HIGHLIGHTS

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Highlights

Markus Hölscher reviews some of the recent literature in green chemistry

Direct ester condensation with water-tolerant Zr and Hf catalysts

Replacements for current chemical processes by more environmentally benign alternatives is a highly desirable aim for many reactions, especially for fundamental reactions used in large-scale synthesis such as ester condensations. Ishihara and Yamamoto from Nagoya University and the University of Chicago, respectively and their coworkers investigated the catalytic performance of HfCl$_4$·2THF and ZrCl$_4$·2THF and found highly active systems. Due to the sensitivity of these compounds towards moisture they extended their work and reported very recently on the use of HfOCl$_2$·8H$_2$O and ZrOCl$_2$·8H$_2$O as efficient and water-tolerant catalysts for direct ester condensations (*Adv. Synth. Catal.*, 2004, **346**, 1275–1279).
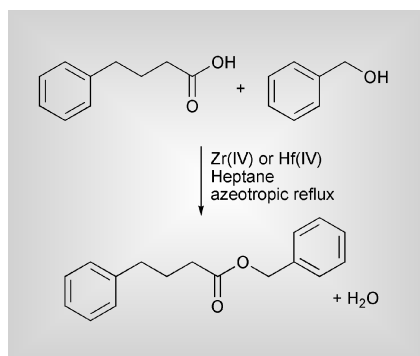

The hydration of the catalysts was found to be crucial for catalytic performance, since fully hydrated oxychlorides showed nearly full conversion and selectivity in the reaction of 4-phenylbutyric acid and benzyl alcohol (heptane, azeotropic reflux, 7 h), whereas partly dehydrated catalysts yielded poor conversions. In the case of Zr these findings were related to the tetrameric [Zr$_4$(OH)$_8$·16(H$_2$O)]$^{8+}$ cation structure of the catalyst. Several alcohols including secondary alcohols and phenol were tested as well as different carboxylic acids. The catalysts could be recycled without loss of activity and selectivity by simply adding hydrochloric acid,

followed by extraction of the organic phase with Et$_2$O. The resulting aqueous phase could be reused directly for the next condensation.

Alkylarene oxidation with molecular oxygen

Polycene oxidation has received much attention because the corresponding reaction products are interesting compounds for organic semiconductors and transistors. Numerous catalytic oxidation systems have been reported, however environmentally friendly methods are scarce. Mizuno *et al.* from the University of Tokyo discovered that molecular oxygen converts a variety of alkylarenes to different oxidation products in a selective and efficient way when a heterogeneous Ru(OH)$_x$/Al$_2$O$_3$ catalyst is used (*Org. Lett.*, 2004, **6**, 3577–3580).
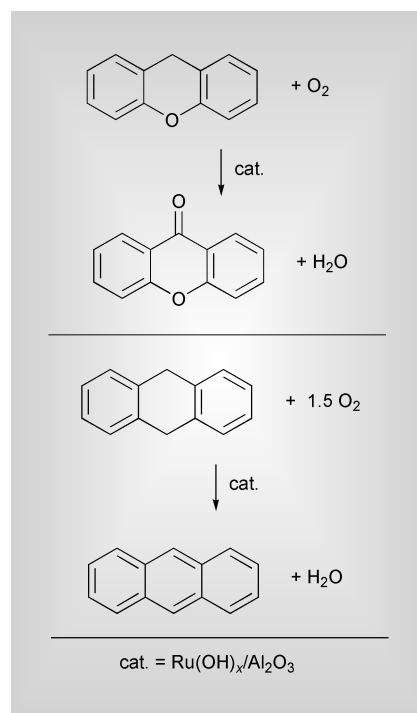
Prototypical test examples were xanthene and 9,10-dihydroanthracene, which were converted to xanthen-9-one and anthracene with conversions of 99% and selectivities of 99% and 93%,

respectively. ICP analyses confirmed the absence of Ru metal in the filtrate after separation of the catalyst. Also the reaction stopped immediately when the catalyst was removed from the reaction system, indicating a truly heterogeneous process. Various alkylarenes were tested, which led to the interesting result that monoactivated substrates such as toluene and xylene could not be oxidized. In contrast substrates with one benzylic methylene group like xanthene and fluorene were selectively oxidized at this position to the corresponding ketones in very high yields. The catalyst could be recycled without loss of activity and selectivity.

Incorporation of bromide into supported Pd catalysts enhances H$_2$ to H$_2$O$_2$ oxidation

H$_2$O$_2$ is an environmentally friendly oxidizing agent and demand for it is increasing continuously. It is used *e.g.* in the paper industries and for water purification as well as waste water treatment. Currently H$_2$O$_2$ is produced by the anthraquinone process, which is a multistep process with certain limitations and disadvantages. A direct oxidation of H$_2$ to H$_2$O$_2$ using a "green" method would be an interesting alternative. Choudhary *et al.* from the National Chemical Laboratory, Pune discovered that the addition of bromide ions to supported Pd catalysts drastically enhances the catalytic efficiency (*Chem. Commun.*, 2004, 2054–2055). No matter which carrier was used (alumina, zirconia, silica, gallia and H-β-zeolite) all catalysts showed poor performance with H$_2$O$_2$ yields between 0.0 and 3.9% in the absence of bromide. However, when the catalysts were impregnated with the corresponding ammonium halide remarkable effects could be observed. In all cases the incorporation of bromide into the catalyst resulted in a drastic increase in H$_2$O$_2$ production with yields ranging between 23.3% (silica carrier) and 29.7% (alumina carrier). The introduction of chlorine, fluorine or iodine yielded very poor results (not significantly higher than the halogen free

catalyst) or even resulted in complete inactivity. The H$_2$O$_2$ yield could be increased further to *ca.* 35% when the optimum amount of bromide (determined to be *ca.* 0.2 mmol g^{-1}) was present in the catalyst. Also it was found that the brominated catalyst activity for H$_2$O$_2$ decomposition was markedly reduced. Leaching of Pd was not observed. The underlying mechanisms of bromide action have yet to be fully revealed.

