic species across the interfacial boundary. Salts of tetrakis(3,5-bis(trifluoromethyl)phenyl)borate have proven highly satisfactory for catalyzing reactions of diazonium and oxonium species, including diazo coupling, Friedel-Crafts alkylation, nitrosation, acid-mediated hydrolysis of esters [Ichikawa, 1988]. The bulky anion is very stable to acid and oxidants.



Regarding catalyst removal, those anchored to an insoluble resin are the easiest, for they require simple filtration at the end of the reaction. These catalysts have both advantages and defects: reactions are slower, and their activity may be more sensitive to environment, e.g., the degree of cross-linking of the resin.

New biphasic systems composing of a hydrocarbon and a fluorocarbon (perfluorinated alkanes, ethers, or tertiary amines) which are largely immiscible are valuable for conducting water-sensitive reactions. Successful hydroformylation of alkenes has been demonstrated [Horvath, 1994] using a rhodium catalyst bound to a phosphine ligand which is soluble in the fluorous phase. Reaction occurs when reactants come into contact with the catalyst in that phase or at the interphase, with assistance of a PTC.

Triphase reactions [Regen, 1982a] have received attention from a few investigators. In the most common systems the catalyst is present in the solid phase (insolubilized ammonium and phosphonium salts, crown ethers, cryptands on resins, silica gel or alumina) together with two immiscible liquids. In some situations the triphase reaction has unique attractiveness. Thus macrolide formation in good to excellent yields has been achieved without resorting to high-dilution technique by stirring mesyloxy carboxylic acids with a resin-bound phosphonium mesylate in toluene/aqueous potassium bicarbonate [Regen, 1982b].

In phase transfer reactions, particularly those involving a solid, mass transfer is critical. Accordingly many more experimental parameters influence the triphasic reactions.

1.1. SUBSTITUTIONS

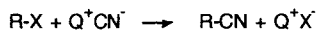
Many polar organic reactions were improved when conducted in polar aprotic solvents such as DMF and DMSO. The advent of phase transfer techniques then brought about an operational option which is often superior. In practically every case, common substitution reactions can profit by adopting this inexpensive but expedient protocol. Among the major advantages are convenience of execution including workup, remarkable absence of side reactions related to solvolysis, applicability to industrial scale reactions where cost is also critical.

Generally, the structure-reactivity relationship of substrate (typically alkyl halides) in simple substitution reactions under PTC conditions follows that established for S_N2 process in dipolar aprotic solvents [Smiley, 1960]. Thus in alkyl halides the trend of primary > secondary > tertiary halides is observed. Variation of the leaving group brings about gradation of reactivity in the rank of R-OMs > R-Br > R-Cl, while R-I and R-OTs behave poorly, due to strong association of I⁻ and TsO⁻ ions with quaternary ammonium and phosphonium ions. Characteristic of the S_N2 mechanism for PTC substitution reactions inversion of configuration is usually observed.

1.1.1. With Cyanide Ion

One of the most thoroughly studied aliphatic substitution reactions concerns the preparation of nitriles from alkyl halides (except iodides) and sulfonates (tosylates excluded). Quaternary onium salts and crown ethers and cryptands have been used successfully in the liquid-liquid PTC reaction [Liotta, 1974a; Cinquini, 1975].

If under anhydrous conditions using equimolar quantity of an onium cyanide, the reaction proceeds almost instantaneously and explosively even at room temperature [Simchen, 1975]. However, the so-called anhydrous conditions is not rigorously free of water, a trace of which must be present. However, as water content is increased further, the rate is depressed.

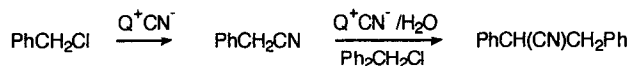


The solid-liquid PTC reaction proceeds better with 18-crown-6 than tetra-*n*-butylammonium bromide, probably indicating the differential efficiencies for transporting the anion from the solid to the organic phase. At least in some cases evidence adduced the formation of a ternary substrate-catalyst-solid reagent complex.

For industrial applications such as the preparation of nitrile intermediates of ibuprofen [Hampl, 1990] and Nylon-8 [Nanba, 1988] the cost excludes crown ethers as catalysts.

Treatment of clays with quaternary ammonium salts forms suitable catalysts which are easily recovered and reused [Lin, 1991].

Attention must be paid to avoid side reactions arising from alkylation of highly reactive nitriles. For example, phenylacetone nitrile initially formed by the reaction of benzyl chloride and sodium cyanide is susceptible to benzylation when the pH of the aqueous medium rises (by reaction of NaCN with water to produce NaOH and HCN). Slow addition of NaCN minimizes the undesired alkylation [Coates, 1973].



Naked cyanide (from solid MCN and catalytic amount of a crown ether) in acetonitrile or benzene is an excellent nucleophile, capable of displacing the chlorine atom from chlorotrimethylsilane [Zubrick, 1975].

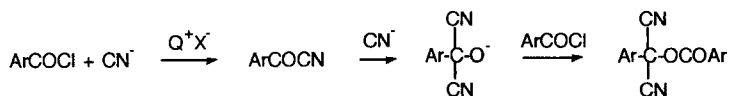
Glutaronitrile. [Liotta, 1974]

A magnetically stirred mixture of 1,3-dichloropropane (5.08g, 45 mmol), dry KCN (11.7 g, 180 mmol), 18-crown-6 (1.01 g, 3.8 mmol) in acetonitrile (25 mL) is refluxed. After 1.5 h the completed

reaction (GC monitoring) is cooled, filtered, and reduced to ca. one-third volume. Addition of water, extraction with dichloromethane, drying over MgSO_4 , evaporation in vacuo, and distillation gives glutaronitrile (4.10 g, 96.8%).

Displacement of vinyl halides becomes possible in the $\text{KCN}/18\text{-crown-6}$ system in the presence of $(\text{Ph}_3\text{P})_4\text{Pd}$ [Yamamura, 1977].

Sensitive nitriles such as cyanofornates are obtainable in 62-94% yields from the chlorofornates [Childs, 1976]. Aroyl cyanides are accessible more conveniently by PTC reaction of the aroyl chlorides with NaCN [Koenig, 1974]. The moderate yields, when the substrates are more electron-deficient, are due to dimer formation.



In conjunction with acetone cyanohydrin, 1,4-addition of the naked cyanide ion to enones (including cholestenone) can be effected.

1.1.2. With Halide Ions

The conversion of one alkyl halide to another or a mesylate to an alkyl halide is relatively facile with both liquid-liquid and solid-liquid phase transfer catalysis. For alkyl fluoride preparation (RCl being better substrates than RBr) it requires a higher temperature therefore quaternary phosphonium salts are employed [Landini, 1974a]. An ion exchange resin with residential quaternary ammonium ions (e.g., Amberlyst A-26) may be converted to the fluoride and used in the PTC reaction [Cainelli, 1976].

The displacement using concentrated hydrohalogenic acids is feasible in the presence of a quaternary ammonium salt [Landini, 1992] which has a great accelerating effect.

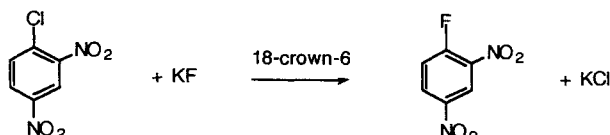
Olefins and alcohols are formed as side products but alcohols are absent when the reaction is conducted with a $\text{KF}/\text{crown ether}$ system [Liotta, 1974b]. Secondary halides are prone to elimination because naked fluoride ion is also a strong base.

Water content in the reaction media is critical for fluoride displacement [Dermeik, 1985; Landini, 1991]. When quaternary ammonium salts are used as catalysts and KF as reagent, 0.33 mole of water per mole of KF would be optimal. This ratio is a compromise between fluoride transfer and catalyst stability.

Alkyl mesylates are better substrates because of mesyloxy ion is a better leaving group than halide ions and the weaker association with the cation makes catalyst regeneration more efficient.

Phase transfer conditions are also suitable for the conversion of sulfonyl chlorides to the corresponding fluorides [Bianchi, 1977].

Aromatic fluorides such as 2,4-dinitrofluorobenzene can be prepared by halogen exchange with the KF/crown ether system [Bram, 1988].



Exchange between any other pair of halogen atoms in alkyl halides is perhaps of less significant values in the preparative sense. However, equilibria in favor of one direction are definitely more easily controlled in the two-phase system, for example by using an aqueous solution containing an excess metal halide to overwhelm the phase transfer catalyst. Alternatively, setting up the equilibrium with equimolar amount of a salt in water and replace the aqueous phase with fresh aliquot. After several cycles the organic phase should contain the exchange product as the major component. The nature of the cation in the added salt must also be considered, as equilibrium is dependent on the unequal (saturated) aqueous solubilities of M^+X^- and M^+Y^- .

A study comparing the catalytic activity for halogen exchange indicates cryptands > a quaternary phosphonium bromide > crown ethers [Cinquini, 1975]. Radioactive drugs containing ^{82}Br , ^{123}I , and ^{131}I isotopes have been prepared [Liu, 1985] by the halogen exchange technique using crown ether catalysts.

1.1.3. With Oxide Anions

The displacement of alkyl halides with hydroxide ion under liquid-liquid phase transfer catalysis is not particularly straightforward, although high conversion of 1-bromooctane to *n*-octanol has been realized using ammonium salts with four *n*-butyl or larger alkyl groups [Herriott, 1972], there are intrinsic problems in such reactions. Ether formation and elimination are serious side reactions, and the hydrated hydroxide ion is quite a difficult to transfer into the organic layer. In order to maintain an effective level of Q^+OH^- it requires high concentration of metal hydroxide in the aqueous phase which is detrimental to the quaternary cations at even moderate temperatures, thus limiting operating temperatures in the 50°-60°C range.

The formation of 1-adamantanol in 92% yield from 1-bromoadamantane [Slobodin, 1988] is an extraordinary case, contributed by steric effect.

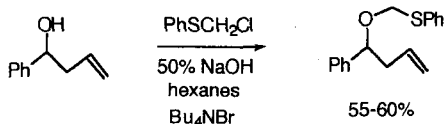
Betaine salts $R_3N^+CH_2COO^-$ seem to be 10- to 50-fold more active than ordinary quaternary alkylammonium salts in promoting the hydroxide displacement reaction [Starks, unpublished]. Involvement of carboxylate intermediates is likely.

An amazingly efficient interconversion of mesitoic acid and its esters can be performed under PTC conditions. The esters are formed in essentially a solid-liquid phase transfer conditions [Loupy, 1986]. Mesitoic esters (even *t*-butyl mesitoate) are saponified on treatment with KOH-crown ether complexes in benzene or toluene [Pederson, 1967] or KOH-cryptands [Dietrich, 1973], by way of acyl-oxygen bond cleavage. (-)-Menthol was recovered from the menthyl ester. (For the more conventional transesterification between phenol and isopropenyl acetate under solid-liquid phase transfer conditions, see [Barry, 1988].)

n-Octyl Mesitoate. [Loupy, 1986]

Mesitoic acid is added to finely powdered KOH (containing 15% w/w water) and a small amount of Aliquat 336. The resulting mixture is shaken at room temperature for 10 min, while it is treated with 1-bromooctane at midpoint. The reaction is completed by heating at 85°C for 2 h. Yield of the ester is 88%.

