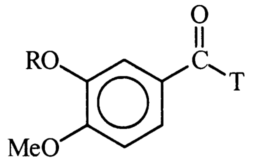
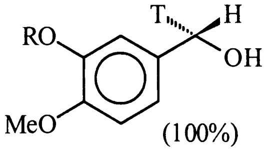
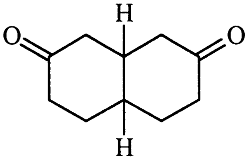
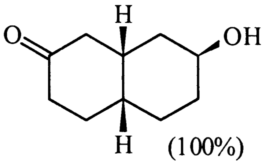
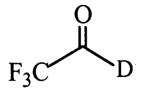
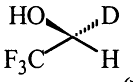
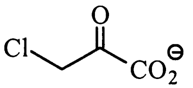
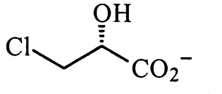
Miscellaneous Reductions

Asymmetric reduction of carbonyl compounds and production of isotopically labelled species has been achieved. A system based on deuterated formate and formate dehydrogenase provides the best system for the introduction of deuterium through nicotinamide-cofactor catalysed process[40] (Table 2).

Table 2

Substrate	Enzyme (cofactor)	Product (ee%)	Ref.
	HLADH (NADH)	 (100%)	41
	HLADH (NADH)	 (100%)	42
	HLADH (NADH)	 (>97%)	43
	L-LDH (NaDH)	 (98%)	44

HLADH = Horse liver alcohol dehydrogenase
L–LDH = L-lactic dehydrogenase

11.4 Enzymes Catalysed Hydrolytic Processes

As already stated enzymes have great potential as catalysts for use in synthetic organic chemistry. The applications of enzymes in synthesis have so far been limited to relatively small number of large scale hydrolytic processes used in industry and to a large number of small scale synthesis of products used in research. Following are given some of the applications of enzymes in hydrolytic processes.

11.4.1 Enantioselective Hydrolysis of Meso Diesters

Pig liver esterase has been used for the enantioselective hydrolysis of the following meso substrates (Table 3).

12. Aqueous Phase Reactions

12.1 Introduction

The use of water as a solvent for carrying out organic reactions was non-existent till about the middle of the 20th century. In view of the environmental concerns caused by pollution of organic solvents, chemists all over the world have been trying to carry out organic reactions in aqueous phase. The advantage of using water as a solvent is its cost, safety (it is non-inflammable, and is devoid of any carcinogenic effects) and simple operation. Water has the highest value for specific heat of all substances. It's unique enthalpic and entropic properties has led the chemists to use it as a solvent in organic reactions. Water has an abnormally low volatility because its molecules are associated with each other by means of hydrogen bonds. In fact, the H bonding is the main reason why covalent compounds have low solubility in water. Ionic material become hydrated and polar materials take part in the hydrogen bonding, so they are soluble.

Under high pressure and temperature, ordinary water behaves very differently.[1] The electrolytic conductance of aqueous solutions increases with increase in pressure. However, for all other solvents the electrical conductivity of solutions decrease with increase in pressure. This unusual behaviour of water is due to its peculiar associative properties.[2]

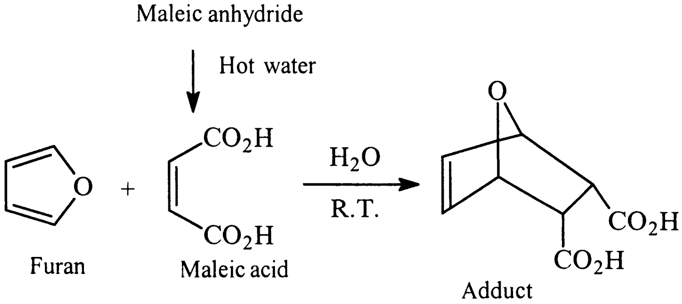
Water becomes less dense due to thermal expansion with increase in temperature. The density of water is 1.0 g/cm^3 at room temperature, which changes to 0.7 g/cm^3 at 306 °C. At critical point, the densities of the two phases become identical and they become a single fluid, which is called supercritical fluid. The density of water at this point is ~ 0.3 g/cm^3. In the supercritical region, most of the properties of water vary widely. The most important of these is the heat capacity at constant pressure, which approach infinity at the critical point. Also, the dielectric constant of dense, supercritical water ranges from 5 to 20 on variation of applied pressure.

As the temperature of water increases to the critical point, its electrolytic conductance rises sharply independent of the pressure. This is attributed to decrease in its viscosity over this range. However, near the supercritical point, the conductance begin to drop off.

Following are given some of the reactions which have been carried out in aqueous medium.

12.2 Diels-Alder Reaction

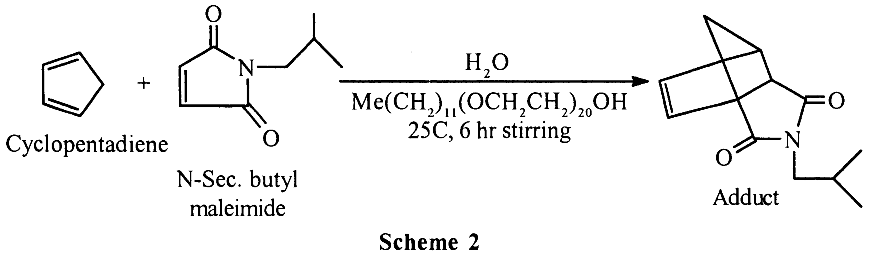
The most important method[3] to form cyclic structures is the well-known Diels-Alder reaction. However, the first Diels-Alder reaction in aqueous media was carried out in the beginning of the 19th century.[4] Thus, furan reacted with maleic anhydride in hot water to give the adduct (Scheme 1).



Scheme 1

The product obtained was a diacid (Scheme 1) showing that the reaction occurred via the formation of maleic acid from maleic anhydride.

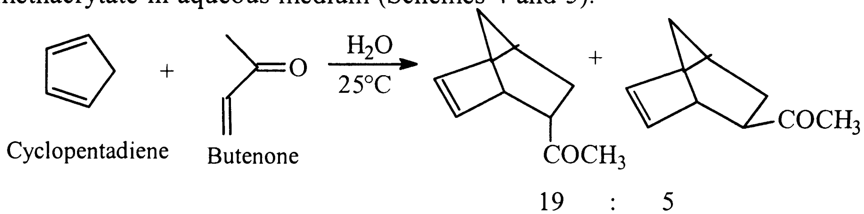
A typical reaction of cyclopentadiene with N-sec. butylmaleimide gave quantitative yield of the adduct (Scheme 2).[5]



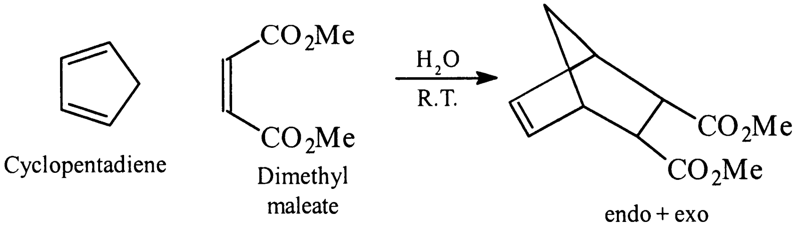
Scheme 2

However, it was only in 1980 that Breslow[6] observed that the Diels-Alder reaction of cyclopentadiene with butenone in water (Scheme 3) was more than 700 times faster than the same reaction in isooctane.

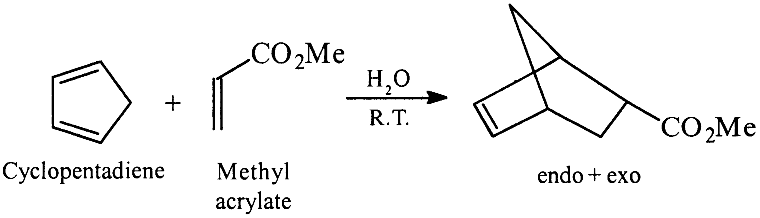
Similarly, cyclopentadiene reacted with dimethyl maleate or methyl methacrytate in aqueous medium (Schemes 4 and 5).



Scheme 3

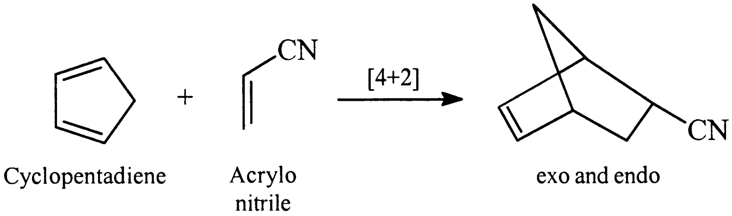


Scheme 4

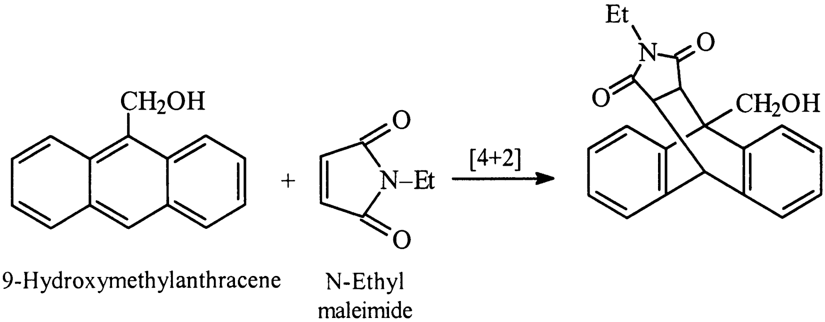


Scheme 5

The following two reactions (Schemes 6 and 7) have also been found to proceed in quantitative yield.[6]



Scheme 6

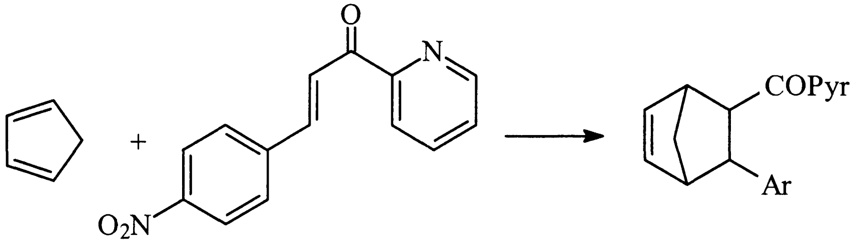


Scheme 7

It has been found that in the Diels-Alder reaction (Scheme 7), the rate increased 2.5 times if the reaction was carried out in a 4.86 M aqueous solution of LiCl. In this case LiCl is a prohydrophobic ('salting out') agent. However, the rate decreased considerably if the reaction was carried out in presence of 2.0 M aqueous solution of guanidinum perchlorate. In this case, guanidinium perchlorate is an antihydrophobic ('salting-in') agent.

It has been demonstrated[7] that the use of 'salting-out' prohydrophobic agents considerably increased the yields of cyclo-adduction of the diene carboxylates with a variety of dienophiles in water at ambient temperature. Similar results were obtained by using corresponding sodium or ammonium carboxylates.

It is well known that the conventional Diels-Alder reactions in aprotic organic solvents are catalysed by Lewis acids. In view of this, the use of Lewis acids in aqueous Diels-Alder reactions has been investigated and the reaction was found to occur much faster (Scheme 8).[8]



Scheme 8

The above reaction (Scheme 8) in aqueous $Cu(NO_3)_2$ proceeded about 800 times faster than in water alone and 2,50,000 times faster than in acetonitrile.

It is appropriate to state that the reaction between cyclopentadiene and methyl acrylate (Scheme 5) proceed about four times faster in formamide and six times faster in ethylene glycol than it does in methanol.[9] Similar results were reported by Liotta et al.[10] These solvents, viz. formamide and ethylene glycol are referred to as 'water-like' solvent systems. Also addition of LiCl in 'water-like' solvents led to a further rate increase. In this case, it is noteworthy that addition of traditional 'antihydrophobic' additives like urea also increased the rate (rather than retarding the rate) of the Diel-Alder reaction.[11]

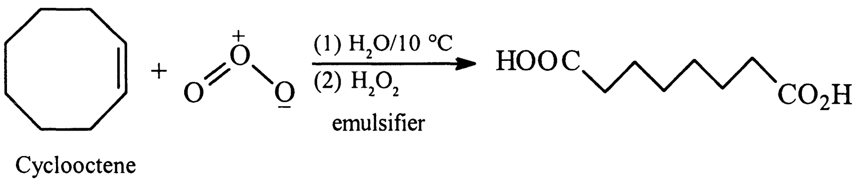
The Diels-Alder reaction in aqueous medium has tremendous synthetic potentialities.[11a] This technique has been used in the field of terpenes, steroids and alkaloids.

Due to the convenience of conducting Diels-Alder reactions, in aqueous phase, this methodology has found a number of applications in pharmaceutical industry. Some interesting applications are:

(i) Synthesis of antifungals based on aqueous Diels-Alder reaction.[12]

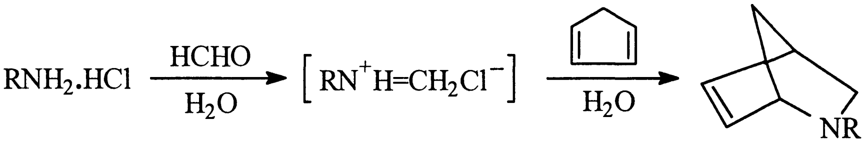
(ii) Intramolecular version of Diels-Alder reaction with a dienecarboxylate was used in synthetic study of the antibiotic ilicicolin H.[13]

(iii) Synthesis of α,ω-alkane dicarboxylic acid by the reaction of cyclooctene with ozone in H_2O at 10° followed by treatment with H_2O_2 in presence of an emulsifier (Scheme 9).[14]



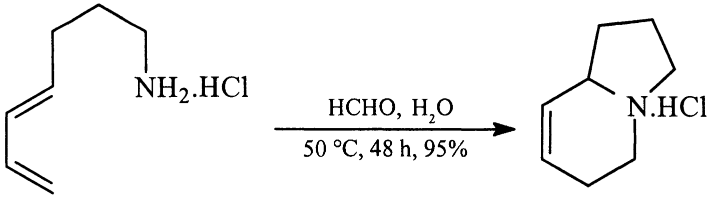
Scheme 9

(iv) A hetero-Diels-Alder reaction for the synthesis of heterocyclic compounds with nitrogen- or oxygen-containing dienophiles are particularly useful.[15] The first example of hetero-Diels Alder reaction was reported in 1985 by Grieco. In this reaction an iminium salt (generated *in situ* under Mannich-like conditions) reacted with dienes in water to give aza-Diels-Alder reaction products (Scheme 10) which are useful in the synthesis of alkaloids.[16]



Scheme 10

The intramolecular aza-Diels-Alder reaction[17] also occurs in aqueous media. This reaction gave fused ring system (Scheme 11).

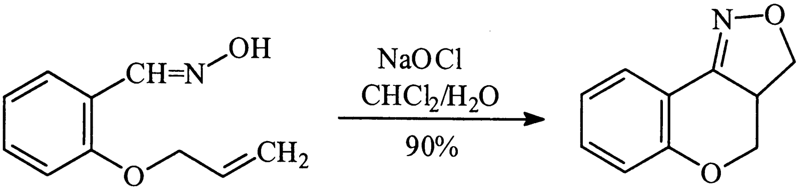


Scheme 11

For more details, refer to a review on hetero Diels-Alder reactions.[18]

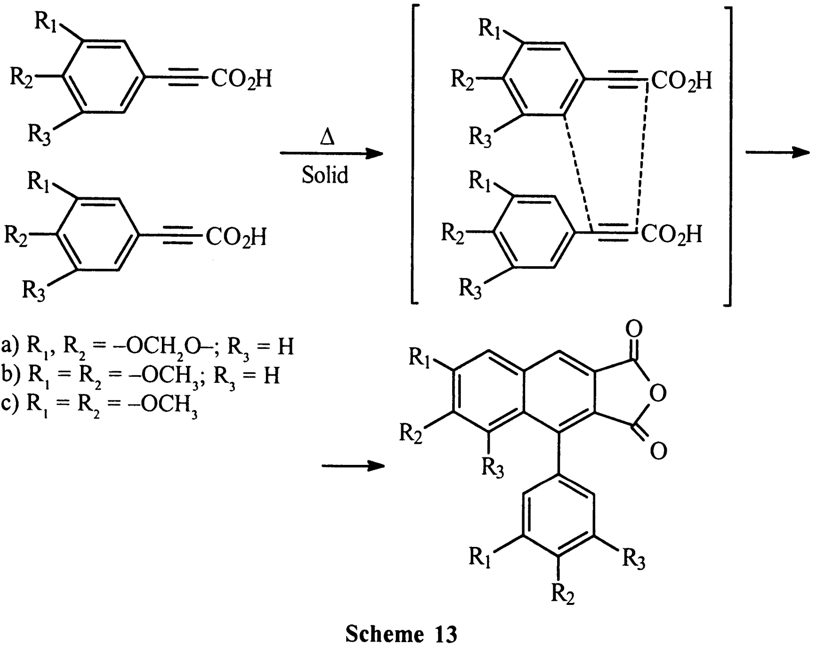
(v) A convenient one-pot synthesis of a variety of heterocyclic products by the reaction of an appropriate oxime with NaOCl in H_2O/CH_2Cl_2 (Scheme 12) has been achieved.[19]

Also see Diels-Alder reaction in ionic liquids, which is considered to be better than in aqueous medium (Chapter 14).



Scheme 12

Diels-Alder reaction can also be performed in the solid phase. Thus, phenylpropiolic acid derivatives upon heating at 80 °C give the products (anhydrides) in 20-50% yields (Scheme 13).[20]



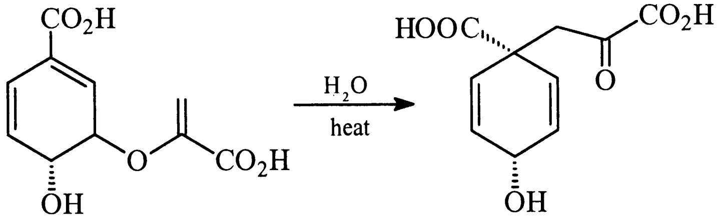
Scheme 13

12.3 Claisen Rearrangement

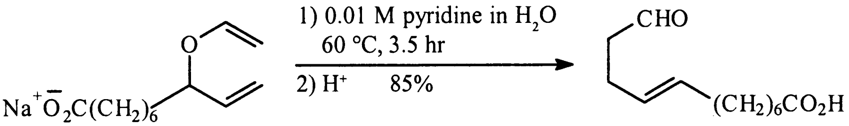
The thermal rearrangement of allyl phenyl ethers to o-allyl phenol and its mechanism is very well known to organic chemists.[21] Both the aliphatic and aromatic Claisen rearrangements involve a 3,3-sigmatropic shift.[22] There are reviews providing usefulness of this rearrangement reaction.[23]

The first reported use of water in promoting Claisen rearrangements was in 1970.[24] The first example of the use of pure water for Claisen rearrangement of chorismic acid is given (Scheme 14).[25]

A simple aliphatic Claisen rearrangement, a [3,3]-sigmatropic rearrangement of an allyl vinyl ether in water gave the aldehyde (Scheme 15).[26]



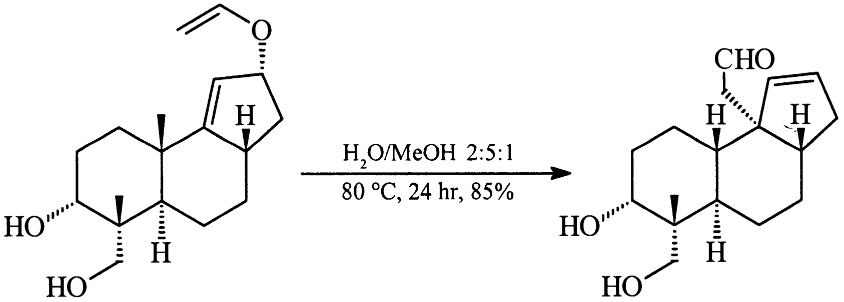
Scheme 14



Scheme 15

The corresponding ester also underwent similar rearrangement. Similarly both allyl vinyl ether and 2-hepta-3,5-dienyl vinyl-ether underwent 3,3-shift. The best results were obtained in 2/1 methanol-water; the rates were about 40 times than those in acetone solvent.[27]

A special feature of the Claisen rearrangement in aqueous medium is that it is not necessary to protect the free hydroxyl group (Scheme 16).[28]



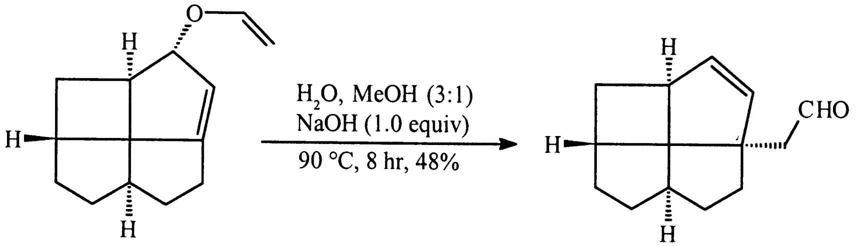
Scheme 16

The above rearrangement for protected analog under usual claisen condition resulted in elimination of acetaldehyde.[29]

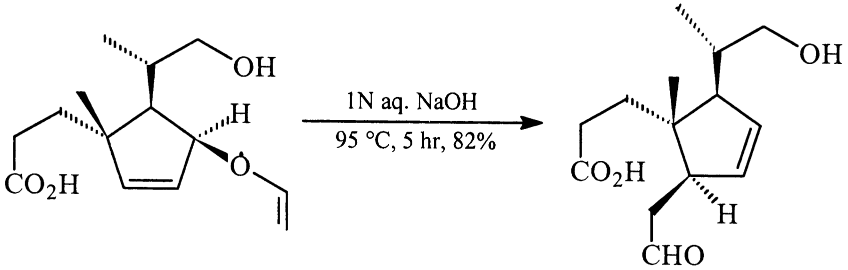
Following are given some of the important applications of Claisen rearrangement in aqueous solution.

(i) Synthesis of fenestrene aldehyde having trans ring fusion between the two 5-membered rings (Scheme 17).[30]

(ii) The Claisen rearrangement of the allyl vinyl ether (Scheme 18) gave the aldehyde in 82% yield.[30]

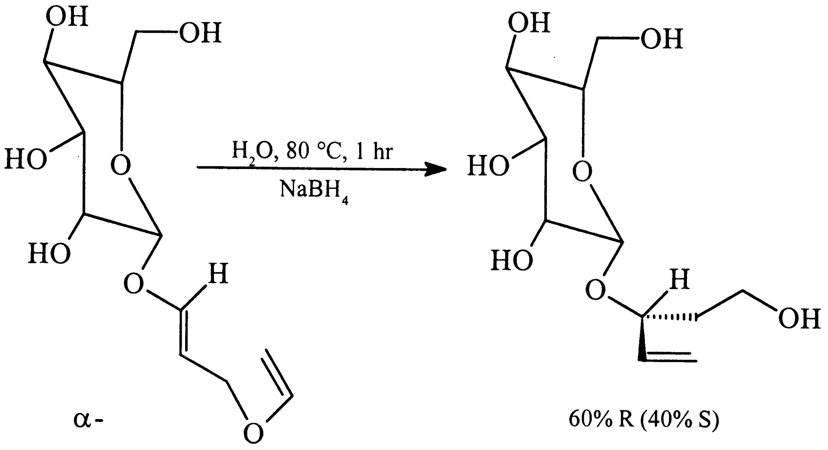


Scheme 17

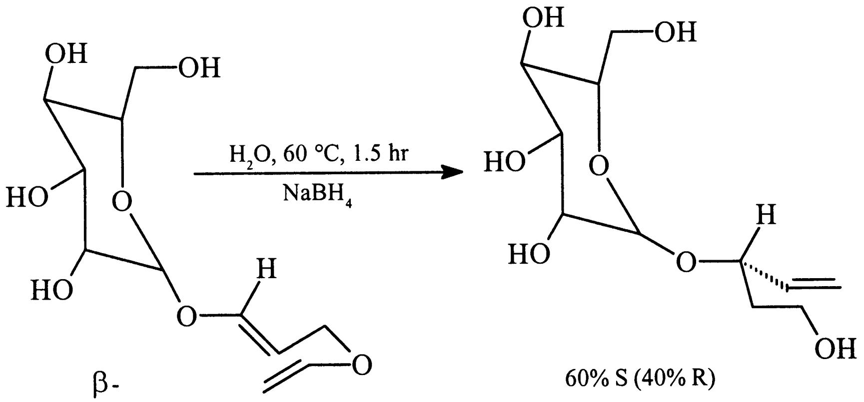


Scheme 18

(iii) Claisen rearrangements of 6-β-glycosylallyl vinyl ether (Scheme 19) and of 6-α-glycosylalkyl vinyl ether (Scheme 20) has been successful in aqueous medium.[31] In both these reactions $NaBH_4$ was added so that the formed aldehyde gets converted into the corresponding alcohol.