Environmentally benign synthesis of cyclic amines with Cp*Ir catalysts

The functionality of *N*-heterocyclic compounds has made them interesting building blocks in pharmaceutical chemistry and synthetic organic chemistry. In particular, pyrrolidine, piperidine and morpholine derivatives occur very frequently in biologically active compounds, which explains the significant research efforts that were made during past decades to make such compounds available. With regard to sustainability, the *N*-heterocyclization of primary amines with diols is an advantageous approach since easily available starting materials can be employed in a one step synthesis generating only water as a byproduct. Fujita, Yamaguchi and coworkers were interested in such intermolecular Ir-catalyzed cyclizations and reported on the catalytic performance of Cp*Ir complexes, which are interesting candidates for these transformations (*Org. Lett.*, 2004, **6**, 3525–3528). During optimization of the test reaction, in which benzyl amine and 1,5-pentanediol were cyclized to *N*-benzyl piperidine it was shown that in the presence of NaHCO$_3$ as base the yields were as high as 99% at a reaction temperature of 90 °C. Other carbonates and hydrogen carbonates were less effective as bases and a poor yield of only 28% was achieved in the absence of base. A variety of alcohols were tested as substrates and the corresponding products could be obtained in yields between 63 and 94%.
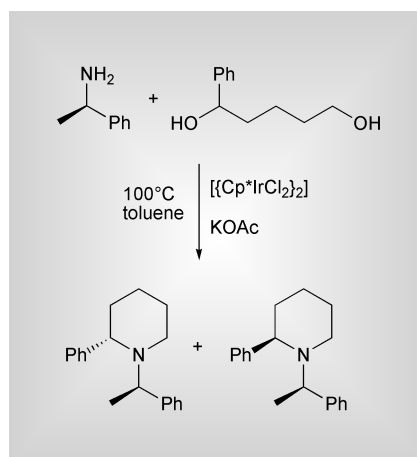
An asymmetric version of this reaction was also established by cyclizing enantiomerically pure (*R*)-1-phenylethylamine and 1-phenyl-1,5-pentanediol yielding a diastereomeric mixture of the corresponding *N*-(1-phenylethyl)-2-phenyl-piperidines (92% de). Hydrogenation of this diastereomeric mixture with Pd–C catalysts yielded (*S*)-2-phenylpiperidine in 96% yield (78% ee).

Ionic liquids as safer reaction media in exothermic polymerizations

Industrial production of chemical products must consider a number of safety issues, and explosions due to thermal runaway are one of the major concerns. Although well studied in many cases, reaction systems using conventional solvents are often not fully understood with regard to energy release during the conduction of exothermic reactions.

MacFarlane *et al.* from Monash University studied the performance of ionic liquids (IL) in thermal polymerizations of styrene and acrylonitrile by using an accelerating-rate calorimeter (*Angew. Chem.*, 2004, **116**, 5477–5480). The IL chosen was *N*-butyl, *N*-methyl pyrrolidinium bis(trifluoromethanesulfonyl)-amide [P$_{1,4}$][tf$_2$N]. Earlier studies had already shown that the tf$_2$N anion is thermally stable for short periods of time up to 394 °C. By plotting the rate of self-heating over the temperature for the above mentioned polymerization carried out in neat styrene, it became clear that the reaction had several exotherms including high-temperature processes around 400 °C. When the reaction was carried out in the IL, the self-heating was drastically reduced at all temperatures with no exothermic activity above 200 °C. At 100 °C the maximum heat rate was less than 0.03 °C min^{-1}, whereas in neat styrene the heat rate amounted to more than 0.1 °C min^{-1} (the maximum was 0.45 °C min^{-1} at 400 °C in neat styrene). The IL also had a significant influence on the pressure build up, with much smaller pressures in the presence of IL. This is beneficial in terms of safety since the IL absorbs the heat from the reaction mixture and in this way delays or quenches polymer decomposition reactions, which further protects the reaction from runaway. Furthermore the time available for safety measures is increased in the IL system, as was shown in temperature–time plots. In the neat styrene system the temperature and pressure rapidly increase from 200 °C to 400 °C and from below 50 psi to over 200 psi, with potentially catastrophic consequences. In the IL system the temperature only rises up to values between 200 °C and 300 °C and this process requires significantly more time. These results suggest the polymerization to be inherently safer when conducted in IL.

On the issue of enantioselectivity of chiral pesticides: a green chemistry opportunity†‡

Although the concept of green chemistry encompasses the manufacture and use of single enantiomer pesticides and pharmaceuticals, it generally does so rather indirectly through articles, editorials, and presentations on the production processes; for example, much attention is paid to research on asymmetric catalysis. In addition, the overwhelming emphasis is on pharmaceuticals. The importance of single- or enriched-enantiomer pesticides is just being realized by the agrochemical industry, and more information is needed by green chemistry advocates on the decreased risk provided by use of such products.

Up to 25% of the members of several classes of pesticides are chiral; that is, they exist as two mirror image isomers called enantiomers. It is known that enantiomers usually differ in their biological properties because of their differential interaction with enzymes or other naturally occurring chiral molecules. This leads to differences in microbial degradation rates, which means that one enantiomer is more persistent in the environment than the other. For example, considerable research has been conducted on the enantioselective degradation of phenoxypropionic acid herbicides, especially dichlorprop and mecoprop. In most cases, exposure of these racemic herbicides to natural soils, either through field application or in laboratory microcosms, results in faster microbial degradation of one of the enantiomers. Dichlorprop (2,4-dichlorphenoxy-2-propionic acid) was shown to be enantioselectively transformed in the surface soil after application to an experimental field.[1]

The S-(−)-enantiomer exhibited a half-life of about 4 days and the R-(+) about 8 days. This is a fortuitous situation, since the (+)-enantiomer is known to be the active herbicide while the (−)-enantiomer is simply "ballast". Metalaxyl, an acylanilide fungicide, has been shown to degrade enantioselectively in most of the soils tested in laboratory microcosms. Ruelene, an organophosphorus insecticide with a center of asymmetry at the phosphorus atom, also degrades selectively in a variety of soils.

Enantiomers also usually differ in their toxicity, both to target and non-target species. More often than not, only one enantiomer is target-active, or one is more target-active than the other. The other enantiomer then is inactive or less active, and simply adds an extra pollution load to the environment. The two S-enantiomers of the widely used chloroacetamide herbicide metolachlor (metolachlor has two chiral centers, so has two R- and two S-enantiomers) are about 10 times more toxic to target weeds than the two R-enantiomers.[2] All the fungicidal activity of metalaxyl resides with the R-enantiomer. The cholinesterase inhibition activity of chiral OP pesticides, as well as the very toxic OP nerve gases, is enantioselective. The enantiomers of malathion are selective in their effects; the R-(+)-enantiomer is more acutely toxic than the S-(−)-enantiomer to a variety of anthropods and to rats. Recent research has shown the (+)-enantiomer of fipronil, a phenylpyrazole broad spectrum insecticide, to be more toxic to *Ceriodaphnia dubia* than the

(−)-enantiomer. The (−)-enantiomer of fipronil was shown to have significantly more androgen and progesterone activity than the (+), while the (−)-enantiomer of o,p′-DDT has much more estrogen activity than the (+)-enantiomer.

