β-Cyclodextrin as a Catalyst in Organic Synthesis

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Abstract: This *mini-review* outlines recent (until the end of 2006) key developments in the use of β-cyclodextrin as a catalyst in organic synthesis. β-cyclodextrin is a water soluble supramolecular catalyst especially useful for transformations such as oxirane ring-opening, aziridine oxidation of alcohols, hydrolysis of phosphate esters and amidation of acids. It has been used for the selective synthesis of 2,6-naphthalene dicarboxylic acid, introduction of protecting groups and for ester cleavage. Interestingly, it has also been used in the aza-Michael addition of amines to conjugated alkenes, in photo-Reimer-Tiemann reactions and as a phase transfer catalyst.

Keywords: β-cyclodextrin, oxidation and reduction, protection and deprotection, phase transfer catalyst, aqueous medium.

This Paper is Dedicated to Professor Steven Langford on the Occasion of his 40th Birthday.

INTRODUCTION

α, β, and γ-cyclodextrin are cyclic oligomers of D-glucose that are hexamers, heptamers and octamers respectively [1] with the secondary hydroxyl glucoses C-2 and C-3 on the more open face and the primary C-6 hydroxyl on the secondary inside face [2]. β-cyclodextrin (β-CD) is a cyclic heptamer composed of seven glucose units joined "*head-to-tail*" by α-1,4 links and is also called cycloheptaamylose or cyclomaltoheptaose (Fig. **1**). It is produced by the action of the enzyme *cyclodextrin glycosyl transferase (CGT)* on hydrolysed starch syrups. CGT is obtained from Bacillus macerans, B. *circulans* or related strains of Bacillus. As a result of its cyclic structure, β-CD has the ability to form inclusion compounds with a range of molecules, those of which generally have a molecular mass of less than 250 g/mol. Some other physical properties of β-CD are: Empirical formula $C_{42}H_{70}O_{35}$ (Mol. Wt. 1134.99), cavity diameter ~6.6 Å; heat capacity ~1342 J $Mol^{-1}K^{-1}$; p*K*a (25 ^{o}C) 12.20 and solubility in water 0.0163 mol L^{-1} (25 ^{o}C). β-CD is a cyclic oligosaccharide shaped like a truncated cone as shown below and has a hydrophobic cavity in the centre. It's ability to bind organic molecules in the hydrophobic pocket has provided a basis for the construction of receptor models [3]. It is widely accepted that the binding forces involved in the inclusion complex formation are van der Waals interactions, hydrophobic interactions, hydrogen bonding and electrostatic interactions between guest molecules and β-CDs [4].

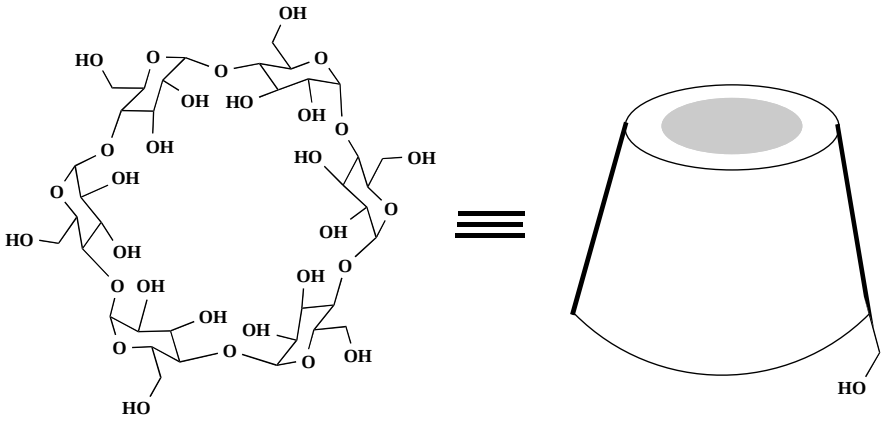

Fig. (1). General structure of β-Cyclodextrin.

β-CD is used in many fields such as foods, cosmetics, toiletries, agrochemicals and pharmaceuticals. Cyclodextrin chemistry is fast becoming one of the important fields of supramolecular chemistry. The possession of a hydrophobic cavity makes CD an attractive subject for study. Its exterior, bristling with hydroxy groups, is polar, whereas the interior of the cavity is non-polar, relative to the usual external environment (which is in most cases water) [5]. Because of the great potential of cyclodextrin as an environmentally benign method for catalytic process, much attention has been focused on its organic reactions in water. β-CD as a catalyst, is attractive since it is inexpensive and can also be readily recovered and reused.

Due to their hydrophobic cavity, CDs provide a microenvironment for organic reactions [6], where by they catalyse reactions through non-covalent interactions. As such, they have been recognised as versatile enzyme mimics [7] and also as supramolecular hosts for organometallic complexes [8]. This current mini-review discusses the use of β-CD as a supramolecular catalyst in organic reactions.

β-CD MEDIATED OXIDATION AND REDUCTION

β-CD mediated water reactions are very useful both from an economic and an environmental point of view and also for the practical convenience of not having to handle flammable anhydrous organic solvents or toxic and expensive reagents. β-CD, apart from being non-toxic, is also considered metabolically safe [9]. Borate β-CD forms inclusion complexes with hydrophobic substrates and is used to catalyse the oxygenation of alkenes (**1**) with *t*-BuOOH (70% in water) in water to give butyldioxy-propanols (**2a**) and (**2b**) (19:1) [10]. Aryl substituted alkenes readily give the major product as (**2a**)

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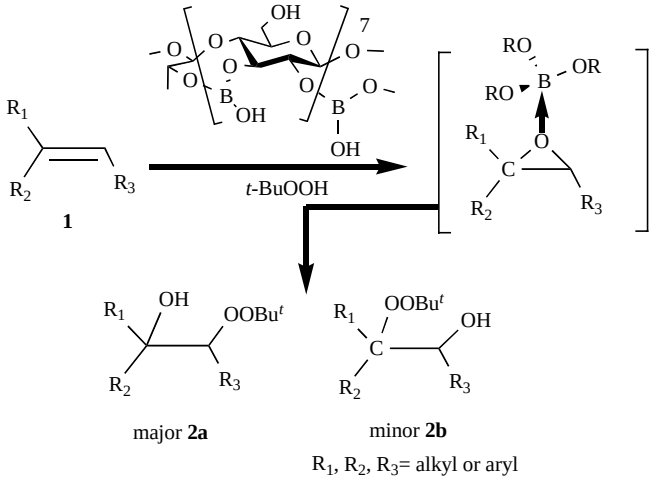
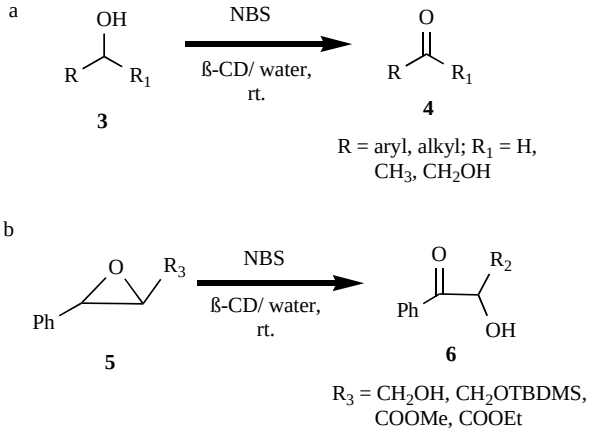
while in case of aliphatic alkenes only norbornene yields the corresponding dioxy-alcohol in moderate yield, as illustrated in Scheme **1**.