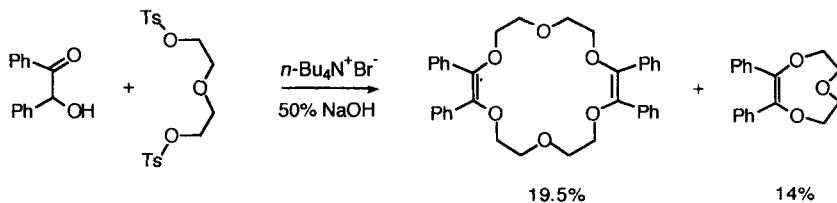
While the alkylation of secondary alcohols with chloromethyl phenyl sulfide under standard conditions gives only 10-30% yield of the ethers, along with large quantities of bis(phenylthio)methane, the PTC route is superior for the preparation [Rawal, 1993].



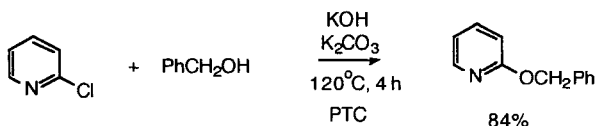
For the synthesis of unsymmetrical ethers under PTC it is better to pair larger alcohols with smaller alkyl halides. Optimal conditions consist of excess alkyl chloride (as solvent if possible), more than fivefold excess of 50% NaOH over the alcohol, and 3-5 mole % of *n*-Bu₄N⁺ HSO₄⁻ as catalyst at 25°-70°C [Freedman, 1975].

Optically pure oxetanes are similarly made by cyclization of 1,2,2-trisubstituted 1,3-propanediol monomesylates [X. Hu, 1995]. The corresponding reaction of the tosylates is slow.

Enediol ethers are readily formed by reaction of benzoin with alkyl tosylates under PTC conditions [Merz, 1977]. It gives unsaturated crown ethers in better yields than conventional method.



Replacement of the chlorine atom of 2- and 4-chloropyridine with an alkoxy group (e.g., benzoyloxy) is accomplished by heating the substrate with a suspension of powdered KOH and K_2CO_3 in dry toluene containing the alcohol and a little tris(3,6-dioxahexyl)amine [Ballesteros, 1987].



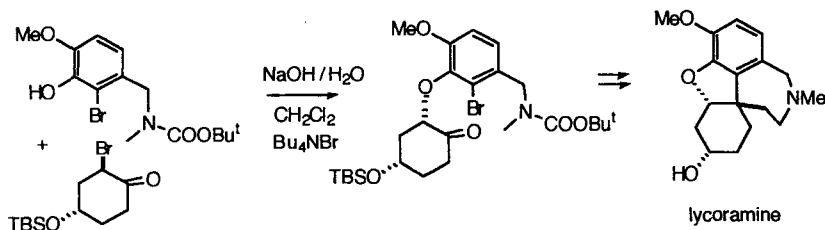
Ordinarily aliphatic alcohols cannot be methylated with dimethyl sulfate, but the reaction proceeds readily in the presence of a tetra-*n*-butylammonium salt [Merz, 1973a].

O-Alkylation of phenols is easily conducted by their addition to a two-phase system of aqueous NaOH, dichloromethane solution of the alkylating agent and $\text{Bn}(\text{nBu})_3\text{N}^+\text{Cl}^-$ [McKillop, 1974]. The extremely high chemoselectivity which is not complicated by *C*-alkylation is noteworthy. Under similar conditions catechols are converted in good yields (76-86%) to methylenedioxyarenes using dibromomethane as alkylating agent [Bashall, 1975].

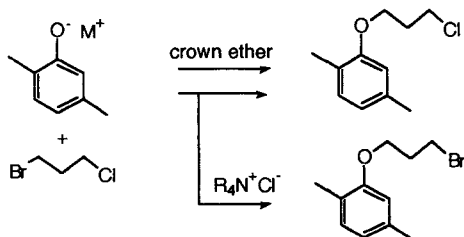
Methylenedioxyarenes. [Bashall, 1975]

To a vigorously stirred refluxing mixture of dibromomethane (0.15 mol) and Adogen 464 (1 mmol) in water (20 mL) is added a solution of a catechol (0.1 mol) and NaOH (0.25 mol) in water (50 mL) during 2 h, while oxygen is being excluded from the system. After the addition the mixture is heated for a further 2 h before workup.

A recent significant employment of PTC alkylation is in a convergent synthesis of lycoramine [Parker, 1992]. Formation of the *cis*-2-aryloxy-4-siloxycyclohexanone was the result of a kinetic process.



The PTC alkylation of 2,5-dimethylphenol with 1-bromo-3-chloropropane [Reinholz, 1990] illustrates the importance of catalyst structure. In the presence of accessible catalysts (e.g., crown ether complexes, RNMe_3X), which form relatively tight ion pairs with anions such as OH^- and which do not activate anion appreciatively, the major product is the aryl 3-chloropropyl ether. On the other hand, bulky ammonium salts which belong to the anion activating group also gives considerable amounts of the 3-bromopropyl ether, owing to activation of Br^- to effect an exchange of the chlorine in the initiate product.



An unusual procedure for *O*-alkylation of 2-naphthol consists of mixing sodium 2-naphthoxide and the alkylating agent in a molten quaternary salt (best results in molten *n*- Bu_4NBr) [Badri, 1992]. The reaction rates and selectivity are better than in DMF. Work up is by ether extraction of the cooled mixture.

Formation of ester from $\text{RCOONa}/\text{H}_2\text{O}$ and $\text{R}'\text{CH}_2\text{X}$ in a two-phase system was observed when an amine was added [BASF, 1912]. However, more than fifty years lapsed before the catalytic role of an ammonium salt generated in situ was determined [Hennis, 1967]. One alkyl group of the ammonium ion must be quite long, and benzylammonium salts are not useful.

Anion exchange macroreticular resins (e.g., Amberlite IRA-904) in which the anion is replaced by a carboxylate undergo alkylation (best with alkyl iodides). Esters are released in 50-90% yield [Cainelli, 1975].

Various other PTC techniques are effective for *O*-alkylation of the carboxylate ion. A correlation of crown ether/cryptand structure with rate of benzyl acetate

formation from benzyl chloride and potassium acetate in acetonitrile at room temperature has been made [Knöchel, 1975]. The reaction of an acyl chloride with an alkyl halide in the presence of an alkali metal bicarbonate and a phase transfer catalyst (Bu_4NBr or PEG-400) in acetonitrile at 80°C to give an ester [Y. Hu, 1992] actually proceeds via the metal carboxylate.

Methyl esters can be converted to other alkyl esters by sequential saponification and *O*-alkylation [Doecke, 1991; O'Donnell, 1991]. Amino acid methyl esters generally undergo transesterification without racemization, except the highly sensitive compounds such as the phenylglycine derivative.

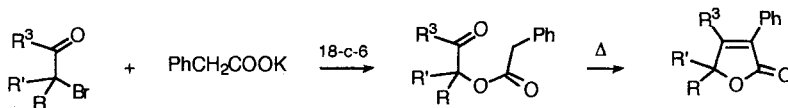


In the solid-phase peptide synthesis, immobilization of the first amino acid to the Merrifield resin is quantitative when carried out by a 18-crown-6 promoted reaction with the Boc-amino acid potassium salt in DMF [Roeske, 1976]. Microwave as energy source shortens the time for a solid-liquid phase transfer reaction [Bram, 1990].

n-Octyl Acetate. [Bram, 1990]

In an open flask is placed potassium acetate, 1-bromooctane and 10 mol% Aliquat 336. The mixture is irradiated in a commercial microwave oven (600 W; final temp. 187°C) for 1-2 min. The yield of the ester is 98% by GC.

The displacement of α -halocarbonyl compounds, including 3-chloro-2,4-pentanedione [Cativiela, 1995], is readily achieved. A 2-phenyl-2-butenolide can be obtained on continued refluxing a mixture of potassium phenylacetate, an α -bromocarbonyl compound in acetonitrile in the presence of 18-crown-6 [Dehm, 1975]. Occurrence of an intramolecular Claisen condensation from the ester is reconcilable with various factors.



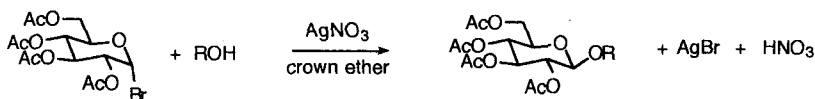
A solution to the technical difficulties in permethylation of sugars is to subject the peracetyl derivatives to bromomethane in benzene-water in the presence of *n*-

$\text{Bu}_4\text{N}^+ \text{HSO}_4^-$ [Di Cesare, 1980]. Sequential saponification and methylation are catalyzed by the phase transfer agent.

Methyl Tetra-*O*-methyl-*D*-glucopyranosides. [Di Cesare, 1980]

Penta-*O*-acetyl- α -*D*-glucopyranoside (1.17 g, 3 mmol) and tetrabutylammonium hydrogen sulfate (0.102 g) are added to benzene (15 mL) which contains a suspension of powdered NaOH (5 g). The vessel is blanketed under an atmosphere of bromomethane and stirred at room temperature for 4 h. The reaction mixture is filtered over Celite which is washed with ether (20 mL). The combined organic solutions are washed with water (2x20 mL), dried over MgSO_4 , concentrated under reduced pressure, and chromatographed on silica gel to afford methyl tetra-*O*-methyl- α -*D*-glucopyranoside (292 mg, 39%) and methyl tetra-*O*-methyl- β -*D*-glucopyranoside (421 mg, 56%).

A modified condition for the Koenigs-Knorr reaction in the presence of a crown ether has been reported [Knöchel, 1974b].

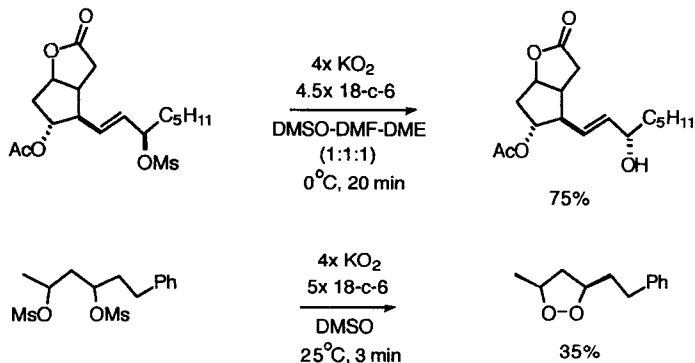


An unusual report claimed the successful reaction of 2-propenyl bromide with carboxylate ions [Klan, 1992].

Acetylation of alcohols (and anilines) with acetyl chloride is rapid using powdered sodium hydroxide and $n\text{-Bu}_4\text{N}^+ \text{HSO}_4^-$ in an organic solvent [Illi, 1979]. Under such conditions it is possible to selectively acetylate the phenolic hydroxyl group of estradiol. Better results for *t*-butoxycarbonylation of alcohols and phenols with di-*t*-butyl carbonate are obtained when phase transfer technique is employed [Houlihan, 1985]. Of course all these *O*-acylation processes do not proceed by direct displacement.

The radical anion superoxide is available commercially in K and Na salts. The use of these salts in organic synthesis has been limited by their poor solubility in the common solvents. With the advent of crown ethers the problem is largely solved, although polar organic solvents are still required. The dialkyl peroxide product from reaction with an alkyl bromide is the result of two $\text{S}_{\text{N}}2$ steps intervened by reduction of the alkylperoxy radical intermediate with another superoxide radical anion [R.A. Johnson, 1975].

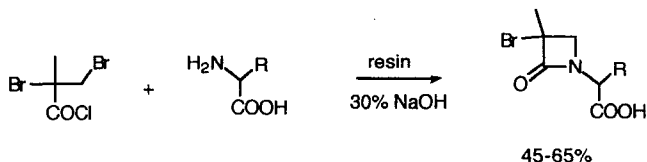
When DMSO is used as solvent or cosolvent the superoxide substitution reaction leads directly to the inverted alcohol. Approximately four equivalents of KO_2 are needed for completing the reaction [Corey, 1975].