Single enantiomer drugs are now routinely synthesized or separated from their racemic mixtures and compose a large fraction of the total pharmaceutical market. On the other hand, the great majority of chiral pesticides are produced and marketed as their racemates, equal mixtures of the two enantiomers. In the last five or so years, however, single-enantiomer or enriched-enantiomer pesticide formulations have been developed and are being marketed and their use promoted, both in the USA and in Europe. This is a "green chemistry" development and has advanced more rapidly in Europe. For example, mecoprop and dichlorprop, mentioned earlier, are decreed by several European governments to be used only as the active R-enantiomers. Metolachlor has been enriched by its manufacturer (now Syngenta) to contain 86% of the active S-enantiomers, which allows a 40% reduction in the amount of the herbicide applied, with the same effect. Several of the currently popular pyrethroid pesticides are now marketed as single enantiomer or enriched products. The U.S. Environmental Protection Agency Office of Pesticide Programs is receiving more requests for registration of single- or enriched-enantiomer pesticides. With the increasing complexity of new
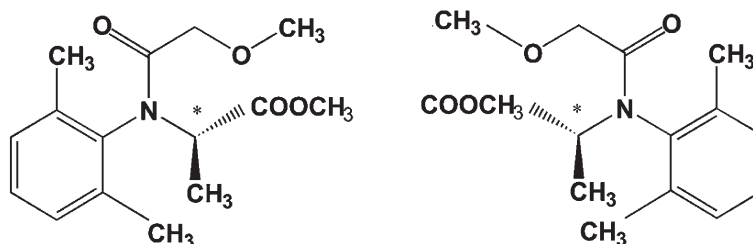
The 2 enantiomers (mirror image isomers) of metalaxyl
* indicates a chiral center at the carbon atom

pesticide structures (which increases the possibility of chiral centers), more routes for production of single-enantiomer compounds, and the increase in green chemistry consciousness by the agro-chemical industry, the number of requests are likely to increase.

To make accurate risk assessments, it is necessary to combine pesticide exposure with various toxicity effects. As indicated above, enantiomer exposure data has begun to accumulate. However, there is a dearth of enantiomer-specific effects data. In some cases manufacturers have determined the activity of separated enantiomers of new pesticides; this is presumably done as a prerequisite for marketing single-enantiomer products, so these tests are often limited to those required for registration. Although it is rare to find enantiomer effects data in the literature, enough exist to establish that such effects should be expected to differ for most enantiomer pairs.

One complicating factor in inclusion of enantioselectivity data in risk assessment is the possible shift of selectivity of degradation with changes in environmental conditions, leading to a corresponding shift in enantiomer persistence. One illustration of this is the behavior of the herbicide metalaxyl during degradation in various soils. In a study conducted in our laboratory, its loss was measured in four soil-water slurries. The active R-(+)-enantiomer of the pesticide disappeared faster in all 4 soils—much faster in one of the soils, with a high degree of enantioselectivity. The conclusion was that microbial degradation leads to longer persistence of the unnecessary enantiomer. However, subsequent research by another group[3] using a wide variety of soils showed that not only the rate of degradation of metalaxyl enantiomers, but even the enantiomer preference, changed with pH of the soil.

In another case,[4] it was shown that ecosystem disturbance (deforestation) and treatment (nutrient amendments and warming at 5 °C above ambient temperature) shifted enantiomer selectivity of soil microbial populations for biodegradation of three pesticides—ruelene (crufomate), dichlorprop and methyl dichlorprop. For example, soil microorganisms in most forest samples from Brazil preferentially removed the (+)-enantiomer of dichlorprop acid, the active form of the herbicide, while the microbes in pasture samples almost exclusively preferred the (−)-enantiomer.

The facts that 1) the relative persistence of enantiomers depends upon environmental conditions, and can even be reversed if conditions change, and 2) the effects of non-target active enantiomers on non-target species are not usually known argue, of course, for more research.

Microbial degradation studies should be conducted with important chiral pesticides using a wider variety of soil/sediment and natural water matrices in order to establish correlations between environmental properties and enantioselectivity. Such studies could be enhanced by sharing samples—for example, investigators using conventional analytical techniques to study microbial degradation of pesticides that happen to be chiral could submit their sample extracts for reanalysis to others who have the analytical tools for chiral separation. On the other hand, enetiomer effects/toxicity studies are more demanding in that they require separated enantiomers. Such separations are usually achievable but require extra time and equipment, including preparative chiral HPLC columns. However, a few enantiomers of important pesticides are available from chemical standard suppliers.

The ultimate goal of such

enantiomer-specific research should be development of a predictive capability for enantioselectivity so that a science-based approach can be made toward production of single-enantiomer pesticides. Such products would relieve the environment of thousands of tons of unnecessary chemicals that, in the worst cases, may have adverse impacts. This would surely be an advance in green chemistry—2 of the 12 principles of Green Chemistry, numbers 1 and 4, state: "It is better to prevent waste than to treat or clean up waste after it is formed" and "Chemical products should be designed to preserve efficiency of function while reducing toxicity".

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A green look at the aldol reaction

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Aldol reactions have been and are widely applied for the preparation of β-hydroxy aldehydes, β-hydroxy ketones or α,β-unsaturated aldehydes or ketones through addition or addition-elimination reactions of aldehydes and ketones. The study of the aldol reaction from the point of view of its greenness must have in mind first of all that a general synthetic method must be based on complete and efficient conversions of well defined selectivity and that greenness is more a term for comparison than an absolute kind of qualification. This comparison, when referred to the aldol reaction, applies here to the diverse modifications of the reaction. Thus, the original poorly selective, but highly atom economic catalytic procedures, have been improved by several authors by introduction of stoichiometric forms of activation in the search for better selectivities. However, the success in these improvements has been accompanied by higher levels of hazard and waste. The study of the greenness of the aldol reaction is completed by a short overview of recent contributions intended to achieve efficient, safe and clean conversions that are susceptible to becoming general green synthetic procedures. Interesting contributions are highlighted for reactions carried out under solvent-less conditions, in water, ionic liquids and supercritical fluids, with activation by microwaves, or with use of heterogeneous catalysis and especially of biocatalysis and biomimetic catalysis. Promising methods based on reduction of unsaturated ketones or on rearrangement of allylic alcohols have also recently been described.

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. The aim of this article is to present a first green view of the well

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established and current methods of the aldol reaction and to introduce recent contributions, some of them susceptible to becoming general green synthetic procedures.

In order to evaluate the greenness of a particular process attention must be paid in the first instance to issues related to safety, health and protection of the environment, due to reactants (substrates and reagents), auxiliaries (mainly solvents) and waste. This enumeration is obviously incomplete, but can be useful at present. The question about how green a reaction is most frequently refers to a particular conversion, to the comparison between two or more alternative processes for the same synthetic target, or between the synthetic pathways for the manufacture of alternative compounds. Several approaches based on the twelve principles of Green Chemistry formulated by Anastas and Warner and on the twelve more green principles due to Winterton have been developed in order to give an adequate answer to that question.[6–8] However, the present study deals with general procedures and a slightly different approach is needed. Indeed, comparison can now be done between reagents, catalysts and solvents, not with particular substances, but rather with classes of compounds. This comparison should show to what extent synthetic features achieved by diverse procedures are paralleled by modifications in hazard and production of waste.

