CHAPTER 7

Synthesis of β-hydroxyl ketones in water: A green protocol under metal-free conditions

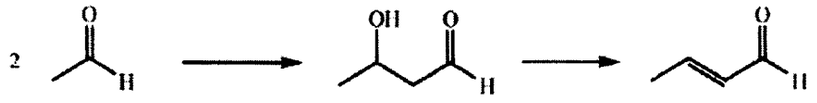
7.0 Synthesis of β-hydroxyl ketones in water: A green protocol under metal-free conditions

7.1 Introduction

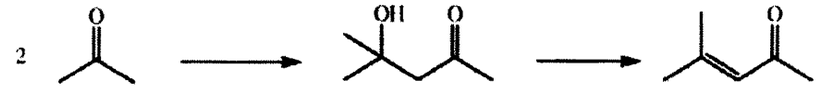
The aldol reaction is one of the most powerful and best known C–C forming synthetic reactions, universally present in basic and advanced organic chemistry texts and amply reviewed in organic synthetic books and series [1–4]. The reaction has industrial relevance either in bulk production, or in the fine chemical and pharmaceutical industry [5] The aldol reaction has a particular interest in that it may be qualified as one of the natural synthetic methods in the sense that important biogenetic pathways are based on aldol conversions and its application opens access to highly functionalised natural and non-natural substances, related for instance, to carbohydrates.

Selectivity

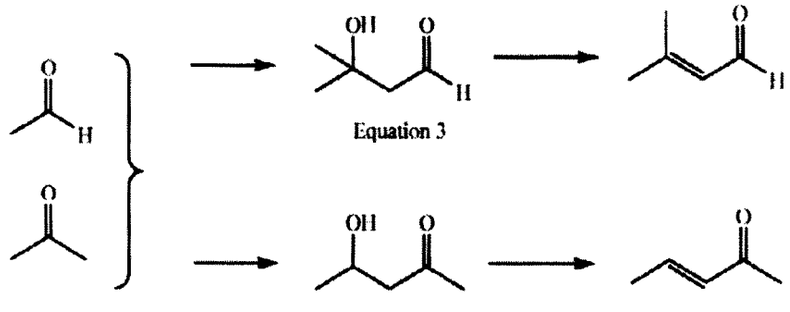
A general synthetic method, especially when intended to be environmentally benign, should be based on complete conversions of well-defined selectivity. Inversion of selectivity trends at will would be desirable. It may be convenient then to have a look at the structural possibilities for selectivity that the aldol reaction offers. Aldol reactions lead to b-hydroxy aldehydes (aldols) or to b-hydroxy ketones (ketols) through an addition reaction (aldolization) or to the α, β-ur saturated aldehydes or ketones that result from a subsequent dehydration (aldolcondensation) (Scheme 1, eqns 1 and 2). The reaction may involve two molecules of the same aldehyde or ketone (selfaldolization or self-condensation) or two different substances (cross-aldolization or cross-condensation). In any case, one of the molecules reacts as a carbonacid (donor) that adds to the carbonyl group of the other one (acceptor). In cross-reactions two donor–acceptor combinations are possible, unless one of the reactants has no α-hydrogen atoms (eqns 3 and 4). Condensations require two hydrogen atoms at the a-carbon atom of the donor aldehyde or ketone (eqn 5). Asymmetric ketones with α and α' hydrogen atoms can react as donors to give two different ketols (eqns 6 and 7), or two enones when dehydration is possible.



Equation 1

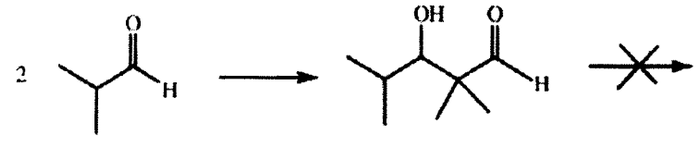


Equation 2

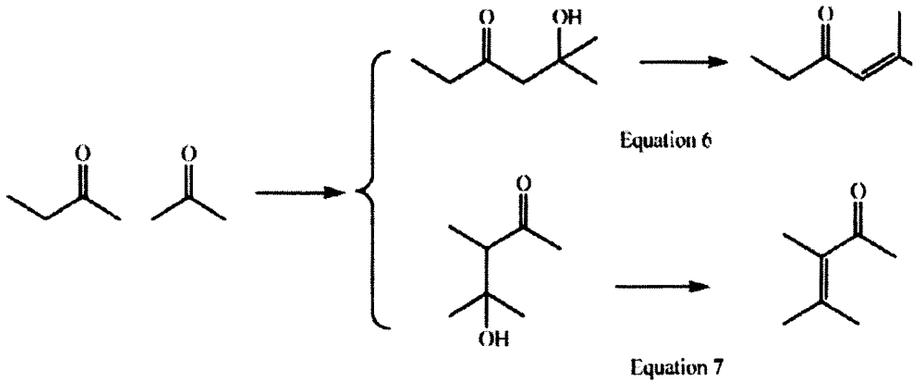


Equation 3

Equation 4



Equation 5



Equation 6

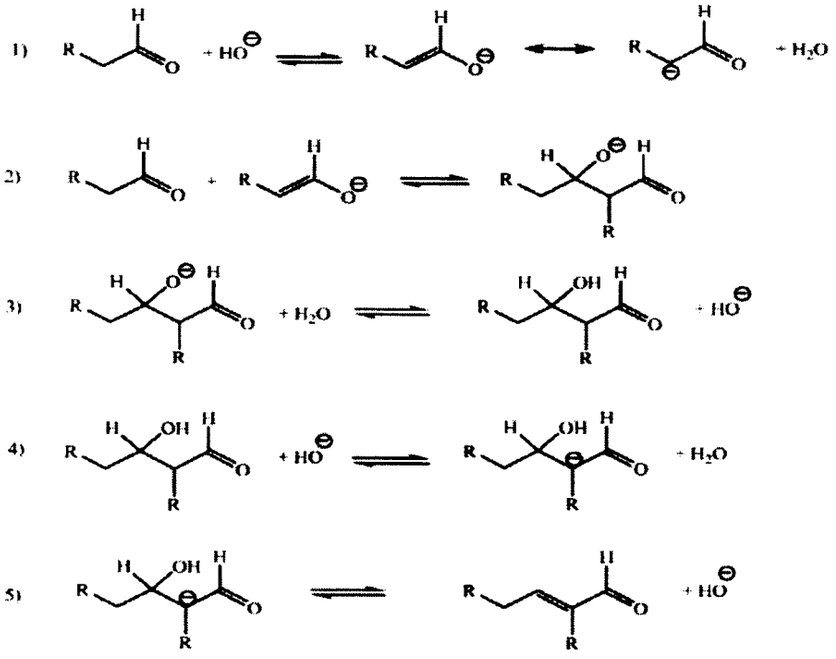
Equation 7

Scheme 1

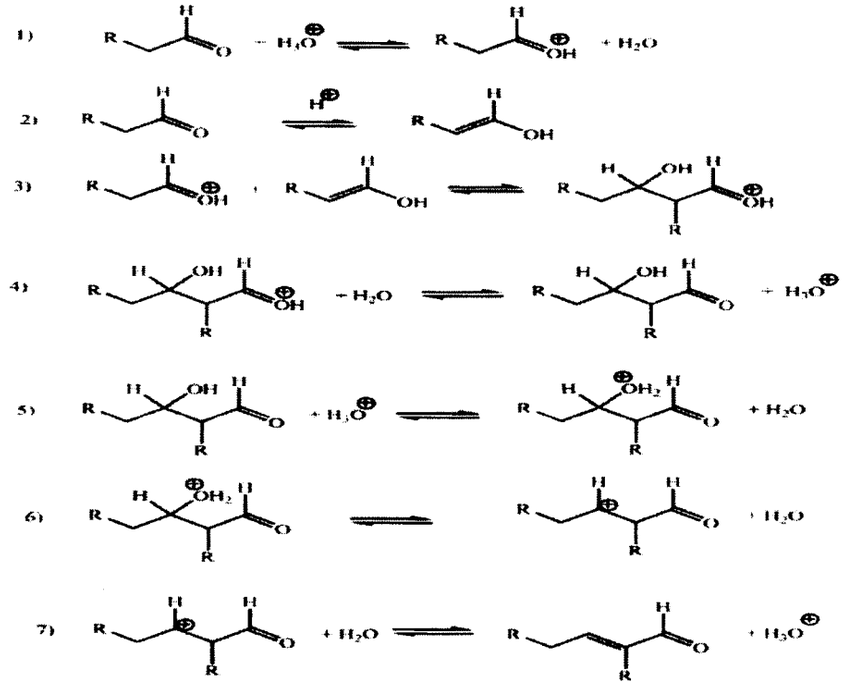
Aldol reactions were first carried out under simple general basic or acid homogeneous or heterogeneous catalytic conditions. Stoichiometric methods have been developed since the 1950s in order to overcome limitations in the scope and selectivity of those catalytic reactions. In these stoichiometric methods the donor is quantitatively deprotonated and the resulting enolate used directly or after conversion into a silyl enol ether or a boron enolate. A return to catalytic procedures has occurred recently in the search for asymmetric and for atom economically efficient procedures.