A linear polycarbonate is produced when potassium carbonate is mixed with α, α' -dibromo-*p*-xylene in the presence of a crown ether [Soga, 1977].

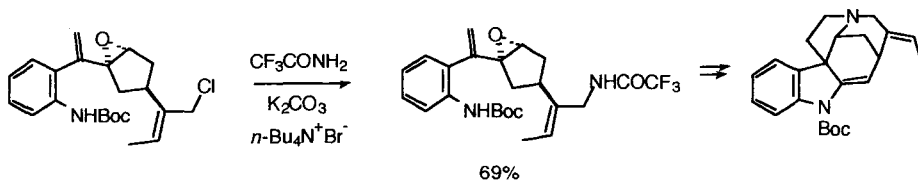
1.1.4. With Other Nucleophiles

Studies on the phase transfer reaction of amines, amides and imides are extensive. *N*-Alkylation of amines, particularly the heteroaromatics, have been studied [Dou, 1976]. The reaction of α -amino acids with 2,3-dibromo-2-methylpropanoyl chloride in the presence of an ion-exchange resin (Duolite-A109) and 30% NaOH to afford β -lactams [Okawara, 1981] involves *N*-acylation and intramolecular *N*-alkylation.



Introduction of a *N*-dialkylaminoethyl group to the ala² residue of an antitumor cyclic hexapeptide, without racemization, is readily performed by the PTC technique [Itokawa, 1993].

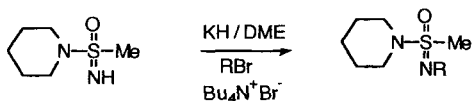
It is definitely more convenient to apply the solid-liquid PTC method to the Gabriel synthesis [Landini, 1976]. With solid potassium phthalimide and a chiral secondary bromide the reaction was demonstrated to be an S_N2 process. A method for α -amino acid synthesis involves alkylation of trifluoroacetamide with α -bromocarboxylic esters under the solid-liquid PTC conditions [Landini, 1991b]. In connection to indole alkaloid synthesis this technique saved the effort [Angle, 1993] while the allylic chloride failed to react with sodium trifluoroacetamide.



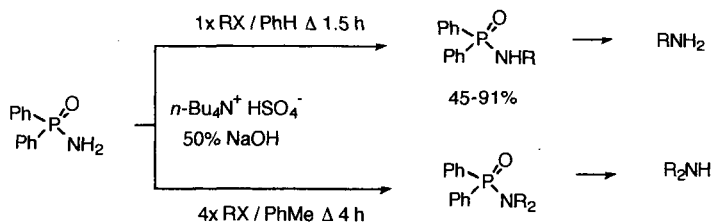
N-Octylphthalimide. [Landini, 1976]

A stirred mixture of 1-bromooctane (3.86 g, 20 mmol) potassium phthalimide (4.63 g, 25 mmol) and hexadecyltributylphosphonium bromide (1.01 g, 2 mmol) in toluene (10 mL) is refluxed until all the bromo compound disappears (GC monitoring). After 2 h (98% conversion) the reaction is terminated by cooling, the solid is filtered and washed with ether (30 mL). The combined solutions are eluted through silica (10 g) and the eluent is washed with 10% NaOH, H₂O, and dried over Na₂SO₄. Evaporation of the solvent affords the product (4.66 g, 90%); m.p. 47°-49°C.

The imino nitrogen of sulfoximines is not easy to alkylate by conventional methods. Here the solid-liquid PTC technique offers an excellent solution [C.R. Johnson, 1993].



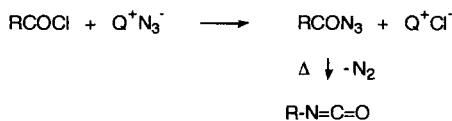
Phosphinamides are also readily *N*-alkylated. The phosphinamide alkylation [Zwierzak, 1977] can be controlled to proceed to the monoalkylated or dialkylated stage by temperature and quantities of the alkylating agent. The products are hydrolyzed to give the corresponding amines on treatment with hydrogen chloride.



Since alkyl azides are relatively easy to prepare by conventional displacement method, the PTC protocol [Reeves, 1976; Hassner, 1986] has a somewhat diminished

value. A more interesting report is that the quaternary ammonium chloride catalyzed reaction of poly(vinyl chloride) in moderately nonpolar solvents such as THF [Takeishi, 1973].

Acyl azides are similarly prepared [Brandström, 1974]. At higher temperature they undergo Curtius rearrangement to provide the isocyanates. The latter compounds are also obtainable from reaction of alkyl halides and sodium cyanate at temperatures $<100^{\circ}\text{C}$ [Zenner, 1972].

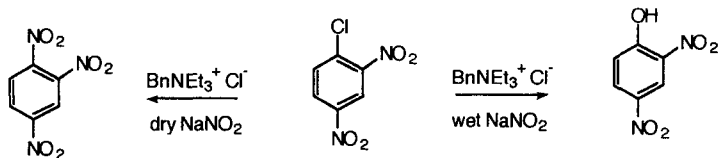


Primary nitroalkanes are the major products when alkyl bromides and an alkali metal nitrite react under phase transfer conditions [Kimura, 1976; Zubrick, 1975]. Yields are slightly lower than the $\text{NaNO}_2/\text{DMSO}$ method. It is remarkable that the reaction of 2,4-dinitrochlorobenzene with dry and wet sodium nitrite leads to 1,2,4-trinitrobenzene and 2,4-dinitrophenol, respectively [Bhati, 1991].

Reaction of 2,4-Dinitrochlorobenzene with Potassium Nitrite. [Bhati, 1991]

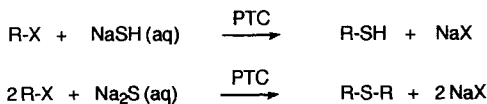
2,4-Dinitrochlorobenzene (2.02 g, 0.01 mol), KNO_2 (1.70 g, 0.02 mol) and benzyltriethylammonium chloride (0.227 g, 0.001 mol) in toluene (25 mL) are stirred magnetically at 70°C for 6 h. The toluene layer is separated, washed with water (3x10 mL), dried over Na_2SO_4 , filtered, and evaporated to leave 1,2,4-trinitrobenzene which is recrystallized from methanol (1.51 g, 71%).

2,4-Dinitrochlorobenzene (2.02 g, 0.01 mol), KNO_2 (1.70 g, 0.02 mol) and benzyltriethylammonium chloride (0.227 g, 0.001 mol) in toluene (25 mL) is stirred with NaHCO_3 (3.3 g, 0.04 mol) in water (5 mL) at 70°C for 5 h. Workup in the same manner gives 2,4-dinitrophenol (1.63 g, 89%).



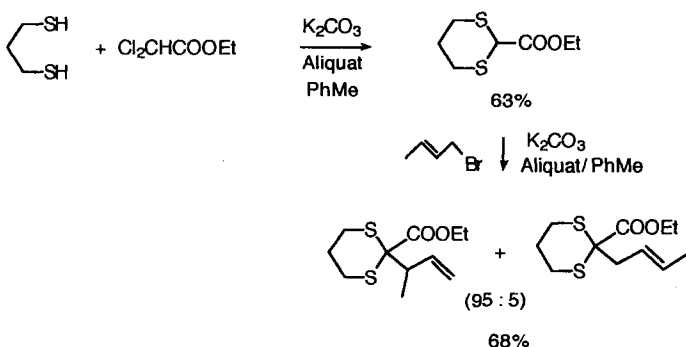
Thiols and symmetrical dialkyl sulfides are generated, often in yields approaching quantitative, when sodium hydrogen sulfide and sodium sulfide, respectively, are alkylated [Jursic, 1989; Landini, 1974b]. Sulfides are also easily synthesized from alkyl- and arylthiols using NaOH as base in the aqueous phase. The

high nucleophilicity of thiolate anions enables the use of secondary halides as alkylating agents [Herriott, 1975].



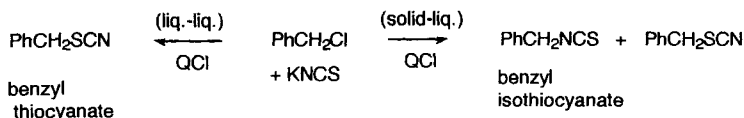
Activated chloroarenes undergo reaction with sodium sulfide under PTC conditions. Of interest are the results from liquid-liquid and solid-liquid reactions of *p*-chloronitrobenzene [Pradhan, 1992]; only nitro group reduction was observed in the former but bis(4-nitrophenyl) sulfide was produced when Na₂S and the catalyst were present as solid.

Thioacetals are formed from *gem*-dihalides by the PTC displacement reaction. Interestingly, activated 1,3-dithianes thus prepared undergo allylation with transposition [Lissel, 1982], in contrast to reactions with NaH as the base.



Dialkyl disulfides are now available from the reaction of alkyl chlorides or bromides with sulfur in the presence of sodium hydroxide and polyethylene glycol-400 in benzene at 65°C [Wang, 1995].

For reaction with ambident anions the choice of catalyst and conditions may be critical for product formation. Thus the displacement of an alkyl halide with KSCN is effectively catalyzed by sulfonium salts with bulky and hydrophobic groups [Kondo, 1988]. With benzyl chloride the affords BnSCN exclusively by liquid-liquid PTC, but solid PTC at 180°C can give rise to variable amounts of BnNCS also, the ratio of the two isomers being dependent on the structure of the catalyst [Dehmlov, 1990].



Preparatively viable displacement of alkyl halides with sodium bisulfite [Lantzsch, 1977] is surprising because a divalent anion needs to be transferred. Dichloromethane has been converted to $\text{ClCH}_2\text{SO}_3\text{Na}$ in 72% yield during 6 h at 90°C under the influence of Et_4NCl .

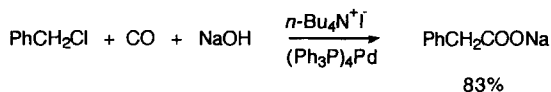
Aqueous hydrochloric acid is a mediocre reagent for the conversion of *n*-alkanols to 1-chloroalkanes. Improved rate and yield of the reaction are observed in the presence of a quaternary phosphonium salt [Landini, 1974a] or ammonium salt [Jursic, 1988]. Alternatively, the transformation is more expediently achieved in a column of silica gel containing a quaternary phosphonium salt [Tundo, 1987]. The method is particularly useful for the conversion of water soluble alcohols.

1-Chlorooctane from Octanol. [Jursic, 1988]

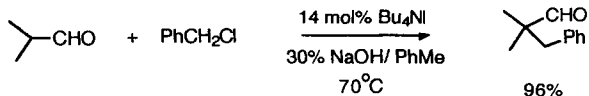
Octanol (13 g, 0.1 mol) hexadecyltrimethylammonium bromide (1 g, 0.0025 mol) and 37% HCl (205 mL, 2.5 mol) are heated at reflux overnight. After cooling the organic layer is separated and the aqueous solution is extracted with petroleum ether (3x100 mL). The organic solutions are combined, washed with 10% Na_2CO_3 solution (50 mL), dried over Na_2SO_4 and evaporated. The oily residue is taken up with ether, passed through silica gel to remove some of the ammonium salt, and distilled to afford 1-chlorooctane (13 g, 87%).



A triphase reaction among an organic halide, carbon monoxide, and sodium hydroxide is catalyzed by a combination of *n*- Bu_4NI and $(\text{Ph}_3\text{P})_4\text{Pd}$ to give the sodium alkanoate [Cassar, 1976]. Benzyl, aryl, heterocyclic, and vinyl halides are reactive.