General properties of substrates, reagents, solvents and waste, especially their toxicity and their connection to the sources of industrial bulk chemicals will be taken into account. Atom economy of the present general procedures will be based on the stoichiometry of the reactions and defined through molar waste of the reaction. Thus, grams of concomitants for each mole of product will be used here, instead of the generally accepted atomic yield or the E-Factor, which is more convenient if particular substances are involved.[9] Harmless and ecologically non-significant concomitants, namely water, nitrogen, or oxygen or alkaline, and alkaline earth metal salts in catalytic amounts are not taken into account in the estimation

of molar waste. Solvents are assumed to be recovered, although risks associated with their use or their susceptibility to contribute to contamination must be considered.

The aldol reaction

Aldol reaction is here understood in its strict sense of a C–C forming reaction which involves aldehydes and ketones as reactants. However currently developed catalytic aldol producing reactions which start from α,β-unsaturated ketones or from allylic alcohols as precursors of the enolates will be briefly introduced because of their green significance. The related Knoevenagel, Reformatsky, Perkin, Mannich, Stobbe, or Darzens reactions and other conversions of carbonyl compounds with nitroalkanes, esters, or amides will be studied elsewhere. Additionally, only intermolecular aldol reactions will be considered here.

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 β-hydroxy aldehydes (aldols) or to β-hydroxy ketones (ketols) through an addition reaction (aldolization) or to the α,β-unsaturated aldehydes or ketones that result from a subsequent dehydration (aldol condensation) (Scheme 1, eqns 1 and 2). The reaction may involve two molecules of the same aldehyde or ketone (self-aldolization 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
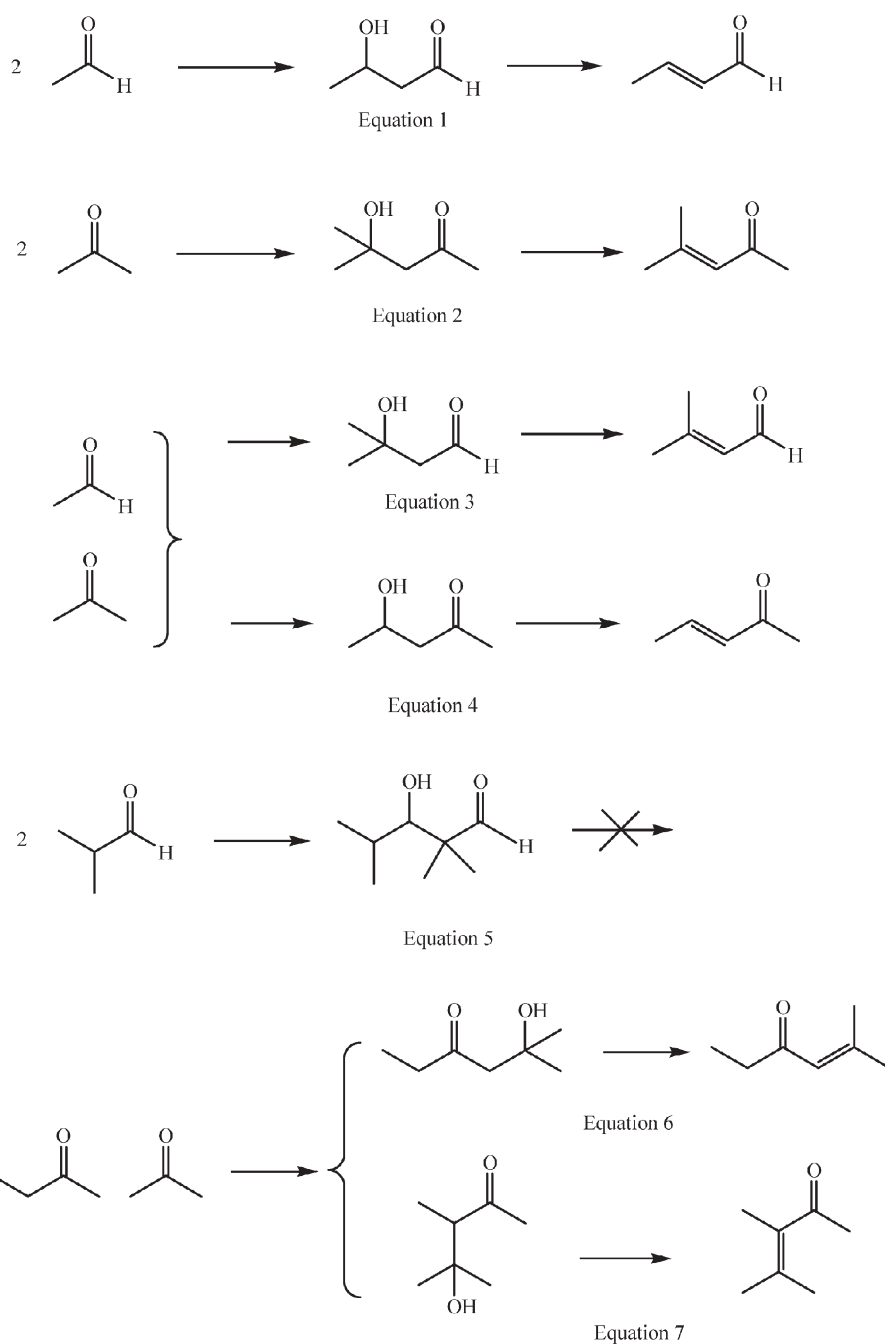
Scheme 1

the reactants has no α-hydrogen atoms (eqns 3 and 4). Condensations require two hydrogen atoms at the α-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.
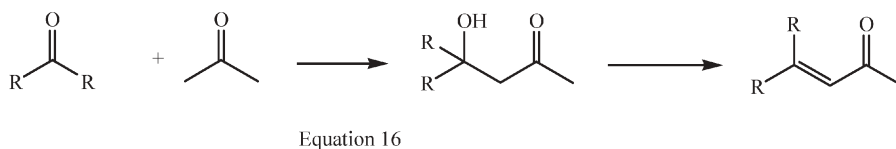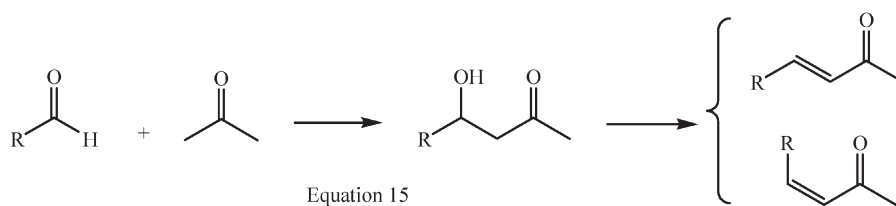
Aldehydes, other than formaldehyde, and asymmetric ketones have a prochiral carbonyl group which becomes chiral whenever they react as acceptors (Scheme 2, eqns 8 and 9). The same is true for α-methylene groups of aldehydes or ketones when they react as donors (eqns 10 and 11). α-Methyne groups are either chiral or achiral, but not prochiral, and their topicity is not modified on reaction as carbonacid centres (eqns 12 and 13). When a single stereogenic centre is generated or preserved aldol additions lead to a 1 : 1 mixture of a pair of enantiomers (eqns 8 to 13), unless the reaction becomes enantioselective. If the addition involves two prochiral centres, two enantiomeric pairs of *erythro/threo* (or *syn/anti*) diastereoisomers may result and the addition is then susceptible