Oxidation of alcohols with *N*-bromosuccinimide (NBS) in the presence of β-CD yields corresponding carbonyl compounds (**4**, Scheme **2a**) [11]. The reaction is selective and no further oxidation to acids was observed. This method tolerates several functional groups such as nitro, amino, methoxy, phenols and alkene. Interestingly, during the oxidation of vicinal diols only the secondary hydroxy group α- to the benzene ring is selectively oxidised. Further, oxidation of epoxides with NBS and β-CD provides α-hydroxyketones (**6**, Scheme **2b**), while other functional groups (such as primary OH, TBDMS, OMe, OEt) remain unreactive.



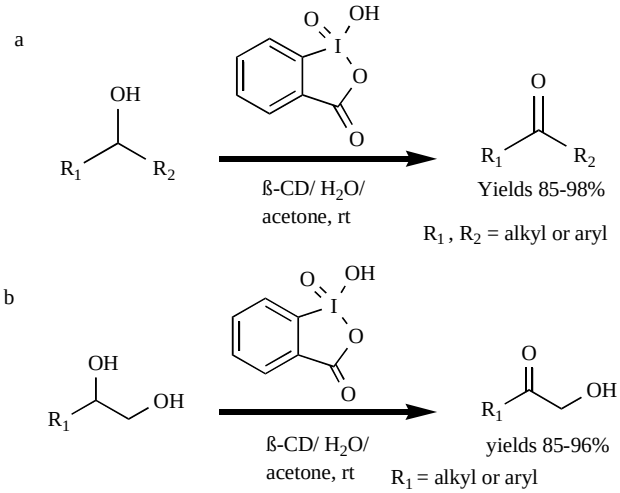
Scheme 1. Preparation of dioxy-alcohol.



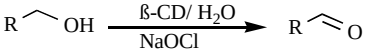
Scheme 2. Use of β-CD in oxidation of (a) alcohols (b) epoxides.

In 2003, Rama Rao and coworkers [12] used the same strategy, utilising hypervalenet iodine (*o*-Iodobenzoic acid) in a water/acetone mixture in the presence of a catalytic amount of β-CD for the oxidation of alcohols to their corresponding aldehydes (1^o OH) and ketones (2^o OH) (Scheme **3**). No further oxidation to acids was observed in the case of aldehyde products and it was observed that arylalcohols gave better yields than the aliphatic alcohols. The oxidation is also selective for the secondary hydroxyl group α- to the benzene rings in the case of vicinal diols. Both the β-CD and iodobenzoic acid were recycled and reused without loss of their activity.

The oxidation of alcohols in excellent yields, at 50°C without transition metals can be obtained using catalytic amounts of β-CD and NaOCl in a mild and green method (Scheme **4**) [13]. This method is cheap and the cyclodextrin can be recovered by the addition of organic solvents such as ethyl acetate or acetone after the reactions [13].



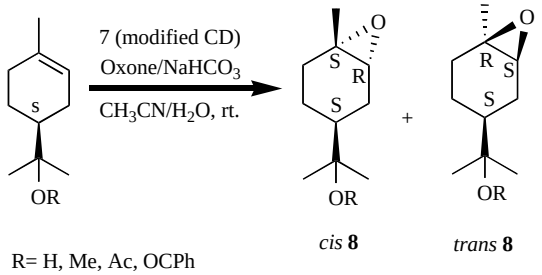
Scheme 3. Oxidation of alcohols to corresponding aldehydes and ketones.



Scheme 4. Oxidation of alcohol.

A facile, substrate-selective and transition metal-free oxidation of benzylic and allylic alcohols to their respective aldehyde has also been reported [14]. The reactions are catalysed by β-CD and NaOCl, with water as the solvent. Modified bridged keto-cyclodextrins have also been utilised in catalytic amounts for the oxidation of alcohols to aldehydes in the presence of hydrogen peroxide in aqueous media at room temperature [15].

It has been reported earlier by Davies *et al*. that cyclodextrin dioxiranes, which are generated *in situ* from keto-cyclodextrins and oxone, can be used for the catalytic oxidation of phenols, amines, and sulfoxides [16]. Wong group have described β-CD modified ketoesters as useful tools for the selective epoxidation of alkenes, as is illustrated in Scheme **5** [17]. Their methods described the preparation of β-CD modified ketoesters (**7**) by functionalisation of the primary hydroxyl rim of the β-CD with pyruvyl chloride (Fig. **2**). The functionalise β-CD has been used for stereoselective alkene epoxidation (*S*)-terpenes, (**8**, 2.5:1) offering mixtures of *cis*- and *trans*- products. However, terpenes bearing bulky groups oxidise less selectively (*cis/trans* = 1.6:1). As described in the year 1998 by group of Tang that the methyl pyruvyl (**9**) is effective for alkane oxidation with oxone as the terminal oxidant [18].



Scheme 5. Steroselective epoxidation of (s)-Terpenes.

The epoxidation of alkenes has been studied in detail by the Bola group [19] utilising a series of β-CD derivatives in the presence of oxone. Recently they have been involved in the oxidation of anilines using hydrogen peroxide as a stoichiometric oxidant in the presence of the ketoester modified β-CD [20]. However, unmodified β-CD does not catalyse the epoxidation of styrene in the presence of hydrogen peroxide, as it does in presence of oxone [19]. This is also

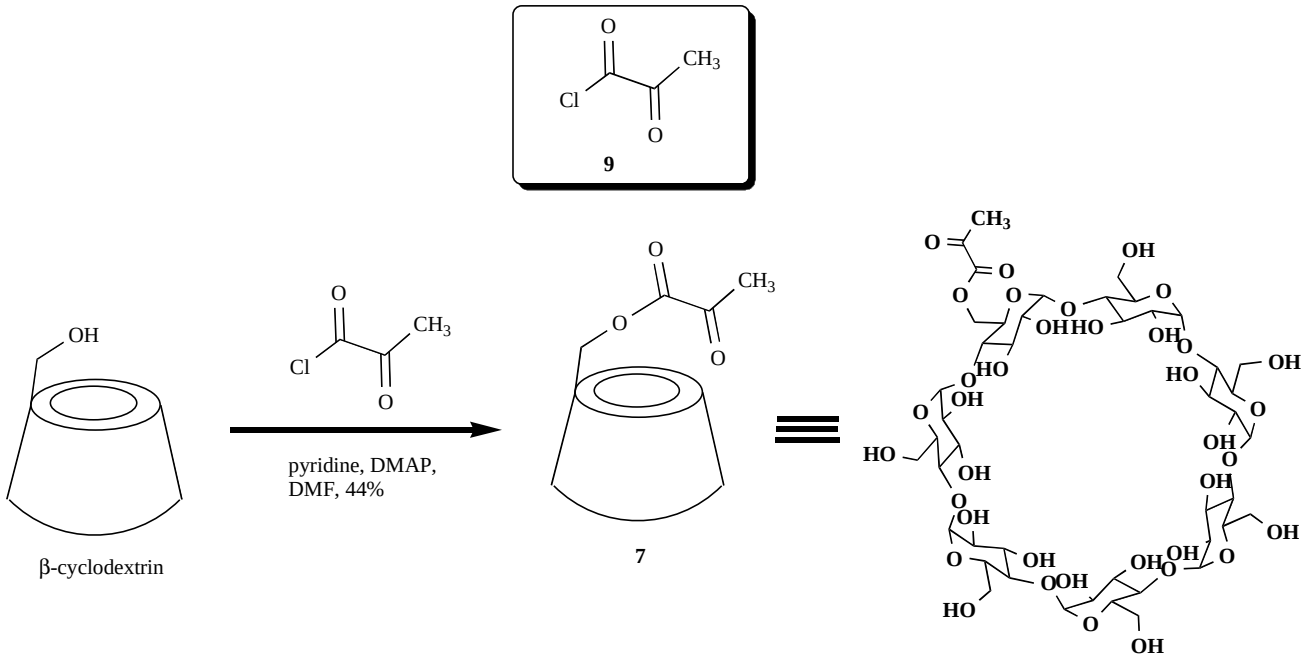
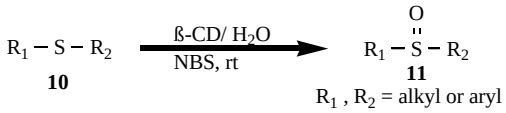


Fig. (2). General synthesis of β-CD modified ketoester.

an advantage for amine oxidation as there are no dioxirane intermediates [20].