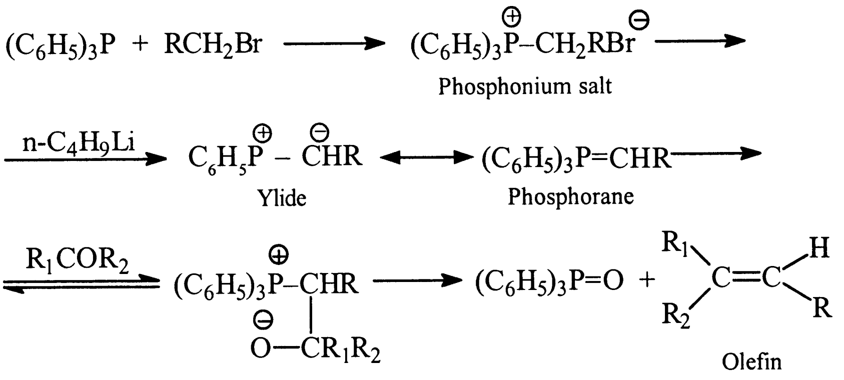
Scheme 19



Scheme 20

12.4 Wittig-Horner Reaction

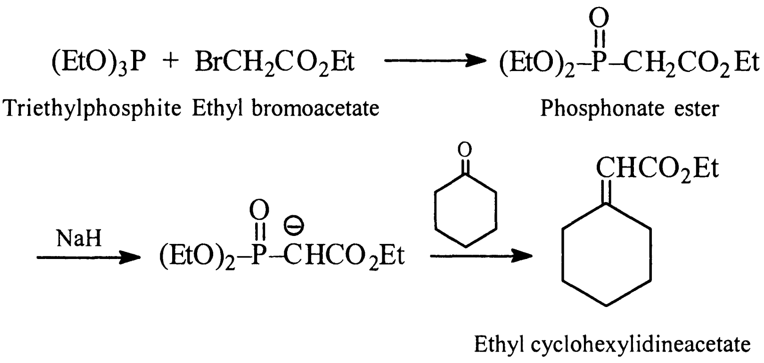
The original wittig reaction[32] has been extensively used for the preparation of olefins from alkylidene phosphoranes (ylids) and carbonyl compounds (Scheme 21).



Scheme 21

In the above reaction the ylide is unstable and is generated *in situ* for reaction with the carbonyl compound.

A modification of the above reaction, known as the Wittig-Horner reaction or Horner-Wadsworth-Emmons reaction uses phosphonate esters. Thus, the reaction of ethyl bromoacetate with triphenylphosphite gives the phosphonate ester, which on treatment with base (NaH) and reaction with cyclohexanone gives α,β-unsaturated ester, ethyl cyclohexylidineacetate in 70% yield (Scheme 22).



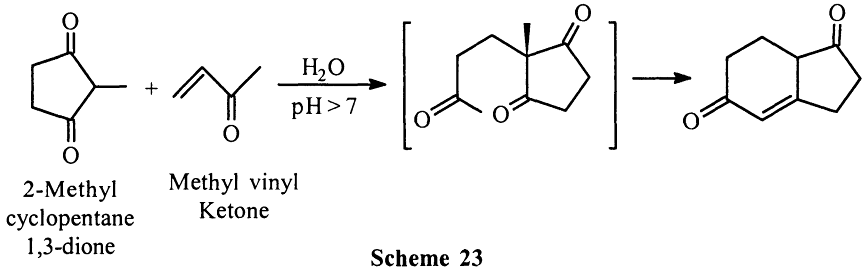
Scheme 22

The above reaction is sometimes performed in an organic/water biphase system.[33] It is now reported[34] that in the above reaction (Scheme 22) in place of strong base like NaH, a PTC can be used in aq. NaOH with good results. In the above reaction (Scheme 22) the base used is NaH or any other strong base. It has been found that the reaction proceeds with a much weaker base, such as K_2CO_3 or $KHCO_3$. Even compounds with base and acid sensitive functional groups can be used directly. In a typical example, under such conditions, β-dimethylhydrazoneacetaldehyde can be obtained efficiently.[35]

12.5 Michael Reaction

It is an addition reaction[36] between an α,β-unsaturated carbonyl compound and a compound with an active methylene group (e.g., malonic ester, acetoacetic ester, cyanoacetic ester, nitroparaffins etc.) in presence of a base, e.g., sodium ethoxide or a secondary amine (usually piperidine).

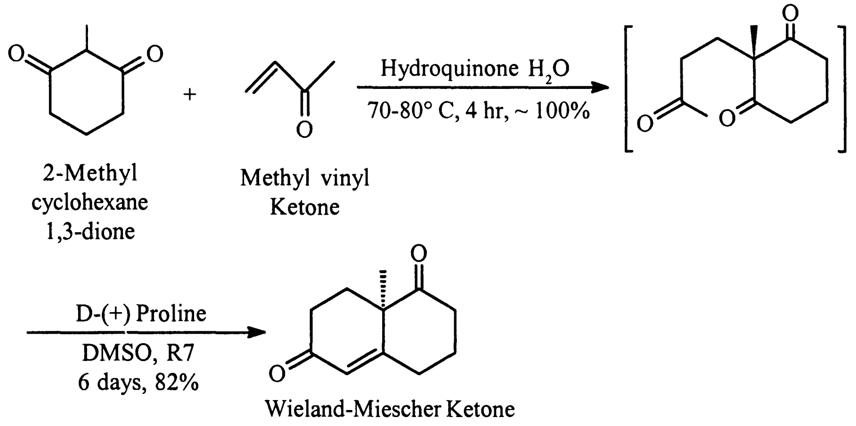
The first successful report of Michael reaction in aqueous medium was in the 1970s. 2-Methylcyclopentane-1,3-dione when reacted with vinyl ketone in water gave an adduct without the use of a basic catalyst (pH > 7). The adduct further cyclises to give a 5-6 fused ring system (Scheme 23).[37]



Scheme 23

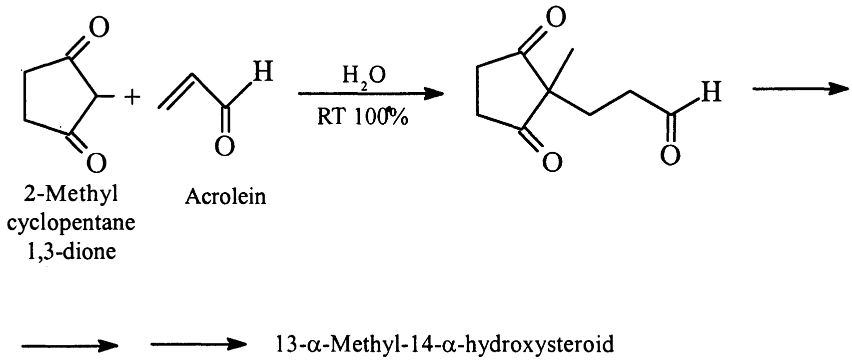
In this reaction (Scheme 23), use of water as solvent gave better yields and pure compound compared to reaction with methanol in presence of a base.

Michael reaction of 2-methyl-cyclohexane-1,3-dione with vinylketone give optically pure Wieland-Miescher ketone (Scheme 24).[38]



Scheme 24

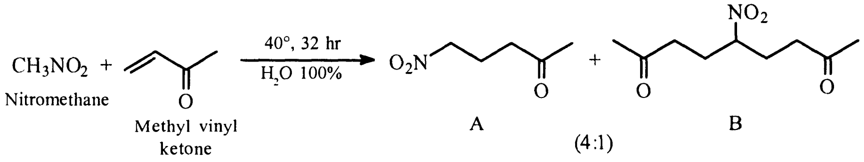
The Michael addition of 2-methyl-cyclopentane 1,3-dione to acrolein in water gave an adduct (Scheme 25) which was used for the synthesis of 13-α-methyl-14α-hydroxysteroid.[39]



Scheme 25

The rate of above Michael addition (Scheme 25) was enhanced by the addition of ytterbium triflate [yb(OTf)$_3$].

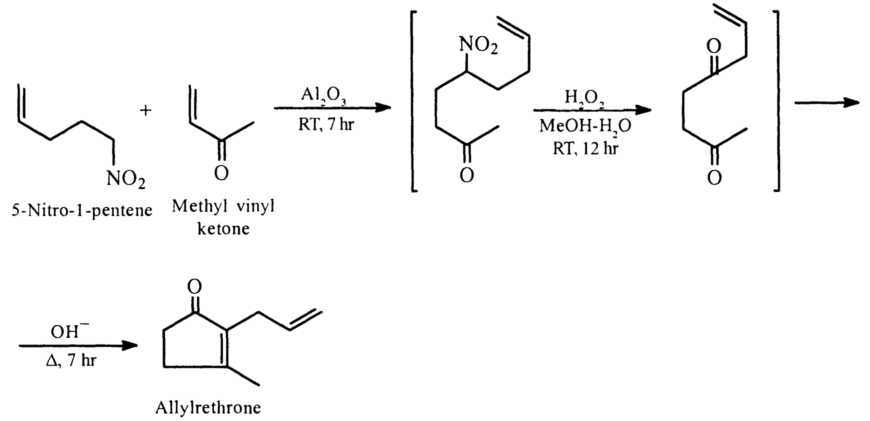
The Michael addition of nitromethane to methyl vinyl ketone in water (in absence of a catalyst) gave 4:1 mixture of adducts (A and B) (Scheme 26).[40]



Scheme 26

Use of methyl alcohol as a solvent (in place of H_2O) gave 1:1 mixture of A and B. The above reaction does not occur in neat conditions or in solvents like THF, PhMe etc. in the absence of a catalyst.

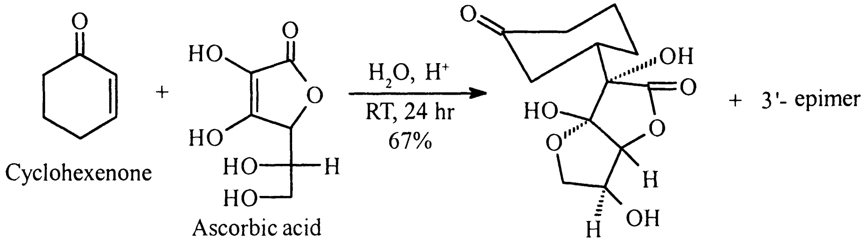
A typical synthesis of allylrethrone, an important component of an insecticidal pyrthroid has been carried out by a combination of michael reaction of 5-nitro-1-pentene and methyl vinyl ketone in presence of Al_2O_3 followed by an intramolecular aldol type condensation (Scheme 27).[41]



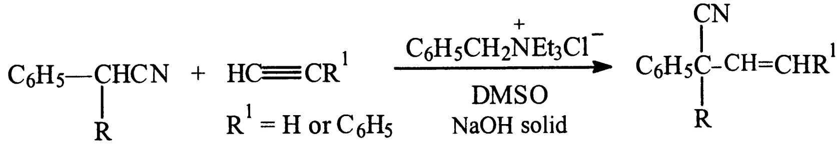
Scheme 27

The Michael addition of cyclohexenone to ascorbic acid was carried out in water in presence of an inorganic acid (rather than a base) (Scheme 28).[42]

The reaction[43] of active nitriles with acetylenes can be catalysed by quaternary ammonium salts (PTC) (Scheme 29).



Scheme 28



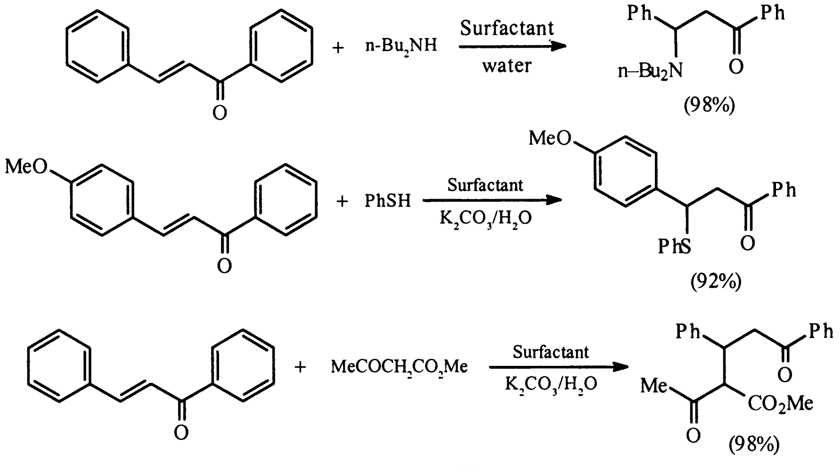
$$C_6H_5\underset{\displaystyle R}{\underset{|}{C}}HCN + HC{\equiv}CR^1 \xrightarrow[\text{DMSO}\ \text{NaOH solid}]{C_6H_5CH_2\overset{+}{N}Et_3Cl^-} C_6H_5\overset{\displaystyle CN}{\overset{|}{\underset{\displaystyle R}{\underset{|}{C}}}}\text{-}CH{=}CHR^1$$

$R^1 = H$ or C_6H_5

$R = CH_3$, isopropyl, benzyl

Scheme 29

Very efficient Michael addition reactions of amines, thiphenol and methyl acetoacetate to chalcone in water suspension have been developed.[44] For example, stirring a suspension of powdered chalcone in a small amount of water containing n-Bu_2NH and a surfactant, hexadecyltrimethylammonium bromide for 2 hr gave the adduct in 98% yield. Similarly adducts were obtained with thiophenol and methyl acetoacetate (Scheme 30).



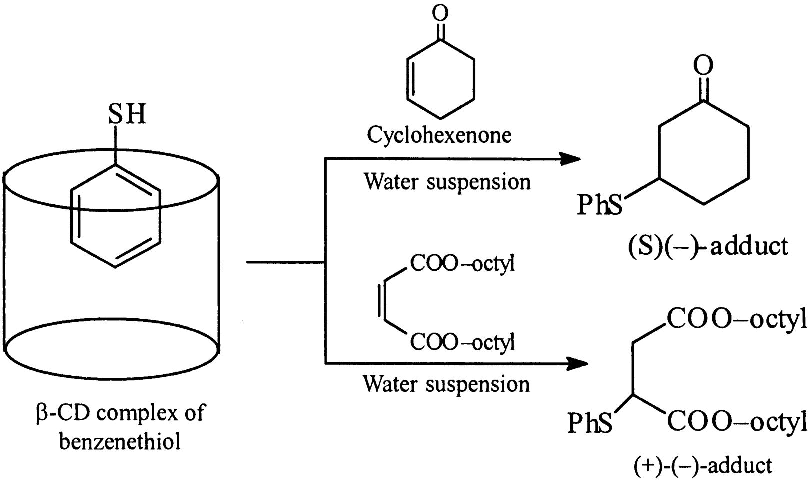
Scheme 30

See also Michael addition in solid state (Sec. 13.2.3).

Asymmetric Michael addition of benzenethiol to 2-cyclohexenone and maleic acid esters proceeds enantioselectively in their crystalline cyclodextrin complexes. The adducts were obtained in 38 and 30% ee respectively. In both cases, the reaction was carried out in water suspension (Scheme 31).[45]

12.6 Aldol Condensation

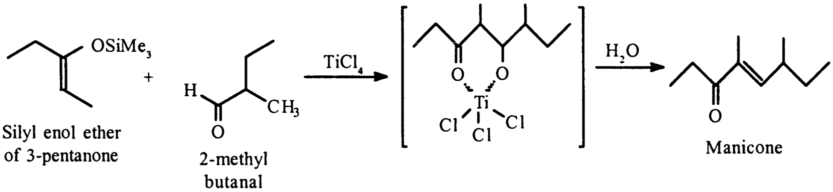
The aldol condensation is considered to be one of the most important carbon-carbon bond forming reactions in organic synthesis in presence of basic reagents. The conventional aldol condensation involve reversible self-addition of aldehydes containing a α-hydrogen atom. The formed β-hydroxy aldehydes



Scheme 31

undergo dehydration to give α,β-unsaturated aldehydes. This has been extensively reviewed.[46] The reaction can occur either between two identical or different aldehydes, two identical or different ketones and an aldehyde and a ketone.

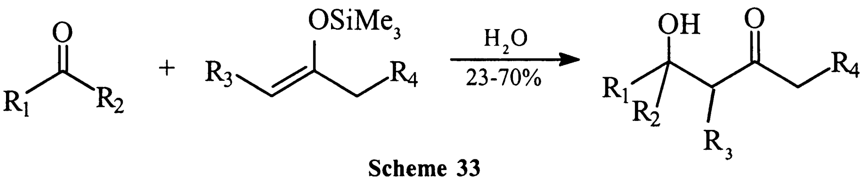
A stereoselective aldol condensation is known as Mukaiyama reaction.[47] It consists in the reaction of an silyl enol ether of 3-pentanone with an aldehyde (2-methyl-butanal) in presence of $TiCl_4$ to yield an aldol product, Manicone, an alarm pheromone (Scheme 32).[48]



Scheme 32

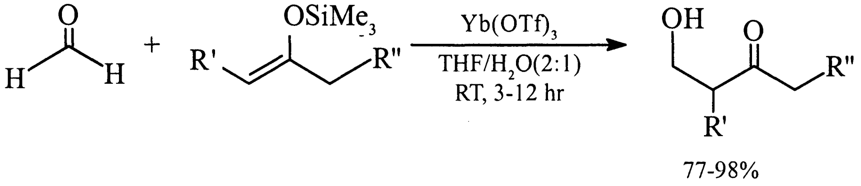
The above reactions are carried out under non-aqueous conditions.

The first water-promoted aldol reaction of silyl enol ethers with aldehydes was first reported in 1986 (Scheme 33).[49]



Scheme 33

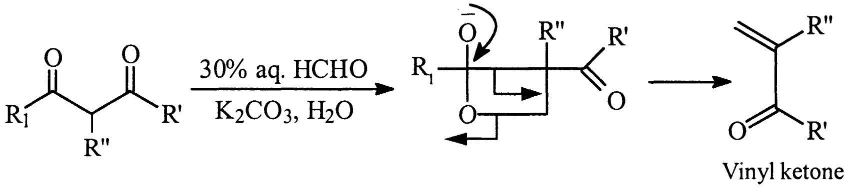
The above reactions were carried out in aqueous medium without any acid catalyst. The reaction, however, took several days for completion, probably because water serves as a weak Lewis acid. The addition of a stronger Lewis acid (e.g., lanthanide triflate) greatly improved the yield and rate of such reactions (Scheme 34).[50]



Scheme 34

It has been found that the dehydration of the alcohols can be avoided in presence of complexes of Zn with aminoesters or aminoalcohols.[51]

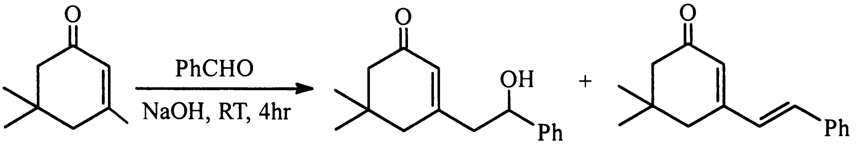
Using the above methodology, vinyl ketones (Scheme 35) can be obtained by the reaction of 2-alkyl-1,3-diketones with aqueous formaldehyde (formalin) using 6-10 M aqueous potassium carbonate as base; the final step involved cleavage of the intermediate with base.[52]



Scheme 35

The reaction of several silyl enol ethers with commercial formaldehyde solution catalysed by yb$(OTf)_3$ were carried out and good yields (80-90%) of the products obtained.[53] Several examples of the aldol condenstion in water have been cited using various aldehydes and silyl enol ethers. The products were obtained in good yield (80-90%).[54] In all the above reactions the catalyst could be recovered and used again and again. The above methodology has been extensively reviewed.[55]

An interesting case of aldol condensation is vinylogous aldol reaction. The γ-hydrogen of α,β-unsuturated ketones, nitriles and esters is 'active' and the electrophilic addition taken place at the γ-position. Thus, the reaction of isophorone with benzaldehyde in water gives only vinylogous aldol addition but with low conversion. However, in presence of CTACI, the condensation product, (E)-benzylideneisophorone, is obtained in 80% yield. Use of tetrabutylammonium chloride (TBACl) gives a mixture of addition and condensation products (Scheme 36).[56]



Isophorone

Water only	24%	–
CTACI	–	80%
TBACI	27%	58%

Scheme 36

Certain aldol condensations have been also carried out in solid state (Sec. 13.2.5).

12.7 Knoevenagel Reaction

The condensation of aldehydes or ketones, with active methylene compounds (especially malonic ester) in presence of a weak base like ammonia or amine (primary or secondary) is known as Knoevenagel reaction.[57,58] However, when condensation is carried out in presence of pyridine as a base, decarboxylation usually occurs during the condensation. This is known as Doebner modification.[59] Some examples are given (Scheme 37).

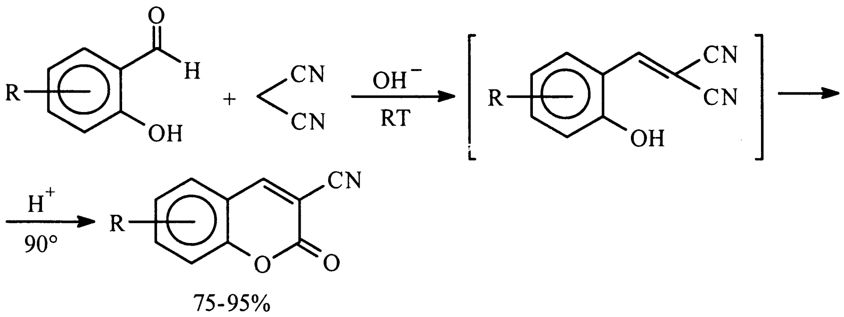
$$\underset{\text{Acetaldehyde}}{CH_3CHO} + \underset{\text{Malonic acid}}{CH_2(COOH)_2} \xrightarrow{\text{Base}} CH_3CH{=}C(COOH)_2 \xrightarrow{-CO_2} \underset{\text{Crotonic acid}}{CH_3CH{=}CHCOOH}$$

$$C_6H_5CHO + CH_2(COOC_2H_5)_2 \xrightarrow[\text{benzene}]{\text{Pyridine}} C_6H_5CH{=}C\,(COOC_2H_5)_2$$

$$\xrightarrow[\text{2) } H_3O^+]{\text{1) hydrolysis}} C_6H_5CH{=}C(COOH)_2 \xrightarrow[-CO_2]{\Delta} \underset{\text{Cinnamic acid}}{C_6H_5CH{=}CHCOOH}$$

Scheme 37

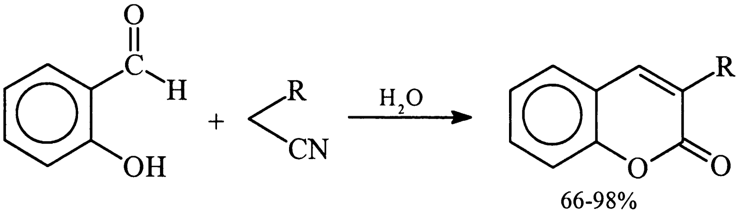
The Knoevenagel reaction has been carried out between aldehydes and acetonitrile in water. Thus, salicylaldehydes react with malononitrile at room temperature in the heterogeneous aqueous alkaline medium to give α-hydroxybenzylidene malononitriles, which are converted directly to 3-cyanocoumarins by acidification and heating (Scheme 38).[60]



R = H, OH, OMe

Scheme 38

In a similar way, use of substituted acetonitriles in the above procedure (Scheme 38) give the corresponding 3-substituted coumarins in 66-98% yields (Scheme 39).



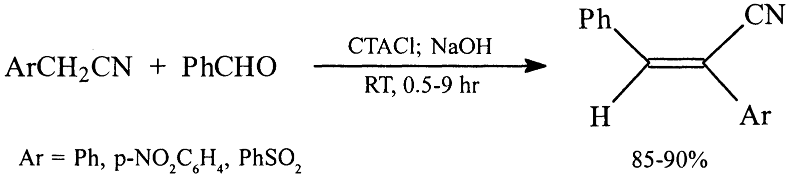
R = CN, CO_2Et, NO_2, Ph, 2-Py

Scheme 39

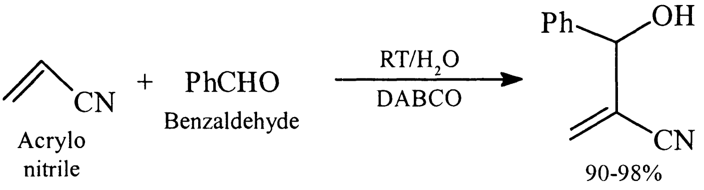
In case of phenylacetonitrile, a catalytic amount of CTABr (0.1 mole/equiv) is used. The above reaction gives better yields in water compared to in ethanol.