General catalytic aldol reactions

Typical bases for reactions carried out under basic catalytic conditions are alkaline or alkaline earth metal hydroxides. The use of basic ion-exchange resins as catalysts may be advantageous. Hydrochloric acid is the most frequent acid catalyst. Alcohols or alcohol–water systems are commonly used as solvents, although low molecular weight aldehydes and ketones react conveniently without solvent [2–5]. All the steps leading to aldolization are reversible (Schemes 2 and 3) and equilibrium constants may not be favourable to the progress of the conversion [6].



Scheme 2



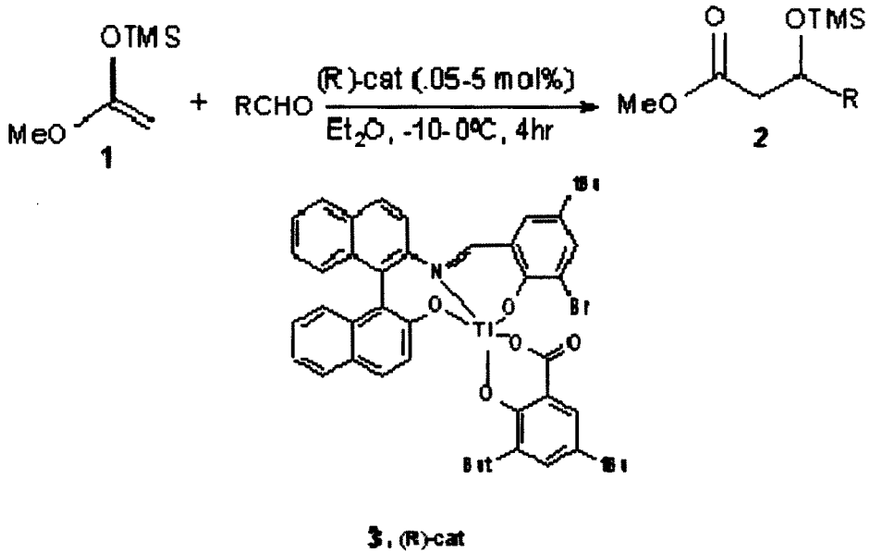
Scheme 3

Mukaiyama-type catalytic aldol addition reactions

In the early eighties work by Mukaiyama and co-workers [7] demonstrated that *in situ* generated Sn(II) enolates add asymmetrically to aldehydes in the presence of stoichiometric quantities of certain chiral diamine ligands as the only chiral inductors. Later on the same group developed the enantioselective aldol addition reaction of silyl enol ethers derived from esters or thioesters to aldehydes catalyzed by sub-stoichiometric quantities of a chiral Lewis acid [8]. In spite of the spectacular advances within the methodology of chiral Lewis acid-catalyzed enantioselective aldol addition reactions between enol silanes derived from either ketone, esters or thioesters and aldehydes [9-11], some aspects remain only partially addressed if at all. For instance, while the majority of the catalytic systems so far developed produce *syn*-aldols, catalytic systems leading to *anti*-aldols are very much less developed. Similarly, chiral catalysts based on fluoride ion sources remain essentially unexplored [12]. Another active research direction in this area seeks water-compatible catalytic systems. Also, problems associated with Mukaiyama-type reactions involving ketones as electrophiles or aldehydes as nucleophilic components remain essentially unresolved. Along with the latest developments in Lewis acid-catalyzed Mukaiyama reactions, it has been discovered very recently that the reaction between enol trichlorosilanes and aldehydes can be efficiently catalyzed by Lewis bases. This has opened a new platform for development and now both Lewis acid-promoted and Lewis base-promoted strategies are available for exploring Mukaiyama type reactions.

Lewis acid mediated reactions.

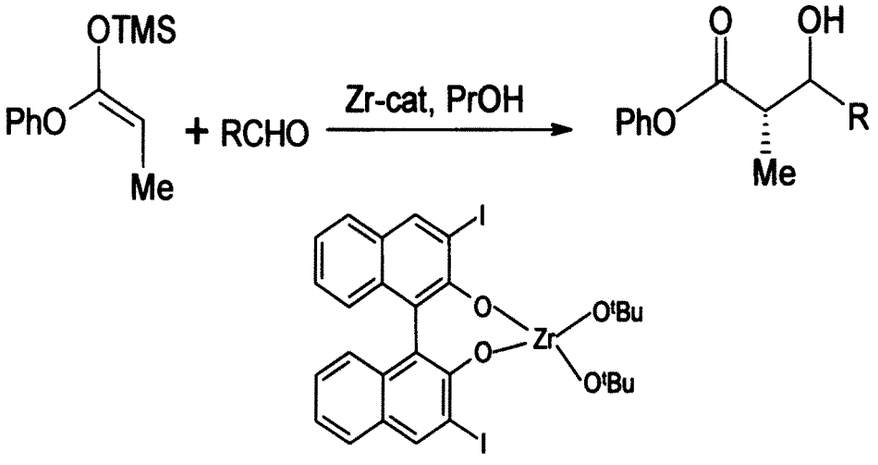
A substantial number of Lewis acids containing early and late transition metals and chiral ligands bearing nitrogen, oxygen and phosphorus donors have been developed to carry out Mukaiyama reactions enantioselectively [9-11]. One important aspect of this reaction is that catalyst activity usually depends on how fast intra- or intermolecular silyl transfer to the aldolate oxygen occurs with simultaneous liberation of the active catalyst. Under low catalyst turnover conditions, requirements for both high catalyst loadings and attenuation of the reaction enantioselectivity as a consequence of the "silicon-catalyzed" achiral aldol pathway can be predicted. In this respect, ligands bearing functional groups that may act as a silyl group shuttle have shown to be effective for improving catalyst turnover and activity. One prominent catalyst that meets these design elements is the titanium Schiff base catalyst **3** [13]. This catalyst is characterized by high activity and tolerance to a wide range of nucleophiles and electrophiles. Under optimized conditions, the simple methyl acetate-derived enol silane **1** adds to aldehydes in the presence of as little as 0.5 mol% of **3** at 0 °C to give adducts **2** in high yields and up to 98% ee (Scheme 4).



Scheme 4 Mukaiyama aldol reactions of trimethylsilyl ketene acetals and aldehydes catalyzed by (*R*)-**3**.

A significant advance in the Mukaiyama reaction has been the ability to produce *anti*-aldols. The majority of catalysts for the Mukaiyama reaction lead to preferential formation of *syn*-aldols irrespective of the configuration of the enolsilane involved and very few have proven to be suitable for producing the cc rresponding *anti*-aldols.

The zirconium catalyst demonstrates this principle (Scheme 5) [14]. The reaction of acetal ketene with aldehydes promoted by this catalyst affords preferentially *anti*-aldol adducts independent of the silyl enolate geometry. An interesting feature of this catalytic system is that the addition of protic additives (alcohols) and small amounts of water are critical for catalyst turnover and formation respectively.