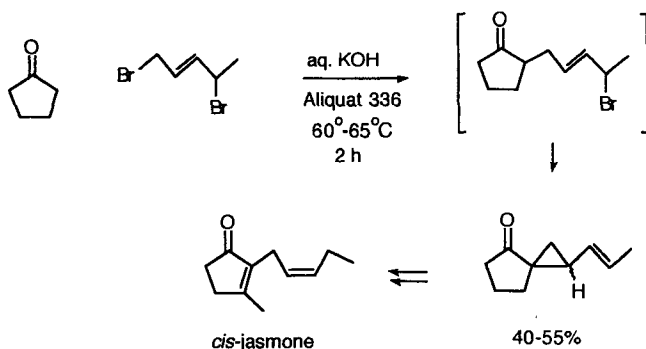


The reductive carbonylation of *gem*-dibromocyclopropanes with a synthesis gas and a Ni-Co system in the presence of a phase transfer catalyst [Grushin, 1991] is an interesting process.



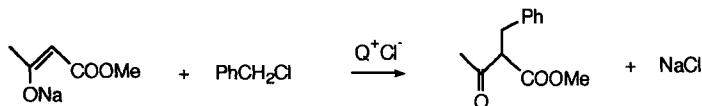
Monoalkylation or dialkylation of benzyl methyl ketone in the absence of solvent is subjected to control by regulating the ratio of the base and alkylating agent [Aranda, 1992].

Sequential alkylation of cyclopentanone with 1,4-dibromo-2-pentene by the PTC technique led to a spirocyclic product in 40-55% yield [Näf, 1978]. The product is a key intermediate for jasmonoid synthesis.



The ambident behavior of enolates toward alkylating agents is influenced by the onium ion structure. With accessible catalysts, the more exposed nitrogen atom such as that in RNMe_3^+ binds more tightly to the oxygen atom of the enolate, enabling higher percentage of C-alkylation.

A suspension of methyl sodioacetoacetate in organic solvent undergoes C-benylation (>90%) with the help of a quaternary ammonium chloride [Durst, 1974]. The result is in contrast to the preferred O-benylation in dipolar aprotic solvents. Note that in benzylation the nature of the electrophile dominates [Jones, 1977].



Aqueous sodium hydroxide rapidly saponifies esters therefore one must resort to using *t*-butyl esters in those β -ketoesters and malonic esters to be alkylated

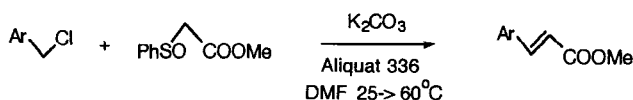
[Jonczyk, 1973]. (Note a method for deliberate removal of one ester group from a malonic ester is by treatment with KOH/18-crown-6 and heat [Hunter, 1977]) On the other hand, methyl and ethyl esters can be used in the ion pair extraction procedure [Brandström, 1972]. With the latter method and the presence of a chiral catalyst it has been possible to obtain optically active allylated products [Fiaud, 1975]. The optical yields are poor.

An expedient procedure [Heizman, 1987] for alkylation of malonic esters espouses the use of catalytic Q^+Cl^- , K_2CO_3 as base, and 5-10% water just enough to promote the reaction. Further improvement by using a combination of the onium salt and a crown ether (or polyethylene glycol) is indicated [Szabo, 1987].

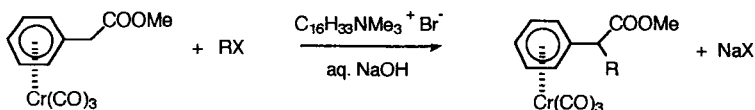
Diethyl cyclopropane-1,1-dicarboxylate. [Heizman, 1987]

Diethyl malonate (32.0 g, 0.2 mol) and 1,2-dichloroethane (40 g, 0.4 mol) are mixed with dry potassium carbonate (69.0 g, 0.5 mol), tetra-*n*-butylammonium bromide (2.0 g, 6 mmol) in benzene (100 mL) which contains water (1mL). The stirred mixture is refluxed for ca. 20 h, cooled, and filtered. The filtrate together with benzene washings (for the solid) is evaporated, and the residue distilled to give the product (31.6 g, 85%); b.p. 115°C/22 torr.

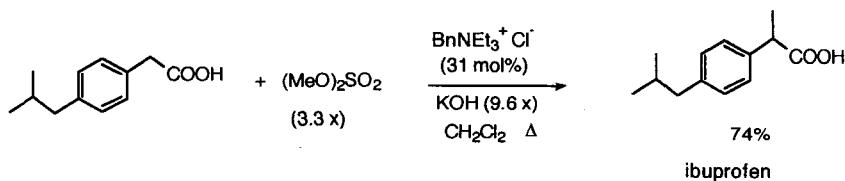
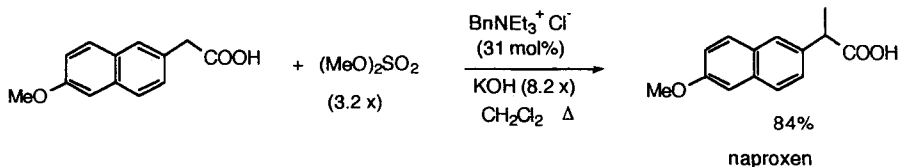
Benylation of α -sulfeinyl esters followed by in situ β -elimination constitutes a useful method for the synthesis of cinnamic esters. This process is adaptable to solid-liquid phase transfer technique [Xu, 1987].



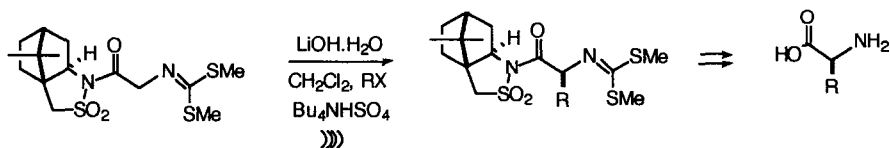
When arylacetic esters are complexed by the tricarbonylchromium group, the enhanced acidity of the benzylic proton enables an extremely rapid alkylation [des Abbayes, 1977b] such that even a methyl ester can be largely preserved.



A practical methylation of arylacetic acids which leads to naproxen and ibuprofen consists of three PTC reactions [Canicio, 1985]. Esterification followed by *C*-methylation is terminated by saponification. The base is solid KOH suspended in dichloromethane, 3.2-3.3 equivalents of dimethyl sulfate is present.



Amino acid synthesis from glycine is facilitated by protection of the functional groups as imine and ester or amide as such derivatives undergo *C*-alkylation readily. Phase transfer technique is advantageous for the transformation [O'Donnell, 1978] which is also adaptable to asymmetric synthesis [O'Donnell, 1994; Oppolzer, 1994] (For analogous alkylation, see [Eddine, 1995]). The condensation of the benzylidene derivative of glycine ester with an aromatic aldehyde is efficient in the presence of potassium carbonate and benzyltriethylammonium chloride in acetonitrile [Wu, 1986]. Thus β -hydroxy α -amino acids are readily obtained from such oxazolidine products by acid hydrolysis.

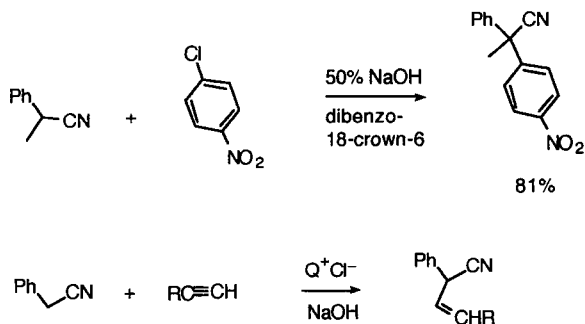


Alkylation of a Chiral *N*^α-Bis(methylthio)methyleneglycinamide. [Oppolzer, 1994]

lithium hydroxide hydrate (50 equiv.) is added to the sultam-derived *N*-protected glycinamide (1.0 equiv.), Bu_4NHSO_4 (1.1 mol. equiv.) and an alkyl halide (1.2 mol. equiv.) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (30:1, 10 mL/mmol) at -10°C , and the mixture is immediately sonicated for 2-8 min. The workup procedure involves filtration, evaporation of the filtrate, trituration of the residue with ether (50 mL/mmol) to remove Bu_4NX , and washing the solution (with water and brine), drying, and concentration. The product is recrystallized.

Activated nitriles, particularly arylacetonitriles, have been subjected to extensive PTC alkylation studies using NaOH as base. Under such conditions a

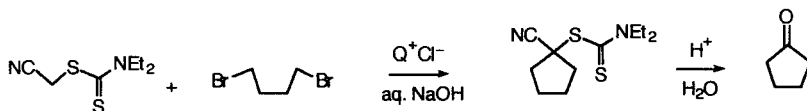
secondary or tertiary alkyl ester group present in the alkylating agent can survive [Makosza, 1969a]. Arylation by *p*-chloronitrobenzene and 4-nitrobenzophenone has been realized [Makosza, 1974b]. A remarkable vinylation with acetylenes was observed [Makosza, 1966b] in the presence of DMSO.



An excellent methylation of phenylacetonitrile with dimethyl carbonate is by passing a gaseous mixture (dimethyl carbonate in fourfold excess) over a catalytic bed of corundum spheres coated with 5 wt% K₂CO₃ and 5 wt% polyethylene glycol 6000 at 180°C [Tundo, 1989]. The selectivity is 99% at 98% conversion, only trace amounts of the dimethylated product are detectable.

Alkynylation of α -substituted phenylacetonitriles occurs with β,β -dichlorostyrene as alkylating agent under PTC [Jonczyk, 1993].

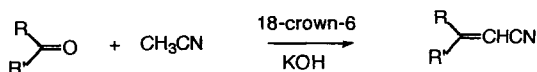
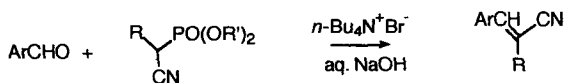
The diethylaminodithiocarbamate of thioglycolenitrile has been developed into a formyl anion synthon or carbonyl 1,1-dianion synthon by virtue of PTC alkylation [Masuyama, 1976]. Thus, reaction with 1,4-dibromobutane followed by acid hydrolysis leads to cyclopentanone.



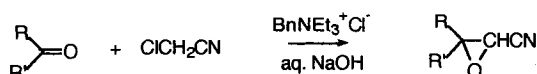
The ion pair extraction procedure allows the use of alkyl iodides because stoichiometric quantity of the quaternary ammonium salt is added [Brandström, 1972]. (For alkylation of β -ketosulfoxides by this protocol, see [Samuelsson, 1971]).

When aromatic aldehydes and cyanomethanephosphonates react under such conditions the products are the unsaturated nitriles (Emmons-Wadsworth reaction)

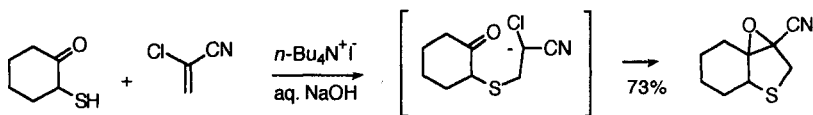
[D'Incan, 1977]. Actually the direct condensation of carbonyl compounds with excess acetonitrile is the most cost effective method [Gokel, 1976].



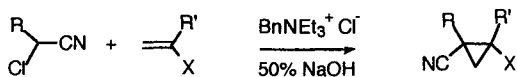
The Darzens reaction is mechanistically akin to the above condensation; only that after the C-C bond formation an intramolecular displacement occurs instead of dehydration. Accordingly the PTC technique is well suited for the Darzens reaction [Jonczyk, 1972; Makosza, 1974]. An interesting variant pertains to the formation of an epoxide by a tandem Michael addition-Darzens reaction [McIntosh, 1977].