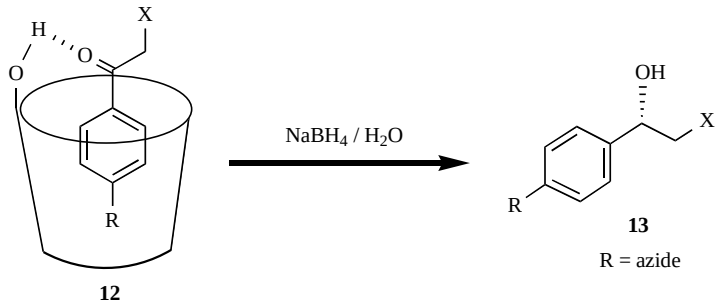
Rao and coworkers have developed a simple and highly selective method for the oxidation of sulfides (**10**) to sulfoxides (**11**) with NBS, catalysed by β-CD in water at room temperature in excellent yields (Scheme **6**). The obtained product was selective without further oxidation to sulfones [21]. In a related process, Pandit and coworkers studied the use of β-CD in the selective oxidation of sulphides to corresponding sulfoxides using ultrasound in aqueous media in the presence of hydrogen peroxide. The utilisation of ultrasound proved to be excellent for this transformation, enhancing the rates of reaction and selectivity of the oxidation towards the desired product [22].



Scheme 6. Oxidation of sulfides to sulfoxides.

The reduction of substituted aryl and alkyl ketones using sodium borohydride in the presence of β-CD provides products with optical yields up to 36% *ee* [23]. Rao and co-workers attempted the reduction of α-azido aryl ketones (**12**) to their corresponding alcohols (**13**) using sodium borohydride in water and in the presence of β-CD (Scheme **7**) and obtained good optical yields [24].

Enantioselective reduction of aromatic and aliphatic ketones has been studied by the Woggon group, applying β-CD complexes with ruthenium metal (**15**) as shown in Fig. (**3**) [25]. Mono (*O*-6-tosyl)-β-



Scheme 7. Reduction of aryl ketones.

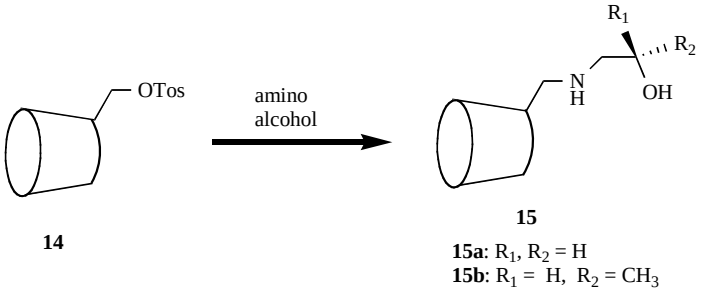
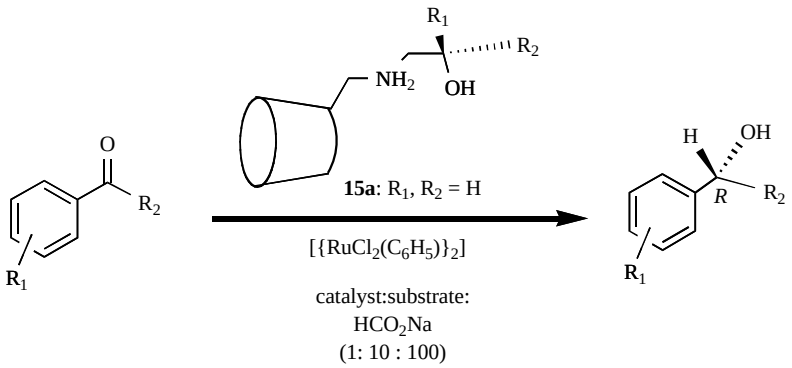
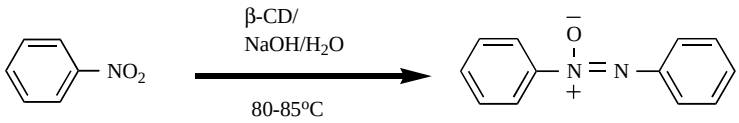


Fig. (3). Enantioselective reduction of aromatic and aliphatic ketones.



Scheme 8. Asymmetric reduction of ketones in water.



Scheme 9. Reduction of nitroarenes.

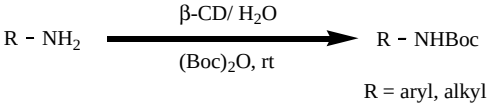
CD (**14**) can be prepared by the tosylation of β-CD, and is then converted in good yields, to the amino-alcohol linked β-CD (**15a**) and (**15b**) [26]. For catalytic reactions, the ruthenium complexes were formed *in situ* with β-CD and treated with ketones at room temperature under an argon atmosphere in the presence of excess sodium formate as the hydrogen source (Scheme **8**) [25]. For CD-catalysed asymmetric reactions, it should be noted that the following criteria are required: a phenyl ring in the substrate to form the CD inclusion complex and a functional group that is able to interact with the hydroxy groups of the CD, in order to attain rigidity for chiral recognition.

To date, the use of supramolecular catalysts for asymmetric reduction of ketones in water is not known outside of this example, and therefore the reaction is quite useful.

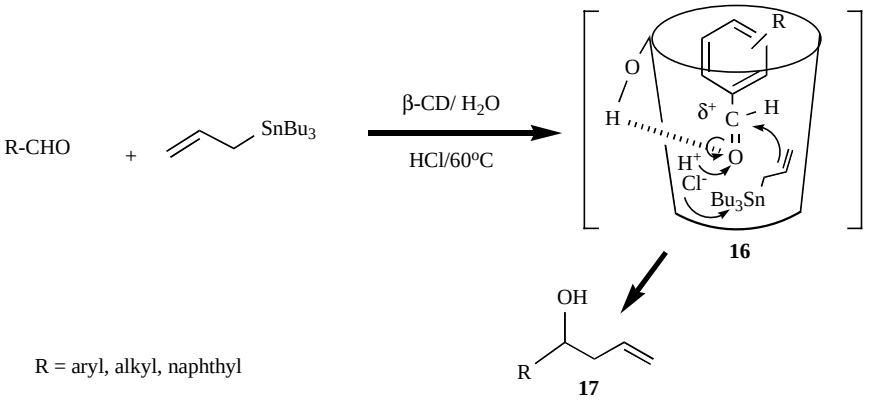
Reductions by OH^- have thus far only been reported in organic solvents because the reducing ability of OH^- in water is extremely low as a result its stabilisation by hydration. Recently, the group of Liu and Lu investigated the β-CD catalysed reduction of mono nitroarenes by hydroxide ions in alkali water (Scheme **9**) [27]. Here the OH^- may act as a one-electron reductant and the water as the source of protons. The first step of the reduction most likely involves the single electron transfer from OH^- to the nitroarene. This may be explained in terms of the combination of the electronic effects of the substituents and the spatial orientation effects of the nitroarene in the β-CD cavity. Nitroarenes with electron withdrawing groups in which the nitro groups are favourable orient towards the OH^- and would be readily reduced [27]. Since the reactive radicals could not have a lifetime long enough to escape the CD cavity for dimerisation, two CDs cooperate in such a way that the two anion radicals encapsulated in them would dimerise without diffusion outside the cavity.