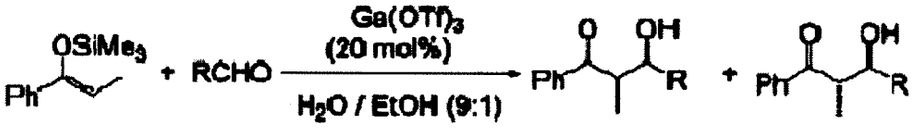


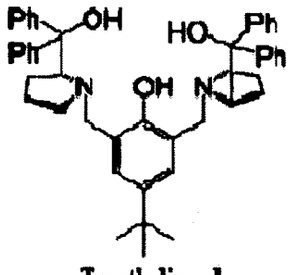
Zr-cat

Scheme 5

Enantioselective Mukaiyama aldol reactions in aqueous media, although incipient, constitute another important advance in the area [15]. Two main difficulties need to be addressed for such reactions to work efficiently. Firstly, many cations (*i.e.* Lewis acids) hydrolyse very easily in water and, secondly, chiral ligand coordinated metal complexes tend to be unstable in water. One attractive solution to address these issues is based upon the concept of multicoordination. Both transition metals and rare earth metals upon coordination to newly designed chiral ligands have provided effective Lewis acid catalysts for aldol reactions in aqueous media [16].

Mukaiyama aldol reactions that are tolerant of higher water/organic solvent ratios have been described recently, including complexes obtained from gallium(III) and chiral semi-crown ligands, particularly Trost's ligand, *vide infra*, which provides uniformly good results (Scheme 6) [17].





Trost's ligand

Scheme 6

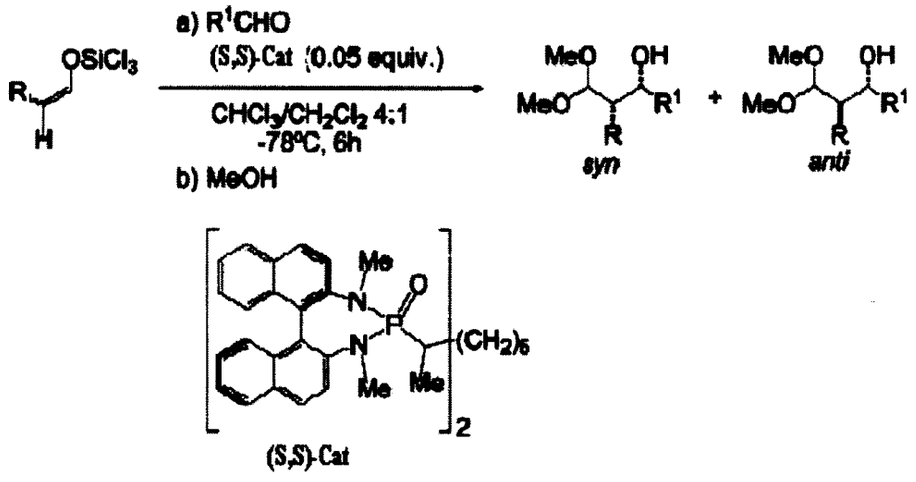
Although most organic materials have limited solubility in water, these findings show that protic, less volatile solvents or mixtures of protic solvents and water are suitable for aldol reactions, and have opened the way for exciting new research in the area.

Lewis base mediated reactions.

All of the Lewis acid catalyzed Mukaiyama reactions, except for those promoted by chiral carbenium ions [18] imply the participation of a metal-based catalyst which activates the electrophilic component of the reaction. A conceptually different approach is based on the activation of the nucleophilic component such as has been achieved by using trichlorosilyl enolates as nucleophiles and chiral phosphoramides as Lewis base catalytic promoters [19]. Replacement of a chlorine by coordination of the phosphoramide oxygen to the silicon appears to lead to a cationic silicon enolate intermediate species that subsequently binds to the electrophilic carbonyl to effect aldolization. For this latter step, two independent pathways are proposed: a boat-like transition structure

with low facial selectivity which would lead to the *syn*-isomer and a chair-like transition structure involving a second molecule of phosphoramide, which would lead to the *anti*-product. The relative importance of both reaction pathways depends on the size and concentration of the catalyst as well as the architecture of the substrate. This method is particularly suitable for alkyl (aryl) methyl ketones, substrates that have proven to be very difficult in the context of typical Mukaiyama procedures.

The development of this approach has resulted in the first method for carrying out catalytic enantioselective cross-aldol reactions of aldehyde [20]. Under optimized conditions, geometrically defined trichlorosilylenolates of aldehydes undergo high yielding addition to aldehydes in the presence of phosphoramide. The *syn*-adducts are the predominant species obtained from (*Z*)-enolates, while (*E*)-configured enolates (Scheme 7).



Scheme 7

Direct catalytic aldol addition reactions

Activation of the donor carbonyl component *via* metal enolate or silyl enol ether formation usually requires a previous and irreversible synthetic operation that may be one-pot (metal enolates) or may require a separate reaction with subsequent isolation of the activated intermediate (silyl enolates). In either case, stoichiometric quantities of reagents are required. From several aspects, direct methods that allow the cross aldol reaction of otherwise unmodified carbonyl donors present much interest, especially if a sub-stoichiometric amount of the promoter (catalyst) is sufficient. Indeed, biochemical aldol reactions such as those catalyzed by aldolases and catalytic antibodies perfectly meet the atom economy principle by using unmodified carbonyl donors. The use of aldolases and catalytic antibodies, however, is little implanted in practical synthesis presumably because they still present a narrow substrate scope. The development of purely chemical methods for the direct, catalytic aldol addition reaction had been awaiting small molecules capable of simultaneously activating the donor and the acceptor carbonyls. Such small molecules now are known and can be grouped into artificial metal complexes and purely organic molecules (organocatalysts) – either natural or designed.

Metal complexes as catalysts

Inspired by the mode of action of type II aldolases, the first examples of metal complex-induced direct asymmetric aldol addition reactions were reported by Shibasaki using catalyst ((R)-LLB). The catalyst design is based around the general principle of two center catalysis (Fig. 1) [21] Two sites of opposite character can be identified in the metal complex: a basic site and an acidic site,

each capable of independently activate in close proximity both the donor ketone (substrate 2) and the acceptor aldehyde (substrate 1), respectively. The chiral backbone of the catalyst can induce a preferential orientation of both substrates thus resulting in the production of an unequal stereoisomeric distribution of aldol products.

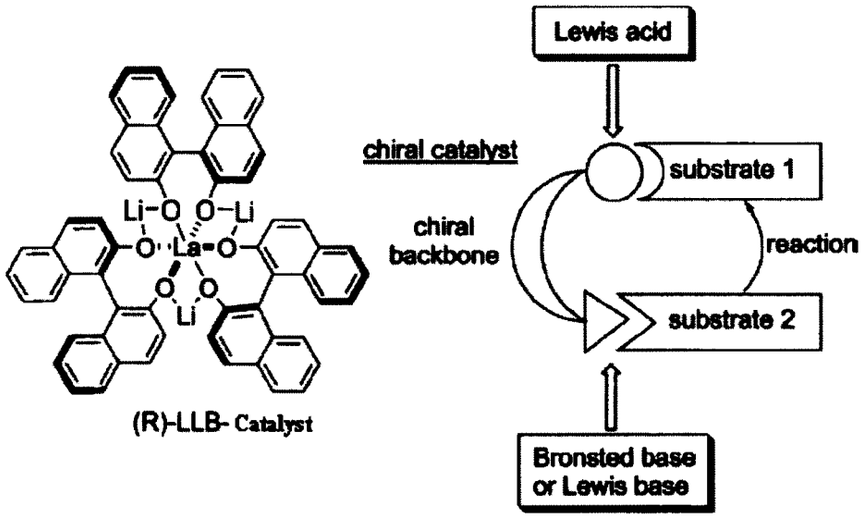


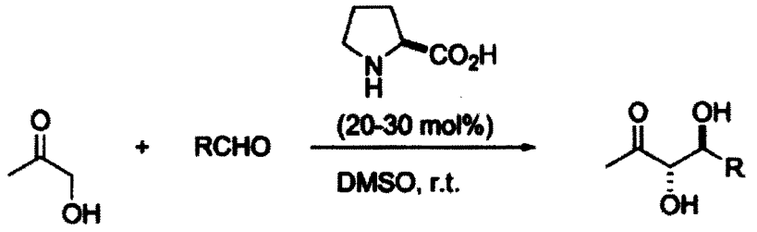
Figure 1.