R	Ph	Me	Ph	-(CH ₂) ₄ -	-(CH ₂) ₄ CH(Me)-	Ph
R'	H	Me	Me			Ph
Yield (%)	75	60	80	65	78	55



The less well known analogy, that is cyclopropanation, can also be effected [Jonczyk, 1976]. However, the electronic characteristics of the reaction partner play an important role. Thus phenyl vinyl sulfone gives open-chain Michael adducts only.



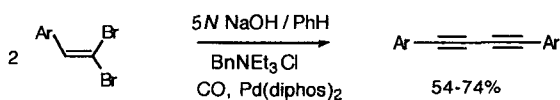
X = CN, SO₂Ph, COOBu^t

cis + trans

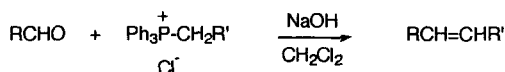
Other compounds that have been submitted to PTC alkylation include tosylmethyl isocyanide [Van Leusen, 1975], cyclopentadiene [Makosza, 1968], indene [Makosza, 1966a], fluorene [Makosza, 1967]. The indene products are 3-substituted, due to isomerization.

1.3. CONDENSATIONS

Symmetrical 1,4-diaryl-1,4-butadiynes are obtained when β,β -dibromostyrenes are treated with carbon monoxide in the presence of a Pd(0) catalyst under PTC conditions [Galamb, 1983]. The function of CO is unknown.

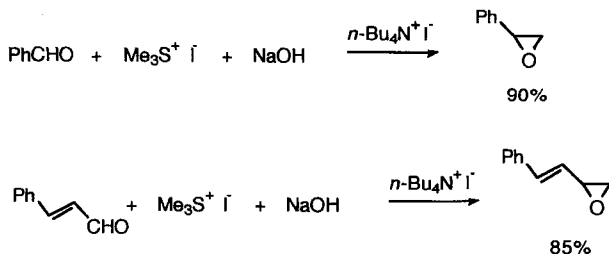


Like conventional alkylation reactions, the Wittig and related reactions suffer from the stringent requirement of anhydrous and hence expensive solvents and reagents. Also like the results discussed in the above section, relief by the application of PTC method has been partially fulfilled. For the Wittig reaction, the use of aqueous NaOH as base is successful for aldehydes [Märkl, 1973; Hünig, 1974; Tagaki, 1974].



The condensation involving α -phosphonocarbanions and aldehydes may be effected without adding a phase transfer catalyst [Mikolajczyk, 1976], indicating an autocatalytic activity of the phosphonates.

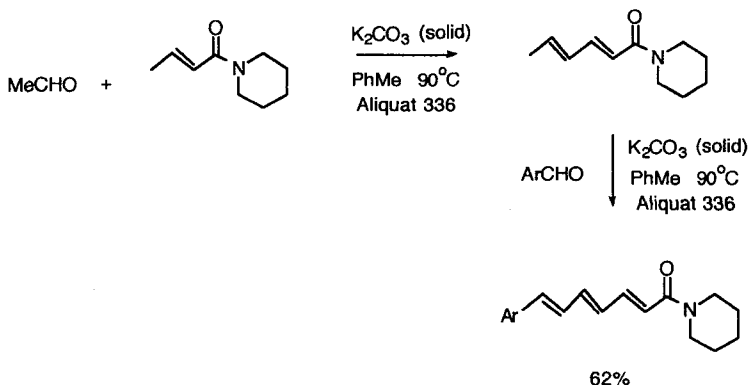
Formation of epoxides from carbonyl compounds and sulfonium ylides under the PTC conditions ($\text{Me}_3\text{S}^+\text{I}^-$, $n\text{-Bu}_4\text{N}^+\text{I}^-$ / CH_2Cl_2 -NaOH(aq.)) has been confirmed [Merz, 1973b], as the quaternary ammonium salt is an essential component. Excellent yields of epoxides are produced from aldehydes, and the reaction delivers moderate enantiomeric excess when chiral catalysts are used [Hiyama, 1975]. Ketones react very sluggishly, perhaps because iodide ion is present. The use of sulfonium chloride and benzyltriethylammonium chloride appears to remedy the situation [Rosenberger, 1980].

2-Phenyloxirane [Merz, 1973]

To a solution of benzaldehyde (10.6 g, 0.1 mol) and *n*-Bu₄NI (0.5 g, 1.35 mmol) in CH₂Cl₂ (100 mL) is underlayered 50% NaOH. After addition of Me₃S⁺I⁻ (20.4 g, 0.1 mol) the mixture is vigorously stirred and heated at 50°C for 48 h, and poured onto ice. The organic layer is separated, washed with water, and dried. Distillation gives the oxirane product (11 g, 92%).

The behavior of the dimethyloxosulfonium methylide give inferior results, and it effects cyclopropanation of conjugated ketones in the same manner as the homogeneous reaction.

Aldol condensation such as that shown below [Dehmlow, 1981b] is very useful for the construction of polyunsaturated carboxylic acid derivatives.



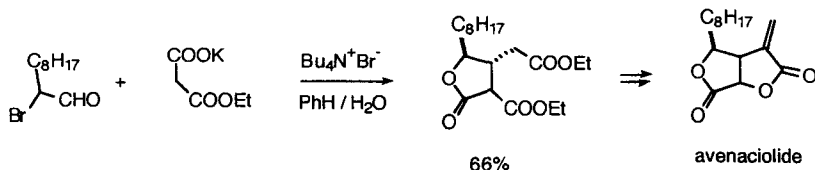
It is possible to achieve enantioselective aldol condensation [Ando, 1993] and Robinson annulation [Bhattacharya, 1986] by using chiral catalysts such as the quaternized quinine alkaloids. Formation of tight ion-pairs (hydrogen bonded) of the enolates are indicated [Reetz, 1993].

Aldol Condensation of 2-Methyl- α -tetralone. [Ando, 1993]

A column of Amberlyst-A26 (Cl⁻ form, 2.5 g, 10 mmol) is transformed into the OH⁻ form by passing through a 1N NaOH solution and washed to neutral pH with water and rinsed with methanol. The column is treated with *N*-benzylcinchonium bromide (464 mg, 1.0 mmol) in methanol (20 mL). Another wash with methanol the elutes are combined and neutralized with 1N hydrofluoric acid. Evaporation of the solvent leaves a residue which is dehydrated by coevaporated three times with 1:1 benzene-acetonitrile. Further drying over P₂O₅ at 40°C overnight gives the quaternary ammonium fluoride (428 mg).

The catalyst (49 mg, 0.12 mmol) in THF (8 mL) at -78°C under argon is successively added benzaldehyde (0.11 mL, 1.1 mmol) and a solution of 1-trimethoxysilyl-2-methyl-3,4-dihydronaphthalene (233 mg, 1.0 mmol) in THF (2 mL). After 6 h, water (2 mL) is added and the mixture is warmed to room temperature and concentrated. The residue is taken up in methanol (10 mL) and treated with 1N HCl (0.3 mL) for 2 h. Workup followed by chromatography gives the aldol products (198 mg, 74%, Erythro : threo = 7:3) [70% ee for the erythro aldol and 20% ee for the threo aldol].

The preparation of a γ -lactone in 66% yield from an α -bromoaldehyde, potassium ethyl malonate [Sakai, 1980] greatly simplifies the synthesis of avenaciolide. The lactone formation under phase transfer catalysis involves esterification (*O*-alkylation), intramolecular Claisen condensation, Michael addition and decarboxylation.

**1.4. ELIMINATIONS AND ADDITIONS****1.4.1. β -Eliminations**

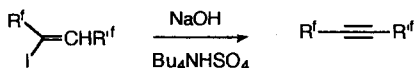
Dehydrohalogenation by the PTC procedure is of relatively little synthetic value. However, it may be mentioned that 18-crown-6 is a promoter for the conversion of *cis*- β -bromo-*p*-styrene to the acetylene by KF [Naso, 1974]. The effect is particularly prominent in acetonitrile.

Generally, the ion-exchange equilibrium hinders β -dehydrohalogenation under PTC conditions. As elimination proceeds the concentration of halide ion increases, rendering the [OH⁻] negligible in the organic phase and the reaction stops. Ion pair extraction conditions are highly successful but the requirement of equimolar $Q^+ OH^-$ is uneconomical. A better method [Makosza, 1991] involves the addition of a weak organic acid YH (e.g., CF_3CH_2OH , Ph_3COH , 2-methylindole) to the system to form a

lipophilic anion (strong base, weak nucleophile) and enter the organic layer as Q^+Y^- , which is an effective reagent. The YH product suffers deprotonation at the phase boundary and the reagent is replenished.

It has been observed that dehydrobromination is strongly promoted by the formation of a third liquid phase which is rich in the catalyst [Mason, 1991].

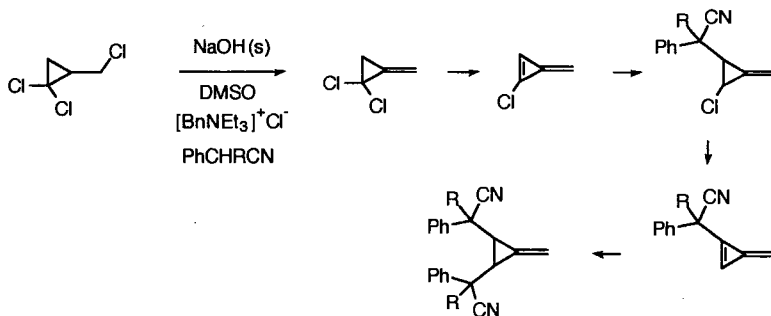
A useful method for the synthesis of unsymmetrical 1,2-bis(perfluoroalkyl)-ethynes is to dehydroiodinate the iodoalkenes with sodium hydroxide in the presence of a quaternary ammonium salt [Sanchez, 1993].



vic-Dibromides are debrominated by sodium thiosulfate when catalytic amount of a phosphonium bromide and sodium iodide are added [Landini, 1975]. The results are comparable to the conventional method using NaI in acetone.

Double dehydrohalogenation of *vic*-dihalides by use of powdered potassium hydroxide is effective with various phase transfer catalysts [Dehmlow, 1981a]. The efficiency is lower with the dichlorides than the dibromides.

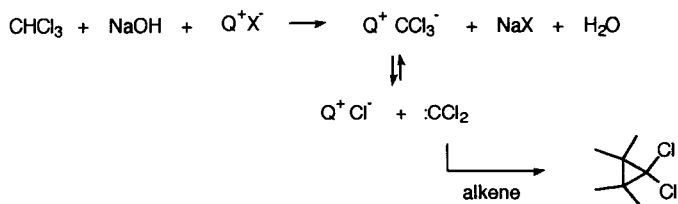
The reaction of 2-chloromethyl-1,1-dichlorocyclopropane with α -substituted phenylacetonitriles leads to 2,3-disubstituted 1-methylenecyclopropanes [Jonczyk, 1994] through a series of dehydrochlorination. With phenylacetonitrile itself only displacement of the primary chloride is observed.



1.4.2. α -Eliminations

Trihalomethanes undergo α -elimination on exposure to a strong base (e.g., *t*-BuOK) to give dihalocarbenes which can be intercepted with alkenes. The α -elimination is a stepwise process via the trihalomethide ions. In the presence of relatively good nucleophiles the carbene intermediates are rapidly destroyed and dihalocyclopropane

formation is suppressed. The discovery of the dramatic increase in the yield of dichlorocarbene adduct of cyclohexene (0.5% → 60-70%) on addition of a quaternary ammonium chloride [Starks, 1968, 1971; Makosza, 1969b] was indeed exciting. Of particular interest is the fact that accessible catalysts (R₃NMe₃Br, Et₄NBr, etc.) are among the best, yet they are very poor catalysts for displacement reactions. Tetramethylammonium chloride is apparently the most active catalyst to promote formation of the monoadduct from a diene [Dehmlow, 1982a].