The reaction of benzaldehyde with acetonitrile does not occur in water only but requires the presence of catalytic amount of CTACl or TBACl to give high yields of the corresponding arylcinnamonitriles (Scheme 40).[57]

Knoevenagel-type addition product can be obtained by the reaction of acrylic derivatives in presence of a 1,4-diazabicyclo[2.2.2]octane (DABCO) (Scheme 41).[61]



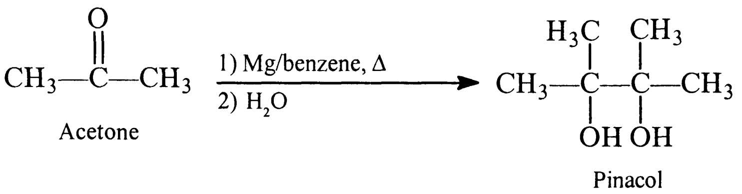
Scheme 40



Scheme 41

12.8 Pinacol Coupling

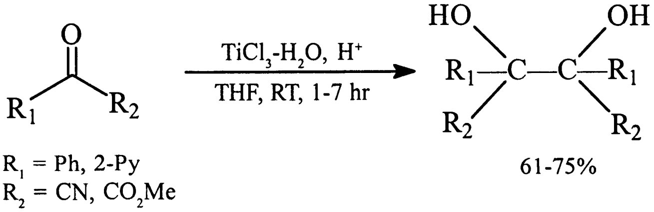
Ketones are known to react with Mg/benzene to give 1,2-diols by heating with magnesium in benzene followed by treatment with water. Thus, under these conditions acetone give pinacol (Scheme 42)



Scheme 42

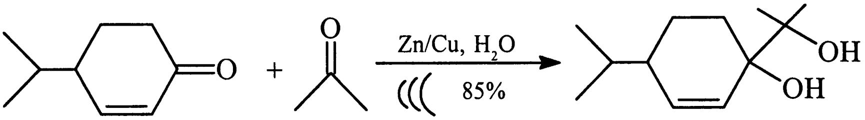
This is known as pinacol coupling. The use of Zn-Cu couple to couple unsaturated aldehydes to pinacols was recorded as early as 1892.[62] Subsequently chromium and vanadium[63] and some ammonical-$TiCl_3$[64] based reducing agents were used.

It has now been found[65] that pinacol coupling takes place in aromatic ketones and aldehydes in aqueous media in presence of Ti(III), under alkaline conditions. However, in presence of acids, only the substrates (aromatic ketones and aldehydes) having electron withdrawing group like CN, CHO, COMe, COOH, COOMe, pyridyl (activating groups) only underwent pinacol coupling[66] (Scheme 43). In case of nonactivated carbonyl compounds, it was necessary to use excess of the substrate as a solvent.[67]



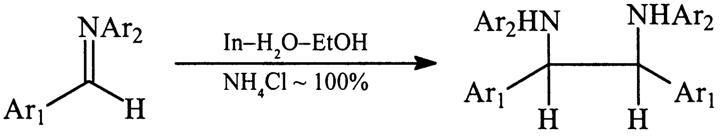
Scheme 43

The coupling reaction between an α,β-unsaturated carbonyl compound and acetone using a Zn-Cu couple and ultrasound in an aqueous acetone suspension (Scheme 44) gave the corresponding product.[68]



Scheme 44

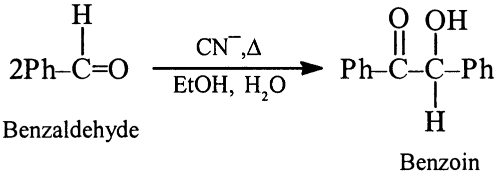
An interesting example is the coupling of aldimines to give vicinal diamines (Scheme 45) by indium in aqueous ethanol in presence of small amount of ammonium chloride, which accelerates the reaction.[69]



Scheme 45

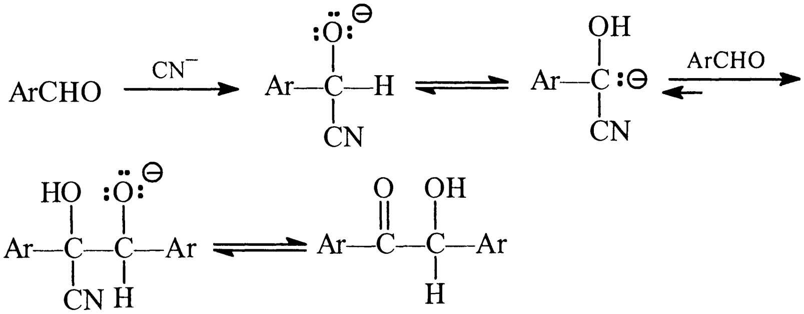
12.9 Benzoin Condensation

It consists in the treatment of aromatic aldehydes with sodium or potassium cyanide, usually in an aqueous ethanolic solution to give α-hydroxy ketones (benzoins) (Scheme 46).[70]



Scheme 46

Benzoin condensation can be considered to occur through a formal Knoevenagel type addition (Scheme 47). The key step of the reaction is the loss of the aldehydic proton, which gives rise to the cyanohydrin anion. In this case the acidity of the proton is increased by the electron-withdrawing power of the cyano group.



Scheme 47

It is found that benzoin condensation of aldehydes are strongly catalysed by a PTC (quaternary ammonium cyanide in a two phase system).[71] In a similar way, acyloin condensations are easily effected by stirring aliphatic or aromatic aldehydes with a quaternary catalyst (PTC), N-laurylthiazolium bromide in aqueous phosphate buffer at room temperature.[72] The aromatic aldehydes reacted in a short time (about 5 min). However, aliphatic aldehydes require longer time (5-10 hr) for completion. Mixtures of aliphatic and aryl aromatic aldehydes give mixed α-hydroxy ketones.[73]

On the basis of extensive work, Breslow found that the benzoin condensation in aqueous media using inorganic salts (e.g., LiCl) is about 200 times faster than in ethanol (without any salt).[74] The addition of γ-cyclodextrin also accelerates the reaction, whereas the addition of β-cyclodextrin inhibits the condensation.

12.10 Claisen-Schmidt Condensation

Normally Claisen-Schmidt condensation involves the condensation of aromatic aldehydes (without α-hydrogen) with an aliphatic aldehyde or ketone (having α-hydrogen) in presence of a relatively strong base (hydroxide or alkoxide) to form α,β-unsaturated aldehyde or a ketone (Scheme 48).[75]

$$C_6H_5CHO + CH_3CHO \xrightarrow{NaOH} C_6H_5CH{=}CHCHO$$

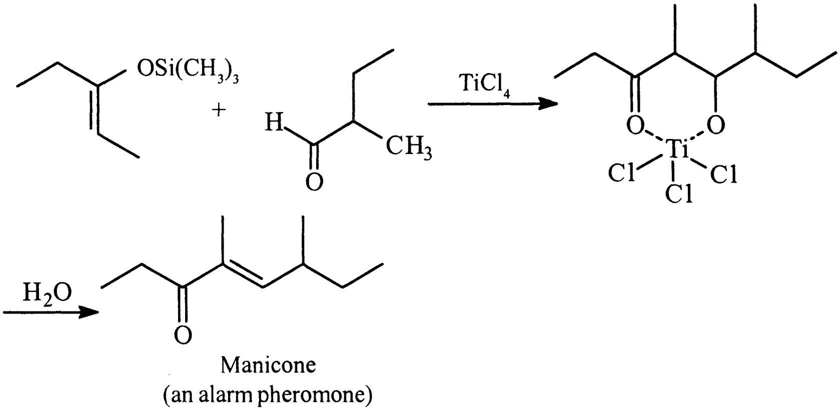
Cinnamaldehyde

$$C_6H_5COCH_3 + C_6H_5CHO \xrightarrow[EtOH]{NaOH} C_6H_5COCH{=}CHC_6H_5$$

Benzalacetophenone
(chalcone)

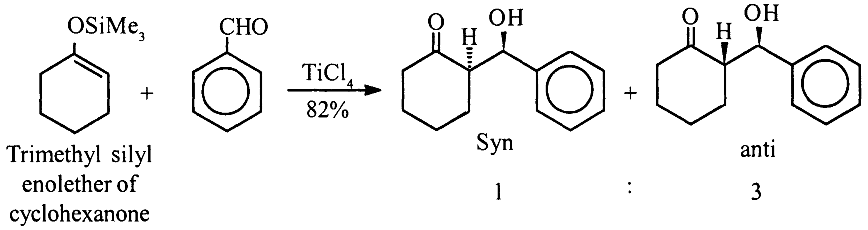
Scheme 48

A related reaction, known as Mukaiyama reaction[76] involves the reaction of silyl enol ether of the ketone with an aldehyde in an organic solvent in presence of $TiCl_4$ (Scheme 49) (see also Scheme 32).



Scheme 49

It has been shown[77] that trimethyl silyl enol ether of cyclohexanone with benzaldehyde occurs in water in presence of $TiCl_4$ in heterogeneous phase at room temperature and atmospheric pressure (Scheme 50).

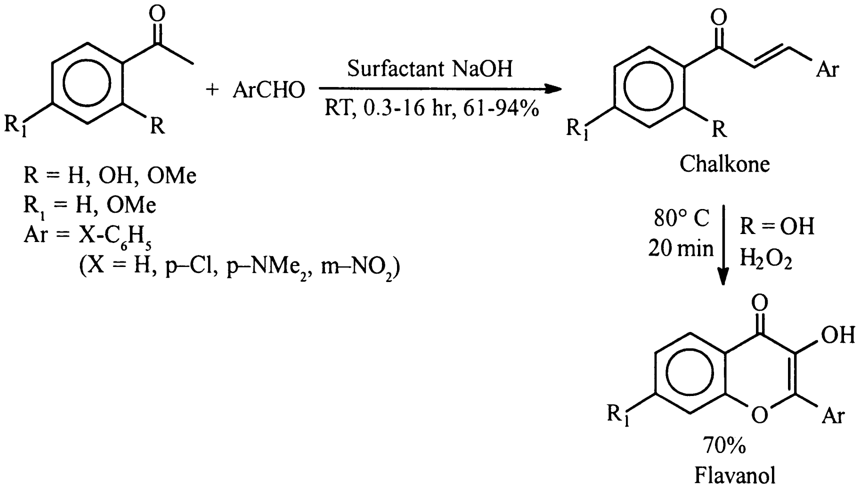


Scheme 50

Better yields are obtained under sonication conditions. The reaction is favoured by an electron-withdrawing substituent in the para position of the phenyl ring in benzaldehyde.

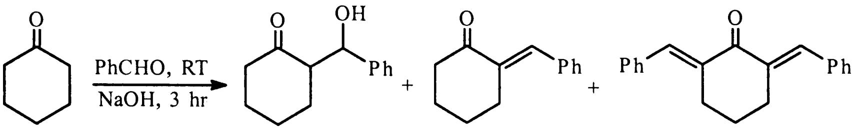
Claisen-Schmidt reaction of acetophenones with aromatic aldehydes in presence of cationic surfactants such as cetylammonium compounds, CTACl, CTABr, $(CTA)_2SO_4$ and CTAOH in mild alkaline conditions give chalcones, which on cyclisation give flavanols (Scheme 51).

The reaction of cyclohexanone with benzaldehyde in water gives high yield of a 1:1 threo-erythro mixture of the ketol. However in presence of CTACl, the bis-condensation product in obtained quantitatively (Scheme 52).[78]



R = H, OH, OMe
R_1 = H, OMe
Ar = X-C_6H_5
(X = H, p–Cl, p–NMe_2, m–NO_2)

Scheme 51

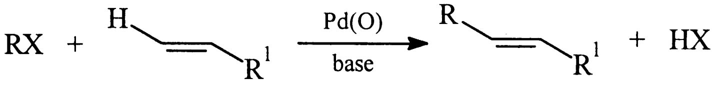


Water only	91%	9%	–
with CTACl	–	–	100%

Scheme 52

12.11 Heck Reaction

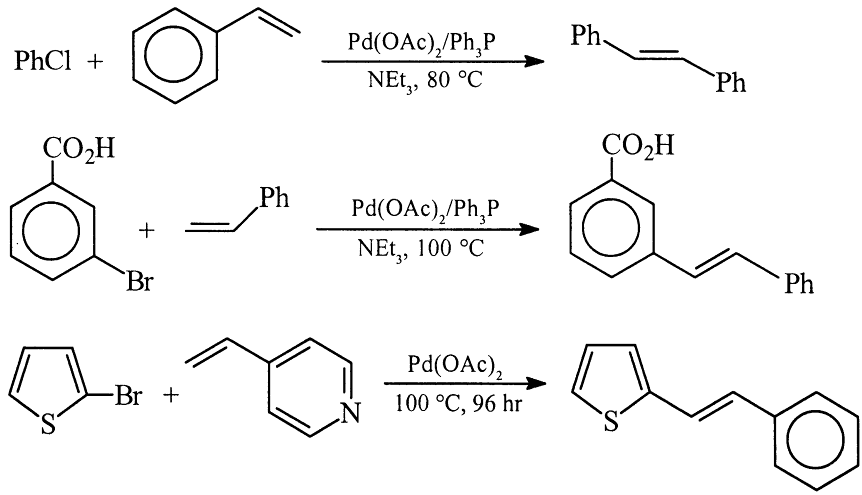
The Heck reaction, a synthetically used palladium catalysed reaction involves the coupling of an alkene with a halide or triflate in presence of Pd(O) catalyst to form a new alkene (Scheme 53).



R = aryl, vinyl or alkyl group without β-hydrogens on a sp^3 carbon atom
X = halide or triflate (OSO_2CF_3)

Scheme 53

Heck reaction uses mild base such as Et_3N or anions like OH^-, $^-OCOCH_3$, CO_3^{2-} etc. Some other applications of Heck reaction are also given (Scheme 54).



Scheme 54

The traditional technique for carrying out the Heck reaction is to use anhydrous polar solvents (eg., DMF and MeCN) and tert. amines as bases.

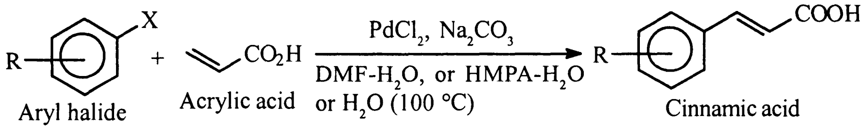
Recently it has been found that the Heck reaction can proceed very well in water. In fact, the role of water in the Heck reaction, as well as other reactions catalysed by Pd(O) in presence of phosphine ligands is: (i) transformation of catalyst precursor into Pd(O) species and (ii) the generation of zero-valent palladium species capable of oxidative addition by oxidation of phosphine ligands by the Pd(II) catalyst precursor can be affected by water content of the reaction mixture.

It has been found that the Heck reaction can be accomplished under PTC conditions[79] with inorganic carbonates as bases under mild conditions at room temperature. Such conditions can be used in case of substrates, like methyl vinyl ketone, which do not survive the usual conditions of Heck arylation (action of base at high temperature). Subsequently, it has been shown that the Heck reaction can be carried out in water and aqueous organic solvents, catalysed by simple palladium salts in presence of inorganic bases like K_2CO_3, Na_2CO_3, $NaHCO_3$, KOH etc.[80]

An interesting application of the Heck reaction is the synthesis of cinnamic acid by the reaction of aryl halides with acrylic acid (Scheme 55).

Use of acrylo nitrile in place of acrylic acid in this method (Scheme 55) yield the corresponding cinnamonitriles. Most of the products obtained in Heck-reactions are almost exclusively (E) isomers. However, the reaction of acrylonitrile give a mixture of (E) and (Z) isomers with ratio 3:1, close to that observed under conventional anhydrous conditions.[81]

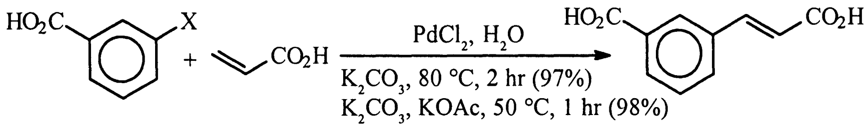
The Heck reaction can also be performed under milder condition by addition of acetate ion as given in (Scheme 56).



$X = I, Br$

$R = H$, p-Cl, p-OMe, p-Me-, p-Ac, p-NO_2, p-CHO, p-OH, m-COOH etc.

Scheme 55



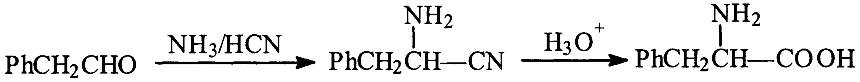
Scheme 56

A number of other application of the Heck reaction have been described in literature.[82]

The Heck reaction has also been performed in ionic liquids (for details see Sec. 14.3.3).

12.12 Strecker Synthesis

This method is used for the synthesis of amino acids by the reaction of an aldehyde with ammonia followed by reaction with HCN to give α–aminonitrile, which on hydrolysis give the corresponding amino acid (Scheme 57).[83]

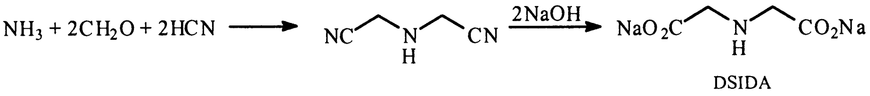


$$PhCH_2CHO \xrightarrow{NH_3/HCN} PhCH_2\overset{\overset{\displaystyle NH_2}{|}}{C}H{-}CN \xrightarrow{H_3O^+} PhCH_2\overset{\overset{\displaystyle NH_2}{|}}{C}H{-}COOH$$

Scheme 57

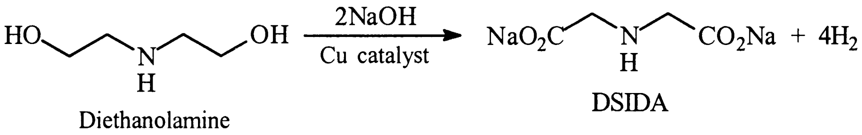
The α-aminonitrile can also be obtained by the treatment of the aldehyde with HCN followed by reaction of the formed cyanohydrin with ammonia. This method is known as Erlenmeyer modification.[84] A more convenient route is to treat the aldehyde in one step with ammonium chloride and sodium cyanide (this mixture is equivalent to ammonium cyanide, which in turn dissociate into ammonia and HCN). This procedure is referred to as the Zelinsky-Stadnikott modification.[85] The final step is the hydrolysis of the intermediate α-aminonitrile under acidic or basic conditions.

Using strecker synthesis, disodium iminodiacetate (DSIDA) an intermediate for the manufacture is Monsantos' Roundup (herbicide) was synthesised.[86]



Strecker Synthesis of DSIDA

In the above synthesis hydrogen cyanide, a hazardous chemical is used and this requires special handling to minimise the risk to workers and the environment. An alternative green synthesis of DSIDA was developed by Monsanto.



Alternative Synthesis of DSIDA

The new method avoids the use of HCN and CH_2O and is safer to operate.

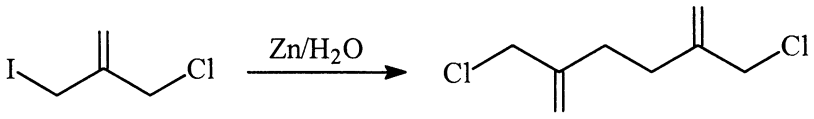
12.13 Wurtz Reaction

It involves coupling of alkyl halides with sodium in dry ether to give hydrocarbons.[87] An example is the synthesis of hexane (Scheme 58).

$$\underset{\text{Propyl bromide}}{CH_3CH_2CH_2Br} \xrightarrow[\text{ether}]{\text{Na}} \underset{\text{Hexane}}{CH_3(CH_2)_4CH_3}$$

Scheme 58

It has been shown[88] that the Wurtz coupling can be carried out by Zn/H_2O (Scheme 59).



Scheme 59

12.14 Oxidations

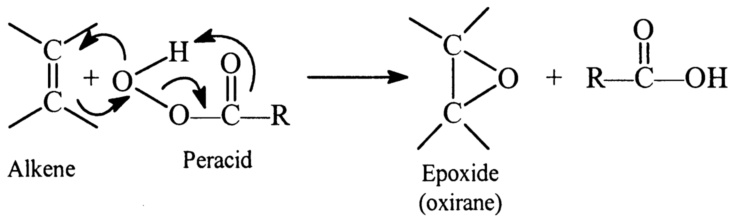
One of the most widely investigated process in organic chemistry is oxidation. A large number of reactions involving oxidation are used in industries besides being of interest in the laboratory. A number of oxidizing agents with different substrates have been described.[89]

Oxidations have been known to be carried out in aqueous medium for a long time. The well known oxidation of arenes with $KMnO_4$ in aqueous alkaline medium is very well known.[90] However, the yields are considerably increased by using $KMnO_4$ in presence of a phase transfer catalyst particularly in the oxidation of toluene. Also, H_2O_2 in water has been used quite frequently in many organic solvents. It is environment-friendly since it forms water as a secondary product.

In the present unit, some innovative and recent oxidations by chemical reagents in aqueous media are given. Enzymatic oxidations have also been known to occur in water. However, this subject will be discussed in a separate section. Following are given some of the important reactions in aqueous medium.

12.14.1 Epoxidation

Peracids are known to react with alkenes to give stable three-membered rings containing oxygen atom, called epoxides or oxiranes (Scheme 60).

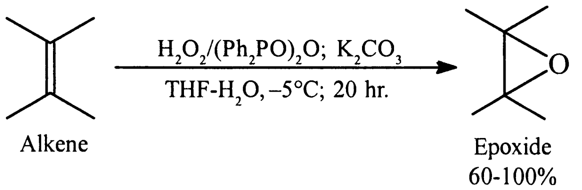


Scheme 60

A number of peracids can be used. The reaction takes place in nonpolar solvents such as dichloromethane and benzene. The above epoxidations are stereoselective and take place by syn addition to the double bond, as established by x-ray analysis of the products obtained. As the cis alkene gives only cis epoxide and trans alkene gives trans epoxide, the reaction must be concerted, i.e., the one step mechanism retains the stereochemistry of the starting alkenes.

It has now been found[91] that epoxidation of simple alkenes with m-chloroperoxybenzoic acid in aqueous solution of $NaHCO_3$ (pH ~ 8.3) at room temperature proceeds well and gives good yields of the epoxides. Using this procedure some of the alkenes like cyclopentene, cyclohexene, cycloheptene, cyclooctene, methyl cyclohexene, (+)-3-carene have been reacted with m-chloroperbenzoic acid at 20 °C for 30 min to give 90-95% of the epoxide. Styrene could be epoxidized at 20 °C (1 hr) giving 95% yield. α-Methylstyrene and trans-β-methylstyrene could be epoxidized at 0 °C in 1 hr giving 63% and 93% respectively yields of the epoxides. In aqueous medium, the reaction occurs in heterogeneous phase, but this does not effect the reactivity, which sometimes is higher than in homogenous organic phase.

For direct epoxidation of simple alkenes by H_2O_2, the peroxide must be activated (Scheme 61). This is done in buffered aqueous tetrahydrofuran (THF), 50% H_2O_2 activated by stoichiometic amounts of organophosphorus anhydride.

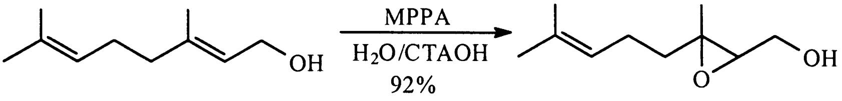


Scheme 61

Using this method a variety of alkenes could be epoxidized.[92] The epoxidation of electron-deficient olefins can be achieved with H_2O_2 in presence of sodium tungstate as a catalyst.[93] The epoxidation of alkene has also been effected with a variety of oxidizing reagents such as $PhlO_4$, NaClO, O_2, H_2O_2, ROOH, $KHSO_5$ etc. in aqueous medium in presence of metalloporphyrins.[94]

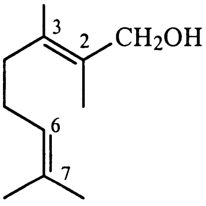
On an industrial scale, epoxidation of alkenes is generally carried out by using hydrogen peroxide, peracetic acid or t-butyl hydroperoxide (TBHP).[95] A novel safe and cheap method for epoxidation has been developed.[96] It consist in using nacent oxygen generated by electrolysis of water at room temperature by using Pd black as an anode. Using this method cyclohexene could be epoxidized in good yield. In this illustration, water is used as a reaction medium as well as a reagent.