Since that report, a few metal-complexes have been documented to be capable of promoting direct asymmetric aldol reactions under catalytic conditions [22] Most of these catalysts are effective with loadings in the 1–20 mol% range. Some catalysts performance can be greatly affected by additives which are used to optimize catalyst turnover or to minimize formation of side-products such as dehydration products. Examples are the use of molecular sieves and the use of water or a KHMDS/water mixture. To date, the substrate scope for these catalytic systems is relatively narrow. Methyl ketones (acetone, acetophenone) are the best suited carbonyl donors, but they have to be used in large excess in most cases.

Also, the efficiency with respect to the substrate aldehyde employed decreases in the order highly-α-branched > less-α-branched > unbranched ≈ aromatic.

Organocatalysis

Aldol addition reactions of unmodified ketones or aldehydes promoted by purely organic molecules without assistance of any metal are another important modern achievement in the area. Since the pioneering finding by List, Barbas III and co-workers that 30 mol% of the simple amino acid, L-proline could promote the aldol addition reaction of acetone to an array of aldehydes in up to > 99% ee [23], the concept of small organic molecules as catalysts has received great attention. Apart from acetone, hydroxyacetone also behaves nicely in reactions with aldehydes in the presence of L-proline to afford the corresponding *syn*-diols in high enantioselectivities and variable yields, (Scheme 8) [24,25].

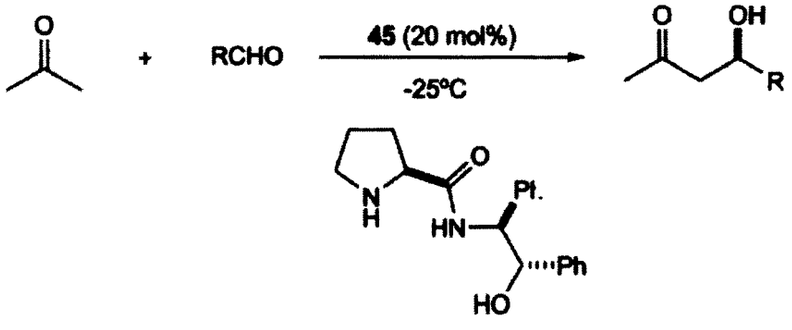


Scheme 8

The catalytic cycle of the proline-catalyzed aldol addition reaction proceeds *via* an enamine intermediate. Enamine-mediated mechanisms are also prominent in aldol reactions catalyzed by the aldolase I type enzymes and catalytic antibodies, where enamine formation is considered to be the rate limiting step of the process.

Two limitations associated with the proline-catalyzed aldol reaction are the relatively large amount of proline required (20–30 mol%) and the low enantioselectivities obtained when aromatic aldehydes are employed. In a recent

repot [26], modified proline, (Scheme 9), have been shown to alleviate these limitations.

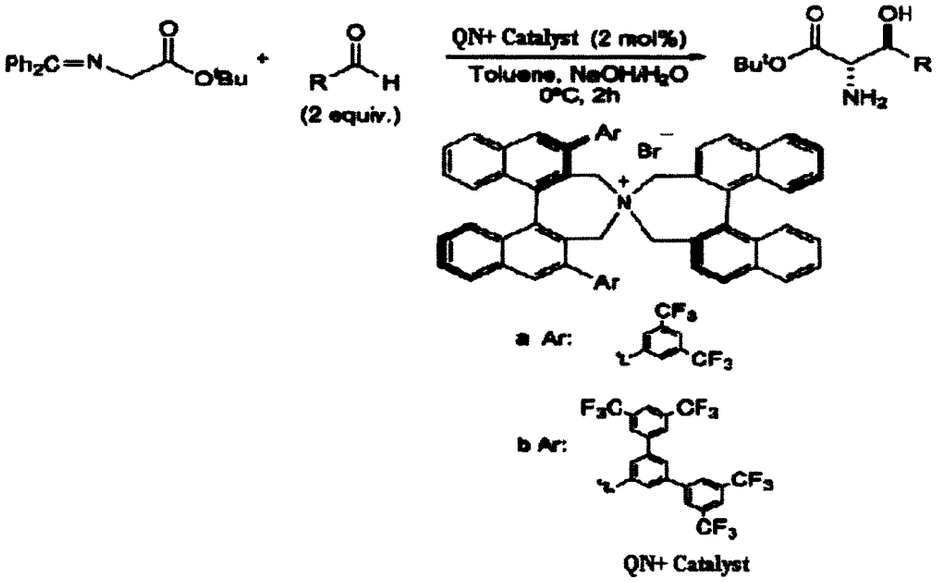


Scheme 9

Two additional developments in the field of direct aldol addition reactions catalyzed by chiral organic molecules other than L-proline and its congeners have been documented. One of the strategies is based on the use of a 1:1 mixture of chiral 1,2-diamines and a protonic (carboxylic, sulfonic or phosphonic) acid [27]. It has been shown that these systems are able to promote the reaction of acetone or some other symmetric ketones with a narrow array of aromatic aldehydes or cyclohexyl carbaldehyde. The formation of considerable amounts of dehydrated aldol product in some instances and the low *syn:anti* selectivity attained are some limitations at present. A mechanism is proposed for this reaction that is reminiscent of the proline-mediated aldolization, wherein the protonated amino group mimics the role played by the carboxylic group of proline.

The second alternative, (Scheme 10), is based upon the use of some chiral quaternary ammonium salts derived from binaphthyls under phase-transfer conditions [28]. As little as 2 mol% of the chiral ammonium salts are capable of forming the aldol addition products derived from glycine Schiff bases and aldehydes in good yields, moderate *anti:syn* selectivity. Finally, organocatalysis

for direct aldol additions in aqueous systems is still not well developed. Although proline and several chiral diamines do promote the addition reaction of acetone, (di)hydroxyacetone and other ketones to aldehydes in buffered aqueous media, the obtained diastereo- and enantioselectivities are still disappointing [29,30].



Scheme 10

Solvent free catalytic aldol reactions

Aldol reactions of small molecular weight aldehydes and ketones are carried out under catalytic conditions without any solvent. This is the case for acetaldehyde, butanal, acetone, or cyclohexanone. However, few recent reports of aldol condensations of higher molecular weight aldehydes or ketones under solvent-free conditions have been described. Thus, excellent condensation yields have been obtained by simple mixture of donor, acceptor and a molar equivalent of sodium hydroxide by grinding them together with a mortar and pestle or in a vibrating mill and a quite simple isolation of products (Scheme 4) [31,32].

Microwave activation has proved convenient for Claisen–Schmidt and related reactions carried out with or without solvent, either directly or by use of acetals [33-35]