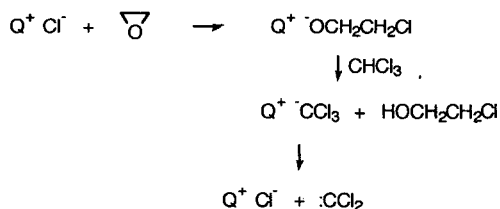
1-Phenyl-2,2-dichlorocyclopropane. [Makosza, 1969b]

A mixture of styrene (10.4 g, 0.1 mol), chloroform (12 g, 0.1 mol), benzyltriethylammonium chloride (0.4 g) and 50% NaOH (20 mL) is vigorously stirred at 40°C for 4 h. Upon dilution with water, separation into layers and distillation, 1-phenyl-2,2-dichlorocyclopropane (15 g, 80%) is obtained.

Under PTC conditions, efficient dichlorocyclopropanation of alkenes is due to rapid transfer of the Cl₃C⁻ anion to the organic phase so that once the carbene is surrounded by a great number of alkene molecules once it is generated, there is much less opportunity for the carbene to encounter the destructive hydroxide ion. From the quaternary ammonium ion structure one might surmise a close ion pairing with the Cl₃C⁻ species.

Trialkylamines are also active in promoting the reaction [Isagawa, 1974], and in fact they are the preferred catalysts for :CBr₂ addition to alkenes [Makosza, 1975b]. (Addition of small amount of ethanol [Makosza, 1973] or pinacol [Dehmlow, 1988] to the reaction media also gives better results in the :CBr₂ addition.) The transferred reagent may be R₃N⁺CHX₂ CCl₃⁻ which are formed by reaction of trialkylammonium dihalomethylide (R₃N⁺CX₂⁻) with the trihalomethane.

For synthetic application to substrates which are sensitive to aqueous NaOH a suspension of sodium trichloroacetate may be used as the dichlorocarbene source [Dehmlow, 1976]. Dichlorocarbene is also generated from ethylene oxide, chloroform in the presence of Q⁺Cl⁻ [Nerdel, 1965]. The Cl₃C⁻ ion is formed by proton abstraction of chloroform by the 2-chloroethoxide ion. Various epoxides are converted to dichlorocyclopropanes by reaction with dichlorocarbene [Tabushi, 1976].



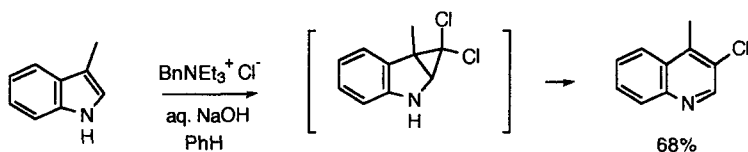
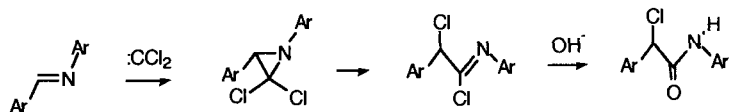
Dihalocarenes are electrophilic, therefore they show discrimination toward alkenes. Electron-deficient alkenes such as α,β -unsaturated sulfones often react with X_3C^- instead of the carbene [Shostakovskii, 1974].

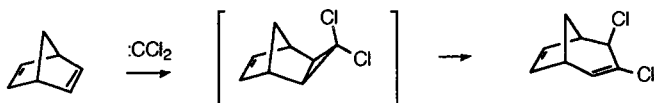
Dichlorocarbene adds to the C=N bond of imines. Some adducts suffer ring opening [Makosza, 1974a]. Cycloaddition involving the C=C double bond of pyrrole and indole is followed by ring expansion in situ [Kwon, 1976]. Strained dihalocyclopropanes (e.g., derived from norbornene and norbornadiene) behave similarly [Kraus, 1972; Dehmlow, 1972].

Bromochlorocarbene is generated from a mixture of dibromomethane, trichloromethylbenzene, and potassium hydroxide in the presence of tetrabutylammonium hydrosulfate [Balcerzak, 1991]. The probable intermediates are dibromomethide ion and chlorodibromomethane which are formed by deprotonation and chlorine abstraction, respectively.

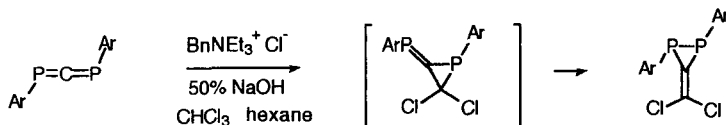
exo-3,4-Dibromobicyclo[3.2.1]oct-2-ene. [Kraus, 1972]

Norbornene (5.0 g), bromoform (135 g), benzyltriethylammonium chloride (0.1 g) and 50% NaOH (110 g) are mixed and stirred vigorously at room temperature for 91 h. After dilution with water and filtration the mixture is washed several times with water, dried over CaCl_2 , evaporated, and distilled to afford the dibromo compound (6.9 g, 48%); b.p. $100^\circ\text{C}/0.5$ torr.

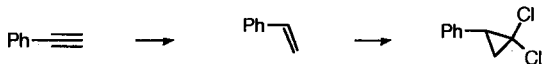




P,P'-Diaryl-3-dichloromethylenediphosphiranes are prepared [Yoshifuji, 1991] by a cycloaddition-rearrangement process.



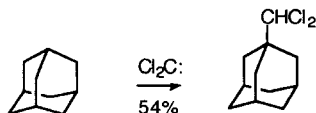
Certain cationic transition metal complexes serve a dual catalytic role in homogeneous and phase transfer catalysis. For example, after effecting the semi-hydrogenation of phenylacetylene, dichlorobis(1,10-phenanthroline)iridium(III) chloride is capable of promoting dichloropropanation [Goldberg, 1986].

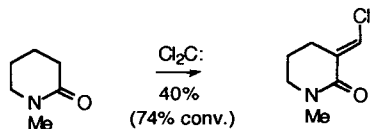
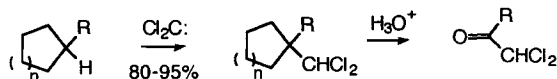


1,1-Dichloro-2-phenylcyclopropane. [Goldberg, 1986]

A 1% solution of phenylacetylene in chloroform is hydrogenated in the presence of dichlorobis(1,10-phenanthroline)iridium(III) chloride at 60°C under 10 atm hydrogen for 2 h. The mixture (containing styrene and ca. 10% ethylbenzene) is stirred with 50% NaOH at 40°C for 12 h to give the dichlorocyclopropane in 80% yield (85% styrene conversion).

Dichlorocarbene insertion into C-H bond is of little synthetic value, except for the preparation of 1-dichloromethyladamantane [Tabushi, 1970] and dichloromethyl ketones from acetals of aldehydes [Steinbeck, 1978]. The formation of α -chloromethylation of *N*-methyl- δ -valerolactam [Marcos, 1986] is a formal C-H insertion, but more likely it proceeds by alkylation of the lactam with dichlorocarbene.

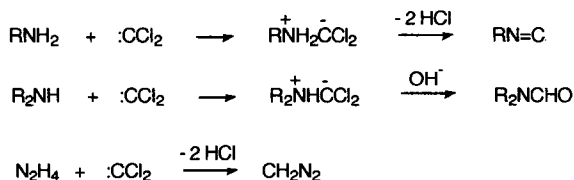




1-Dichloromethyladamantane. [Tabushi, 1970]

To a vigorously stirred mixture of adamantane (13.6 g), 50% NaOH (200 mL), benzene (20 mL) and benzyltrimethylammonium chloride (0.4 g) at 40°C was dropwise added chloroform (80 mL) during 6 h. After a further stirring of 0.5 h workup gives the product (b.p. 114°-115°C/8 torr) in 54% yield (91% based on consumed adamantane).

The one-step synthesis of isonitriles [Weber, 1972a, b] from primary amines constitutes a superior method to the standard procedure via the formamides. Secondary amines afford formamides under the same conditions [Graefe, 1974]. An economical method for the generation of diazomethane from hydrazine is based on PTC [Sepp, 1974].

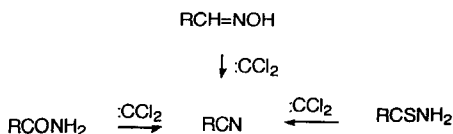


Diazomethane. [Sepp, 1974]

A Vigreux column (with takeoff sidearm connected to a condenser and topped by an addition funnel) is mounted on a two-neck flask which is then charged with KOH pellets (80 g, 1.4 mol), water (20 mL), chloroform (48 g, 0.4 mol), ether (200 mL), 18-crown-6 (0.2 g, 0.8 mmol), and finally 85% hydrazine hydrate (11.76 g, 0.2 mol). Upon sealing the second neck with a rubber stopper the reaction mixture is vigorously stirred and heated. Foaming starts and yellow distillate appears. After collection of about 100 mL distillate in the ice-cooled 500 mL Erlenmeyer receiver (originally containing 50 mL ether), ether is replenished from the addition funnel at the rate approximately equal to the distillation, which is stopped when the distillate becomes colorless. A 48% yield based on hydrazine is obtained. (Small amount of hydrazine can be removed if dichloromethane is used as solvent, and the distillate is washed with water {10 mL per 100 mL distillate}). The yield is

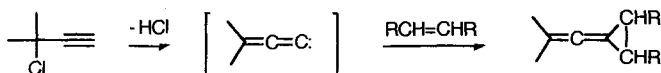
decreased by about 10%. Also a lower yield of diazomethane is observed when NaOH/*n*-Bu₄NOH are used instead of KOH/crown ether.

Dehydration of primary amides, aldoximes, and elimination of hydrogen sulfide from thioamides have been observed [Saraie, 1973]. These processes may involve interaction of the carbene with the oxygen or sulfur atom of the substrates.



Of limited value is the conversion of alcohols to chlorides by dichlorocarbene generated in the PTC system [Sasaki, 1973].

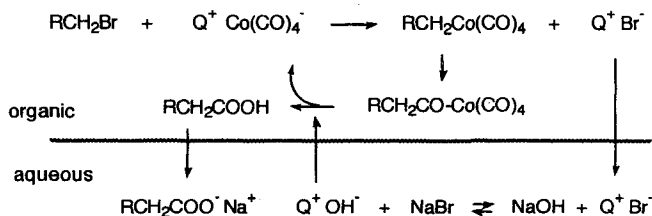
Dimethylvinylidenecarbene is generated from 3-chloro-3-methylbutyne by 1,3-dehydrochlorination under anhydrous conditions. The PTC method [Julia, 1984; Patrick, 1974; Sasaki, 1974] is better not only in terms of convenience but also in yields.



The generation of *N*-carbethoxynitrene by α -elimination and trapping with a triorganoborane is best conducted in a two-phase system with a quaternary ammonium chloride [Akimoto, 1981].

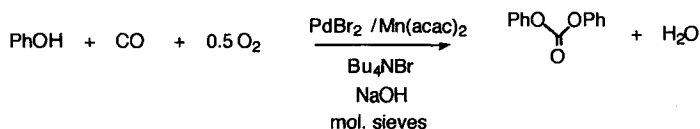
1.4.3. Addition Reactions

Homologation of halides to form carboxylic acids involving carbon monoxide is usually considered as carbonylation reaction. As carbon monoxide is concerned the two bond-forming steps to its carbon atom constitute an α -addition. The use of PTC to effect such a reaction in the presence of a metal carbonyl (e.g., Co₂(CO)₈) is most fruitful, as the halides are protected from solvolytic destruction, active metal carbonyl anions are readily transferred to the organic phase and activated by a bulky quaternary ammonium ion in the displacement of the halides. The decomposition of the intermediates by hydroxide ion after acyl migration is facilitated by the presence of the transferred Q⁺OH⁻ [des Abbayes, 1983, 1985].