Regioselective epoxidation of allyl alcohols in presence of other C=C bonds by using monoperphthalic acid (MPPA) in presence of cetyltrimethyl ammonium hydroxide (CTAOH) (which controls the pH of the aqueous medium) (Scheme 62).[97]

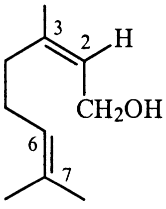


Scheme 62

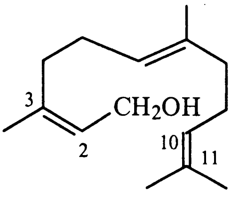
It is interesting to note how the epoxidation takes place at different double bonds in the terpenoids viz. geraniol (I), nerol (II), farnesol (III) and linalool (IV) with MPPA by carrying out the reaction at different pH.



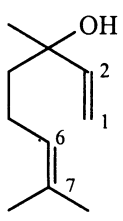
Geraniol
I



Nerol
II



Farnesol
III



Linalool
IV

It has been found[98] that 2,3-epoxidation takes place in I, II and III with MPPA in aqueous medium at pH 12.5 and in about 90% yields. In I, II and IV

6,7-epoxidation takes place in aqueous medium at pH 8.3 in about 60-90% yields. The 10,11-epoxidation takes place at pH 12 in 88% yield. In case of linalool (IV), 1,2-epoxidation does not take place. It is appropriate to state that 6,7-epoxidation of geraniol (I) has been reported earlier with t-C_4H_9OOH/VO $(acac)_2$ in benzene (refluxing) and 2,3-epoxidation achieved by using m-chloroperbenzoic acid.[99]

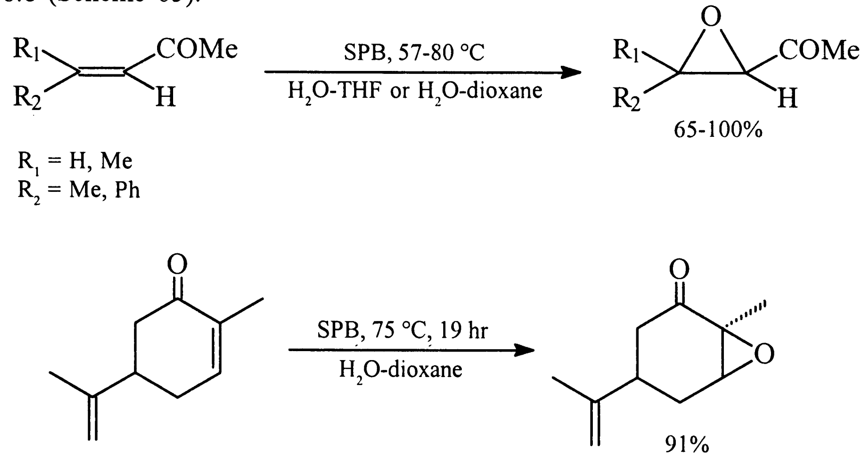
It is interesting to note that attempts to epoxidise linalool and its analogues with MPPA in organic solvents give the tetrahydrofuran and tetrahydropyran derivatives.

Epoxidation of α,β-unsaturated carbonyl compounds in aqueous media can be achieved traditionally by Michael reaction with alkaline hydroperoxides.[100] It has been reported that the epoxidation of α,β-unsaturated carbonyl compound can be conveniently accomplished[101] by using sodium perborate (SPB) in aqueous media at pH 8 to give α,β-epoxyketones (Scheme 63).

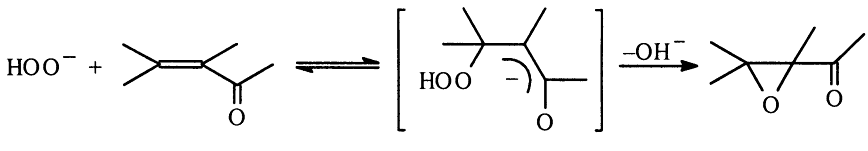
The epoxidation of α,β-unsaturated carbonyl compounds with hydrogen peroxide under basic biphase condition, known as the Weitz-Scheffer epoxidation (Scheme 64)[102] is a very convenient and efficient method for giving the epoxides.

The reaction (Scheme 64) has been used for the epoxidation of a number of α,β-unsaturated aldehydes, ketones, nitriles, esters and sulfones etc.

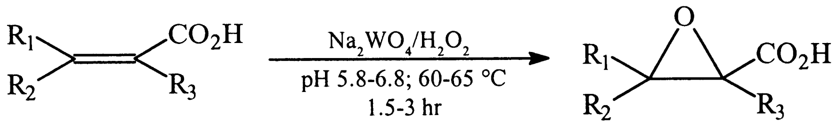
The epoxidation of α,β-unsaturated carboxylic acid is difficult. However, the epoxidation can be achieved with H_2O_2 in presence of Na_2WO_4 at pH 5.8-6.8 (Scheme 65).



Scheme 63



Scheme 64



R_1, R_2, R_3 = H, Me, Br

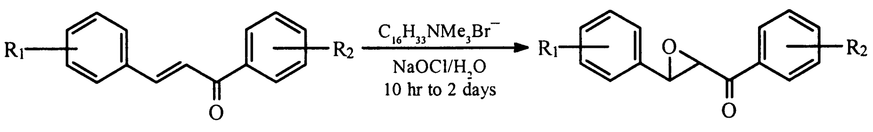
Scheme 65

The above reaction is known as Payne's reaction[103] using the modified procedure of sharpless.[104]

Alternatively the above epoxidation of α,β-unsaturated carboxylic acids can be achieved by using ozone-acetone system and buffering the reaction with $NaHCO_3$[105] in 75-80% yield.

Epoxidation of fumaric acid can be achieved by using ozone in water at neutral pH in quantitative yield.[106]

The epoxidation of chalkones with NaOCl (commercially available) in water suspension proceeded very efficiently[107] in presence of a PTC hexadecyltrimethylammonium bromide in excellent yields (50-100%) (Scheme 66).



$R_1 = R_2 = H$
R_1 = p-Br; R_2 = H
R_1 = H; R_2 = p-Br
R_1 = m-Me; R_2 = H
R_1 = p-Cl; R_2 = H

R_1 = p-MeO; R_2 = H
R_1 = p-Me; R_2 = H
R_1 = H; R_2 = p-Me
$R_1 = R_2$ = p-Cl
$R_1 = R_2$ = p-Me

Scheme 66

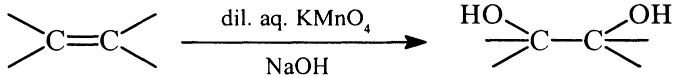
12.14.2 Dihydroxylation

In case of alkens, one can get either syn- or anti-dihydroxylation.

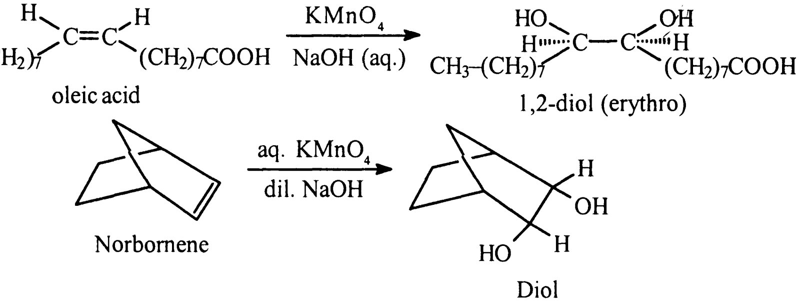
12.14.2.1 Syn-Dihydroxylation

One of the earliest known method of syn-dihydroxylation of alkenes is by treatment with dilute $KMn0_4$ solution in presence of sodium hydroxide (Scheme 67). In fact the change in purple colour is the basis for the presence of double bond and this is known as Baeyer's test for unsaturation.

This method is used for syn-hydroxylation of oleic acid and norbornene (Scheme 68).



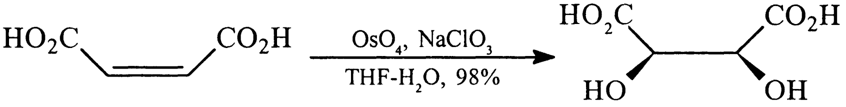
Scheme 67



Scheme 68

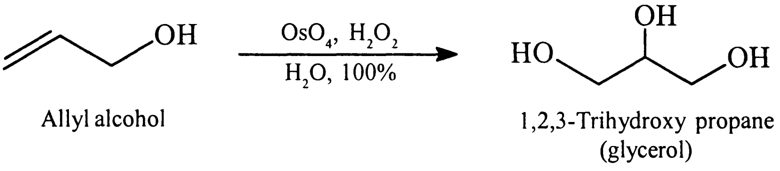
There are numerous other examples of syn-dihydroxylation of alkenes in the literature.

Osmium tetroxide in dry organic solvent[108] was subsequently used for syn-dihydroxylations of alkenes. In fact, only a catalytic amount of osmium tetraoxide was needed; the reaction was done in presence of chlorate salt as primary oxidant. The reaction is normally carried out in water-tetrahydrofuran solvent mixture (Scheme 69). Silver or barium chlorate gave better yields.



Scheme 69

The syn-hydroxylation of alkenes can also be effected by hydrogen peroxide in presence of catalytic amount of $Os0_4$. This procedure was used earlier in solvents such as acetone or diethyl ether.[109] By this method allyl alcohol is quantitatively hydroxylated in water (Scheme-70).[110]

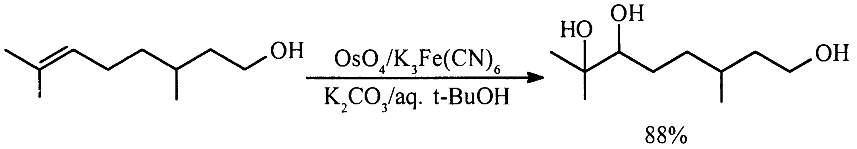


Scheme 70

Following are given some other methods used for syn-dihydroxylation of alkenes:

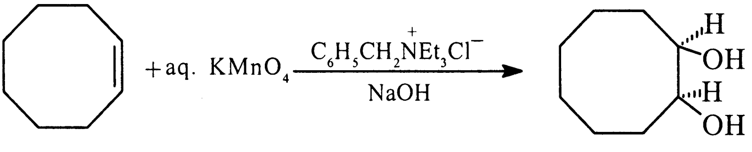
(i) Osmium-tetroxide-tertiary amine N-oxide system.[111] The reaction is carried out in aqueous acetone in either one or two phase system.

(ii) $K_3Fe(CN)_6$ in presence of K_2CO_3 in aqueous or tertiary butyl alcohol provides a powerful system for the osmium-catalysed dihydroxylation of alkenes (Scheme 71).[112] Using this method even alkene having low reactivity or hindered alkenes could be hydroxylated.



Scheme 71

Syn-hydroxylation of olefins has also been carried out with $KMnO_4$ solution using a PTC catalyst under alkaline conditions. Thus, under alkaline conditions, cyclooctene gives[113] 50% yield of cis 1,2-cyclooctane diol compared to an yield of about 7% by the classical technique (Scheme 72).



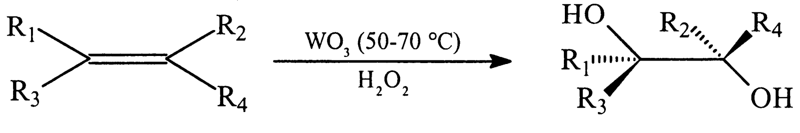
Cyclooctene

cis, 1,2-cyclooctane diol
50%

Scheme 72

12.14.2.2 Anti Dihydroxylation

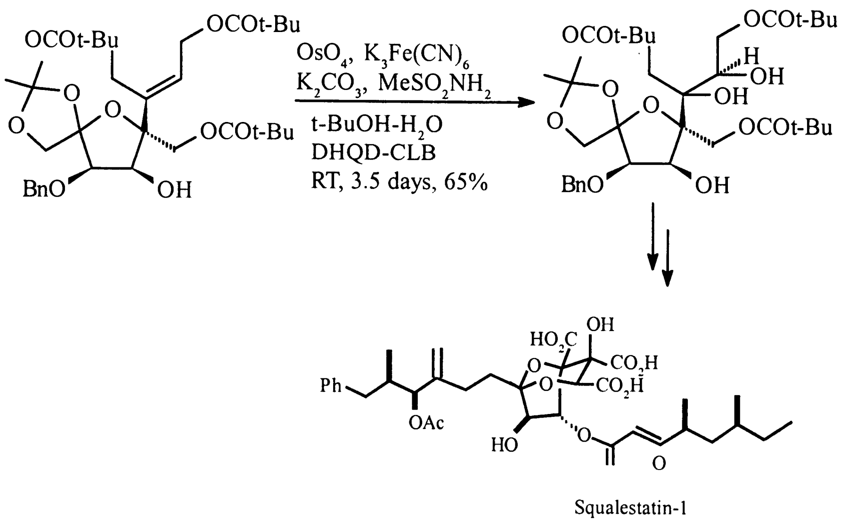
Hydrogen peroxide in presence of tungsten oxide (WO_3) or selenium dioxide (SeO_2) react with alkene to give anti-dihydroxylation products (Scheme 73).[114]



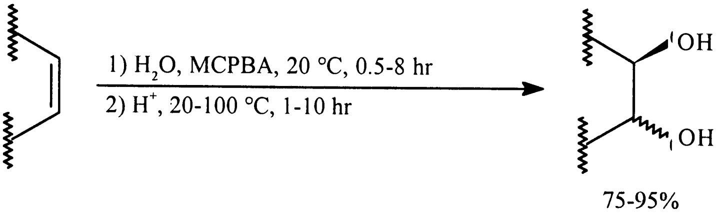
Scheme 73

Using the Sharpless dihydroxylation different types of compounds (having C=C) have been transformed to diols with high enantiomeric-excess levels. This is known as asymmetric dihydroxylation and has a wide range of synthetic applications. A representative example is dihydroxylation used as the key step for the synthesis of squalestatin (Scheme 74).[115]

A one pot procedure for the antihydroxylation of the carbon-carbon double bond can be achieved as shown below (Scheme 75).[116]



Scheme 74



Scheme 75

12.14.3 Miscellaneous Oxidations in Aqueous Medium

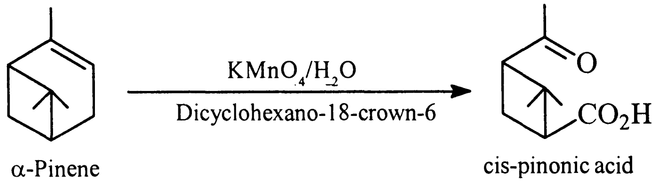
12.14.3.1 Alkenes

The oxidation of alkenes with aqueous solution of $KMnO_4$ in presence of a phase transfer catalyst (e.g. $CH_3(CH_2)_{15}N^+(CH_3)_3Cl^-$) or a crown ether (e.g. 18-crown-6) gives 79% yield of the carboxylic acid. Some examples are given (Scheme 76).

An interesting example is the oxidation of n-octane to 1-octanol (Scheme 77) using *Psuedomonas oleovorans*.[117] This procedure is used for the commercial production of 1-octanol (>98% pure).[118]

$$CH_3(CH_2)_5CH{=}CH_2 \xrightarrow[CH_3(CH_2)_{15}\overset{+}{N}(CH_3)_3Cl^-]{aq.\ KMn0_4} CH_3(CH_2)_4CH_2COOH$$

1-octene   Heptanoic acid



Scheme 76

$$CH_3(CH_2)_6CH_3 \xrightarrow[oleovorans\ H_2O]{Pseudomonas} CH_3(CH_2)_6CH_2OH$$

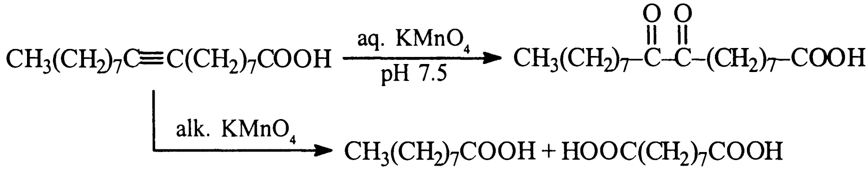
n-Octane   1-Octanol

Scheme 77

12.14.3.2 Alkynes

Alkynes can be oxidised with $KMn0_4$ in aqueous medium to give a mixture of carboxylic acids. Some examples are given below (Scheme 78).

$$R{-}C{\equiv}C{-}R' + 4[O] \xrightarrow{KMn0_4} RCOOH + R'COOH$$



$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH \xrightarrow[pH\ 7.5]{aq.\ KMn0_4} CH_3(CH_2)_7{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}(CH_2)_7{-}COOH$$

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH \xrightarrow{alk.\ KMn0_4} CH_3(CH_2)_7COOH + HOOC(CH_2)_7COOH$$

Scheme 78

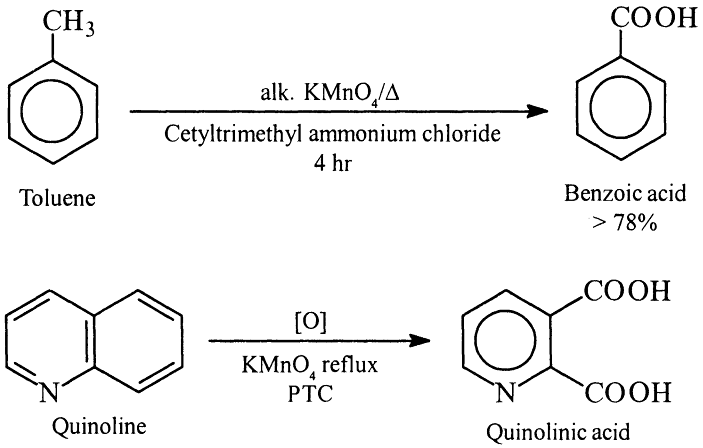
12.14.3.3 Oxidation of Aromatic Side Chains and Aromatic Ring System

Some examples are given (Scheme 79).

12.14.3.4 Oxidation of Aldehydes and Ketones

A number of procedures are available for the oxidation of aldehydes to the corresponding carboxylic acids in aqueous and organic media.[119]

Aromatic aldehydes have been conveniently oxidized by aqueous performic acid obtained by addition of H_20_2 to HCOOH at low temperature (0-4 °C).[120]



Scheme 79

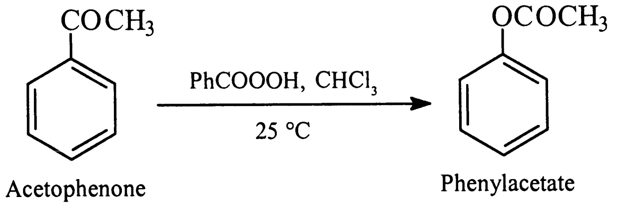
The carboxylic acids precipitate out of the reaction mixture and can be isolated by filtration. Even the hetroaromatic aldehydes like formyl pyridines, formyl quinolines and formylazaindoles can be oxidised by the above procedure to the corresponding carboxylic acids; in this procedure, the formation of N-oxides is avoided.

Chemoselective oxidation of formyl group in presence of other oxidizable groups can be carried out in aqueous media in presence of a surfactant. For example, 4-(methylthio)benzaldehyde is quantitatively oxidised to 4-(methylthio)benzoic acid with TBHP in a basic aqueous medium in presence of cetyltrimethyl ammonium sulphate.[121]

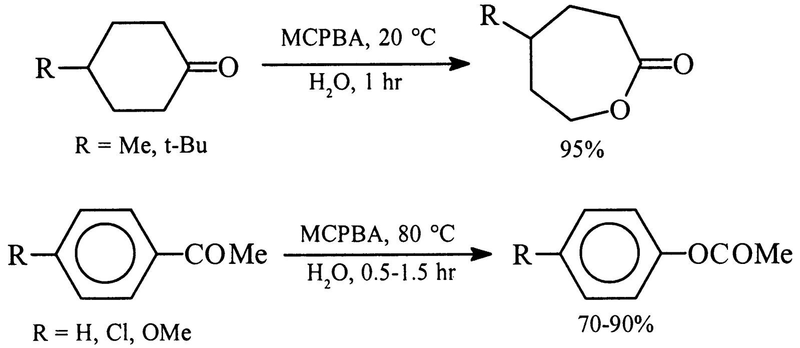
Aromatic aldehydes having hydroxyl group in ortho or para position to the formyl groups can be oxidised with alkaline H_2O_2 (Dakin reaction) in low yields.[122] This reaction has been recently carried out in high yields using sodium percarbonate (SPC; Na_2CO_3, 1.5 H_2O_2) in H_2O-THF under ultrasonic irradiation.[123] Using this procedure following aldehydes have been oxidised in 85-95% yields: o-hydroxybenzaldehyde; p-hydroxybenzaldehyde; 2-hydroxy-4-methoxybenzaldehyde, 2-hydroxy-3-methoxybenzaldehyde and 3-methoxy-4-hydroxybenzaldehyde.

The Baeyer-Villiger oxidation[124] is well known for the conversion of aromatic ketones (e.g., acetophenone) into the corresponding esters (Scheme 80).

The common peracids used are perbenzoic acid, performic acid and m-chloroperbenzoic acid. The reaction is generally carried out in organic solvents. The Baeyer-Villiger oxidation of ketones has been satisfactorily carried out in aqueous heterogeneous medium with MCPBA at room temperature.[125] Some examples using the above methodology are given (Scheme 81).

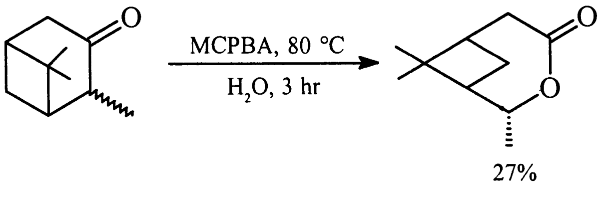


Scheme 80



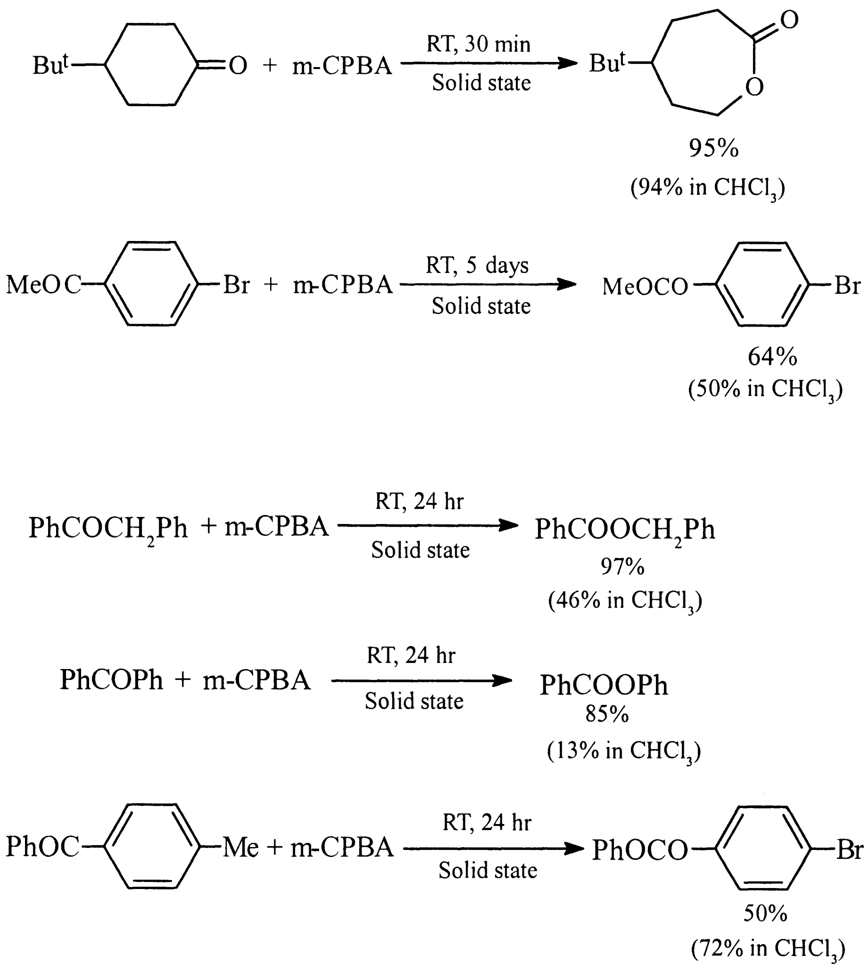
Scheme 81

Using the above procedure, ketones, which are reactive (e.g. anthrone which usually gives anthraquinone) and ketones, which are unreactive or give the expected lactones in organic solvents with difficulty[126] can also be oxidised (Scheme 82).