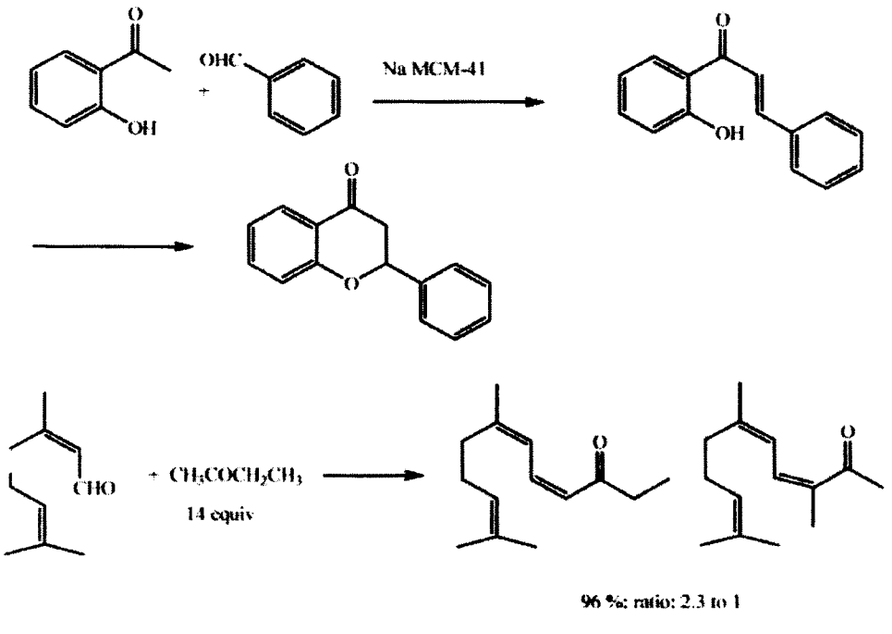
Reactions in ionic liquids

The self-condensation of propionaldehyde and the cross condensation of the same aldehyde and 2-methylpentanal have been performed in ionic liquids. Best results with 1 M hydroxide containing butyldimethylimidazolinium hexafluorophosphate [bdmim][PF6] afford conversion yields comparable to those obtained in parallel condensations in water. Side products due to further aldol condensations of the first products are observed in the ionic liquids. However, significantly better selectivity results for the cross aldol condensation of propionaldehyde and 2-methylpentanal are obtained in
[bdmim][BF4] than in water [36]

Reactions under heterogeneous catalysis

Heterogeneous catalysts for the aldol reaction offer the possibility of simpler separations of the catalyst from the reaction mixture. Though attractive due to their easy design, variety of porous system, hydrophobicity and hydrophilicity, zeolites have not proved good catalysts up to now for those aldol reactions susceptible to being useful in fine chemistry and pharmaceutical industries. Modified hydrotalcites and microporous silica seem more promising and are the object of much current work. Thus, a hydrotalcite modified with potassium t-butoxylate catalyses the condensation of acetone with a variety of substituted benzaldehydes very efficiently, with 100% conversions and isolated yields above 90% (Scheme 11) [37,38]. Although high yields are described for the aldol

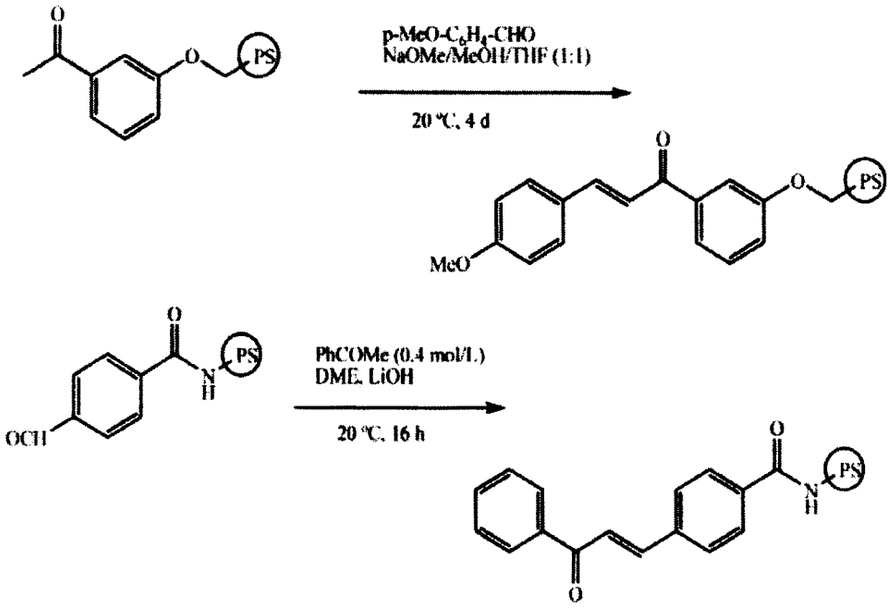
condensation of citral with excess butanone, regioselectivities found are still poor [39].



Scheme 11

Synthesis on solid phase

Aldol reactions and related condensations have been carried out on solid insoluble supports. Either the donor or the acceptor may be linked to the support (Scheme 12). With all the constraints bound to solid supported reagents, this optional method may be convenient for some cross condensations. However, one problem encountered is related to the fact that in solid phase synthesis, reagents have to be used in excess. This can lead to side reactions. For instance, the enone that forms by reaction of a resin-bound aldehyde with a ketone may undergo Michael addition of the excess of ketone [40]



Scheme 12

7.2 PRESENT WORK

Currently, there is a great concern for the environment, which means chemical companies are now finding themselves under increasing legislative and economical pressure to reduce their emissions and waste. This has lead to the creation of 'Green Chemistry', which is defined as [41]:

"*The design of chemical products and processes that reduces or eliminates the use and generation of hazardous substances'.*

An environmentally friendly chemical process is the vital part of the current chemical research and development [42]. Recently, environmentally benign approaches have been developed using solvent-free conditions [43]. Much attention, however, has been focused on the use of water as a green solvent in organic synthesis. In addition to its abundance, economy and safety, water has become a natural substitute and an alternative environmentally benign solvent in organic synthesis [44]. The use of an aqueous medium as solvent also reduces the

harmful effects of organic solvents on the environment. These advantages become even more attractive if such reactions can be performed using reusable catalysts.

The aldol reaction is one of the most powerful and useful reactions utilized in the construction of the carbon-carbon bond [45]. Aldol reaction has been classically conducted in the presence of strong base or acid. [46]. However, under such strong basic or acidic condition, the synthesis of the desired aldol product is plagued by the concomitant α,β-unsaturated ketone, formed through aldol dehydration [46a,c] and other side products from polycondensation, self-condensation of the ketone, Michael addition to the formed enone, and so on. [46a]. To overcome these problems, various Lewis acids [47] or Lewis bases [25,48] have been explored as alternative catalysts. But in most of the cases the ketones need to be modified as silyl enol ethers, ketene silyl acetals, etc.

Aldol reactions in pure water have been reported; however the substrates have to be modified as silyl enol ethers, ketene silyl acetals and boron enolates [49]. Most recently, proline catalysed aldol reactions in aqueous micelles [50] and sodium carbonate catalysed aldol reactions in water have been reported [51]. Zn complexes of proline, lysine and arginine catalysed aldol addition of p-nitrobenzaldehyde and acetone in aqueous medium at room temperature have also been reported [52].

To the best of our knowledge, there is no report of aldol reaction of unprotected ketones in pure water promoted by Amberlite IRA-400 (basic) resin as the heterogeneous catalyst at ambient temperature.

Herein we present the highly efficient and practical aldol reaction of unmodified ketones with reactive aldehydes bearing strong-electron withdrawing

groups in water catalyzed by Amberlite IRA-400 (basic) resin at room temperature.

7.3 EXPERIMENTAL

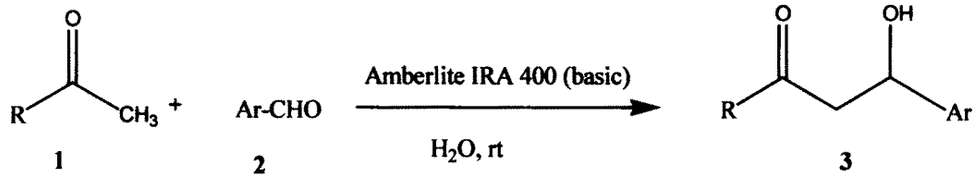
Reagents and solvents were obtained from commercial suppliers and were used without further purification. Melting points were determined in open capillaries and are uncorrected. IR was recorded as KBr pellet on a Thermo Nicolet spectrometer and reported in cm^{-1}. NMR was recorded on Bruker Avance 300MHz spectrometer, for ^{1}HNMR, chemical shifts (δ) are reported in parts per million relative to tetramethyl silane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

Represantative Procedure for the preparation of β-hydroxyl ketones (3).

A mixture of ketone **1** (1.05mmol) and aldehyde **2** (1mmol) in 15ml of water was stirred vogorously at room temperature for several minutes to form enough turbidity and a good dispersion. Then 1gm of resin, Amberlite IRA 400 (basic) was added. The reaction was followed and monitered by TLC. After the reaction was complete, the reaction mixture was filtered by buchner filteration and the solid residue was washed with ethyl acetate and filtered and the filtrate was kept at room temperature. The crystals of β-hydroxyl ketones were developed in about 2hr. Thus separated resin can be reactivated and reused for next batch reaction. In all the cases the product obtained was analytically pure.