β-CD MEDIATED PROTECTION, DEPROTECTION, AND HYDROLYSIS IN AQUEOUS SOLVENTS

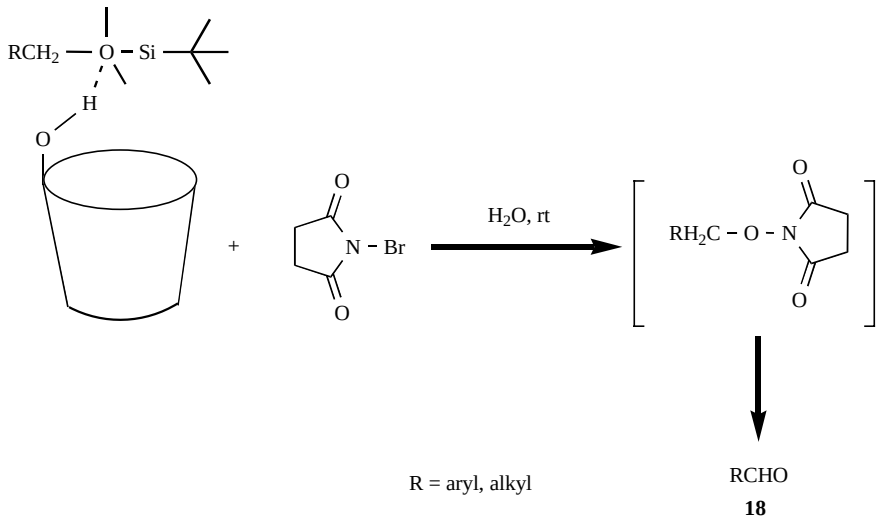
Protection of amino groups is often required during the synthesis of peptides, amino acids and other natural products. The most widely used protecting group is *tert*-butoxycarbonyl (Boc), which has been recognised as the protecting group of choice due to its easy installation, removal, stability towards neucleophiles and strong basic conditions [28]. Recently Rao and coworkers developed a method for protection of aryl and alkyl amines using catalytic amount of β-CD in water under neutral conditions (Scheme **10**). Various reagents and methodologies developed over the years to introduce the Boc- group, using $(Boc)_2O$, have been carried out either in the presence of a base or Lewis acid catalyst [28]. However, the method developed by Rao *et. al.* has some advantages over existing methods, such as in this method they use neutral conditions for the protection of the amines and it is also cleaner, higher yielding and has shorter reaction times [29].



Scheme 10. Boc protection of amines.



Scheme 11. Allylation of aldehydes.



Scheme 12. Oxidative deprotection of *tert*-butyldimethylsilyl.

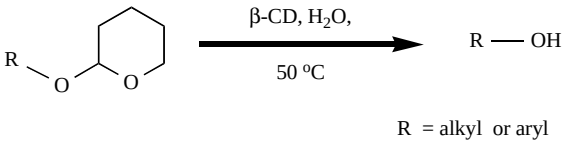
β-CD has been used for allylation of aldehydes with allyltributyltin in water (Scheme **11**) and the method is highly efficient, non-toxic, high yielding and avoids the use of transition metal catalysts [30, 31]. Reactions also take place using catalytic β-CD but as the aldehyde is complexed in the cavity (with the CD-hydroxyl groups forming H-bonds with the carbonyl oxygen of the aldehyde), the attack of the allyltributyltin is delayed, thus the formation of the allyl alcohol (**17**) is a slow reaction (Scheme **11**).

Catalytic amounts of β-CD have been used to catalyse oxidative deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers using NBS at room temperature with water as a solvent (Scheme **12**) [32]. These methods tolerate other functional groups such as hydroxy, methoxy, isopropoxy, methylenedioxy and nitro groups and olefins. No further oxidation to the acid is observed and only the carbonyl product is isolated (**18**) (Scheme **12**), directly depending upon the class of the starting substrate [32].

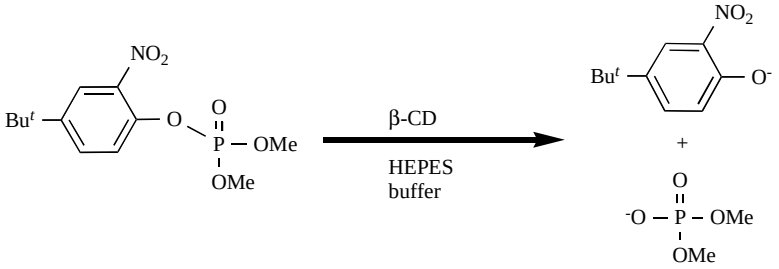
The effect of cyclodextrin on hydrolysis has been studied in several laboratories [33]. The group of Rossi utilised catalytic amounts of β-CD for the hydrolysis of perfluoroalkyl amides of *p*-nitroaniline [34]. Comparative studies have been carried out by the group of Ikeda for the stereospecific acceleration of hydrolysis of *p*-nitrophenyl-D-glycoside utilising α, β, and γ-CD. They also extending the study to compare the hydrolysis of *p*-nitrophenyl-α-D-mannoside, β-D-glucoside and β-D-galactoside in comparison to that of the corresponding β-D-mannoside, α-D-glucoside and α-D-galactoside, respectively [35]. The hydrolysis of tetrahydropyranyl ethers to alcohols has been studied in detail utilising catalytic amounts of β-CD in water under neutral conditions as illustrated in Scheme **13** [36].

Simpson and coworkers [37] synthesised Cu(II) complexes of modified β-CD and used them for the effective and selective hydrolysis of phosphate triesters at neutral pH (in HEPES buffer) and 298 K. The substrates used in this study contain *tert*-butyl groups *para* to the triester phosphate because they promote complexation with the cyclodextrin, and a nitro group which facilitates detection of the hydrolysis product, as illustrated in Scheme **14** [37]. The hydrolysis of this compound was monitored at 435 nm, which corresponds to the wavelength of the phenoxide.

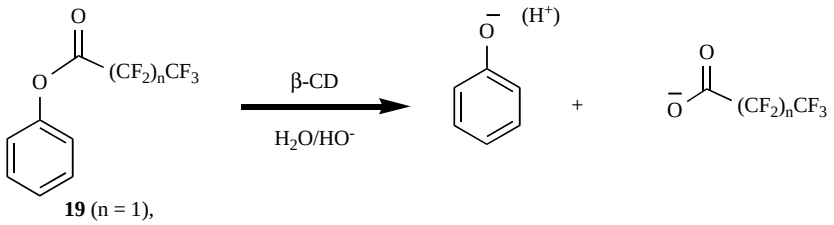
β-CD mediated hydrolysis of phenyl esters of perfluoroalkanoic acids have been described in detail by the group of Ross [38]. The rates of hydrolysis of the ester $CF_3(CF_2)_nCOOPh$ (**19**: n = 1; **20**: n = 2; **21**: n = 6) were measured at pH 6.00 to 9.00 in the presence of β-CD (Scheme **15**). For compounds (**19**) and (**20**) the reaction rate decreases as the concentration of the β-CD increases. It suggests that the substrate forms an inclusion complex with the β-CD. The β-CD reaction involves the ionised OH group at the rim of the CD cavity with poor efficiency due to an unfavourable orientation of the substrates (**19**) and (**20**) in the complex, where as compound (**21**) is strongly accelerated by β-CD because it has a long chain and complexes with the inner cavity [38].



Scheme 13. Hydrolysis of tetrahydropyranyl ethers.



Scheme 14. Selective hydrolysis of phosphate triesters.