Scheme 82

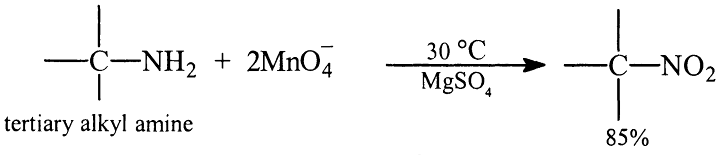
Some Baeyer-Villiger oxidation of ketones with m-chloroperbenzoic acid proceed much faster in the solid state than in solution. In this method, a mixture of powdered ketone and 2-mole equivalent of m-chloroperbenzoic acid is kept at room temperature to give the product.[127] The yields obtained in solid state are much better than in $CHCl_3$. Some representative examples are given as follows (Scheme 83).



Scheme 83

12.14.3.5 Oxidation of Amines into Nitro Compounds

Alkaline $KMnO_4$ oxidises tertiary alkyl amines into nitro compounds (Scheme 84).[128]



$$-\overset{|}{\underset{|}{C}}-NH_2 + 2MnO_4^- \xrightarrow[MgSO_4]{30\ °C} -\overset{|}{\underset{|}{C}}-NO_2$$

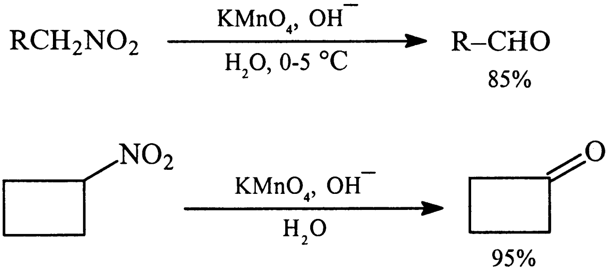
Scheme 84

Primary and secondary alkyl amines remain uneffected under above conditions. Aromatic amines containing a carboxylic or alcoholic groups can be oxidised to nitro compounds by oxone (potassium hydrogen peroxymonosulfate triple salt, $2KHSO_3$, $KHS0_4$, K_2S0_4) in 20-50% aqueous acetone at 18 °C in 73-84% yield.[129]

It is of interest to note that aminopyridine N-oxides are obtained under acidic conditions in organic solvent and usually requires protection of the amino group by acetylation and final deprotection.[130] It has now been possible to obtain N-oxide in good yield from aminopyridine directly by using oxone in water under neutral or basic conditions at room temperature.[131] The selectivity of the reaction depends on the position of the amino group.

12.14.3.6 Oxidation of Nitro Compounds into Carbonyl Compounds

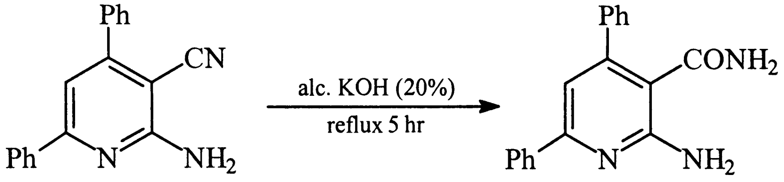
Alkaline $KMn0_4$ oxidises primary and secondary nitro groups into the corresponding carbonyl compounds (aldehydes and ketones respectively) (Scheme 85).



Scheme 85

12.14.3.7 Oxidation of Nitriles

The conversion of nitriles into amides was first reported in 1968[132] by heating the nitrile with alcoholic KOH (Scheme 86).



2-Amino-3-cyano-
4,6-diphenylpyridine

2-Amino-3-carbamoyl-
4,6-diphenylpyridine

Scheme 86

It is now well known that the conversion of nitriles into amides can be carried out under a variety of conditions in presence of metal catalyst.[133]

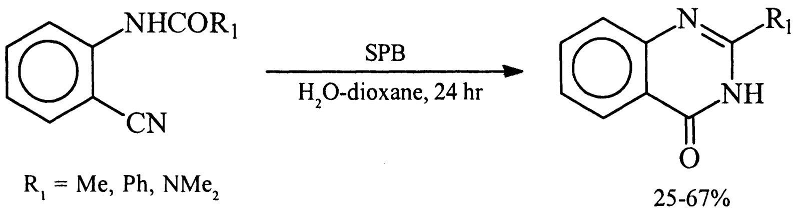
A convenient method[134] has been developed. It involves in using urea-hydrogen peroxide adduct (UHP, H_2NCONH_2, H_2O_2) in presence of catalytic amount of K_2CO_3 in water-acetone at room temperature (Scheme 87).

$$\text{R–CN} \xrightarrow[\text{H}_2\text{O-acetone, R.T.}]{\text{UHP, K}_2\text{CO}_3} \text{R–CONH}_2$$

Scheme 87

Using the above method following nitriles have been converted into corresponding amides in 85-95% yield: benzonitrile, methyl cyanide and chloromethyl cyanide.

Nitriles can also be converted into amides by using sodium perborate (SPB; $NaBO_3$, nH_2O, $n = 1$ to 4) in aqueous media such as H_2O-MeOH[135]; H_2O-acetone[136] and H_2O-dioxan[137]. An interesting application of this reaction is the synthesis of quinazolin-4-(3H)-ones[138] (Scheme-88).



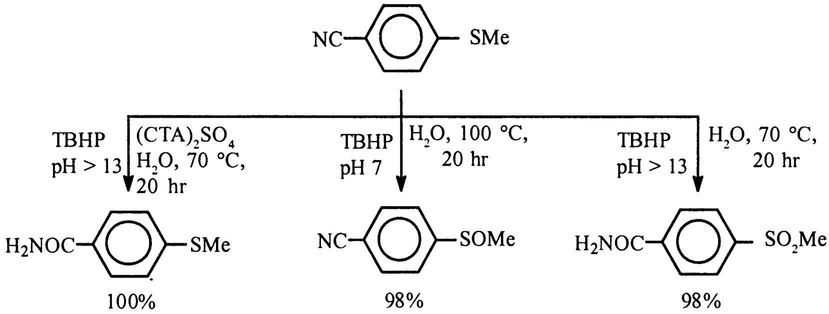
Scheme 88

The quinazolin-4-(3H)-ones are interesting systems to build pharmaceutical compounds.

It has been reported[139] that the CN group of 4-(methylthio)benzonitrile is quantitatively and selectively oxidised to amide by tertiary butyl hydroperoxide (TBHP) in strong alkaline aqueous medium in presence of cetyltrimethyl ammonium sulfate [$(CTA)_2SO_4$] (Scheme 89). TBHP does not oxidise the CN group at pH 7 (even at 100 °C), however in the absence of $(CTA)_2SO_4$, only the methylsulfenyl group is oxidised to methylsulfinyl. But under basic conditions, TBHP converts both groups into amide and sulfonyl groups respectively (Scheme 89).

12.14.3.8 Oxidation of Sulphides

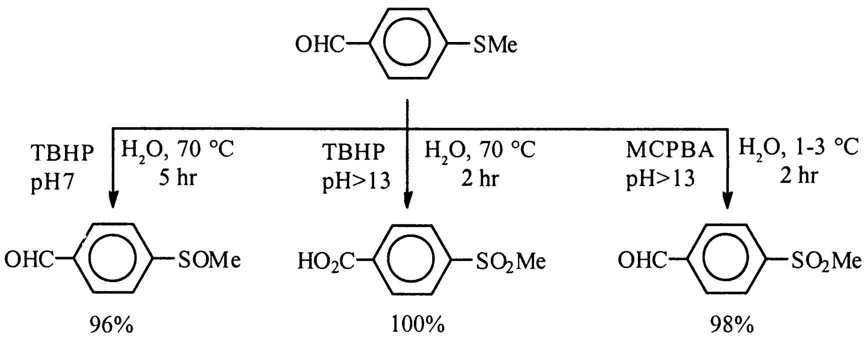
A number of reagents (e.g. H_2O_2/acetic acid) are available for the oxidation of sulphides to sulfoxides and sulphones. These methods are useful only for small scale preparations. On a large scale, an oxidant like oxone in aqueous acetone, buffered to pH 7.8-8.0 with sodium bicarbonate is used.[140] This procedure is economical and environmentally benin. The formation of the oxidation products, viz. sulfoxides or sulphones depend on the equivalent of oxone used, temperature and reaction time. In aqueous medium at pH 6-7 (buffered with phosphate), the reaction is very fast and excellent conversions to sulfoxides and sulphones are obtained.[141]



Scheme 89

Another cheaply available industrial chemical, sodium perborate (SPB) in aqueous methanolic sodium hydroxide oxidises sulphides into sulphones in very good yield.[142] Sulphides can be oxidised to sulphoxides exclusively by using commercial 70% aqueous TBHP in water in the heterogeneous phase at 20-70 °C.[143] Using this procedure some of the sulphides like Et_2S, PhSMe, PhSPh, p-OHC_6H_4SMe can be oxidised quantitatively into the corresponding sulfoxides at 20 °C.

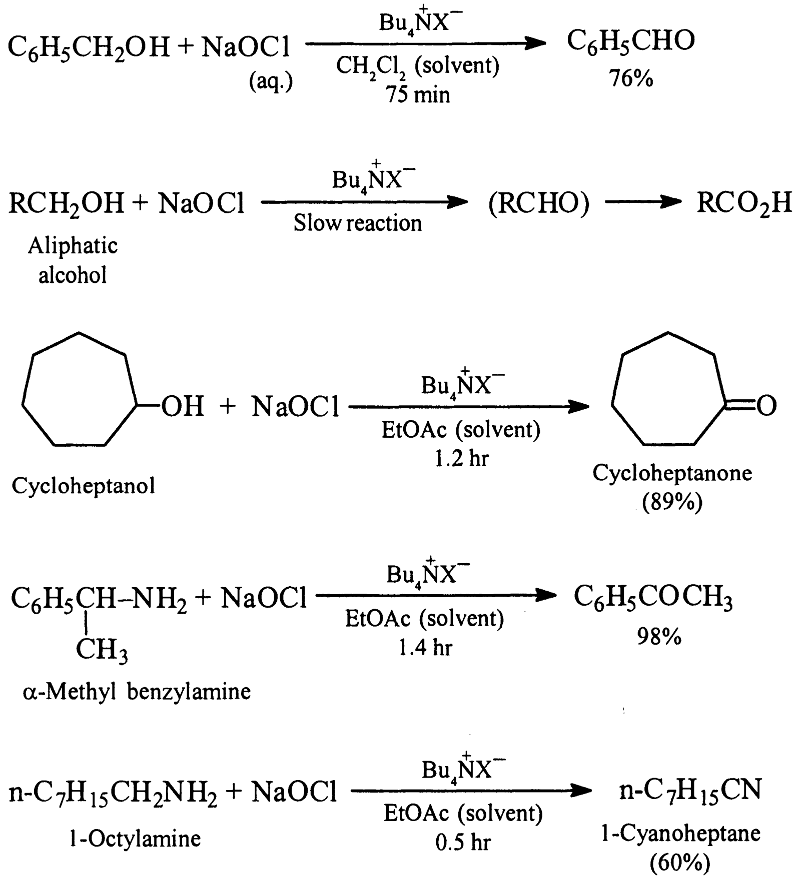
The SMe group of 4-(methylthio)benzaldehyde can be selectively oxidised to the sulfinyl group in water at 70 °C at pH 7 with tertiary butyl hydroperoxide (TBHP) (Scheme-90).[144] However, under strong basic condition both the CHO and SMe groups are oxidised to –COOH and –SO_2Me respectively. By using MCPBA under basic conditions, oxidation of –CHO group is prevented and SMe group is oxidised to SO_2Me in good yield.



Scheme 90

12.14.3.9 Oxidations with Hypochlorite

Hypochlorite is a well known oxidizing agent in the haloform reaction for the oxidation of methyl ketones to carboxylic acids. It has been shown[145] that the hypochlorite anion can be transferred into organic solutions by PTC (quaternary cations). Some of the applications of this technique are given as follows (Scheme 91).



Scheme 91

12.14.3.10 Oxidation with Ferricyanide

Potassium ferri cyanide oxidises 1,2-disubstituted hydrazines in presence of 2,4,6-triphenyl phenol (as PTC) in presence of NaOH[146] to give 1,2-disubstituted azo compounds (Scheme 92).

$$\text{RNHNHR}' + K_3Fe(CN)_6 \xrightarrow[\text{NaOH}]{\text{TPP}} \underset{63\text{-}98\%}{\text{RN=NR}}$$

Scheme 92

Besides what has been mentioned above, a number of oxidations can be performed in aqueous phase in the presence of a phase transfer catalyst (see Chapter 8).

12.15 Reduction

12.15.1 Introduction

Like oxidation, reduction of organic molecules has played an important role in organic synthesis. A number of reducing agents with different substrates have been described.[147]

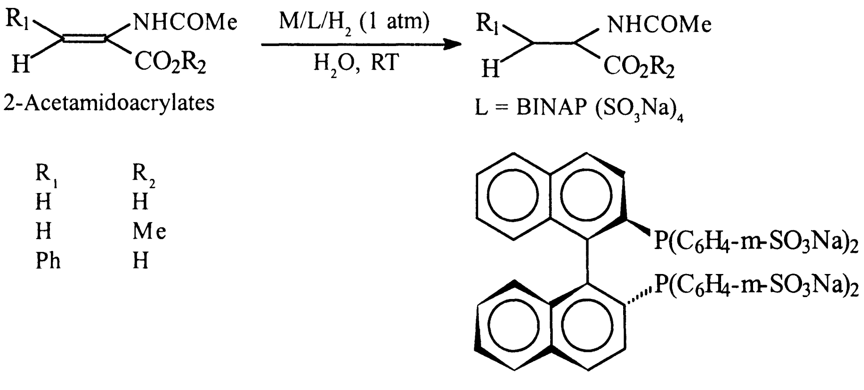
During the past 10 years, there has been considerable progress with respect to the types of bonds which can be reduced and also with respect to regio- and stereo-selectivity of the reduction processes. The only reducing agent which could be used in aqueous medium is sodium borohydride. From a point of view of industrial application reduction in aqueous medium is of paramount importance. It is interesting to note that hydride reductions which at one time seemed impossible to be carried out in aqueous medium have now been accomplished by the development of a number of water-soluble catalysts which give higher yields and selectivities. Even the hydrogenation of aromatic compounds have been accomplished in aqueous media.

In the present unit, some examples of a few novel reduction performed in aqueous medium are described. Enzymic reduction have also been known to occur in water. However, this subject will be discussed in a separate section. Some important reductions in aqueous media are given as follows:

12.15.2 Reduction of Carbon-Carbon Double Bonds

Organic compounds containing carbon-carbon double bond (e.g. alkenes) can be reduced to the corresponding saturated compounds (eg., alkanes) by $Pt0_2/H_2$, Pd/H_2 or Raney Ni/H_2. Even diimide is useful for reducing carbon-carbon double bond in compounds like p-nitrocinnamic acid, cyclohexene 1,2-dicarboxylic acid and oleic acid.

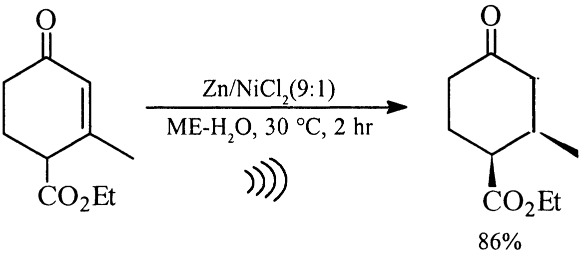
The reduction of carbon-carbon double bonds by the use of water soluble hydrogenation catalysts has received attention.[148] Thus, hydrogenation of 2-acetamidoacrylates with hydrogen at room temperature in water in the presence of water soluble chiral Rh(I) and Ru(II) complexes with (R)-BINAP (SO_3Na) [BINAP is 2,2'-bis(diphenylphosphino-1,1'-binaphthyl] (Scheme 93).[149]



Scheme 93

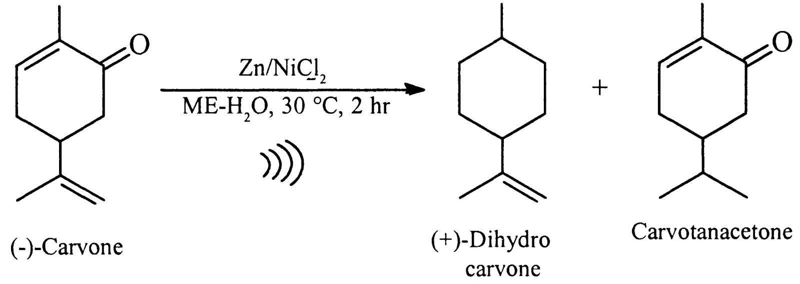
Ruthenium complexes are found to be more stable than the corresponding rhodium analogue; the ee of the final reduced product is found to be 68-88%.

The carbon-carbon double bond of α,β-unsaturated carbonyl compounds is conveniently reduced by using Zn/NiCl$_2$ (9:1) in 2-methoxyethanol (ME)-water system (Scheme 94).[150] Sonication increases the yield.



Scheme 94

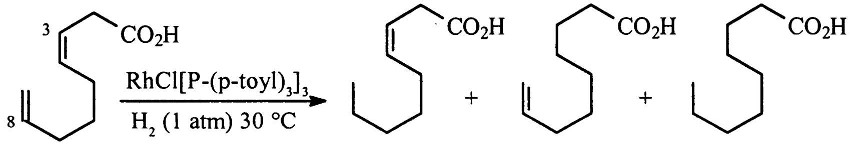
The above procedure (Scheme-94) has been used to selectively reduce (-)-carvone to (+) dihydrocarvone and carvotanacetone in 95% and 83% yields respectively by variation of experimental conditions (Scheme-95).[151]



Scheme 95

Carvone was earlier reduced to dihydrocarvone by using homogeneous hydrogenation technique with hydridochlorotris(triphenylphosphine) ruthenium $(Ph_3P)_3$ RuClH.[152]

Hydrogenation of 3,8-nonadienoic acid (a compound containing an terminal as well as an internal double bond) gives different products depending on the reaction conditions.[153] For example, half hydrogenation of 3,8-nonadienoic acid in anhyd. benzene with $RhCl[P(p\text{-tolyl})_3]_3$ gives major amount (66%) of 3-nonenoic acid (A). However, addition of equal amount of water to the reaction medium gives an inversion of selectivity giving 8-nonenoic acid as the major product (85%). The use of aqueous KOH retards the hydrogenation rate (Scheme 96).



3,8-Nonadienoic acid

A
3-Nonenoic acid

B
8-Nonenoic acid

C
Decanoic acid (capric acid)

	A	B	C
C_6H_6 (4 hr)	66%	10%	20%
C_6H_6-H_2O (2 hr)	0.7%	85%	8%
C_6H_6-KOH aq.(20 hr)	6%	18%	39%

Scheme 96

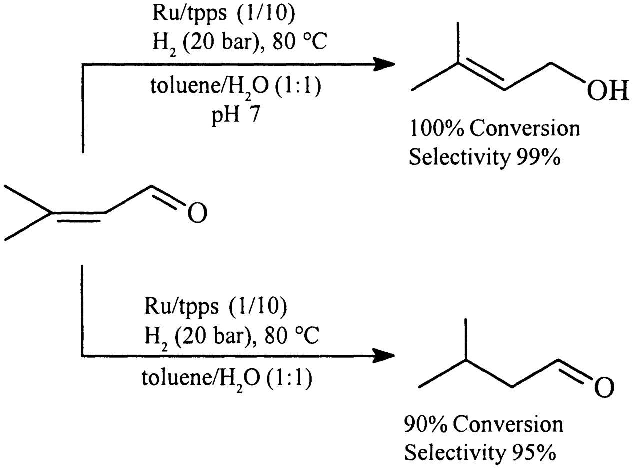
The carbon-carbon double bonds can also be reduced by samarium diiodide-H_2O system.[154]

Chemoselective hydrogenation of an unsaturated aldehyde by transition metal catalysed process[155] (Scheme 97) has been achieved.

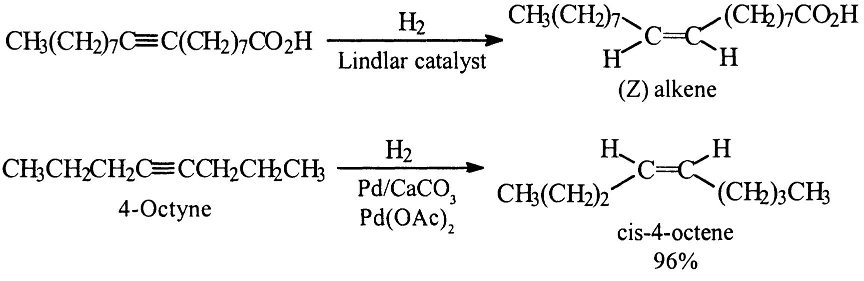
12.15.3 Reduction of Carbon-Carbon Triple Bonds

It is very well documented that the carbon-carbon triple bonds (e.g., alkynes) on catalytic hydrogenation gives the completely reduced product, viz. alkanes. Alkynes can also be reduced partially to give z-alkenes by palladium-calcium carbonate catalyst which has been deactivated (partially poisoned) by the addition of lead acetate (Lindlar catalyst) or Pd-$BaSO_4$ deactivated by quinoline. The lead treatment poisoned the palladium catalyst, rendering it less active and the reaction is more selective. Some examples are given (Scheme 98).

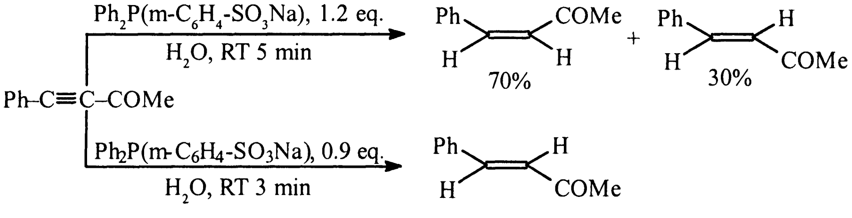
An example of reduction of carbon-carbon triple bond in water is the reaction of disubstituted alkynes (which are electron deficient) with water-soluble monosulfonated and trisulfonated triphenylphosphine (Scheme 99).[156]



Scheme 97



Scheme 98



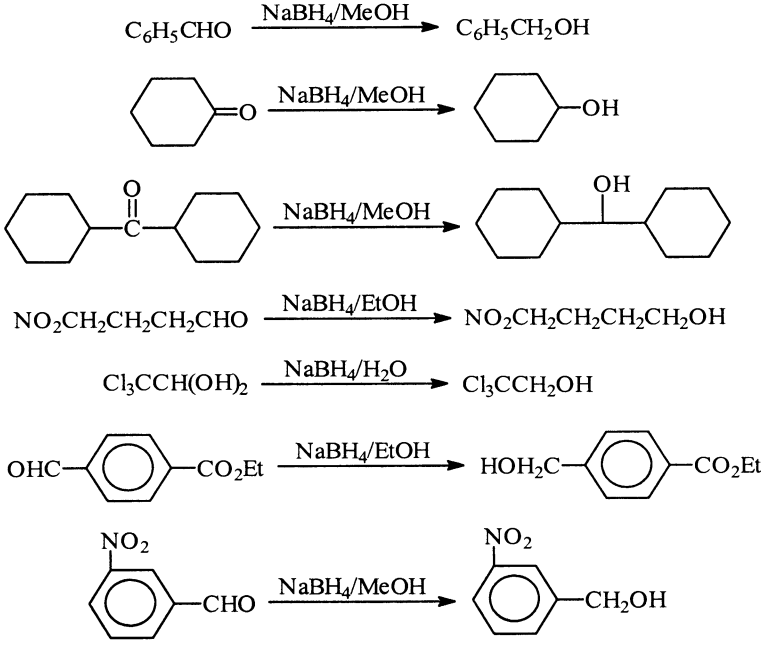
Scheme 99

In the above procedure (Scheme 99), the water acts both as a solvent as well as a reactant, and the amount of phosphine controls the cis/trans ratio of the formed alkenes since it catalyses the cis-trans olefin isomerisation.

12.15.4 Reduction of Carbonyl Compounds

A variety of reagents are available for the reduction of carbonyl compounds. Some of the common reagents are Na-C_2H_5OH, PtO_2/H_2, LAH, $NaBH_4$, Na_2BH_3CN, HCO_2H/EtMgBr, $(Et_2O)SiH.Me$, B_2H_6.[157]

Some of the more common reductions using $NaBH_4$ are given (Scheme 100).