to becoming both diastereoselective and enantioselective (eqn 14). The presence of other chiral centres in the reactants modifies the above situations, but its discussion is beyond the present purpose. On dehydration of aldols or ketols, C–C double bonds form and mixtures of *cis/trans* (*E/Z*) diastereoisomers result, except when the acceptor is either formaldehyde or a symmetrical ketone, or when the reaction is *E*- or *Z*-selective (Scheme 3, eqns 15 and 16).

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. This historical outline provides an adequate scheme for the present discussion.

Equations 8

Equation 9

Equation 10

Equation 11

Equation 12

Equation 13

Equation 14

Scheme 2

Equation 15

Equation 16
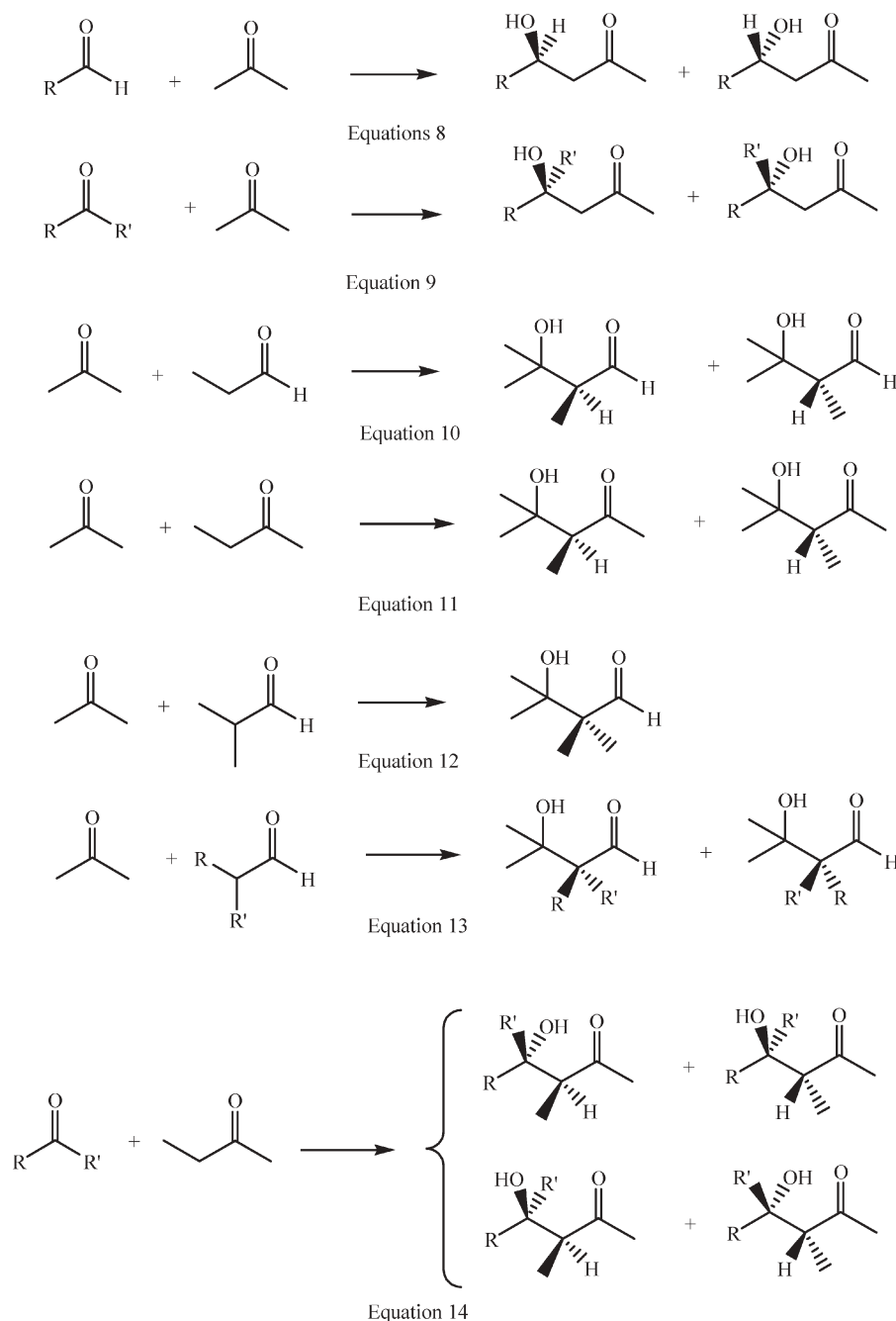
Scheme 3

Safety and environmental impact

Aldehydes and ketones are the starting materials in all procedures based on aldol reactions. It is convenient thus to introduce some comments on these classes of compounds before discussing procedures and reagents.

A great number of simple starting aldehydes and ketones are bulk products and can be considered proximate to the fossil feed-stocks in the synthetic chain. Without going into detail, this feature allows the assumption that few reagent and energy consuming and waste producing conversions are needed for their manufacture. Other aldehydes and ketones are readily available natural products or can be easily prepared from them.