19 (n = 1),
20 (n = 2),
and **21** (n = 6)

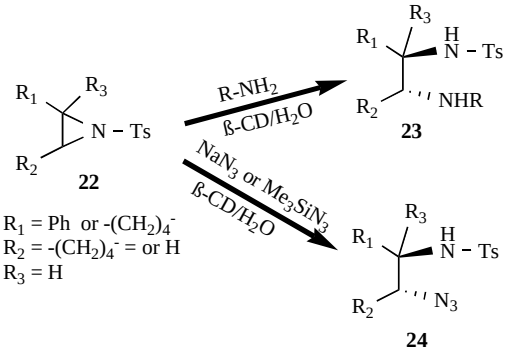
Scheme 15. β-CD metidated hydrolysis of phenyl ester.

Bols and coworkers utilised cyanohydrin modified β-CD derivatives as a supramolecular catalyst for the hydrolysis of nitrophenyl glycosides in the presence of sodium borohydride (as a hydrogen source) [39]. Recently, Lafont *et al.* used a derivative of CD (2-*O*-monobenzyl ether of β-CD) as the precursor to the catalyst for organophosphoryl ester hydrolysis [40].

RING OPENING OF EPOXIDES, AZIRIDINES USING β-CD AS A CATALYST

Regioselective ring opening of epoxides and aziridines with nucleophiles such as aromatic amines, azides, sulphides and alcohols under biomimetic conditions are a synthetically important class of reactions in organic and medicinal chemistry. In 2001, Rao and coworkers described the use of a β-CD catalysed efficient biomimetic cleavage of aziridines (**22**) with aromatic amines and azide nucleophiles [41]. The reaction was carried out in water at room temperature for 24 h to give corresponding diamines (**23**) or azido amines (**24**) in good yield. The β-CD was recycled and resued without loss of activity [41]. In the literature, several methods are available for the opening of aziridines but there are limitations, such as the use of anhydrous organic solvents, moisture sensitive catalysts, hazardous reagents etc., thus making this method developed by β-CD useful for multistep organic synthesis and medicinal chemistry. Following the successive opening of aziridines with aromatic amines and azides, Rao's group have successfuly utilised β-CD for the regioselective ring opening of aziridines with thiophenol in water at neutral pH [42]. The described methodology is simple and highly efficient. They have used β-CD for aziridine ring opening with thiols and amines to yield amino sulphides and diamines [43], which is providing an alternative method for aziridine ring opening. This reaction was generally carried out using boron trifluoride.etherate, CAN and trifluoromethane sulfonic acids (for details see ref. 43, and therein references).

In 2002, Rao and coworkers discovered the use of β-CD for the mild and efficient biomimetic synthesis of α-hydroxymethylaryl-ketones (**26**) *via* ring opening of oxiranes (**25**) in the presence of NBS in water at room temperature (Scheme **17**). The method is simple and environmentally benign, with high potential for future applications in



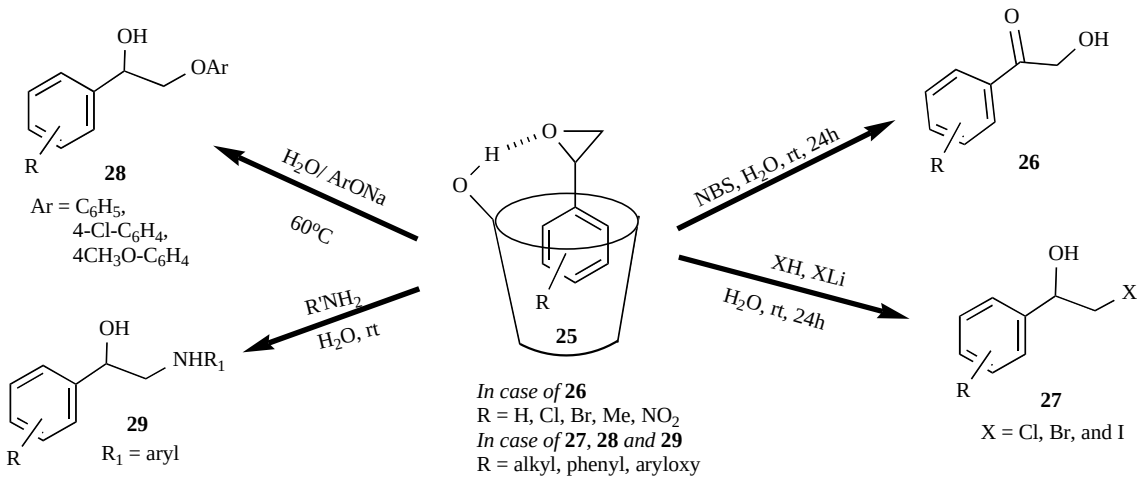
22

R_1 = Ph or $-(CH_2)_4-$
R_2 = $-(CH_2)_4-$ = or H
R_3 = H

23

24

Scheme 16. Ring opening of aziridines.



28

Ar = C_6H_5,
4-Cl-C_6H_4,
$4CH_3O$-C_6H_4

29

R_1 = aryl

25

In case of **26**
R = H, Cl, Br, Me, NO_2
In case of **27**, **28** *and* **29**
R = alkyl, phenyl, aryloxy

26

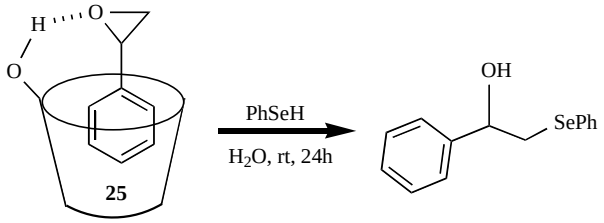
27

X = Cl, Br, and I

Scheme 17. β-CD mediated opening of epoxides.

multistep organic synthesis [44]. They also investigated the use of β-CD for the highly regioselective ring opening of epoxides (**25**) to halohydrins (**27**) with hydrogen or lithium halides using water as the solvent (Scheme **17**) [45]. The method works in a biomimetic fashion with high regioselectivity, which was not possible with earlier methods, due to the inclusion complex formation of epoxides with β-CD which then reacts with hydrogen halides to form halohydrins (**27**). The method is successful for hydrogen halides and lithium halides, where as other metal halides such as sodium and potassium halides were deemed unsuccessful [45]. Ring opening of oxiranes with phenoxides in the presence of β-CD in water yielded β-hydroxy ethers (**28**), in a biomimetic fashion with high regioselectivity [45]. Recently, the Rao group has developed a method for selectively opening aromatic epoxides with aromatic amines, thus affording the corresponding β-aminoalcohol (**29**) (Scheme **17**) in excellent yields with high regioselectivity using catalytic amounts of β-CD [47].