Scheme 100

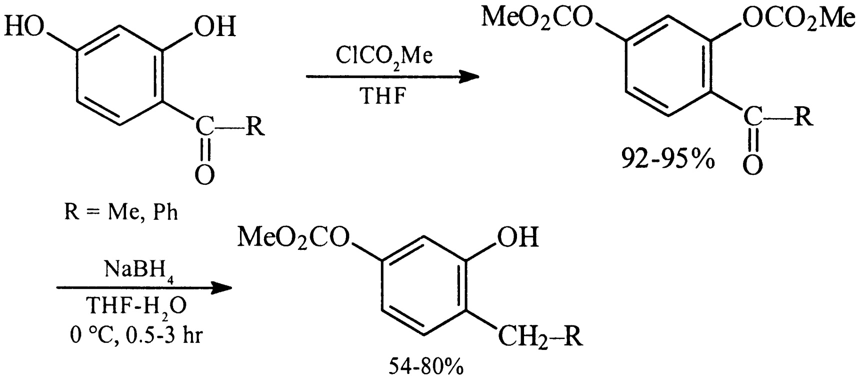
Using sodium borohydride in aqueous medium, 2-alkylresorcinols have been prepared (Scheme 101).[158]

The entire process (Scheme 101) could be carried out as one pot reaction.

The reduction of carbonyl compounds in aqueous media has been carried out by a number of reagents under mild conditions. The most frequently used reagent is sodium borohydride, which can also be used using phase-transfer catalysts[159] or inverse phase transfer catalyst[160] in a two phase medium in the presence of surfactants.

The carbonyl compounds can be quantitatively reduced regio- and stereoselectively by $NaBH_4$ at room temperature in aqueous solution containing glycosidic amphiphiles like methyl-β-D-glactoside, dodecanoyl-β-D-maltoside, sucrose etc.[161] By using this procedure, α,β-unsaturated ketones give

1,2-reduction product (corresponding allylic alcohols) and cyclohexanones give the more stable alcohol.



Scheme 101

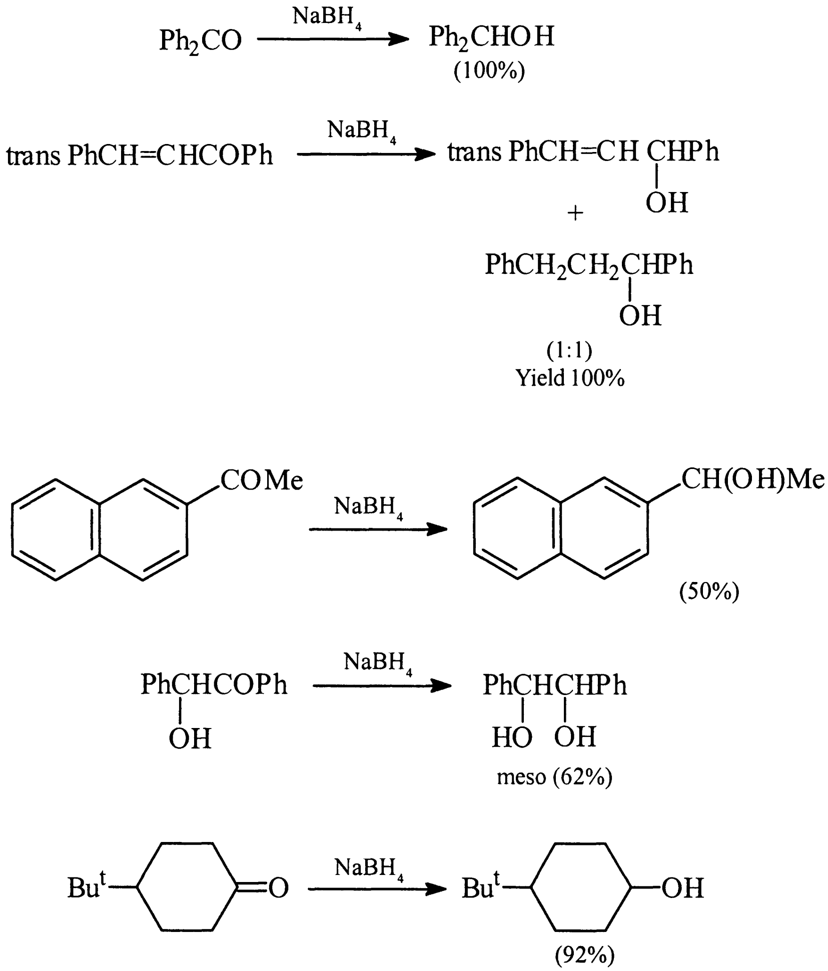
Reduction of ketones with $NaBH_4$ also proceeds in the solid state.[162] In this method a mixture of powdered ketone and 10-fold molar amount of $NaBH_4$ is kept in a dry box at room temperature with occasional mixing and grinding using an agate mortar and pestle for 5 days to give the reduced product. Following ketones were reduced by this procedure (Scheme 102).

Enantioselective hydrogenation of β-ketoesters has been achieved by using a ruthenium catalyst derived from (R,R)-1,2-bis(trans-2,5-diisopropylphospholano)ethane [(R,R)-i-Pr-PPE-Ru] to give β-hydroxy esters with high conversion and high ee under mild conditions (Scheme 103).[163]

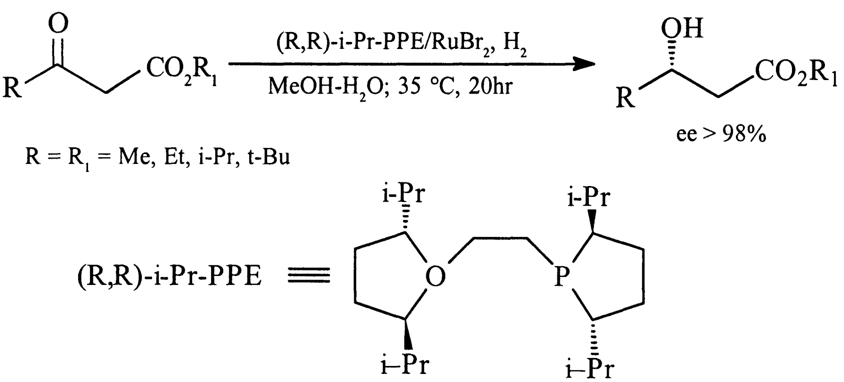
The reduction of aldehydes like benzaldehyde and p-tolualdehyde with Raney Ni in 10% aqueous NaOH give the corresponding benzyl alcohols in 17-80% yields[164] along with the corresponding carboxylic acids as byproducts obviously by cannizzaro reaction. It has been found that in aqueous $NaHCO_3$ under sonication conditions give the corresponding alcohols in good yields.

Another interesting reagent used for reduction of carbonyl compounds is cadmium chloride-magnisum in H_2O-THF system (Scheme 104).[165]

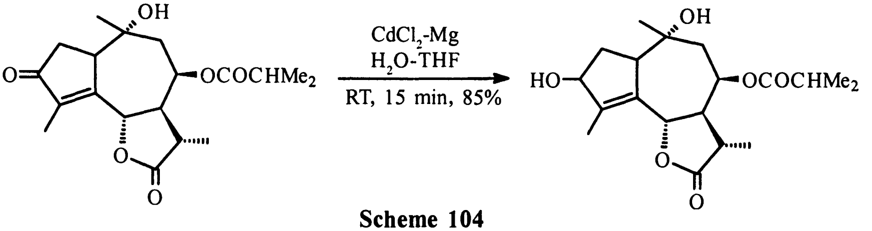
Certain other reagents like samarium iodide in aqueous THF[166], sodium dithionite in aqueous DMF[167], sodium sulfide in presence of polyethylene glycol[168] and metallic zinc along with nickel chloride.[169] Using the latter reagent ($Zn/NiCl_2$), α,β-unsaturated carbonyl compounds can be very readily reduced under ultrasound conditions[170] (Scheme 105).



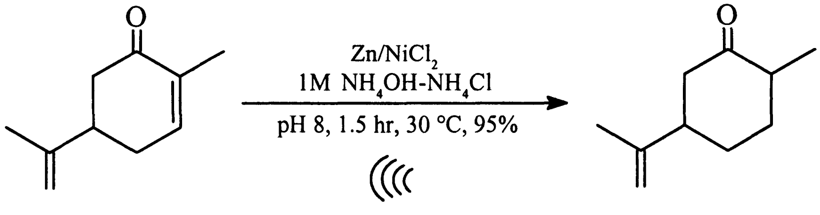
Scheme 102



Scheme 103

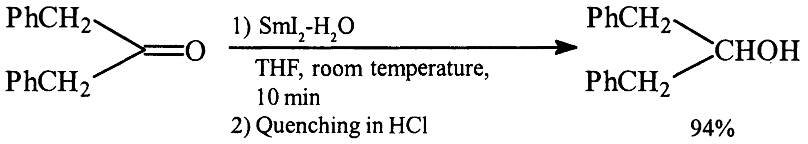


Scheme 104



Scheme 105

Ketones can also be reduced in an aqueous medium by SmI_2-H_2O[171] (Scheme 106).



Scheme 106

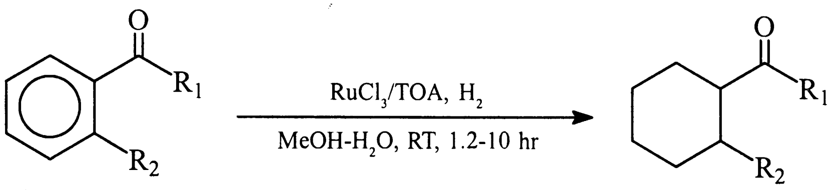
12.15.5 Reduction of Aromatic Ring

The hydrogenation of benzenoids to cyclohexane derivatives is very useful for various methodologies. Aromatic hydrocarbons require drastic conditions for reduction (for example $PtO_2/H_2/CH_3COOH$; Raney Ni/H_2/Pr/Δ, Rh-Al_2O_3/H_2).

It is now possible to reduce aromatic ring in aqueous medium at 50 atm of H_2 and at room temperature with ruthenium trichloride stabilized by trioctylamine ($RuCl_3$/TOA).[172] One such example is given (Scheme 107).

In the given procedure (Scheme 107) the rate of the reaction is 10-12 times the rate in organic solvent and in the aqueous medium, in comparison to cis, the trans isomer is the major product.

The heterocyclic compounds, viz. pyridine, 2-phenylpyridine and 3-methylpyridine can be reduced to the corresponding hexahydro product by Sm-20% HCl in 90-95% yields.[173] However in the reduction of 4-aminopyridine by the above method, the 4-amino group is eliminated giving piperidine as the major product (60%). The heterocyclic compounds can also be reduced in 70-94% yield by SmI_2-H_2O system at 0 °C for 2.5 hr.[174] Using this method 2-amino-, 2-chloro-, and 2-cyano-pyridine on reduction give piperidine, the substituent groups are eliminated.



R_1 = OMe, CO_2Me
R_2 = H, Me, NH_2

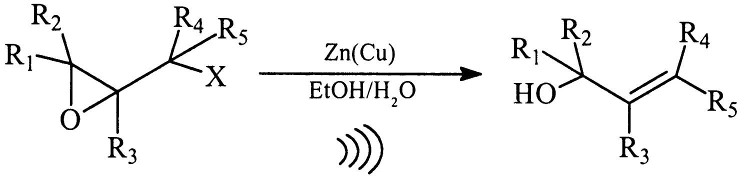
80-90%
cis-trans 6:15

Scheme 107

12.15.6 Miscellaneous Reductions

(i) Reductive removal of halogen from α-halocarbonyl compounds in aqueous medium can be effected by using sodium dithionite[175], zinc[176], chromous sulfate[177] and sodium iodide.[178]

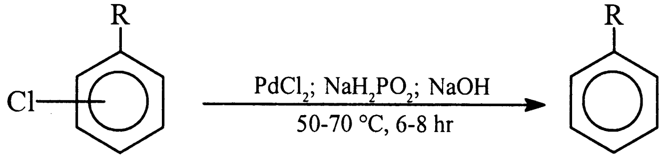
(ii) 2,3-Epoxyallyl halides can be transformed readily into allylic alcohol (Scheme 108) by zinc-copper couple in H_2O under sonication.



89-94%

Scheme 108

(iiii) Reductive dehalogenation in aryl halides can be effected in aqueous alkaline media in presence of $PdCl_2$ with NaH_2PO_2 as a hydrogen source (Scheme 109).[179]

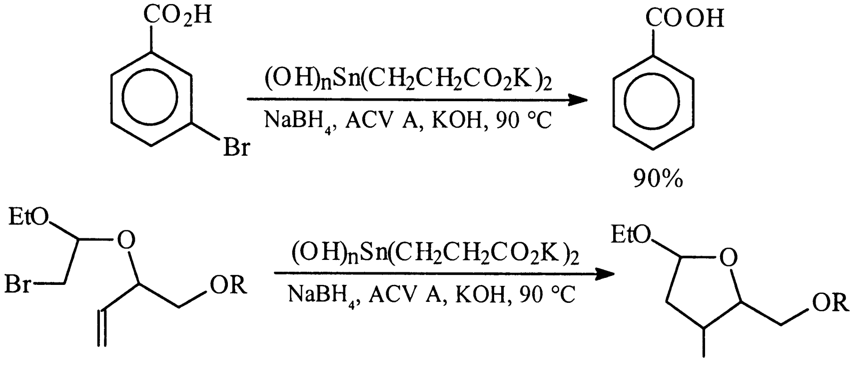


15-94%

Scheme 109

The above method (Scheme 109) does not work in case of nitrogen containing heterocyclic compounds and the yield in case of m-substituted aryl halides is low.

However, m-bromobenzoic acid can be converted into benzoic acid in 90% yield by using water soluble tris[3-(2-methoxyethoxy)propyl] stannane in presence of 4,4'-azobis (4-cyanovaleric acid) (ACVA) or sunlamp as initiator in aqueous $NaHCO_3$.[180] Above debromination can also be effected by using [bis(potassium propanoate)n (hydroxystannate), which in presence of $NaBH_4$ and ACVA affords reductions and free radical cyclisation of aryl and alkenyl bromides (Scheme 110).



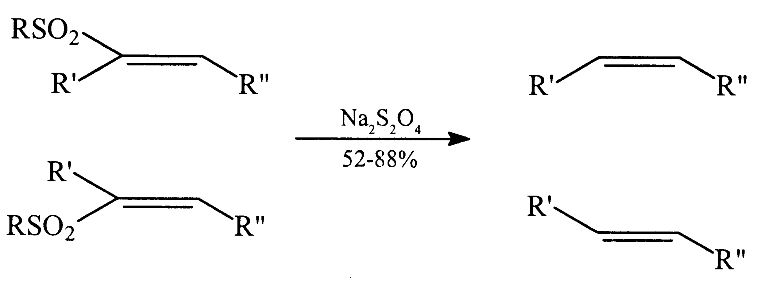
Scheme 110

The hydrogenolysis of halopyridines can be convenient when carried out with 15% aqueous $TiCl_4$ in presence of acetic acid.[181] Aqueous titanium trichloride quantitatively removes cyano group from cyanopyridines. Reductive dehalogenation is also catalysed by SmI_2.

(iv) Groups like azide, sulfoxide, disulphide, activated C=C bond and nitroxide can be effectively reduced by using sodium hydrogen telluride (NaTeH) (prepared *in situ* by the reaction of tellurium powder with aqueous ethanolic solution of $NaBH_4$).[182]

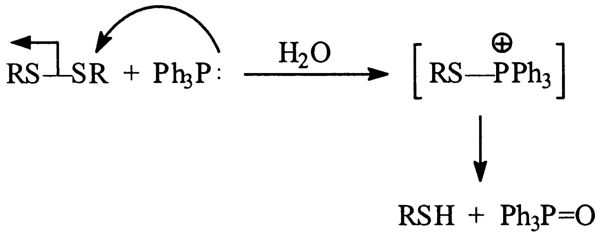
(v) Groups like aldehydes, ketones, olefins, nitroxides and azides can be reduced by sodium hypophosphite buffer solution.[183]

(vi) Vinyl sulphones can be stereospecifically reduced to the corresponding olefins with sodium dithionite in aqueous medium (Scheme 111).[184]



Scheme 111

(vi) Diaryl and dialkyl sulphides can be reduced by triphenylphosphine in aqueous solvents (Scheme 112).[185]



Scheme 112

12.16 Polymerisation Reactions

12.16.1 Polymers

It is well known that most of the polymers are not biodegradable. This problem can be approached in two ways. One way is to recycle the polymer and the other way is to convert it again into the monomers and recycle them again. However, the best way is to make polymers which are biodegradable.

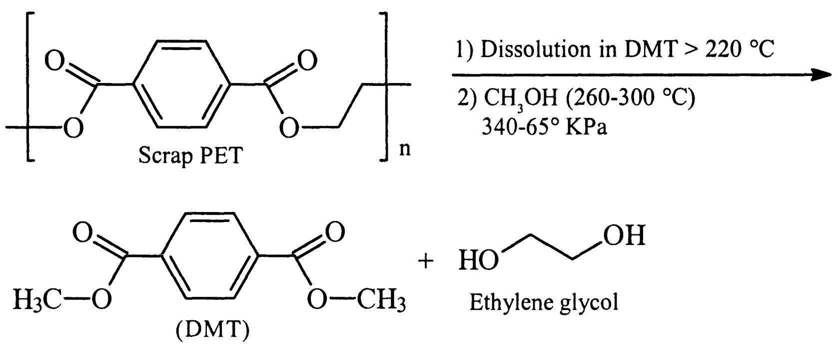
12.16.1.1 Recycling of Polymers

Let us now consider recycling, taking the example of the polyester, polyethyleneterephthalate (PET). It is known that PET is obtained by the polymerisation of dimethylterephthalate and ethylene glycol and is used in different products like beverage and food containers, nonfood containers, trays, luggage, boat parts, tapes etc. Fibres of PET are also used in clothing, carpets, blanckets, cord, rope etc. The recycled PET cannot be reused for food containers, as the impurities present are not sanitized at the temperature used in the melt process. Some of the products made of PET are mixtures with other polymers and contain dyes and other materials. These have to be disposed off by only incineration or land-filled. Also, during incineration the products obtained cause atmospheric pollution.

12.16.1.2 Conversion of PET Materials into Monomers

The process for the conversion of scrap PET into monomers is known as the Petrette process.[186] The flow sheet of the Petrette process for the recovery of monomers from PET scrap is given (Scheme 113).

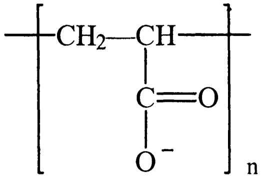
The monomers (DMT and ethylene glycol) are purified and again polymerised to give PET.



Scheme 113

12.16.1.3 To Make Polymers which are Biodegradable

One of the commonly used biodegradable polymer Thermal Polyaspartate polymer (TPA). Prior to the synthesis of TPA, polyacrylate polymer (PAC) was used as scale inhibitor in water handling processes. If not inhibited, the scale formation lead to loss of energy, non-functioning of pumps, boilers and condensers.



PAC

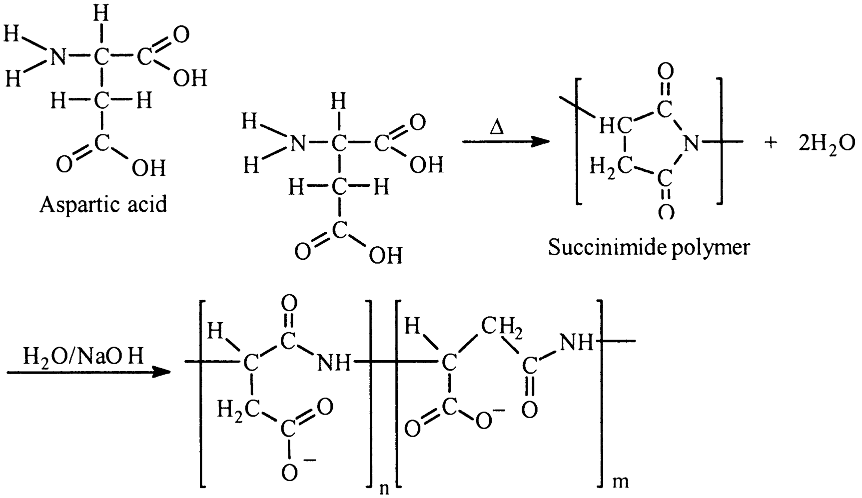
Though PAC is relatively non-toxic and environmentally benign, it is not biodegradable. This causes a disposal problem in waste water treatment facilities, where the PAC must be removed and land filled. The problem for it's disposal has been solved by Donlar Corporation, which has developed a method for the production of TPA (thermal polyaspartate), a biodegerable alternative to PAC.[187] The Donlar's synthesis[188] consists of heating the aspartic acid followed by hydrolysing the formed succinimide polymer with aqueous base (Scheme 114).

The above synthesis is 'green' because it uses no organic solvent, produces little or no waste and the yield is better than 97%.

12.16.1.4 Manufacture of Polycarbonates

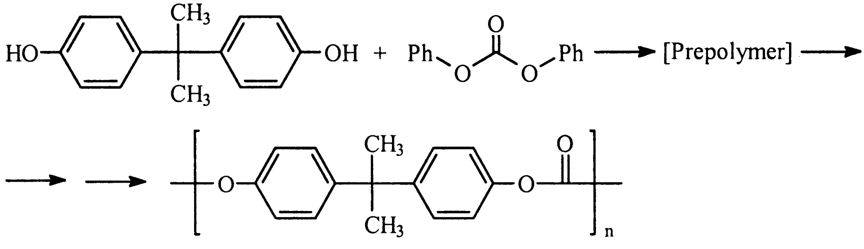
Polycarbonates were earlier prepared by the polymerisation of phenols (e.g., bisphenol-A) using phosgene and methylene chloride. A new process has been developed by Asahi Chemical Industries using solid state polymerisation[189] for producing polycarbonate without phosgene and methylene chloride.[190]

In this process bisphenol-A and diphenyl carbonate directly give low molecular weight prepolymers, which are converted into high molecular weight polymers by crystallisation followed by further polymerisation (Scheme 115).



(TPA)

Scheme 114

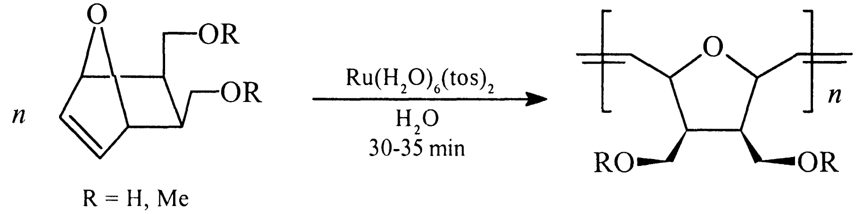


Polycarbonate

Scheme 115

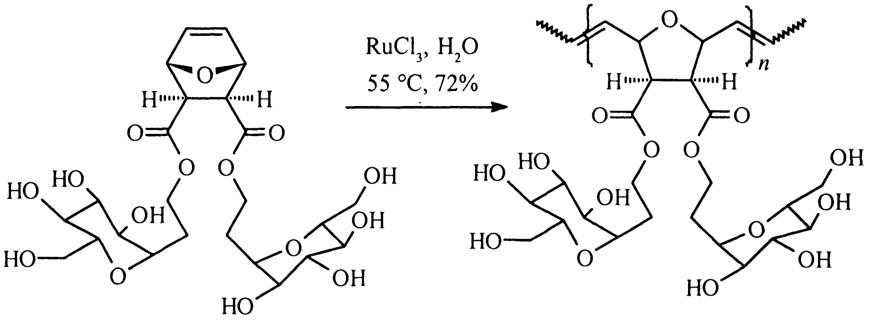
12.16.1.5 Emulsion Polymerisation

Earlier attempts at emulsion polymerization of norbornenes in aqueous solution using iridium complexes as catalysts gave poor yields (10%).[190] However, it was subsequently found that 7-oxaborane derivatives could be rapidly polymerised in aqueous solution in presence of air using some group VIII coordination complexes as catalysts giving a quantitative yield of a ring-opening metathesis polymerisation product (Scheme 116).[191]



Scheme 116

Using the above methodology norbornene could also be polymerised.[192,193] The ruthenium catalyst required for the above polymerisation were obtained by the procedure of Berhard-Ludi.[194] The aqueous catalyst solution could be reused; it was found to be more active. Another Ru(IV) catalyst[195] could also be used for emulsion ring-opening polymerisation of norbornene. The polymers obtained by the later catalysts had very high molecular wieght and had high cis-selectivity. Using this method, neogylcopolymers were synthesised (Scheme 117).