7.4 Results and Discussion

The reactions of ketones **1a-b** and aldehydes **2a-e** proceeded very well under the same conditions to afford **3** in very high yields (Scheme 13).



1 2 3

1a: R=Ph
1a:R=4-Cl-Ph

2a:Ar=Ph
2b:Ar=2-NO_2-Ph
2c:Ar=3-NO_2-Ph
2d:Ar=4-NO_2-Ph
2e:Ar=4-Cl-Ph

Scheme 13. Cross-aldol reactions of ketones 1a-b and aldehydes 2a-e in water catalysed by Amberlite IRA 400 (basic).

The reaction times, yields and purities for the cross-aldol reactions of ketones **1a-b** with aldehydes **2a-e** are listed in Table 1. From Table **1**, it can be seen that the isolated yields are nearly quantitative with high purity under the given reaction conditions. The reactivity orders for the ketones and aldehydes as **1b>1a** and **2d>2e>2c>2b>2a** respectively. The lower reactivity of 2-nitrobenzaldehyde to that of 3-nitro, 4-nitro and 4-chloro benzaldehydes is probably due to the steric effect of the ortho nitro group. The identities of all the aldol products were ascertained by NMR spectra. In the ^{1}H NMR spectra of 3ab and 3bb, the two methylene protons are magnetically nonequivalent, due to strong influence of the *o*-nitro group of the benzene ring and each proton has a double-doublet splitting patterns. The methine proton shows a triplet splitting, fully consistent with their structures.

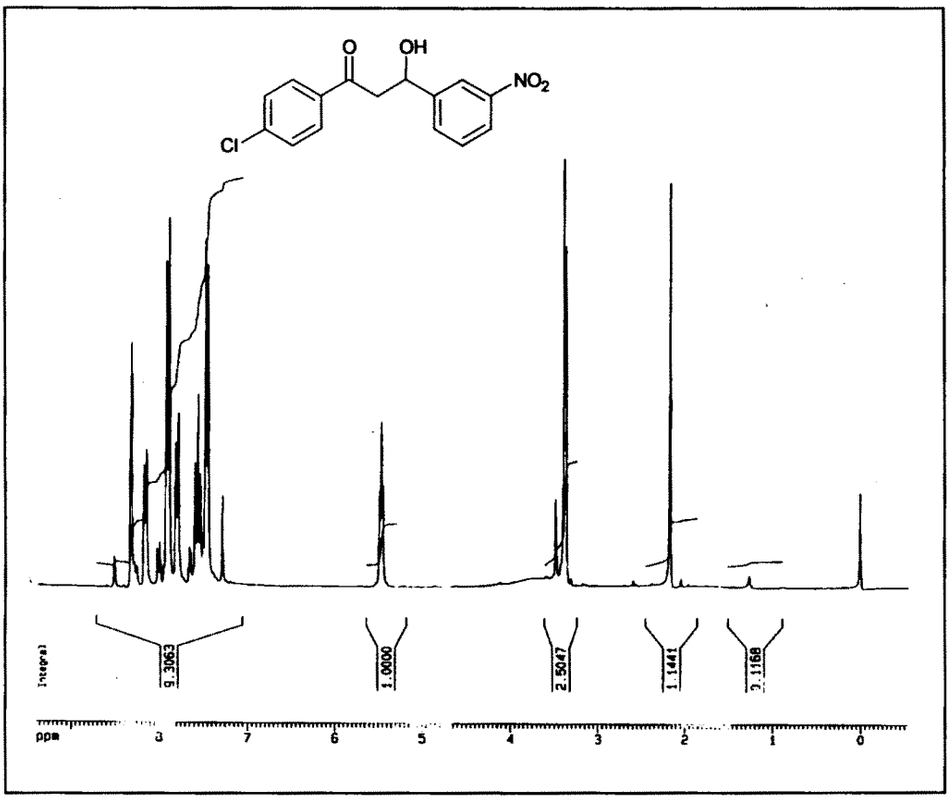
Besides nitrobenzaldehydes, other reactive aldehydes bearing strong electron-withdrawing groups could undergo resin catalysed aldol reactions at room temperature and give selectively the β-hydroxyl ketones. For example 4-chlorobenzaldehyde reacted with acetophenone in the presence of resin in water at ambient temperature for 18hr to produce 3-(4-Chlorophenyl)-3-hydroxy-1-phenyl-1-propanone in 89% yield.

Despite the extremely low solubility of both ketones and aldehydes used in water, the resin, Amberlite IRA 400 catalysed aldol reactions could still proceed efficiently at ambient temperature. The aldol reaction might take place at the interface of the organic reactants with water. The sparsely dissolved ketones and aldehydes in water could also react to give the aldol product in the presence of the resin. It was found that vigorous stirring was required for the success of the aldol reaction. The aldol products 3 could be obtained in practical pure form by simple Buchner filtration and washing the solid residue with ethyl acetate to separate the polymer. And the crystals started develop within 2hr. It should be noted that the separated resin can be regenerated and recycled for the next batch reaction. As an example, the reaction of **1a** and **2c** afforded **3ac** quantitatively in all three subsequent runs.

The aldol synthetic method reported here does not require the preformed silyl enol ethers or ketene silyl acetals which generate significant amount of metal salts as waste and usually demand the use of potentially polluting solvents and low temperatures. Catalysed reactions of acetophenone with aromatic aldehydes are known to give chalcones under nonaqueous solvents [53] or solvent free conditions [54]. Under our reaction conditions, no traces of dehydration products from the initially formed β-hydroxyl ketones, self-condensation products of ketones and

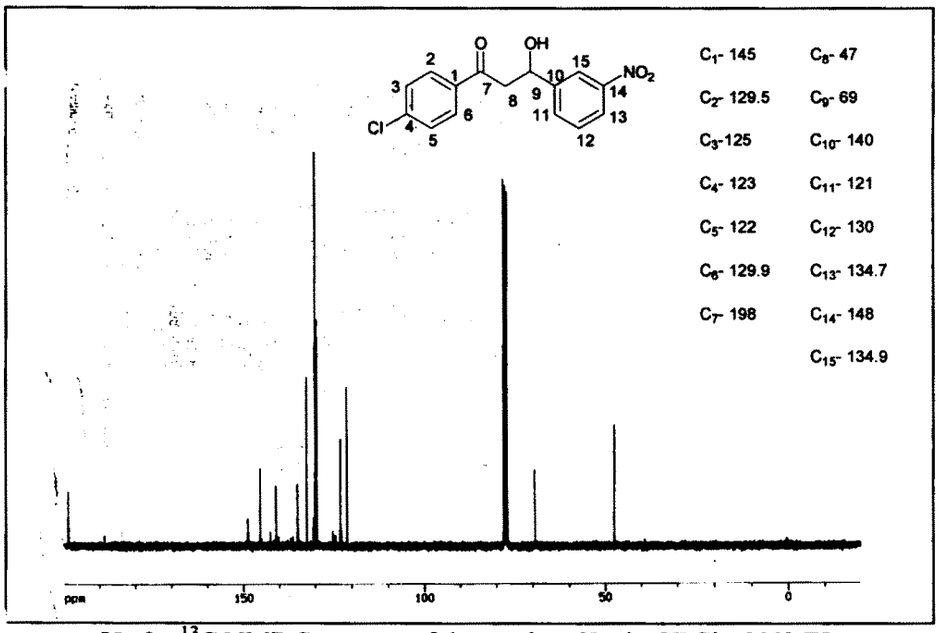
diols resulting from tandem aldol reduction reactions of ketones **1a,b** and aldehydes **2a-e**. β-hydroxyl ketones **3** were the single isolated products with nearly quantitative yields.