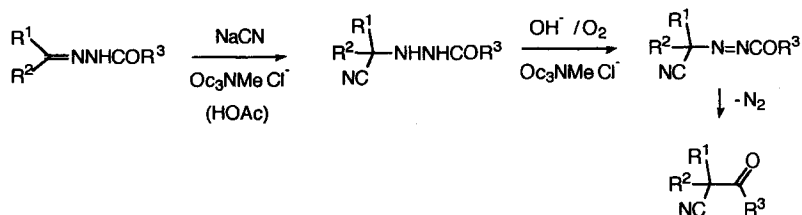
With the use of iron pentacarbonyl as catalyst benzylic halides can be largely converted to dibenzyl ketones [des Abbayes, 1988] by manipulating the conditions to maximize the concentration of the tetracarbonylacetyliron anion in the organic solution while decreasing the transfer rate of OH^- .

Phenol undergoes carbonylation to give diphenyl carbonate when subjected to treatment with carbon monoxide and oxygen in the presence of a phase transfer catalyst, PdBr_2 , $\text{Mn}(\text{acac})_2$, molecular sieves and NaOH [Hallgren, 1981].

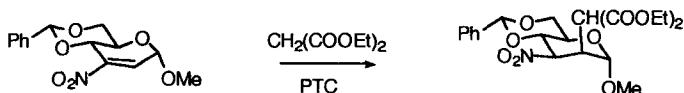


It is interesting that a phase transfer catalyst changes the course for ammonium polysulfide to react with α, β -unsaturated ketones [Krein, 1993].

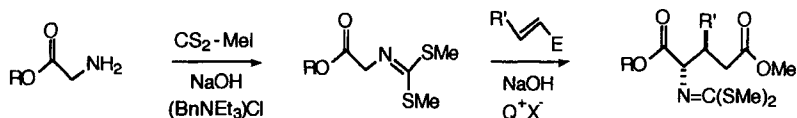
Ketone arylhydrazones are converted to α -cyanoketones on treatment with sodium cyanide in a biphasic system in the presence of acetic acid and air [Chiba, 1991]. The three stages involved in this transformation are nucleophilic addition, oxidation, and extrusion of nitrogen.



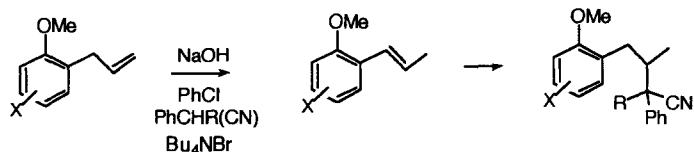
A Michael addition of active methylene compounds to an unsaturated nitrosugar in benzene requires catalysis by a quaternary phosphonium salt [Sakakibara, 1975]. The reaction is highly stereoselective, producing the thermodynamically less stable *manno*-isomers. For accomplishing more routine Michael additions the solid PTC method warrants consideration [Bram, 1985].



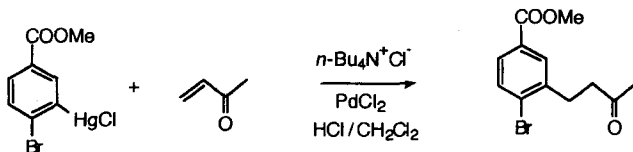
3-Substituted glutamic acid derivatives have been synthesized by a Michael addition. The solid-liquid PTC process is *anti*-selective [Alvarez-Ibarra, 1995].



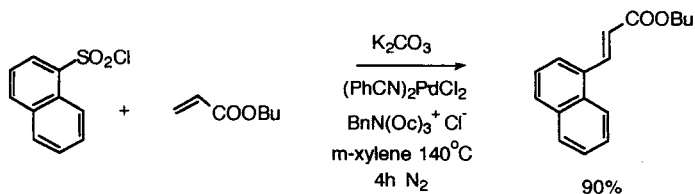
o-Allylarenes containing moderately electron-withdrawing substituents form adducts with phenylacetonitriles under PTC conditions (e.g., NaOH/PhCl, Bu₄N⁺Br⁻) via the isomerized propenylarenes [Lasek, 1993].



The reaction of an arylmercury chloride with methyl vinyl ketone which is Pd(II)-catalyzed [Cacchi, 1985] is a formal Michael addition. This and other Heck reactions benefit from phase transfer catalysis [Jeffery, 1984; Hoffmann, 1989], particularly in dealing with thermally labile substrates. The phase transfer catalyst facilitates the regeneration of Pd(0) species in a Heck reaction [Jeffery, 1994].



An interesting Heck-type reaction has been achieved using an arenesulfonyl chloride instead of an aryl halide under PTC conditions [Miura, 1989].



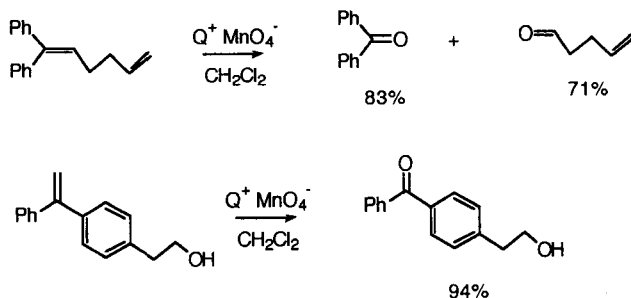
1.5. OXIDATIONS

The assistance from PTC to solving problems in oxidation of organic molecules is even more profound than in other areas. An often encountered difficulty concerning the availability of a compatible solvent is obviated. Strong oxidants which are based on anions with a high valent transition metal core can be transferred from water into inert organic solvents to perform oxidation of substrates. For permanganate anion, all sorts of phase transfer agents are suitable to achieve the objective.

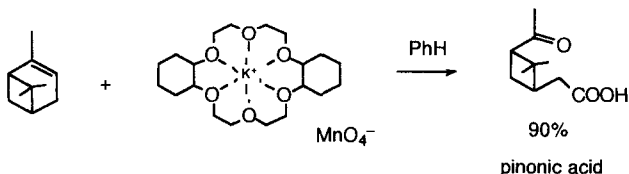
1.5.1. Oxidation of Alkenes, Alkynes, and Arenes

Permanganate oxidation of alkenes by the phase transfer technique is extremely versatile because different sets of products are obtainable by varying conditions. By regulating the pH of the aqueous oxidant which is added to the organic solution containing the catalyst and the alkene, one type of product predominates: *cis*-1,2-diol (basic), α -ketol (neutral), aldehydes/carboxylic acids (acidic), as shown in the case of dicyclopentadiene [Ogino, 1980]. Complex mixture of products usually result if the pH is not carefully controlled. In the solid-liquid PTC system (solid KMnO_4 /catalyst $\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3)_3$) the workup procedure is an important factor: *cis*-1,2-diol (dry workup or basic water), aldehydes (acidic water).

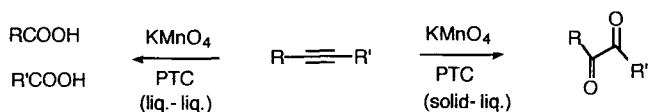
It should be noted that chemoselective cleavage of double bonds are possible [Rathore, 1986].



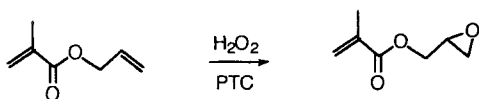
Crown ethers also render KMnO_4 soluble in benzene, therefore many nonpolar compounds are readily oxidized [Sam, 1972]: (*E*)-stilbene \rightarrow benzoic acid (100%), α -pinene \rightarrow pinonic acid (90%), *p*-xylene \rightarrow toluic acid (100%).



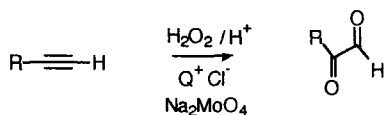
Alkynes afford carboxylic acids [D.G. Lee, 1978] and α -diketones [Gannon, 1987], respectively, when subjected to KMnO_4 oxidation under liquid-liquid and dry solid-liquid conditions.



Industrial epoxidation of alkenes with hydrogen peroxide, cocatalyzed by a phase transfer agent and metalate ion such as tungstate and molybdate [Payne, 1959] is improved by the addition of phosphoric acid [Venturello, 1981]. For long-chain 1-alkenes the optimal pH is about 1.6. Epoxidation of allyl methacrylate gives glycidyl methacrylate with 94% selectivity at 74% conversion [Fort, 1992].

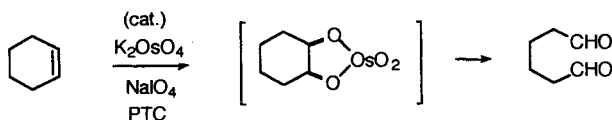


Terminal alkynes afford α -ketoaldehydes with excellent selectivity on oxidation with acidic hydrogen peroxide in the presence of Q^+Cl^- and sodium molybdate [Ballistreri, 1988].



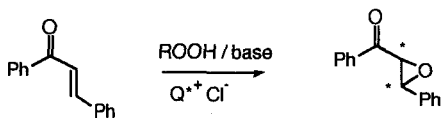
Osmium tetroxide is probably the best reagent for the conversion of alkenes to *cis*-1,2-diols owing to its high selectivity and mildness. Its serious shortcomings in

terms of cost and toxicity have been addressed. In situ recycle of Os(VIII) species by many innocuous and inexpensive cooxidants is quite successful. However, when periodic acid or sodium periodate is used the reaction for nonpolar substrates is very slow. Phase transfer technique is definitely a remedy for this situation; furthermore, the two phase system allows for electrochemical regeneration of HIO_4 so that the process becomes very economical [M.A. Johnson, 1972].



The stronger oxidant RuO_4 is also too expensive to be used stoichiometrically. The same tactic can be applied to oxidation of alkenes to carboxylic acids, and in this case aqueous sodium hypochlorite (+ $n\text{-Bu}_4\text{NBr}$) is an excellent agent to recondition the ruthenium [Foglia, 1977]. The PTC/ RuCl_3 cocatalyst system is also effective for promoting oxidative cleavage of alkenes with hydrogen peroxide [Barak, 1987].

The base-catalyzed epoxidation of electron-deficient alkenes with hydrogen peroxide or *t*-butyl hydroperoxide can take advantage of chiral phase transfer agents (e.g., *N*-benzylquinine chloride) to produce optically active epoxides [Helder, 1976].

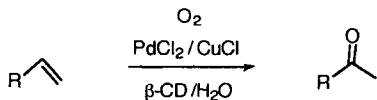


Chalcone Oxide. [Helder, 1976]

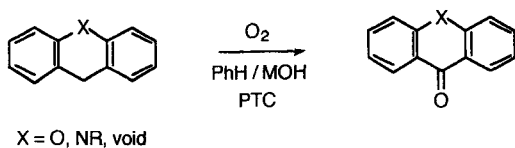
Chalcone (20.4 g) in toluene (125 mL) is treated with NaOH (7.5 g), 30% hydrogen peroxide (90 mL) and cinchonine benzochloride (0.75g) at room temperature. After vigorous stirring for 24 h, a levorotatory product (21.8 g, 99%) is obtained.

The phase transfer technique obviates the problem of nuclear chlorination during epoxidation of dimethyl *o*-propargyloxybenzylidenemalonate with sodium hypochlorite [Bernaus, 1991]. The substrate and the product are less exposed to the reagent under the PTC conditions.