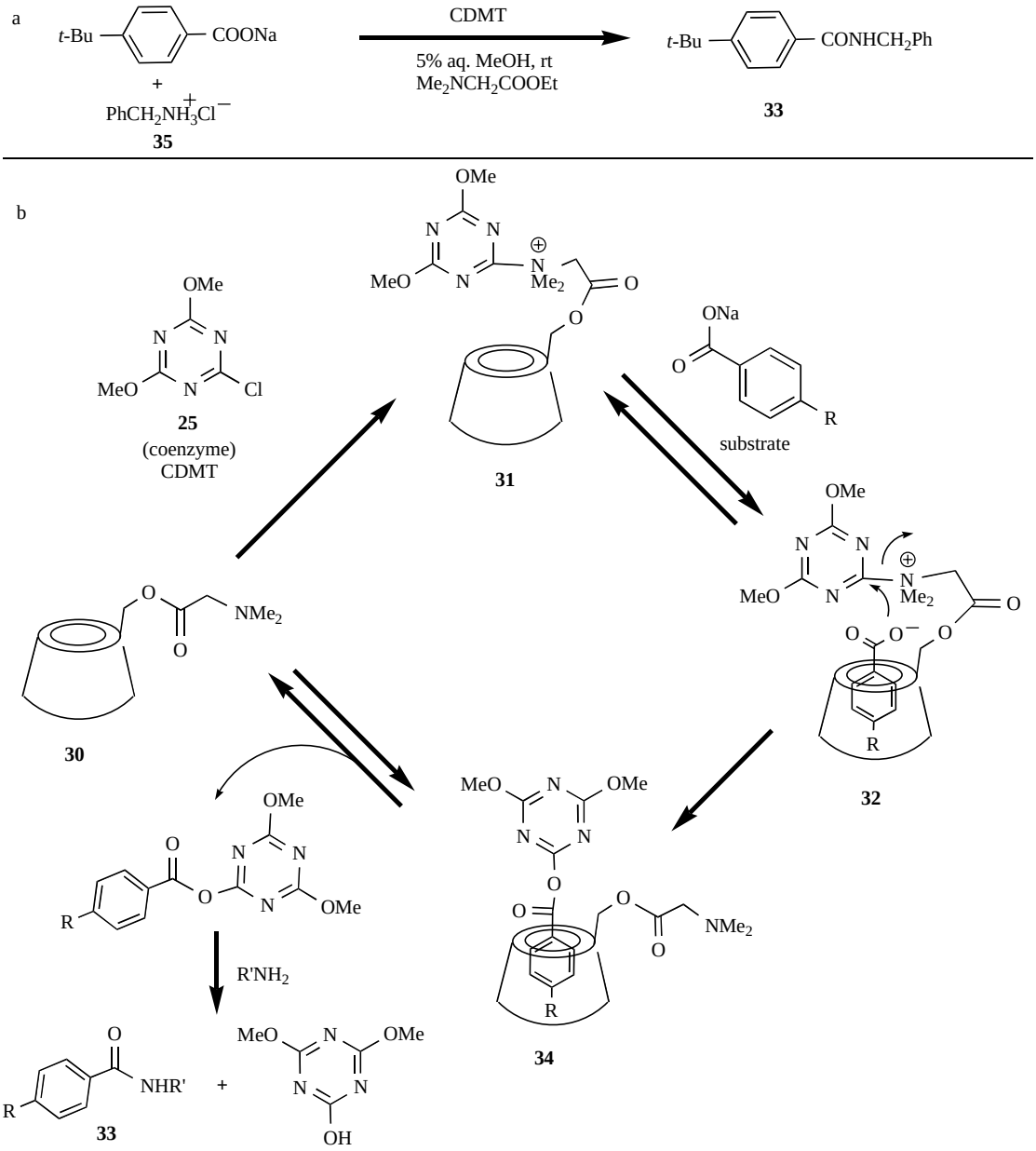
Recently, the synthesis of β-hydroxy selenides has been reported at room temperature in good yield by the highly regioselective ring-opening of epoxides with benzeneselenol in water in the presence of β-CD as a supramolecular catalyst. The β-CD can be recovered and reused without loss of activity (Scheme **18**) [48].



Scheme 18. Regioselective epoxide ring opening with benzeneselenol.

β-CD USED AS A CATALYST IN AMIDATION REACTION

Amidation reactions are important tools for peptide, organic and medicinal chemistry. Kunishima *et al.* studied the effect of CD for the substrate-specific condensation of aromatic carboxylic acids with amines to obtain carboxyamides (**33**) (Scheme **19a**). Here they use CD as a new artificial enzyme that efficiently mimics acyltransferase

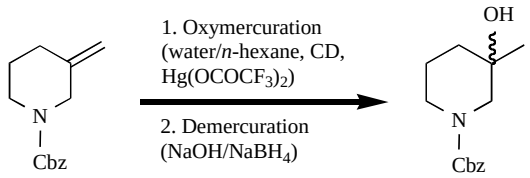


Scheme 19. a) Preparation of amide; b) mechanism of amidation.

[49]. Typical reaction protocol involves methanolic solutions of an ammonium salt (**35**) and CDMT (coenzyme) in equivalent proportions being added to an aqueous solution of sodium carboxylate and stoichiometric amounts of the catalyst (**30**). As shown in Scheme **19b**, (**30**) is activated by coupling with CDMT through the dimethylamino bond to give a holoenzyme (**31**). An aromatic carboxylate ion (the substrate) fits in the cavity of the CD and preferentially interacts with the holoenzyme (**31**) to form an inclusion complex (**32**), where the carboxylate ion attacks triazino group giving the EP complex (**34**). Finally aminolysis of the resulting acyloxytrazine (an activated ester) takes place to precipitate the water-insoluble amide products (**33**) [49]. Recently, amidation of carboxylic acids in a liquid-liquid two phase system using cyclodextrins as an inverse-phase transfer catalyst has been successfully studied [50]. The methodology works as follows; acids are dissolved in an appropriate organic phase and as usual can be expected to selectively transfer to the aqueous phase by the formation of an inclusion complex with CDs, where it then undergoes coupling with triazine. This activated ester then couples with the amine to give a hydrophobic amide, which transfers again to the organic phase [50].

FUNCTIONALISATION OF ALKENES UTILISING β-CD AS A CATALYST

Santos and coworkers have studied enantioselective functionalisation of alkenes using cyclodextrins as inverse-phase transfer catalysts. Hydration by an oxymercuration-demercuration utilising $Hg(OCOCF_3)_2$ and $NaOH/NaBH_4$ respectively in the presence of CD as the catalyst *via* a Markovnikov addition has been achieved (Scheme **20**). Unfunctionalised alkenes such as styrene, failed to react under these conditions. However, the hydration of allylic amines and allyl protected alcohols was successful and moderately enantioselective [51].



Scheme 20. Enantioselective functionalisation of alkenes.

β-CD AS A PHASE-TRANSFER CATALYST: HYDROFORMYLATION

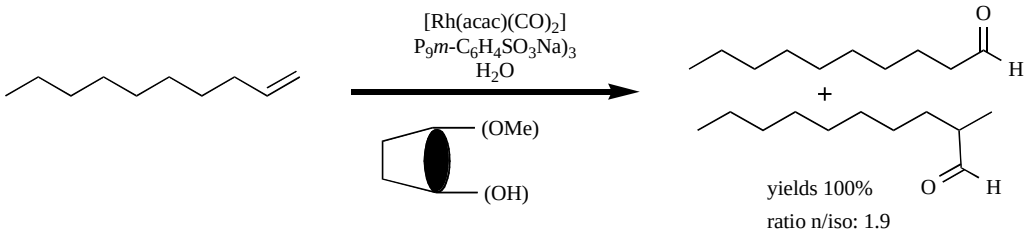
Aqueous-organic biphasic catalysis has become a well established research field for industrial applications [52]. Most efforts in this area are presently directed to the synthesis of new water-soluble ligands and to the development of mass transfer promoters to permit the reaction of water-insoluble starting materials. Hydroformylation is a major industrial process that produces aldehydes and alcohols from olefins, carbon monoxide and hydrogen [53]. The reaction was discovered in 1993 by Roelen [53], who detected the formation of aldehydes in the presence of a cobalt based catalyst. A major improvement was made by the joint efforts of Rhone *et al.* by using rhodium in aqueous media. Extensive research has been carried out related to this process [54]. Monflier and coworkers [55] studied in detailed the synthesis and use of modified CD (randomly methylated α- and β-CD) as a mass transfer promoter in the aqueous biphase hydroformylation of higher olefins and molecular recognition between a water-soluble organometallic complex and β-CD. Monflier *et al.* [56] studied in detail the use of cyclodextrin for hydroformylation utilising biphasic systems, achieving a conversion of up to 100% and a regioselectivity of up to 95% for the Rh-catalysed hydroformylation of dec-1-ene in water (free of organic solvent), in the presence of partially methylated β-CD (Scheme **21**).