7.5 Spectra

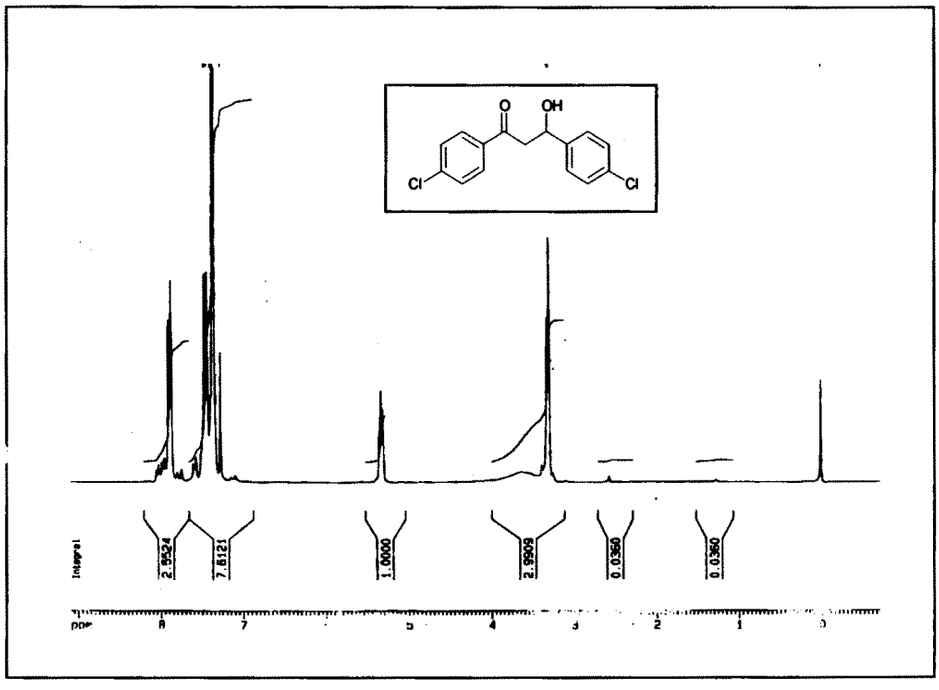


Spectrum No 1. ^{1}H NMR Spectrum of the product **3bec** in $CDCl_3$, 300MHz

In ^{1}HNMR spectra, the above compound (spectrum No.1) shows a doublet at 3.39 ppm (J=6.1 Hz) is due to methylene protons and triplet at 5.46 ppm (J=5.73 and 6.0 Hz) is due to –CH-OH. Aromatic protons resonated as a multiplet in the range of 7.28-8.32 ppm. And ^{13}CNMR (Spectrum No.2) is in total agreement with corresponding structure.

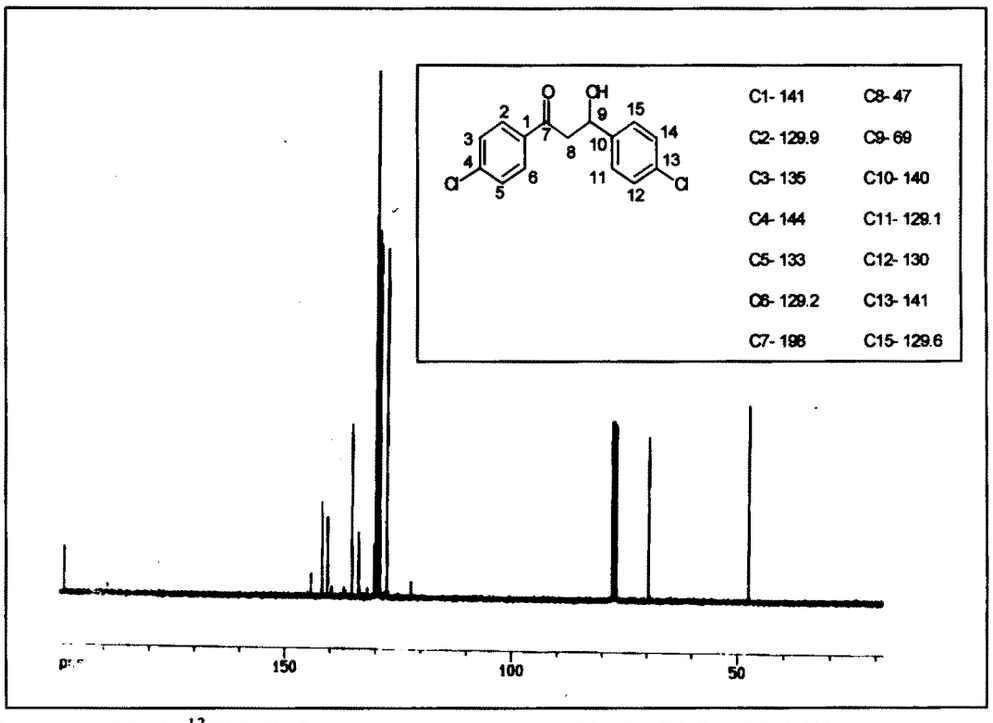


Spectrum No 2. ^{13}C NMR Spectrum of the product **3bc** in $CDCl_3$, 300MHz



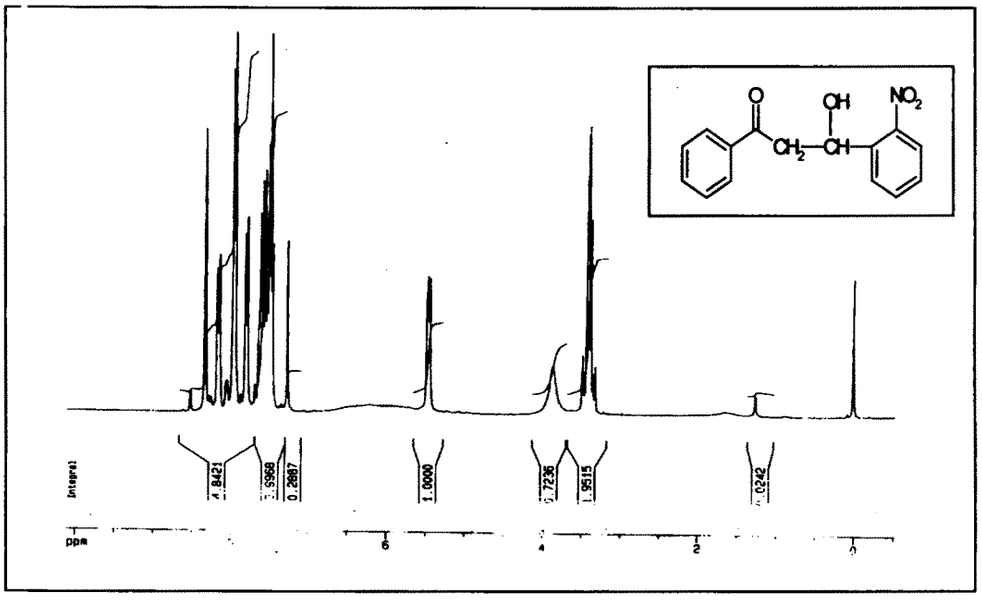
Spectrum No 3. ^{1}H NMR Spectrum of the product **3be** in $CDCl_3$, 300MHz

The ^{1}HNMR spectrum of the **3be** (Spectrum No. 3) exhibited doublet at δ-3.33 ppm (J=4.9 Hz) is due to methylene proton (-CO-CH_2-) and quadrate at δ-5.33 ppm (J=4.8 and 6.6 Hz) is due to CH of –CH-OH- . Aromatic protons exhibited two doublets of doublets at 7.49 (dd, J= 8.4 Hz) ppm and 7.91 (dd, J=6.5 Hz) ppm and OH appeared as a broad singlet at 7.08 ppm which is D_2O exchangable and ^{13}CNMR is in total agreement with corresponding structure (Spectrum No.4).