As for hazards associated with manipulation of aldehydes and ketones, it should be recalled here that all low molecular weight aldehydes are toxic. Formaldehyde and acetaldehyde are irritating to eyes, skin and tracheal tract and, more importantly, they have been reported as carcinogens. Saturated ketones are only moderately toxic, except on prolonged inhalation, when depression of the central nervous system may occur. One of the serious hazards associated with ketones is their ability to react with hydrogen peroxide to give dangerous explosive peroxides, a feature which, in connection with aldol reactions, should be cause for concern only in the work-up of boron enolate aldol reactions (see below).[10] The above comments apply also to the aldol products: hydroxy aldehydes or ketones or their related unsaturated compounds. Thus, crotonaldehyde and methyl vinyl ketone are both included in EPA's "Extremely Hazardous Substances List" and acetaldol, and diaceton alcohol are reported as moderately irritant, toxic on skin contact and narcotic on inhalation.[10]

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 4 and 5) and equilibrium constants may not be favourable to the
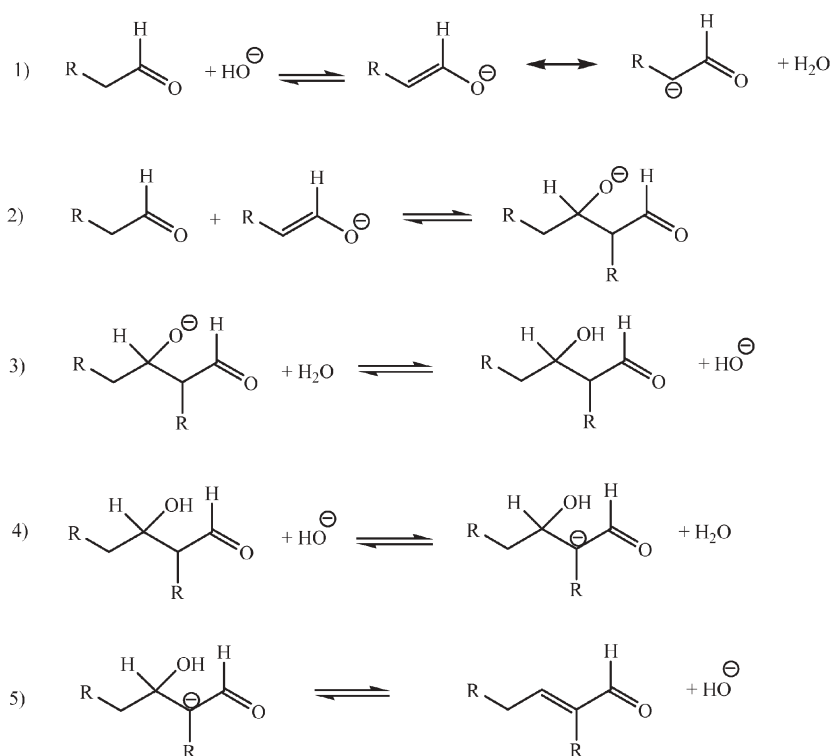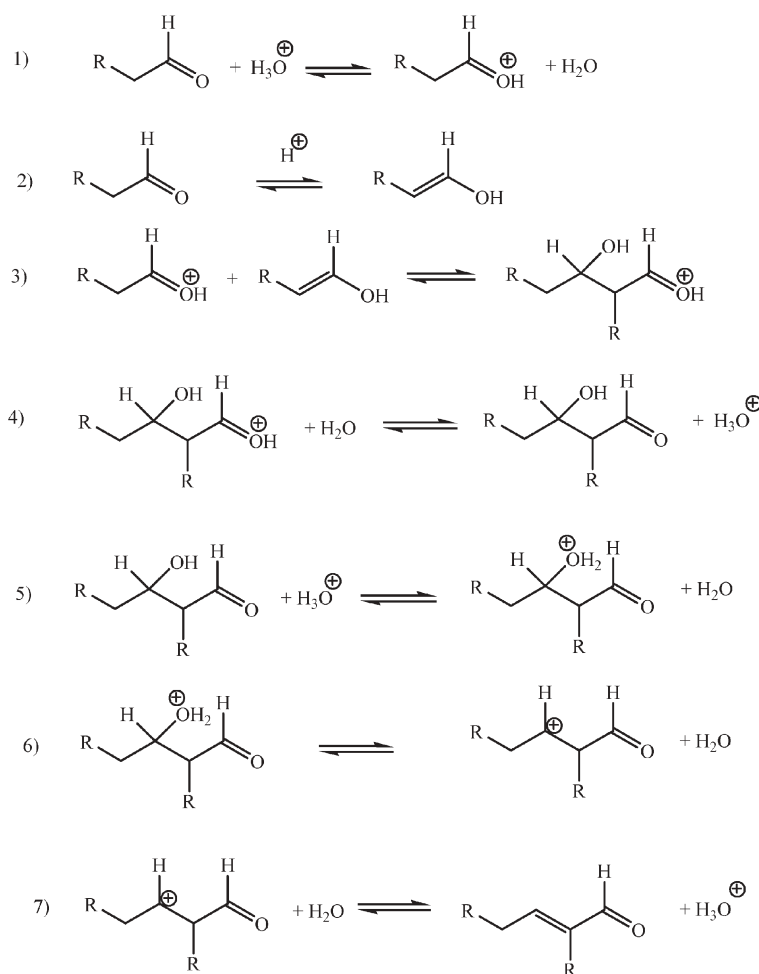
Scheme 4

Scheme 5

progress of the conversion.[11] Recognition of these features is crucial in order to understand reactivities and selectivities and to establish convenient experimental conditions. In general terms steric compression is detrimental for the addition, a feature that accounts for the poor reactivity of ketones as acceptors. Elimination steps are also reversible in theory, but frequently irreversible in practice, especially for acid catalysed reactions, and favoured when the forming ethylenic double bond is conjugated to a phenyl or another unsaturated group. The success of the conversion may depend occasionally on the continuous separation of products from the reacting mixture as they form, or on the practical irreversibility of the dehydration step. Good examples of these are the traditional laboratory scale aldol self-condensation of acetone in a Soxhlet set-up[12] or the Claisen–Schmidt condensations carried out in water or in aqueous ethanol, frequently accompanied by precipitation of the unsaturated aldol adduct.

Linear alkyl aldehydes undergo self-aldolizations (Scheme 6), but only a limited number of ketones afford practical conversions. Control of pH and temperature of the solution is critical for the progress of the reaction to ensure that either addition or condensation results and to avoid oligomerizations, especially of condensation products. Bases are usually employed in catalytic amounts: 2% or 10% molar ratios are usual. This situation is not the same for acid catalysed reactions when about 2–3 equivalents of hydrochloric acid are frequently employed.[3]

The cross reaction of two aldehydes affords a mixture of up to four compounds, which is simplified when one of them cannot participate in the reaction other than as an acceptor, or when different reactivities as acceptors allow one of the possible combinations to predominate in the mixture. Excess of the component which cannot allow self-condensation is then a common practice. A general application of cross aldol condensation is the condensation of aromatic aldehydes with other aldehydes or with ketones, known as the Claisen–Schmidt condensation (Scheme 7).

Aldol reactions of asymmetric ketones may be regioselective. For instance, methyl ketones such as butanone and 2-pentanone react with a variety of aldehydes through their methylene groups. For the Claisen–Schmidt condensation, the general observation is that asymmetric ketones react with the aromatic aldehyde through the less substituted position (a methyl group in practice) under basic conditions and through the more substituted α position (a methylene group) under acid catalysis (Scheme 7).

The reversibility of most additions accounts for aldolizations not being stereoselective. However, *trans* geometry is frequently found in the condensation products of aldehydes with acetaldehyde or with methyl ketones, especially in the Claisen–Schmidt condensation.