Furthermore, the group investigated modified derivatives of CDs for hydroformylation. Heptakis-(2,3-di-*O*-methyl-6-*O*-sulfo propyl)-β-CDs have been prepared and used as inverse-phase transfer catalysts for biphasic mass transfer in Tsuji-Trost and hydroformylation reactions. In terms of activity, the methylated sulfopropyl ether β-CD is much more effective than methylated β-CD [57]. The potential of methylated sulfopropyl ether β-CD derivatives as supramolecular carriers in biphasic Tsuji-Trost reactions catalysed by water soluble palladium complexes of trisulfonated triphosphine, have been studied in detail by Monflier *et al.* (Fig. **4**) [58]. These interesting results are attributed to the formation of an alkene/cyclodextrin inclusion complex as well as the solubility of the modified cyclodextrin in both phases.

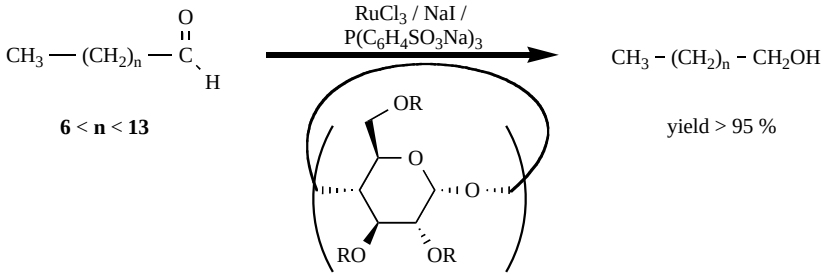
To this date, hydroformylation in the presence of unmodified cyclodextrin, as studied by the Jackson group, has revealed rather disappointing results [59]. Detailed molecular dynamic study of the hydroformylation of olefins promoted by a series of derivatives of cyclodextrin has been utilised in liquid-liquid systems using a biphasic rhodium catalyst by the Wipff group [60].

USE OF β-CD FOR HYDROGENATION REACTIONS

Monflier and coworkers used the chemically modified β-CD {heptakis-(2,6-di-*O*-methyl)-β-CD} as efficient supramolecular carriers for the biphasic hydrogenation of water-insoluble aldehydes



Scheme 21. β-CD used as a phase transfer catalyst.



Scheme 22. Hydrogenation of aldehydes.

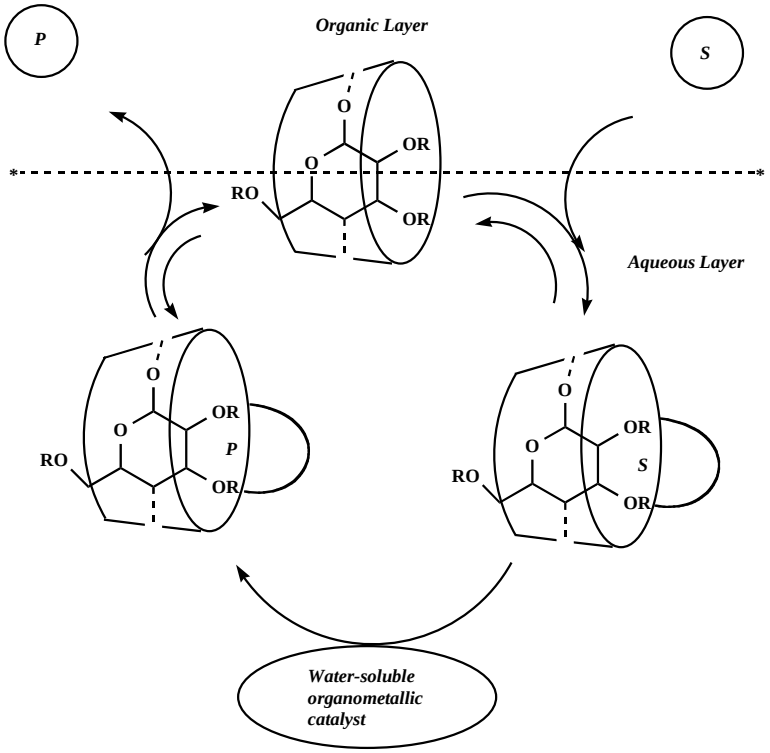
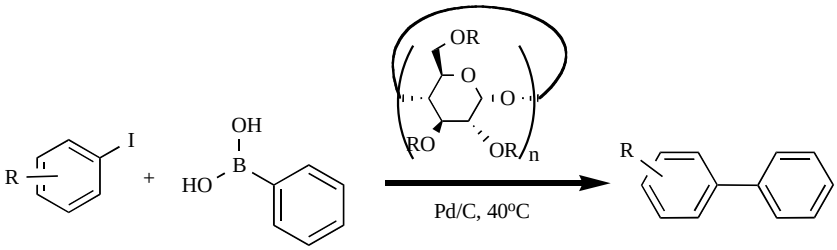


Fig. (4). Model of the aqueous organometallic catalysis mediated by chemically modified CDs (*S* = Substrate and *P* = Product).



Scheme 23. Suzuki-Miyaura reaction.

while the unmodified β-CD exhibited very poor catalytic activity. The modified β-CD has high catalytic activity, simplicity in work-up and is recovered quantitatively [61]. Comparative studies of α-CD, β-CD, and γ-CD demonstrated that aperture size (large aperture for γ-CD or a smaller aperture for α-CD), affected conversion however; modified β-CD has the optimal size for hydrogenation of aldehydes (Scheme **22**) [61].

Recently, the Roucoux group investigated the use of methylated cyclodextrin in the chemoselective hydrogenation of benzene derivatives with nanoparticles under biphasic liquid-liquid conditions [62]. Various methylated cyclodextrins have been used. The selective hydrogenation between reducible exocyclic functionalities such as C=C double bonds and aromatic groups can be easily controlled by the choice of the degree of substitution. Randomly methylated cyclodextrins have been used by Monflier for Suzuki-Miyaura reactions under biphasic conditions utilising ligand free Pd/C- as catalyst [63].

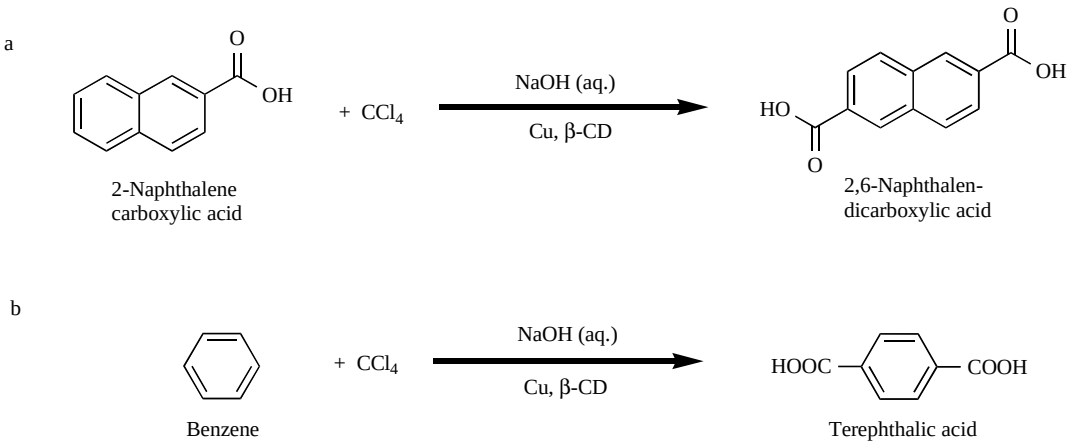
β-CD USED FOR CARBOXYLATION

The group of Shiraishi developed a method for the selective synthesis of 2,6-naphthalenedicarboxylic acid from 2-naphthalene-carboxylic acid using carbon tetrachloride, copper powder, and sodium hydroxide (aq.) in the presence of a catalytic amount of β-CD at 60°C under an argon atmosphere, obtaining 67% yield (Scheme **24a**). They have confirmed by ^{1}H-NMR the presence of the inclusion complex of β-CD and 2-naphthalenecarboxylic acid in aqueous alkaline solution [64]. The solubility of CCl_4 in water is poor however it can be soluble in aqueous alkali solutions when it is included in the cavity of CD. A detailed study of the inclusion of the CCl_4 has been carried out by ^{1}H NMR chemical shifts of β-CD. The included CCl_4 converts into the trichloromethyl radical by reaction with Cu in aqueous alkali solution and then attacks the naphthyl ring. A detailed mechanistic study can been found in reference [64]. However, in the presence of α- and γ-CD the reaction is unsuccessful. After studying the monocarboxylation of naphthalenecarboxylic acid, the group investigated the use of β-CD for the synthesis of terephthalic acid from benzene in one step using water (Scheme **24b**) [65].