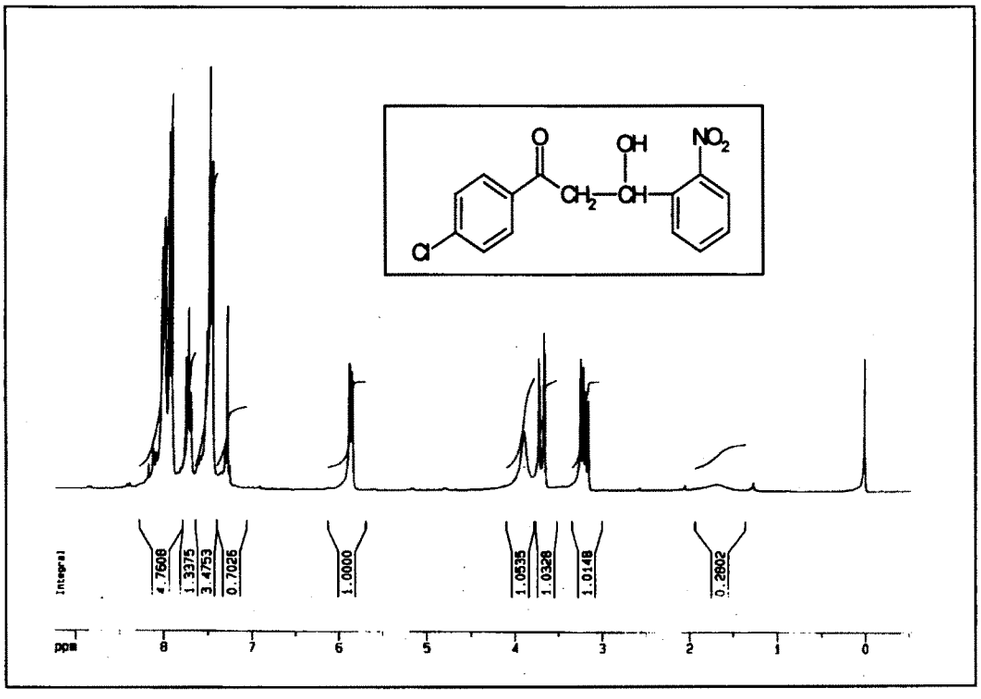


Spectrum No 4. ^{13}CNMR Spectrum of the product **3be** in $CDCl_3$, 300MHz

In the ^{1}H NMR spectra of **3ab** and **3bb** (Spectrum 5 & 6), the two methylene protons are magnetically nonequivalent, due to strong influence of the o-nitro group of the benzene ring and each proton has a double-doublet splitting patterns. The methine proton shows a triplet splitting, fully consistent with their structures.



Spectrum No 5. ^{1}H NMR Spectrum of the product **3ab** in $CDCl_3$, 300MHz



Spectrum No 6. ^{1}H NMR Spectrum of the product **3bb** in $CDCl_3$, 300MHz

The ^{1}HNMR results of the products 3ab,3ae,3bb are summarised in Table 1.

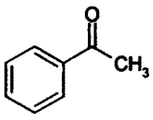
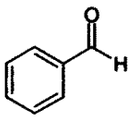
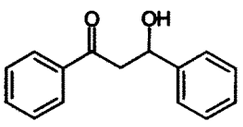
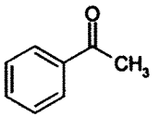
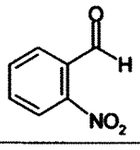
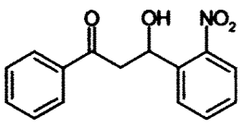
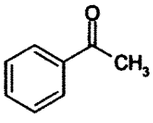
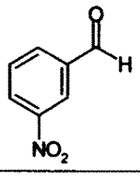
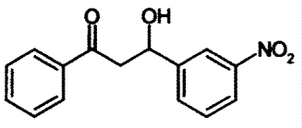
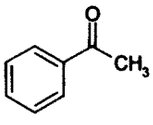
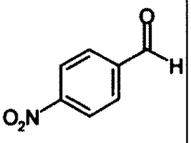
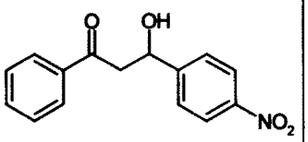
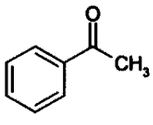
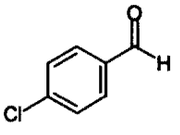
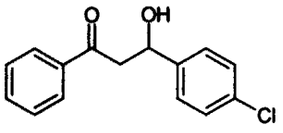
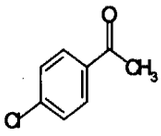
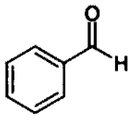
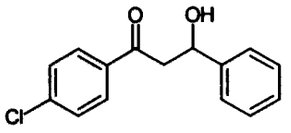
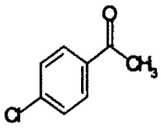
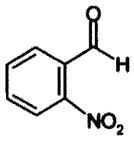
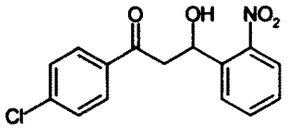
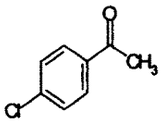
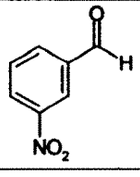
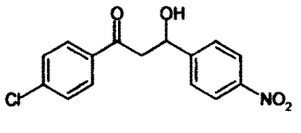
Table 1.

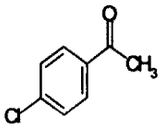
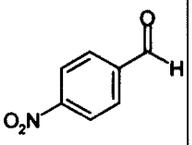
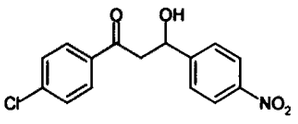
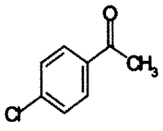
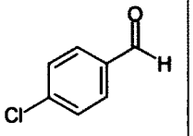
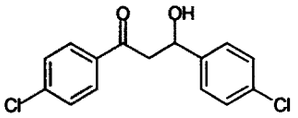
Product	^{1}HNMR Results
3ab	m.p:106-107°C. ^{1}HNMR (300MHz, $CDCl_3$)δ= 3.43(d,d, 2H, CH_2 J=5.8 and 3.3 Hz),3.87 (Br.s, 1H, OH) 5.48 (d.d, 1H, CH, J=3.02 and 2.82 Hz), 7.47-8.18 (m, 9H, Ar-H).
3ae	m.p: 117-118°C. ^{1}HNMR (300MHz, $CDCl_3$) δ= 3.35 (d, 2H, CH_2 J=5.2Hz), 5.34 (t, 1H, CH, J=6.39 and 5.49Hz), 7.27-8.06 (m, 10H, Ar-H, OH).
3bb	m.p:82-85^{0}C ^{1}HNMR (300MHz, $CDCl_3$) δ= 3.67 (d,d, 2H, CH_2, J=1.99 and 2.0 Hz) 3.87 (br,s, 1H, OH) 5.88 (d,d, 1H, CH, J=9.08 Hz) 7.3-8.12 (m, 8H, Ar-H)

7.6 Conclussion

The present contribution describes the utilization of Amberlite IRA 400 (basic) resin as an efficient catalyst for the aldol reactions of unmodified ketones and reactive aldehydes in pure water at ambient temperature. An environmentally friendly and efficient process for the synthesis of β-hydroxyl ketones has been proven to be practical from the aldol reactions of ketones and reactive aldehydes bearing strong electron-withdrawing groups. The current method is very attractive and appealing synthetic process for β-hydroxyl ketones because of the following adventages: (1) 100% atom economical reaction, (2) Very high yield, (3) Simplicity of product isolation, (4) Usage of water as environmentally benign reaction medium and (5) Catalytic usage of Amberlite IRA400 (basic) as a reusable catalyst. The protocol reported in this paper can be easily developed into large-scale preparation of β-hydroxyl ketones.

Table 2. Reaction times, yields for the cross-aldol reactions catalysed by Amberlite IRA 400 (basic)

Srl. No	Ketone **1a,b**	Aldehyde **2a-e**	Time (hr)	Product **3**	Yield (%)[a] & (M.P.°C)
1			24		89 (98-101)
2			18		83 (106-107)
3			18		93 (82-84)
4			18		91 (112-114)
5			24		89 (117-118)
6			20		81 103-107)
7			20		87 (82-85)
8			18		89 (113-115)

9			20		93 (118-120)
10			22		79 (78-80)

[a]Isolated yield. The identities of the products has been ascertained by NMR

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