Frequent side products found in aldol reactions are the carboxylic acids and alcohols (Cannizzaro) or esters (Tischenko) that result from disproportionation of the reacting aldehydes.[2] The accompanying Cannizzaro reaction is frequently encountered in the use of formaldehyde and has industrial significance in the synthesis of pentaerythritol and related products.[5] However, the oligomers that form by further reaction of the aldol products are probably the most important side products of catalytic aldol reactions.
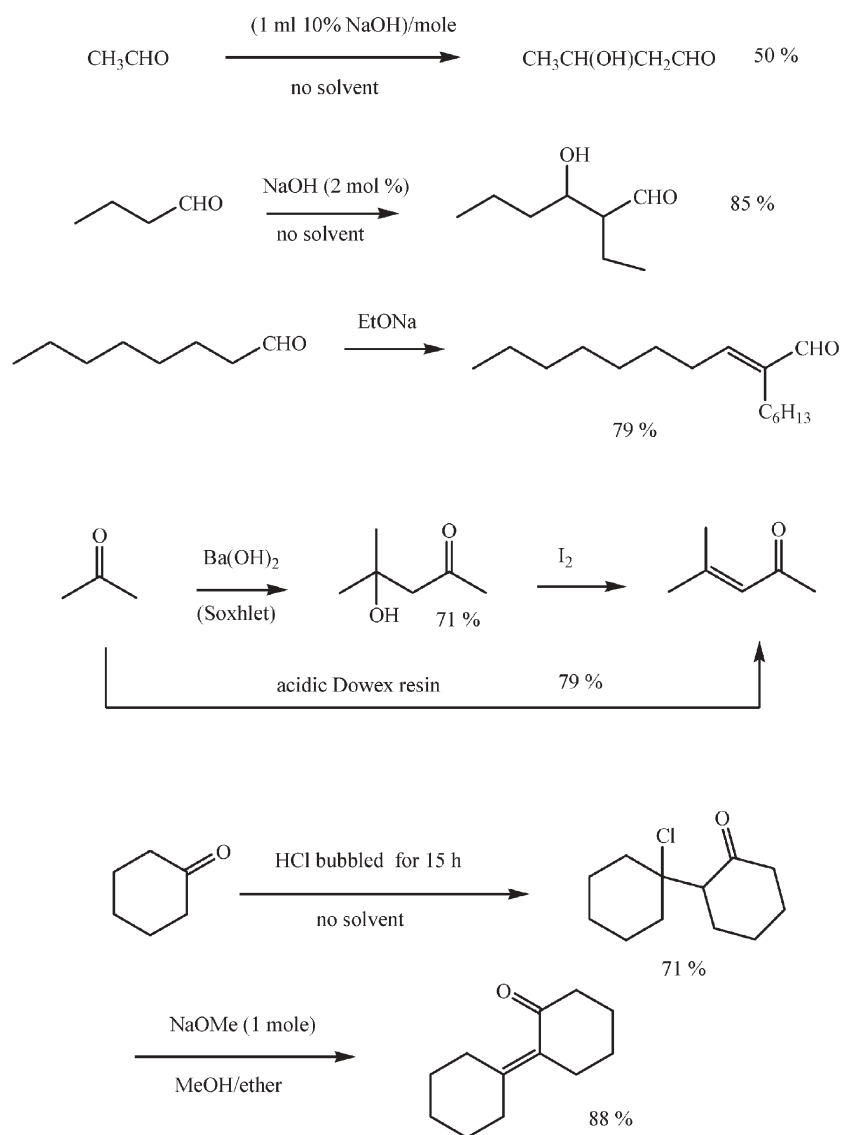
Scheme 6

Safety and environmental impact

In regard to safety and to environmental impact of catalytic aldol reactions, the easily available bases and acids are well known to chemists for their corroding properties, especially to human tissues, and their propensity to cause violent reactions on contact with a great variety of substances. Usual solvents, ethanol and methanol, are moderately flammable and methanol is accumulatively toxic.[10] Their volatility may be a cause of concern and isopropyl alcohol stands as a likely substitute for both.[7]

When attention is addressed to waste, not much should be expected, as long as promoter bases and acids are employed in genuinely catalytic amounts. Atom yield for carbon compounds in aldolization is 100% and only water is split in condensations. Work-up neutralization will lead then to small amounts of alkaline chlorides. Stoichiometric equations justify the assumption of a negligible molar waste for the basic catalysed aldol reaction (Table 1). Still better, ion exchange resins are easily separated and reused. For acid catalysis, the acid must be neutralized in the work-up and the resulting amount of alkaline chloride will depend on the actual amount of catalyst employed.

In view of the above comments, it may be concluded that the catalytic aldol reaction can be regarded as a substantially waste free method, especially when carried out in the presence of catalytic amounts of base or with basic ion-exchange resins. But there are significant limitations as a synthetic method. For instance, it does not provide adequate control of cross reactions; it does not allow the synthesis of the aldols or ketols which should result from ketones as acceptors; there is no convenient regioselectivity control of asymmetric ketones as donors; aldolizations are not stereoselective and the *cis/trans* stereochemistry of aldol condensation products cannot be controlled at will.

Stoichiometric aldol reactions

Stoichiometric aldol reactions provide general methods which overcome a number of the above limitations pointed out for catalytic aldol reactions. A common feature to stoichiometric methods is that no elimination occurs under the reaction conditions and thus aldols or ketols are obtained on work-up. Condensation products, whenever wanted, must be obtained in a separate dehydration step.