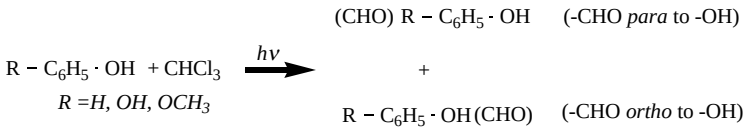
β-CD has also been applied for the eco-efficient catalytic hydro-dechlorination of carbon tetrachloride (CCl_4) in aqueous media at neutral pH [66].

β-CD BASED NAME REACTIONS

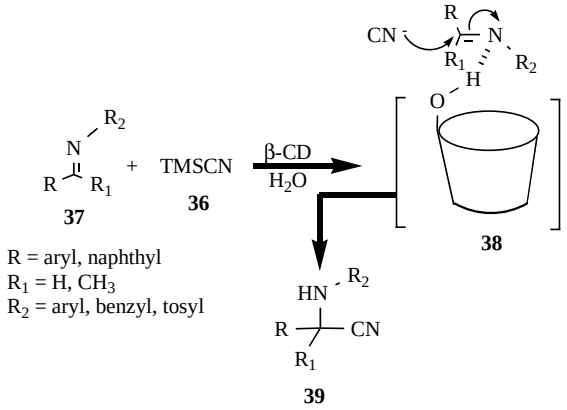
The use of β-CD has also been investigated in named reactions and heterocyclic chemistry. The photo-Reimer-Tiemann reaction of phenols mediated by β-CD, 2,6-di-*O*-methyl-β-cyclodextrin (DMBCD) and hydroxy propyl-β-CD (HPBCD) was described by Ravichandran in 1998 (Scheme **25**) [67]. Phenol is a typical compound, which ejects an electron upon photo-irradiation. When phenol and chloroform are photo-irradiated in aqueous methanol, 4-



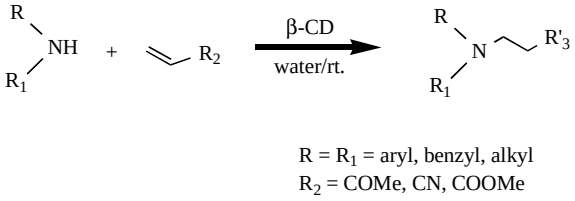
Scheme 24. β-CD mediated carboxylation of aromatic rings.



Scheme 25. Photo-Reimer-Tiemann reaction.



Scheme 26. β-CD mediated Strecker reaction.

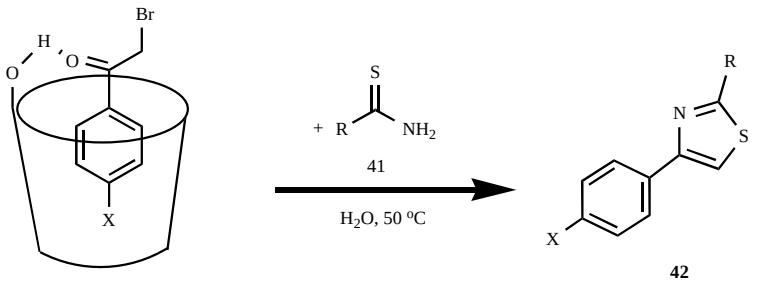


Scheme 27. β-CD mediated aza-Michael addition.

hydroxybenzaldehyde and salicylaldehyde are the major isolated products. The effect of β-CD on the reaction was shown in two respects: 1) the yield of the aldehyde formation was enhanced along with the acceleration of the reaction rate; 2) the *para*/*ortho* ratio was increased. Only β-CD has shown an enhanced yield of 73% with 82.4% selectivity for the formation of 4-hydroxybenzaldehyde against a 62% yield with 66.6 % selectivity for the same compound in the absence of the β-CD. In the presence of DMBCD, a maximum yield of 68%, and 79.6% selectivity for *para* is achieved while in the presence of HP-BCD a remarkably enhanced yield of > 90-94% and *para* selectivity of > 81-100%. Overall, for the photo-Reimer-Tiemann reaction, β-CD and DMBCD showed higher selectivity for the formation of a *para* product; however the use of HPBCD played a key role in enhancing the yield to a maximum of 98%.

Recently the use of β-CD in the Strecker reaction has been investigated by the Rao group [68]. An environmentally benign and highly efficient procedure for the nucleophilic addition of timethylsilyl cyanides (**36**) to imines (**37**). It provides α-amino nitriles (**39**) (Scheme **26**) in good yields *via* hydrogen bonding of the imine nitrogen to the outer OH of the β-CD (**38**). The reaction has been carried out in aqueous medium in the presence of a catalytic amount of β-CD. They have been able to recycle and reuse the β-CD without loss of its activity, for a number of times [68].

Following this success, the group has used this strategy for the aza-Michael addition of amines to conjugated alkenes in water, yielding the corresponding β-amino compounds in excellent yields (Scheme **27**) [69]. The reaction involved *in situ* formation of the β–CD complex with the amine in an aqueous media followed by attack of the olefin at room temperature for 12 hrs, forming the



Scheme 28. β-CD mediated synthesis of thiazoles or amino thiazoles.

corresponding β-amino carbonyl compound in excellent yields [69]. The described method is important in organic chemistry, especially for the synthesis of heterocyclic compounds, which contain a β-amino carbonyl unit. β-amino carbonyl compounds are versatile synthetic intermediates for the synthesis of a variety of biologically important targets or target intermediates (see reference 69 for details).

β-CD has also been used in the synthesis of novel heterocyclic molecules. The reaction of phenacyl bromides (**40**) and thioamide/thiourea (**41**) yields thiazoles or amino thiazoles (**42**), depending on the substrates used (Scheme **28**) [70]. The role of the CD in this reaction is to activate the phenacyl bromide within the cavity, which is followed by attack of the thiamide or thiourea to give the corresponding thiazole or aminothiazole, respectively.

β-CD has been investigated for the synthesis of thiranes from oxiranes and thiourea in water at room temperature under neutral conditions [71]. Again, the β-CD here can be recovered and reused without loss of activity. These reactions also work with α-CD giving similar results however, β-CD is inexpensive and readily available. More recently, Bhosale *et al.* have described the use of β-CD as a supramolecular catalyst in organic synthesis [72].

SUMMARY

This review reveals that β-CD and its various derivatives are extremely active in organic transformations. In several reactions, it is possible to recycle and reuse it without loss of its activity. Most useful of all, β-CD has proven to be a green catalyst as almost all transformations have been carried out in aqueous media or biphasic conditions. It is simple to handle, non-toxic and low costing as compared to other supramolecular catalysts. Hence β-CD is a very useful tool for multistep organic synthesis and in medicinal chemistry.

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