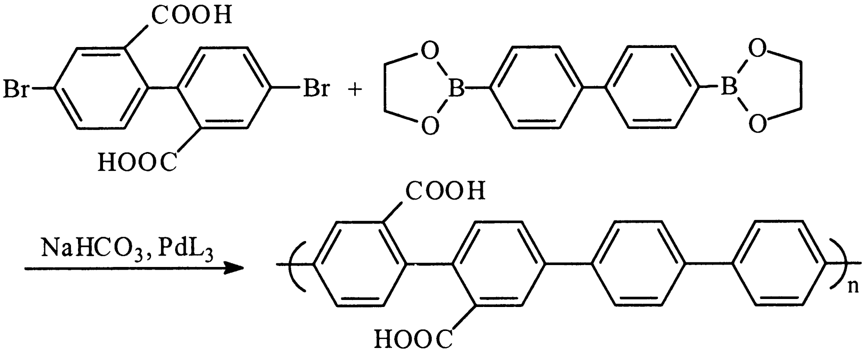


Scheme 117

A non-metallic conducting polymer was synthesised (Scheme 118).[196]

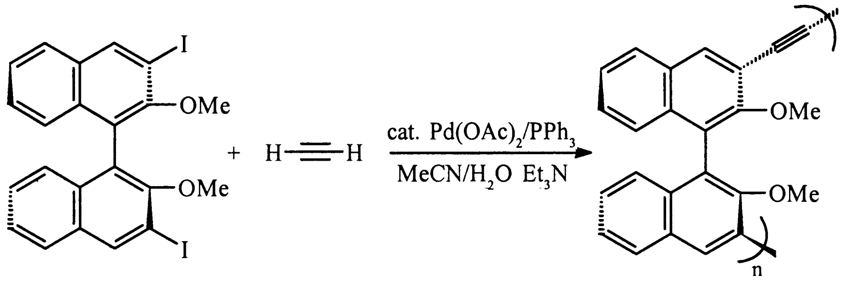
A helical polymer was prepared by using palladium-catalysed coupling between aryl halides with acetylene gas (Scheme 119).[197]

Solid state polymerisation of α-amino acids has been achieved giving rise to high molecular weight polypeptides.



L = $P(C_6H_5)_2(m\text{-}C_6H_4SO_3Na)$

Scheme 118

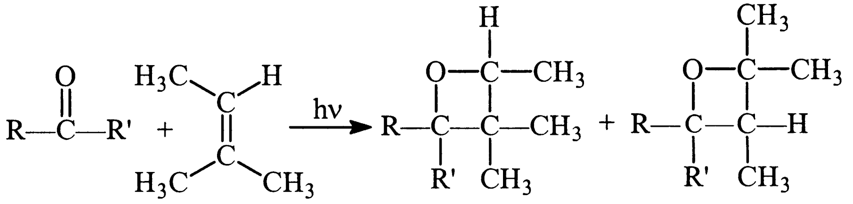


Scheme 119

12.17 Photochemical Reactions

The importance of photochemical reactions can hardly be overemphasized. The earliest known photochemical reaction is the photosynthesis of sugars by plants using sunlight, CO_2 and H_2O in presence of chlorophyll. Some of the common examples of routine photochemical reactions are:

(i) Photochemical cycloaddition of carbonyl compounds and olefins (Paterno-Buchi reaction) to give four membered ether rings (Scheme 120).[198]



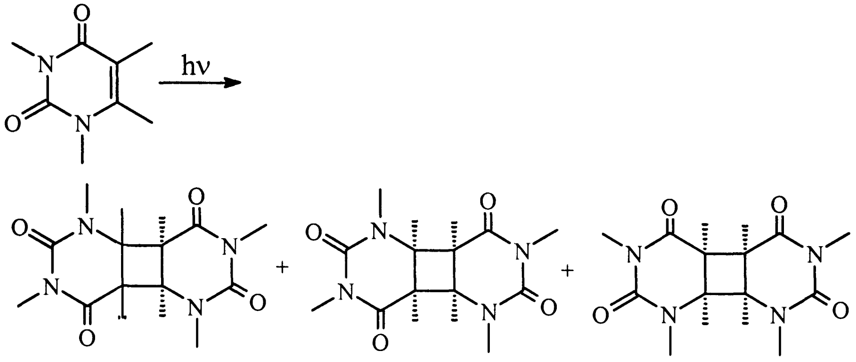
Scheme 120

(ii) Photo fries rearrangements. The phenolic esters in solution on photolysis give a mixture of o- and p-acylphenols.[199]

There are numerous other examples. Most of the photochemical reaction are carried out in solvents like benzene.

In view of the scare of the medium dependence of photochemical reactions, attempts were made for carrying out the reactions in water as a solvent.[200]

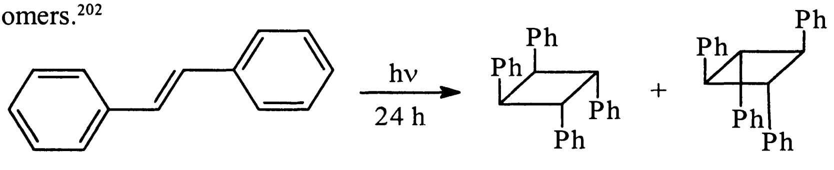
It has been reported in 1980's that the photochemical reactions can be conveniently carried out in aqueous phase. Thus, the photodimerisation of thymine, uracil and their derivatives could be carried out in water giving considerably better yields than in other organic solvents (Scheme 121).[201]



Water	27.8%	63.1%	9.1%	ø = 0.015
Acetonitrile	24.9%	68.2%	6.7%	ø = 0.0047
Methanol	31.4%	68.6%	–	ø = 0.004

Scheme 121. Data taken from reference 201

Organic substrates having poor solubility in water (e.g., stilbenes and alkyl cinnamates) also photodimerize efficiently in water (Scheme 122). The same reaction in organic solvents such as benzene gives mainly cis-trans isomers.[202]



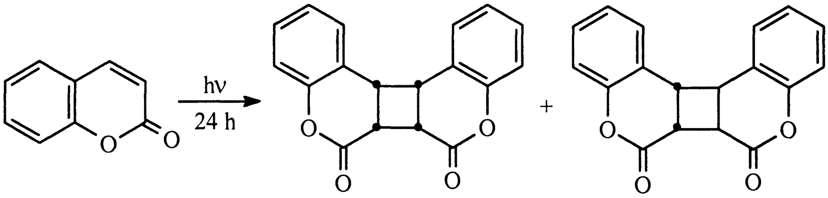
Benzene	0%	0%
Water	12%	10%
Water + LiCl	25%	17%
Water + guanidinium chloride	8%	6%

Scheme 122. Data taken from reference 202

The addition of LiCl (decreasing the hydrophobic effect) increases the yield of dimerisation (Scheme 122), whereas the addition of guanidinum chloride (decreasing the hydrophobic effect) lowers the yield of the product.

Similar results were obtained with alkyl cinnamates.[203]

An interesting example is the photodimerisation of coumarin in water (Scheme 123).



Solvent	Quantum Yield
Benzene	$< 10^{-5}$
Methanol	$< 10^{-5}$
Water	2×10^{-3}

Scheme 123

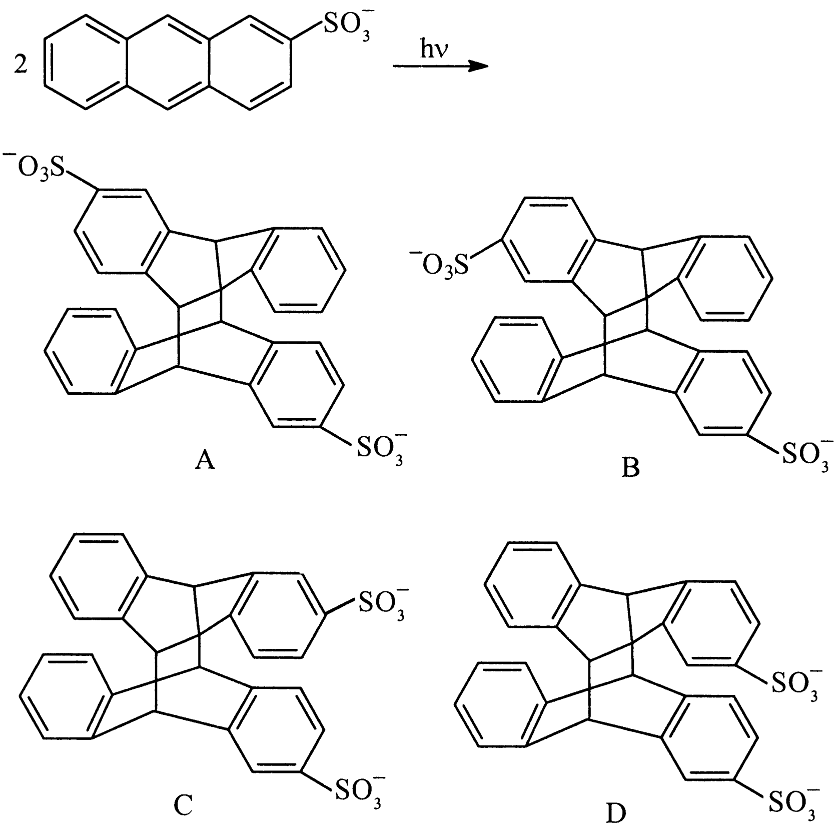
The yield of the dimerisation of coumarin in water (Scheme 123) is 100 times more than that in benzene or methanol.

It has been found that the micelles (formed by carrying out the reaction in presence of a surfactant/water) have a pronounced effect on regio- and stereoselectivity of photochemical reactions.

The photodimerisation of anthracene-2-sulphonate in water gives four products A, B, C, D (Scheme 124). However, if the reaction is carried out in presence of β-cyclodextrin, only the isomer A is obtained.[204] Some other examples of photochemical reactions are:

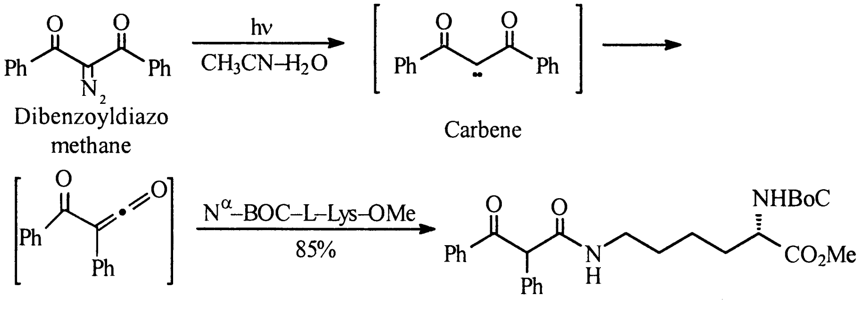
(i) Photoirradiation of dibenzoyldiazomethane in $CH_3CN–H_2O$ in presence of an amino acid derivative gave the addition product (Scheme 125) via the formation of a carbene.[205]

(ii) The photoirridation of o-fluoroanisole in $KCN-H_2O$ gave o-substitution product (catechol monomethyl ether) as the major product along with o-cyanoanisole as the minor product. Similar reaction with p- fluoroanisole gave p-cyanoanisole as the major product along with amount minor of hydroquinol monomethyl ether (Scheme 126).[206]

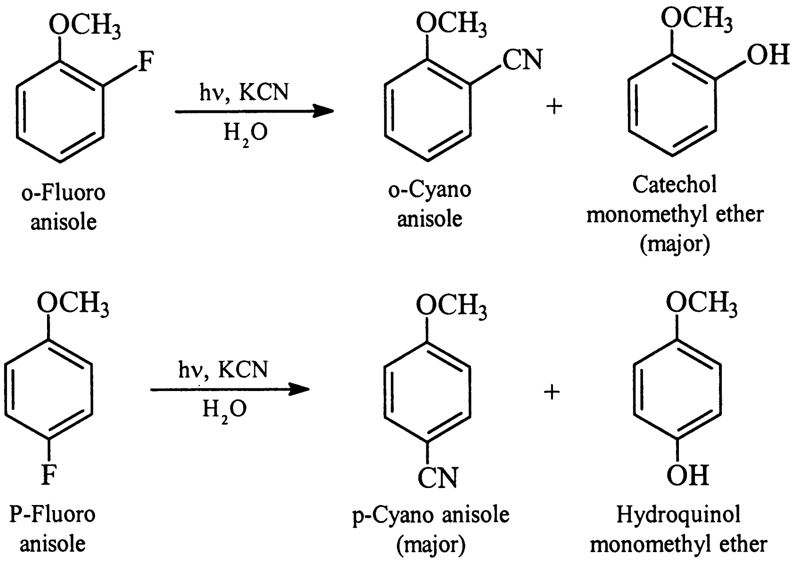


Medium	Product (A : B : C : D)
Water	1 : 0.8 : 0.4 : 0.05
Water + β-CD	A only

Scheme 124. Data taken from reference 201



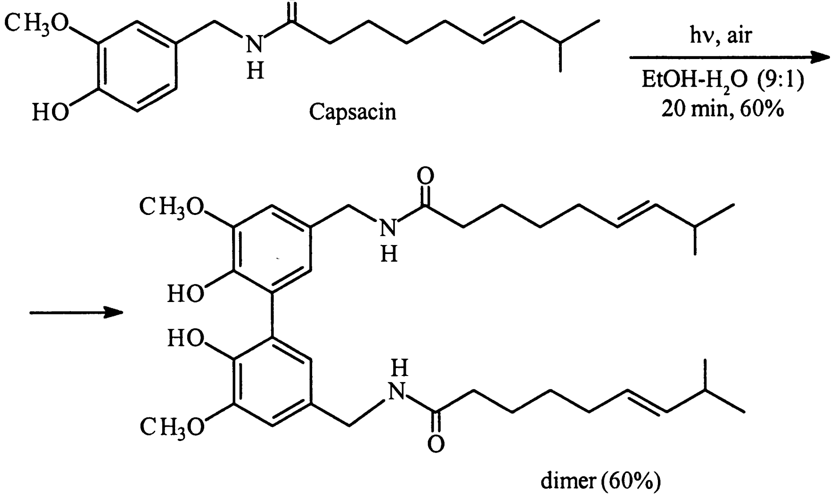
Scheme 125



Scheme 126

In the above reaction (Scheme 126), the use of water influences the chemoselectivity in photochemical substitution reactions.

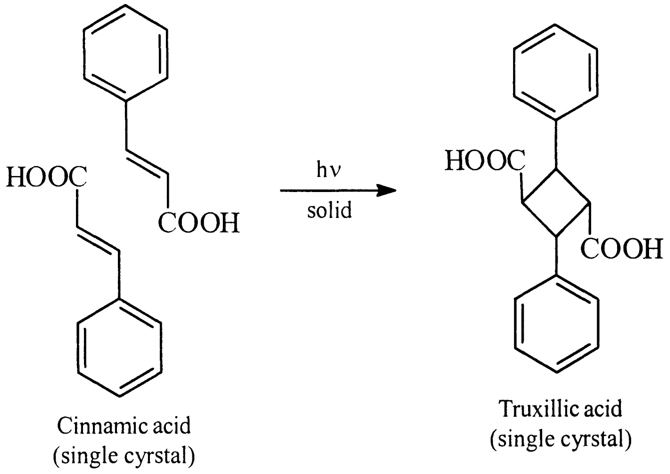
(iii) Photochemical oxidative dimerisation of capsacin in aqueous ethanol gave dimer in 60% yield within 20 min of irradiation (Scheme 127).[207]



Scheme 127

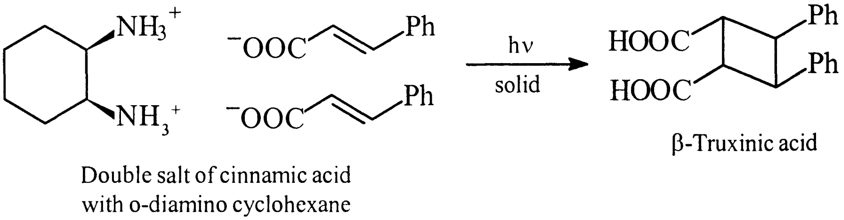
(iv) Photooxidation of phenol is of interest in environmental chemistry.[208]

Photochemical reactions have also been studied in solid state. Thus the photodimerisation of cinnamic acid to truxillic acid has been achieved in the solid state (Scheme 128).[209]



Scheme 128

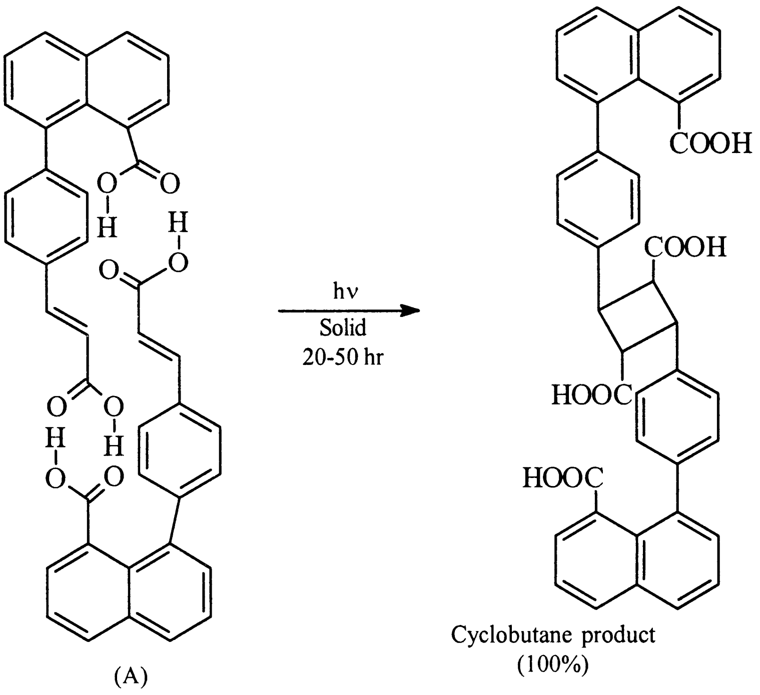
The photodimerisation of cinnamic acid can be controlled by irradiation of its double salts with certain diamines in the solid state. Thus, the double salt crystal of cinnamic acid and o-diaminocyclohexane gave upon irradiation in the solid state, β-truxinic acid as the major product (Scheme 129).[210]



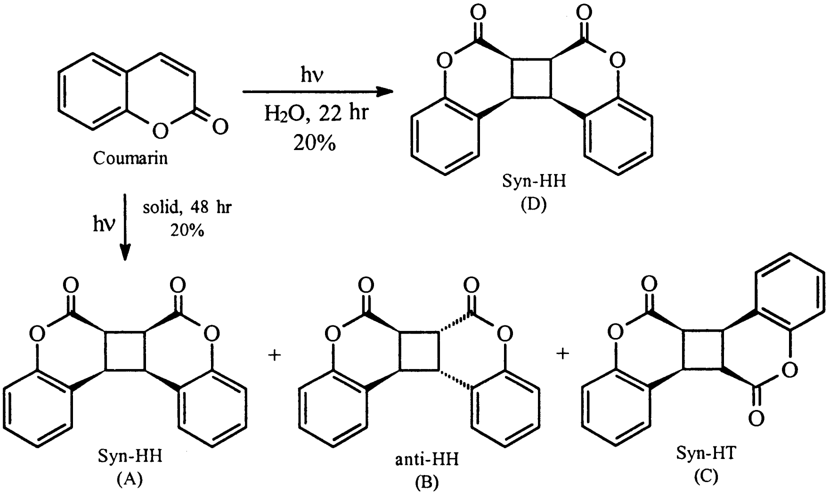
Scheme 129

Similar irradiation of naphthoic acid-derived cinnamic acid (A) in solid state on irradiation for 20-50 hr afforded a single cyclobutane product in 100% yield (Scheme 130).[211]

The photocyclisation of coumarin and its derivatives has been extensively studied.[212] Thus, irradiation of coumarin for 48 hr in the solid state gives a mixture of A, B and C in 20% yields. However, irradiation of an aqueous solution of coumarin for 22 hr affords only the syn-head to head dimer (D) in 20% yield (Scheme 131).

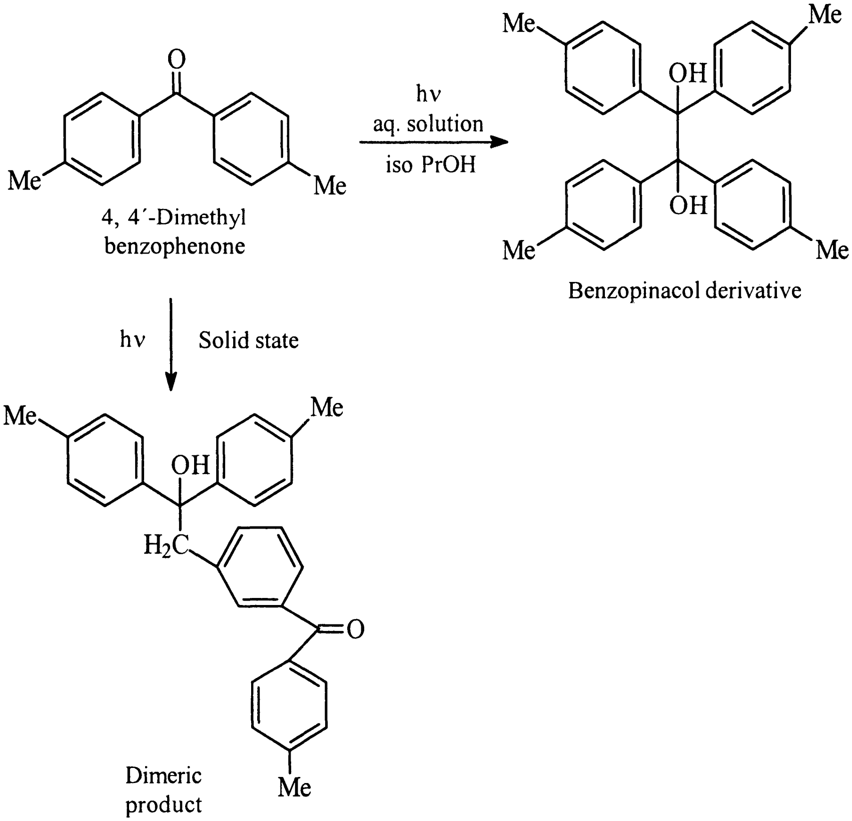


Scheme 130



Scheme 131

It is well recorded that benzopinacol can be obtained quantitatively on photoirradiation of 4,4'-dimethyl benzophenone in isopropylalcohol. However, in the solid state photoirradiation gives the dimeric compound (Scheme 132).[213] Besides the representative example of photochemical reactions in solid phase a large number of illustrations are available.[214]



Scheme 132

12.18 Electrochemical Synthesis

12.18.1 Introduction

The earliest electrochemical synthesis is the so-called Kolbe reaction involving the oxidation of carboxylic acids in forming decarboxylated coupling products (alkanes). At present, the electrochemical synthesis has become an independent discipline. A large number of organic reactions (synthesis) have been achieved by this technique. The essential requirement for conducting an electrochemical reaction is the conductivity of the reaction medium. The most commonly used solvent is water, though organic solvents have also been used. However, there is a distinct advantage in using aqueous solutions over organic solvents.[215] In case of organic solvents, during electrolysis, a complex mixture of products get accumulated in the electrolyte, which leads to loss of expensive solvent. On the other hand, electrolysis of water yield O_2/H^+ and H_2/OH^-. In view of this, the electrolysis of water can be performed at a maintained level of pH without contaminating the electrolytic system.

The electrochemical synthesis are of two types: anodic oxidative processes and cathodic reductive processes. During anodic oxidative processes, the organic compounds are oxidised. The nature of the product of anodic oxidation depends on the solvent used, pH of the medium and oxidation potential.

In cathodic reductive processes, the cathode of electrolysis provide an electron source for the reduction of organic compounds. Generally the rate of reduction increases with the acidity of the medium. Electroreduction of unsaturated compounds in water or aqueous-organic mixtures give reduced products — this process is equivalent to catalytic hydrogenation.

An electrochemical process uses a anode made of metal that resists oxidation, such as lead, nickel or most frequently platinum. The anode is usually in the shape of a cylinder made of wire guage. The usual electrolytes are dilute sulphuric acid or sodium methoxide prepared *in situ* from methanol and sodium. The direct current voltage is 3-100 V, the current density is 10-20 A/dm^3, and the temperature of the medium is 20-80 °C.

Electrochemical reactions are practically as diverse as non-electrochemical reactions. Thus, the combination of electrochemical reactions with catalysts (electrochemical catalytic process), enzymatic chemistry (electroenzymatic reactions) are quite common. The readers may refer to the following references:

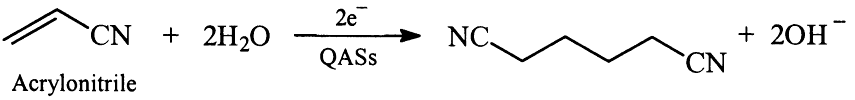
- A.N. Frumkin, in Advances in Electrochemistry and Electrochemical Engineering, P. Delahay and C.W. Tobias, eds., Interscience, New York, Vol. 3.
- Topics in Current Chemistry, E. Steckhan, ed., Springer-Verlag, Berlin, 1987, Vol. 142.
- E. Steckhan, in Topics in Current Chemistry, E. Steckhan, ed., Springer-Verlag, Berlin, Vol. 170.
- D.K. Kyriacou, Basics of Electroorganic Synthesis, Wiley, New York, 1981.
- H. Lund and M.M. Baizer, eds., Organic electrochemistry, Marcel Dekker, New York, 1991.