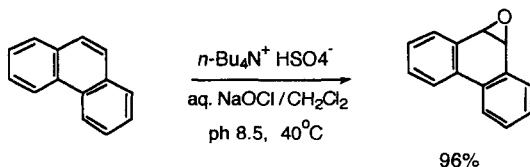
The Wacker oxidation is an industrially important process which is limited to lower alkenes due to solubility and hence rate problems. Using β -cyclodextrin as an inverse PTC to deliver sparingly soluble alkenes to the aqueous phase enhances the rates dramatically [Zahalka, 1986]. This method furnishes very clean products.



As indicated above, permanganate functions as a benzylic oxidant. A similar capability is shown by biphasic ruthenium(III)-H₂O₂ and RuO₄-NaOCl systems [Sasson, 1986] in combination with a phase transfer agent. For rapid oxidation of fluorene, xanthene, acridane, and analogues it only requires air (or oxygen) supply to a benzene solution containing a PTC and a base (aq. NaOH or solid KOH/18-crown-6) [Alneri, 1977].



Some polycyclic arenes undergo nuclear oxidation. For example, an excellent yield of the 9,10-oxide has been obtained from phenanthrene using PTC hypochlorite reaction [Fonouni, 1983]. On subjecting to the Q⁺Cl-tungstate-H₃PO₄-H₂O₂ combination, such compounds suffer ring cleavage to furnish the diacids [Saito, 1986].



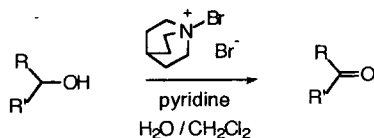
1.5.2. Oxidation of Heterofunctional Compounds

The oxidation of alcohols to carbonyl products under PTC conditions can be achieved by a number of reagents. Controlled oxidation of primary alcohols to the aldehyde stage is often desirable; for benzylic alcohols the system consisting of solid KMnO₄ and N(CH₂CH₂OCH₂CH₂OCH₃)₃ [Okimoto, 1977] and the liquid-liquid reaction involving Q⁺Cl⁻ and aqueous hypochlorite [G.A. Lee, 1976] or Q⁺HSO₄⁻ and aqueous dichromic acid [Landini, 1979] give satisfactory results. Secondary alcohols are of course oxidized to ketones.

An unusual oxidation of benzyl alcohol to benzaldehyde at room temperature involves stirring with iodobenzene in the presence of sodium bicarbonate and

catalytic amounts of palladium(II) acetate and tetrabutylammonium chloride [Choudary, 1985].

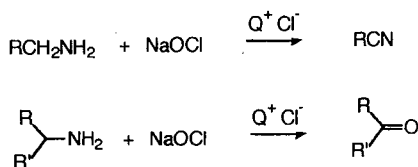
Chromic oxide oxidation of secondary alcohol in the presence of R_4NX has been reported [Gelbard, 1980]. *N*-Bromoquinuclidine in combination with pyridine can oxidize secondary alcohols at room temperature. The two-phase system is better than dichloromethane alone [Blair, 1992]. Apparently quinuclidine functions as a phase transfer catalyst.



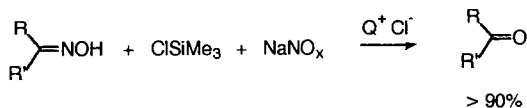
For the oxidation of aromatic aldehydes with aqueous $KMnO_4$ a small amount of [2-(dodecylmethyl-*t*-butylsiloxy)ethyl]trimethylammonium nitrate is recommended as catalyst [Jaeger, 1988]. This salt is stable in water at pH 3-11 and it can be decomposed by fluoride ion in aqueous or non aqueous media. Consequently emulsions which are often formed and interfere with workup when conventional tetraalkylammonium salts are used are avoided.

Excellent yield of benzoic acid is obtained by treatment of benzoin with a combination of potassium superoxide and 18-crown-6 in benzene at room temperature [San Filippo, 1976].

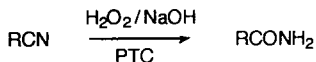
Primary amines of the RCH_2NH_2 type undergo remarkably facile transformation to the nitriles by a PTC hypochlorite, whereas secondary amines give ketones [G.A. Lee, 1976].



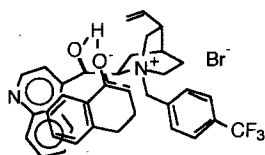
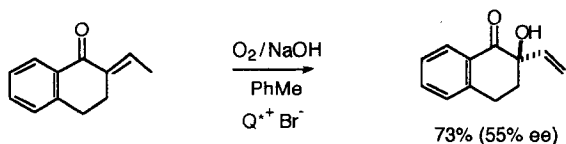
Deoxygenation with a mixture of chlorotrimethylsilane, $NaNO_x$ ($x=2,3$) and a phase transfer agent [J.G. Lee, 1990] probably involves transphasic delivery of NO_x^- to react with the chlorosilane, generating the silyl nitrite or nitrate and thence the purported reagent NO_xCl .



Improvement of the nitrile hydration to primary amides with alkaline hydrogen peroxide by phase transfer catalysts is definite [Cacchi, 1980].



Asymmetric oxygenation of ketones in the presence of chiral phase transfer catalysts derived from cinchonine has good results [Masui, 1988].



O₂ attacks from frontside of enolate

Chiral α -Hydroxyketones. [[Masui, 1988].

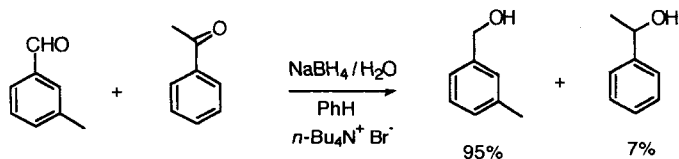
Addition of the ketone (1 mmol) in toluene (10 mL) containing triethyl phosphite (0.2 mmol) and the cinchonium salt (5 mol%) to 50% NaOH (5 mL) is followed by bubbling of an oxygen stream at room temperature. At complete consumption of the ketone the mixture is quenched with water (10 mL) and extracted with benzene. The organic solutions are washed with 10% HCl, H₂O, and brine. Drying, evaporation and chromatography over silica gel furnishes the product.

1.6. REDUCTIONS

Lithium aluminum hydride cannot be exposed to water therefore PTC must involve solid-liquid technique. 15-Crown-5 seems to be a suitable sequester for the lithium ion thereby solubilizing the reducing agent in aprotic solvents. Indeed various functional groups which are affected by lithium aluminum hydride can be reduced in this manner [Gevorgyan, 1985].

Borohydride reduction under phase transfer conditions can discriminate aldehydes from ketones [Rao, 1986]. For rate acceleration in ketone reduction one

may use of a quaternary ammonium salt bearing a β -hydroxyl group [Colonna, 1978]. The method is applicable to reduction of acid chlorides to alcohols [Costello, 1985].



Acid chloride attaching to insoluble polymers can be converted to the aldehydes in 70-96% yields by treatment with iron pentacarbonyl in the presence of Bu_4NBr and NaOH , followed by neutralization with acetic acid [Ungurenasu, 1989].

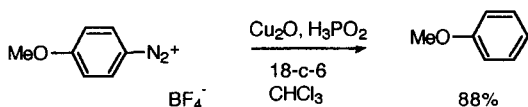
Reductive dehalogenation with sodium borohydride is usually very sluggish. However, octadecane is obtained from the alkyl bromide in 80% yield when the reaction is conducted in hot toluene in the presence of a polyethylene-bound crown ether and tri-*n*-butyltin chloride as catalysts [Bergbreiter, 1987].

Organoazides do not undergo smooth reduction with borohydride, but there is great improvement if the PTC technique is employed [Rolla, 1982]. This reaction can be combined with azide displacement to enable a one-pot preparation of amines from alkyl halides or mesylates.

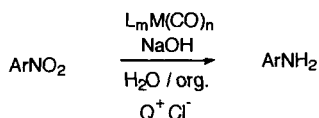
n-Octylamine. [Rolla, 1982]

The stirred mixture of 1-bromooctane (19.3 g, 0.1 mol), sodium azide (16.2 g, 0.25 mol), hexadecyltributylphosphonium bromide (5.1 g, 0.01 mol) in water (50 mL) is heated at 80°C for 8 h. Thereafter the aqueous phase is removed, replaced with toluene (15.5 mL), and treated with a solution of sodium borohydride (11.7 g, 0.3 mol) in water (30 mL) during 0.5 h. Heating at 80°C is resumed and maintained for 16 h to complete the reduction. The amine is extracted from the cooled organic solution (which retains the catalyst) with 10% hydrochloric acid and then recovered (11.4 g, 88%).

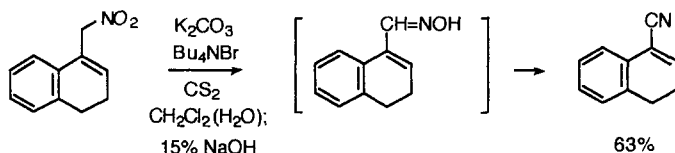
It is possible that the reduction of aromatic diazonium salts in the presence of 18-crown-6 [Korzenowski, 1977] is facilitated by complexation of the cation to loosen the C-N bond.



Nitroarenes are reduced to anilines by the combination of a PTC and $\text{Fe}_3(\text{CO})_{12}\text{-NaOH}$ [des Abbayes, 1977a], $\text{CpV}(\text{CO})_4\text{-NaOH}$ [Falicki, 1988] or the bimetallic catalyst $(1,5\text{-hexadieneRhCl})_2/\text{Co}_2(\text{CO})_8\text{-CO-NaOH}$ [Hashem, 1984]. The actual reducing agents in these reactions may be the carbonylmetal hydride anions. The vanadium hydride is also useful for dehalogenation.



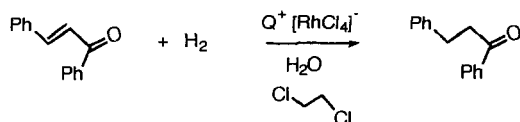
The treatment of allylic nitro compounds with carbon disulfide in the presence of a solid base and a quaternary ammonium salt results in the aldoximes which on further reaction under liquid-liquid phase transfer conditions give conjugated nitriles [Albanese, 1990]. The overall process comprises a reduction followed by dehydration.



1-Cyano-3,4-dihydronaphthalene. [Albanese, 1990]

A mixture of 1-nitromethyl-3,4-dihydronaphthalene (1.89 g, 10 mmol), tetra-*n*-butylammonium bromide (0.32 g, 1 mmol), K_2CO_3 (0.69 g, 5 mmol) in dichloromethane (100 mL, containing 36 μL H_2O) is stirred at room temperature for 15 min, treated with carbon disulfide (0.9 mL, 15 mmol). After 8 h, more carbon disulfide (4 mL, 67 mmol) is added followed by 15% NaOH (10 mL, 44 mmol) in a dropwise fashion over 1.5 h. Stirring continues for 2 h before workup which affords the nitrile (0.98 g, 63%); b.p. 88-89°C/0.3 torr.

Aliquat 336 effectively transfers RhCl_3 from aqueous solution in the form of $[(\text{C}_8\text{H}_{17})_3\text{NMe}]^+ [\text{RhCl}_4]^-$ to organic solvents (preferably 1,2-dichloroethane) to act as hydrogenation catalyst [Blum, 1983]. Selective reduction of unsaturated carbonyl compounds has been demonstrated. Note that tertiary phosphines are poisons.



Exclusive reduction of the double bond of conjugated ketones with sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$ - NaHCO_3 /Aliquat) has also been observed [Louis-Andre, 1985].

An excellent hydrogenation system which is active for arenes and some heteroaromatic compounds operates in two-phase containing the chloro(1,5-hexadiene)rhodium dimer and a Q^+X^- [Januszkiewicz, 1983]. Functional groups such as ketone, ester, and amides are not affected.

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