Following are given some representative examples of electrochemical synthesis.

12.18.2 Synthesis of Adiponitrile

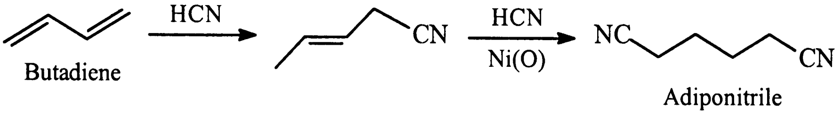
Adiponitrile is used as an important synthon for hexamethylene diamine and adipic acid, which are used for the manufacture of Nylon-66.

It is obtained commercially by the electroreductive coupling of acrylonitrile. By this process about 90% of adiponitrile is obtained.[216] In this process a concentrated solution of certain quaternary ammonium salts (QASs), such as tetraethylammonium-p-toluene sulfonate is used together with lead or mercury cathode (Scheme 133).



Scheme 133

It will be appropriate to mention here that selective hydrocyanation of butadiene catalysed by Ni(O)/triarylphosphite complexes give adiponitrile (Scheme 134).[217]



Scheme 134

12.18.3 Synthesis of Sebacic Acid

Sebacic acid is an important intermediate in the manufacture of polyamide resins. It is obtained on a large scale by saponification of castor oil.[218] It is now obtained by electrochemical process involving the following three steps (Scheme 135).

$$\underset{\text{Adipic acid}}{HO_2C{-}(CH_2)_4CO_2H} \xrightarrow[\text{esterification}]{CH_3OH} \underset{\text{Monomethyl ester of adipic acid}}{CH_3O_2C(CH_2)_4CO_2H} \longrightarrow$$

$$\xrightarrow[55\ ^\circ C]{\text{Electrolysis}} \underset{\text{Dimethyl ester of sebacic acid}}{CH_3O_2C(CH_2)_8CO_2CH_3} \xrightarrow{\text{Hydrolysis}} \underset{\text{Sebacic acid}}{HO_2C(CH_2)_8CO_2H}$$

Scheme 135

In the above process, anodic coupling of the monomethyl ester of adipic acid takes place. The electrolyte is a 20% aqueous solution of monomethyl adipate, neutralised with sodium hydroxide. The anode is platinum-plated with titanium and the cathode is of steel.

12.18.4 Miscellaneous Electrochemical Reactions

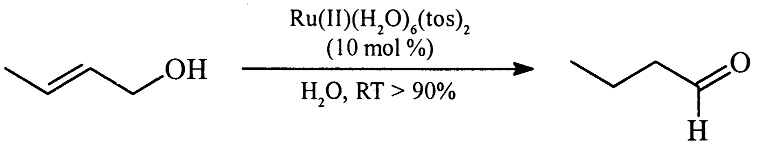
(i) Electrochemical reduction of glucose for the manufacture of sorbitol and mannitol.[220]

(ii) Electrochemical reduction of phthalic acid to the corresponding dihydrophthalic acids.[221]
(iii) Electrochemical coupling of acetone to yield pinacol.[222]
(iv) Electrochemical oxidation of 1,4-butynediol to acetylene dicarboxylic acid.[223]
(v) Electrochemical oxidation of furfural to maltol.[224]
(vi) Electrochemical epoxidation of alkenes.[225]
(vii) Electrochemical conversion of alkenes into ketones.[226]
(viii) Electrochemical oxidation of aromatic rings and side chains to carboxylic acids.[227]
(ix) Electrochemical oxidation of primary alcohols to carboxylic acids.[228]
(x) Electrochemical oxidation of secondary alcohols to ketones.[229]
(xi) Electrochemical oxidation of vicinal diols to carboxylic acids.[230]
(xii) Electrochemical hydroxylation or dehydrogenative coupling of phenols.[231]
(xiii) Electrochemical Kolbe synthesis of hydrocarbons.[232]

12.19 Miscellaneous Reactions in Aqueous Phase

12.19.1 Isomerisation of Alkenes

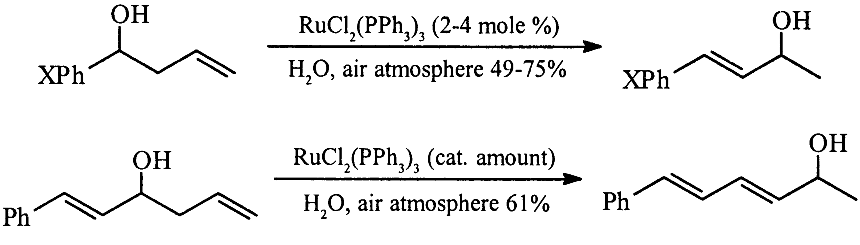
Alkenes are known to isomerise in presence of transition metal complexes. It has been found that isomerisation of allylic alcohols (or ethers) can be performed in aqueous media in presence of Ru(II)(H_2O)$_6$(tos)$_2$ (tos = p-toluene sulfonate) (Scheme 136).[233]



Scheme 136

In the above reaction the initially formed enols and enolethers are unstable and are instantaneously hydrolysed to give the corresponding carbonyl compounds.

Some other examples are given as follows (Scheme 137).[234]



Scheme 137

In both the given examples (Scheme 137) the substrates undergo structural reorganisation involving reshuffling of both the hydroxyl group and the olefin in water. These reactions can be considered as olefin migration followed by an allylic rearrangement.

12.19.2 Carbonylation

Carbonylation is a very important process for the preparation of carboxylic acids (and their derivatives), aldehydes and ketones. It was earlier carried out in presence of transition metal catalysts.[235]

The aryl halides can be converted into the corresponding carboxylic acid by carbonylation in presence of water. The use of PTC is a well established technique for carbonylation of organic halides.[236] Carbonylation of organic halides using various types of phase transfer techniques has been extensively reviewed.[237]

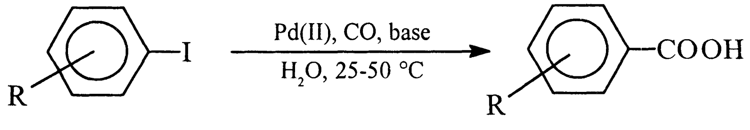
Aryl halides can be carbonylated to give the corresponding carboxylic acids (Scheme 138) under very mild conditions in presence of inorganic bases (like alkaline metal hydroxides, carbonates, acetates etc.) and certain palladium catalysts (like $Pd(OAc)_2$, K_2PdCl, $Pd(NH_3)_4Cl$, $PdCl_2(PPh_3)_2$ etc.). Best results are obtained with simple palladium salt using K_2CO_3 as base (Scheme 138).

$$\mathrm{ArX} \xrightarrow[\mathrm{DMF\text{-}H_2O\ (2:1)\ 25\text{-}50\ ^\circ C}]{\mathrm{Pd(OAc)_2\ (1\ mole\ \%),\ CO,\ K_2CO_3}} \mathrm{ArCOOH}$$

$Ar = p\text{-}ZC_6H_4$ ($Z = NO_2$, Cl, CN, Me, NH_2 etc.)

Scheme 138

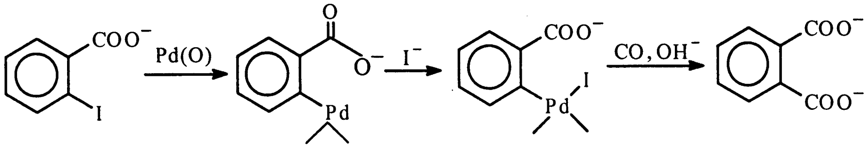
Water soluble aryl iodides can be carbonylated in H_2O in presence of soluble palladium salt or complexes and K_2CO_3 as base at 25-50 °C (Scheme 139).



R = m-, p–COOH
o-, m-, p–OH

Scheme 139

Ortho-iodobenzoic acid cannot be carbonylated under the above conditions (Scheme 139). It, can, however be carbonylated in presence of excess iodide ion to give phthalic acid (Scheme 140).



Scheme 140

In case of water insoluble aryl iodides, the iodine atom is first oxidized to the iodyl group by $NaClO_3$, the formed iodyl derivative (having slightly enhanced solubility in water) are readily carbonylated under mild conditions to give carboxylic acids (Scheme 141).[238]

$$\mathrm{ArI} \xrightarrow{NaClO_3} \mathrm{ArIO_2} \xrightarrow[\text{CO (1 atm), } H_2O\text{, 40-50 °C}]{Na_2PdCl_4\text{, NaOH}} \mathrm{ArCOOH}$$

Scheme 141

Carbonylation of allylic and benzylic chlorides was carried out by transition-metals (as catalysis) to give β,γ-unsaturated acids.[239] However, the above method gave low yields. It is found that carbonylation of benzyl bromide and chloride could be carried out by stirring with an aqueous sodium hydroxide and an organic solvent using a PTC and a cobalt catalyst. Even benzylic mercaptan could be carbonylated to give esters under high pressure and temperature (Scheme 142).[240]

$$\mathrm{PhCH_2X} \xrightarrow[\text{PTC}]{[Co(CO)_4]^-\text{ aq. NaOH}} \mathrm{PhCH_2CO_2Na}$$

X = Cl or Br

$$\mathrm{ArCH_2SH + CO + R'OH} \xrightarrow[\substack{\text{850-900 psi (lb/in}^2\text{)} \\ \text{190 °C, 24 hr, 25-83\%}}]{Co_2(CO)_8\text{, } H_2O} \mathrm{ArCH_2COOR'}$$

Scheme 142

Carbonylation of allyl bromides and chlorides has been achieved in presence of a nickel catalyst in aqueous NaOH at atmospheric pressure.[241] Subsequently it is found that Palladium-catalysed carbonylation of allyl chloride proceeded smoothly in two-phase aqueous NaOH/benzene under atmospheric pressure at room temperature (Scheme 143).[242]

$$CH_2{=}CHCH_2Cl + CO + ROH \xrightarrow[19\text{-}98\%]{Pd} CH_2{=}CHCH_2COOR$$

$R = H, CH_3, C_2H_5$ etc.

Scheme 143

In the above method shown in Scheme 143, addition of surfactants (e.g., $n\text{-}C_7H_{15}SO_3Na$ or $n\text{-}C_7H_{15}CO_2Na$) accelerate the carbonylation.[243]

Some other carbonylation reactions are:

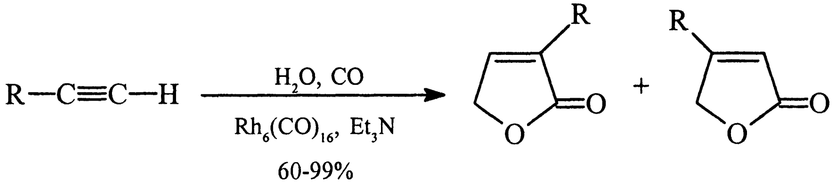
(i) Carbonylation of 1-perfluoroalkyl-substituted 2-iodoalkanes in presence of transition metal catalysts in aqueous media give β-perfluoroalkyl carboxylic acid (Scheme 144).[244]

$$R_f\text{–}CH_2CHR'I + CO + H_2O \xrightarrow[\text{base } 42\text{-}89\%]{\text{Pd, Co, or Rh cat.}} R_f\text{–}CH_2CHR'CO_2H$$

R_f= perfluoroalkyl group

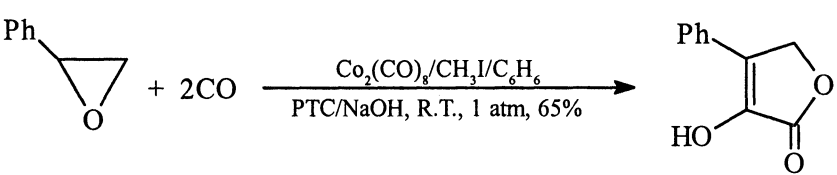
Scheme 144

(ii) γ-Lactones have been obtained by the carbonylation of terminal alkynes in water in presence of rhodium carbonyl (Scheme 145).[245]



Scheme 145

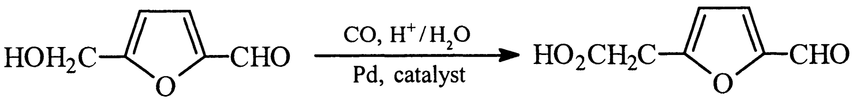
(iii) The reaction of styrene oxide with carbon monoxide is catalysed by a cobalt complex in presence of methyl iodide to give enol (Scheme 146).[246]



Scheme 146

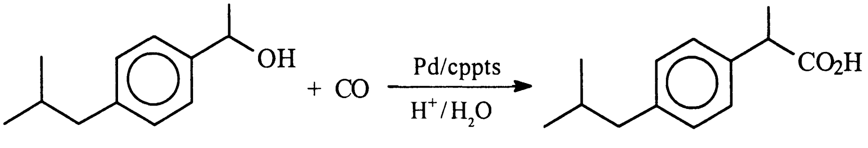
(iv) Carbonylation of methane under acidic conditions by oxygen and CO in water, catalysed by palladium, platinum or rhodium catalysts gives acetic acid.[247]

(v) 5-Hydroxymethyl furfural can be selectively carbonylated to the corresponding acid by using a water soluble palladium catalyst (Scheme 147).[248]



Scheme 147

(vi) Carbonylation of 1-(4-isobutylphenyl)ethanol gives ibuprofen (Scheme 148).[249]



Ibuprofen

Scheme 148

12.19.3 Hydroformylation of Olefins

Hydroformylation of olefins is a chief industrial process for the manufacture of aldehydes and alcohols by reaction with CO and H_2 in presence of a catalyst.[250]

Carbon monoxide and hydrogen have been known to be used for the manufacture of methyl alcohol. Also, the first product to be manufactured by the hydroformylation of propene is butyraldehyde (Scheme 149).[251]

$$\underset{}{CO + H_2} \xrightarrow[300\ ^\circ C]{ZnO,\ CrO_3} \underset{\text{Methyl alcohol}}{CH_3OH}$$

$$\underset{\text{Propene}}{CH_3CH{=}CH_2} + CO + H_2 \xrightarrow[\text{catalyst}]{\text{Rhodium}} \underset{\text{Butyraldehyde}}{CH_3CH_2CH_2CHO}$$

Scheme 149

A number of catalysts were tried for the hydroformylation of olefins. Main among these are:

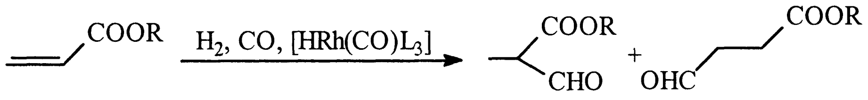
(i) Rhodium combined with phosphorus ligand

(ii) Attachment of a normally soluble catalyst to an insoluble polymer support.

(iii) Transition-metal complexes with water soluble phosphine ligands and water as immiscible solvent for the hydroformylation. Most of the catalysts had a problem arising out of leaching of the catalyst into the organic phase.

Finally a variety of 1-alkenes were hydroformylated with a highly water-soluble tris-sulphonated ligand, P(m-$PhSO_3Na$).[252] Some more effective catalysts involving the use of other sulphonated phosphine ligands have also been developed.[253]

Another unique approach is the concept of support aqueous phase (SAP) catalysis.[254] In this approach, a thin, aqueous film containing a water soluble catalyst adheres to silica gel with a high surface area. The reaction occurs at the liquid-liquid interface. Using this technique, hydroformylation of alkenes like octene, dicyclopentadiene is possible. Through SAP approach, hydroformylation of acrylic acid derivatives is of considerable industrial applications (Scheme 150).[255]

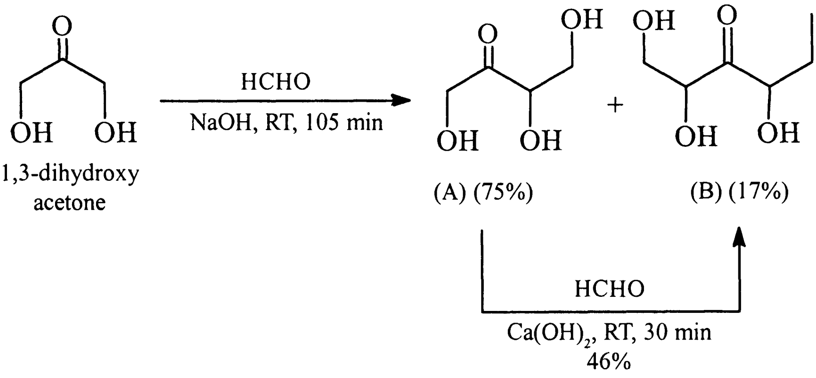


Scheme 150

The major product obtained (Scheme 150) is formylpropionic acids, which are precursors of methacrylate monomers and can be used for a number of important pharmaceuticals. A number of other applications of hydroformylation have been reviewed.[256]

12.19.4 Homologation of 1,3-dihydroxyacetone

In aqueous medium, it is not necessary to protect functional groups. Thus homologation of 1,3-dihydroxyacetone with formaldehyde in presence of base gives the homologated derivatives A and B (Scheme 151).[257]



Scheme 151

The above reaction is known as Tollens reaction.

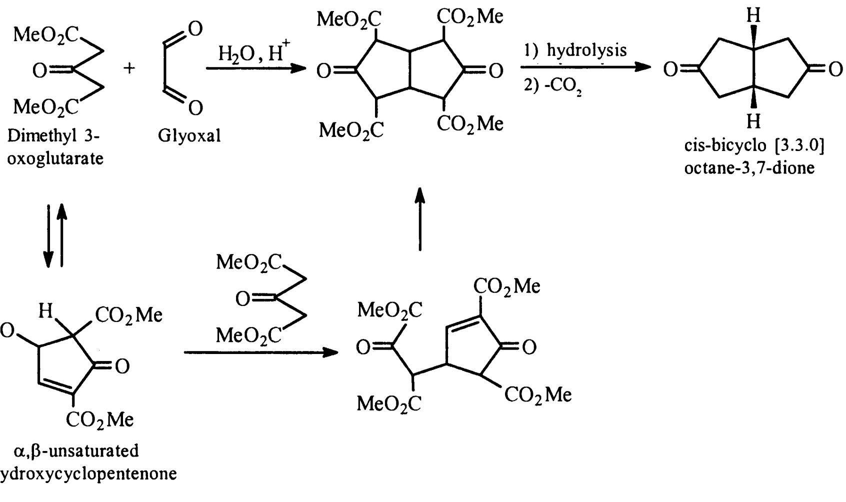
12.19.5 Weiss-Cook Reaction

The reaction of dimethyl 3-oxoglutarate with glyoxal in aqueous acidic solution gives [3.3.0] octane, 3,7-dione-2,4,6,8-tetracarboxylate; and on acid catalysed hydrolysis followed by decarboxylation it gives cis-bicyclo[3.3.0] octane-3,7-dione (Scheme 152).[258] The reaction is believed to involve a double Knoevenagal reaction that gives an α,β-unsaturated γ-hydroxycyclopentenone, which reacts with another molecule of dimethyl 3-oxoglutarate by Michael addition.

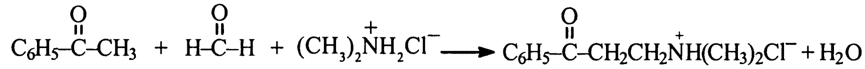
12.19.6 Mannich Type Reactions

The original Mannich reaction consisted in the reaction of a compound containing at least one active hydrogen atom (ketones, nitroalkanes, β-ketoesters, β-cyano acids etc.) with formaldehyde and primary or secondary amine or ammonia (in the form of its hydrochloride) to give products, β-aminoketone derivatives, known as mannich base (Scheme 153).[259]

A new approach (or modification) using preformed iminium salts and imines has been developed. The imines react with enolate (especially trimethylsilyl ethers) to give β-amino ketones. In this reaction $TiCl_4$ was used as a promoter.[260] The general scheme for the synthesis of β-aminoketones is given in Scheme 154.



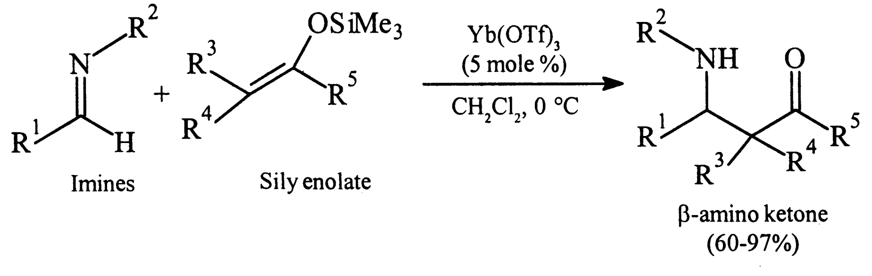
Scheme 152



$$C_6H_5-\overset{O}{\overset{\|}{C}}-CH_3 + H-\overset{O}{\overset{\|}{C}}-H + (CH_3)_2\overset{+}{N}H_2Cl^- \longrightarrow C_6H_5-\overset{O}{\overset{\|}{C}}-CH_2CH_2\overset{+}{N}H(CH_3)_2Cl^- + H_2O$$

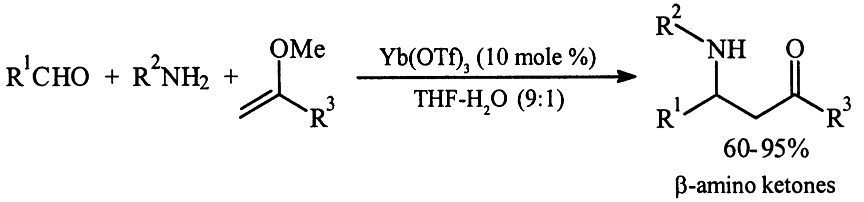
Acetophenone Formaldehyde Dimethylamine hydrochloride β-N,N-Dimethylamino ketone (HCl salt)

Scheme 153



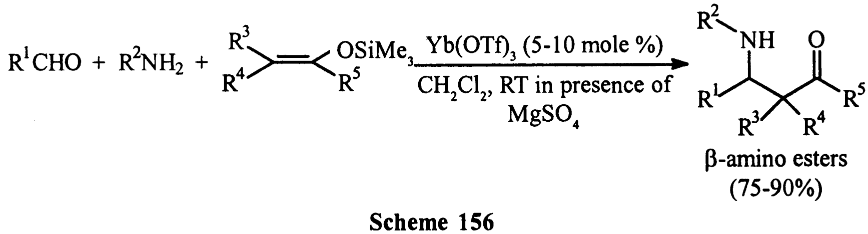
Scheme 154

Vinyl ethers also reacted with imines and amines in presence of catalytic amount of $Yb(OTf)_3$ to give corresponding β-amino ketones (Scheme 155).[261]



Scheme 155

The Mannich type reaction was also used for the synthesis of β-amino esters from aldehydes using $Yb(OTf)_3$ as catalyst (Scheme 156).[262]



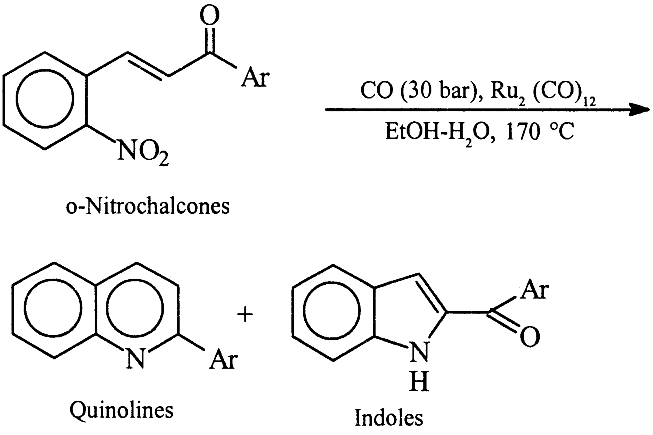
Scheme 156

12.19.7 Conversion of o-nitrochalcones into Quinolines and Indoles

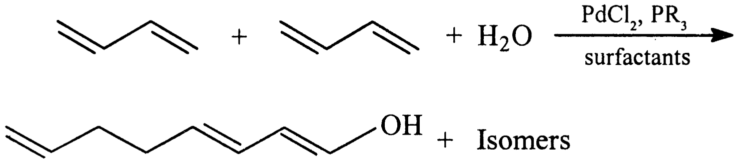
Reduction of o-nitrochalcone under WGSR conditions[263] followed by the cyclisations give rise to the formation of quinolines and indoles (Scheme 157).[264]

12.19.8 Synthesis of Octadienols

The aqueous isomerization of butadiene gives octadienols (Scheme 158).[265]



Scheme 157



Scheme 158

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