Direct enolate aldol reactions

Ketones are moderate carbonacids and strong bases are required for their quantitative deprotonation. Although the variety of bases is larger in practice, lithium diisopropylamide
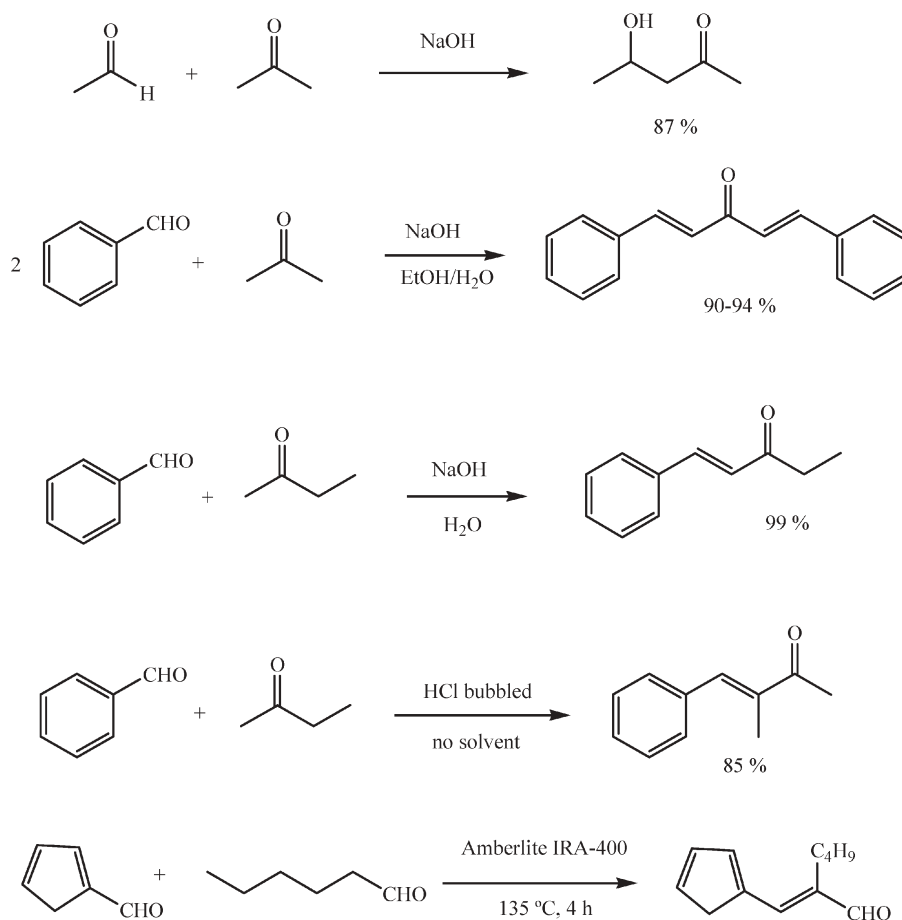
Scheme 7

(LDA) and sodium hydride may be taken here as commonly convenient reagents for the generation of enolates. Protic media are incompatible with these strong bases and tetrahydrofuran is the most frequent solvent. Absolute exclusion of moisture and oxygen are also fundamental experimental precautions. Reactions are carried out by deprotonation of the donor with an equivalent amount of base, and then addition of the acceptor. The immediate reaction adduct is an alkaline aldolate which, on neutralization with an equivalent amount of acid, affords the aldol or ketol (Scheme 8). As a consequence of the prior generation of the enolate, the aldolization is thermodynamically favoured and irreversible in practice: a feature that determines many of the differences found between catalytic and stoichiometric aldol reactions. Thus, ketones now react conveniently as acceptors. However, a significant limitation is met for aldehydes as donors, as their deprotonation is problematic, a feature which is usually circumvented by conversion of the aldehyde to an aldimine (see below). Further, the basicity of enolates may cause proton exchange prior to the addition, a difficulty in cross aldolizations, and constrains the use of reactants with groups sensitive to basic reagents. Exchange with transition metals, such as zirconium or titanium may circumvent this problem.

Regioselective deprotonation of asymmetric ketones that have similar acidity in their α and α′ positions is feasible by the appropriate choice of conditions. Thus, under conditions for kinetically controlled deprotonation (low temperature, short time, strong base in equivalent or excess amounts in the solution), the less substituted enolate predominates and under thermodynamically controlled conditions (near room temperature, adequate time for equilibration, limited amount of base in solution), the more substituted enolate is generated preferentially. (Scheme 8).

Aldol additions of generated lithium enolates are diastereoselective. The trend is determined by the geometry of the enolate and can be predicted with the aid of the Zimmerman–Traxler model, which is usually valid for lithium and boron enolates but not for other alkali metals or tetraalkylammonium ions as counterions. As a general rule, ethyl ketones with bulky carbonyl substituents afford the Z-enolate on deprotonation and this leads to *syn* ketols when added to aldehydes (Scheme 9). The synthesis of acyclic *anti* ketols is usually problematic, but for cyclic ketones no other enolate can result but the E-enolate and *anti* ketols are then obtained. Another effect of the aforementioned metal exchange is that it promotes higher *syn* selectivities.

When attention is paid to safety and environmental issues associated with the aldol addition of stoichiometrically generated enolates, it is found first of all that bases for the quantitative generation of enolates are not bulk products. Although commercially available, tetrahydrofuran solutions of lithium amides are frequently prepared *in situ* from butyllithium and the corresponding amine. Sodium hydride is a commercial product that may ignite spontaneously in moist air and explodes in contact with water, DMSO or DMF ($>25\ ^{\circ}C$). Ethereal solvents are highly flammable, form explosive peroxides, are moderately toxic by inhalation and there is some evidence of carcinogenic activity for THF.[10] For an estimation of the atom economy it would not be unreasonable now to consider the generation of LDA from butyllithium, but restriction to the reagents actually used is preferred at the present level of study (Table 1). Waste comprises isopropylamine and lithium chloride for LDA as base and hydrogen and sodium chloride on use of sodium hydride. Transition metal exchange is certainly accompanied by a substantial increase of molar waste.

Table 1 Stoichiometric equations and molar waste of aldol reactions

Method	Stoichiometric equations	Concomitant products	Molar waste/ g mol^{-1}
General base catalysis	$2CH_3CHO + NaOH$ (cat. am.) $\rightarrow CH_3CH(OH)CH_2CHO + NaOH$ (cat. am.) $CH_3CH(OH)CH_2CHO + NaOH$ (cat. am.) $\rightarrow CH_3CH=CHCHO + H_2O + NaOH$ (cat. am.) $NaOH$ (cat. am.) $+ HCl$ (cat. am.) $\rightarrow$ **NaCl** (cat. am.)$+ H_2O$	NaCl (cat. am.)	≈ 0
Stoichiometric enolate generation	$CH_3COCH_3 + i\text{-}Pr_2NLi \rightarrow CH_3COCH_2 Li + $ **i-Pr$_2$NH**	i-Pr$_2$NH	101
	$CH_3COCH_2 Li + CH_3COCH_3 \rightarrow CH_3COCH_2–C(CH_3)_2OLi$ $CH_3COCH_2–C(CH_3)_2OLi + HCl \rightarrow CH_3COCH_2–C(CH_3)_2OH + $ **LiCl**	LiCl	$+42.5$ $=143.5$
	For NaH as base	H$_2$ NaCl	58.5
Wittig aldol reaction	$RCH_2CHO + H_2NC_6H_{11} \rightarrow RCH_2CH=NC_6H_{11} + H_2O$ $RCH_2CH=NC_6H_{11} + i\text{-}Pr_2NLi \rightarrow [RCHCH=NC_6H_{11}]Li + $ **i-Pr$_2$NH** $[RCHCH=NC_6H_{11}]Li + R'_2CO \rightarrow R'_2C(OLi)CH(R)CH=NC_6H_{11}$ $R'_2C(OLi)CH(R)CH=NC_6H_{11} + HCl \rightarrow R'_2C(OH)CH(R)CH=NC_6H_{11} + $ **LiCl** $R'_2C(OH)CH(R)CH=NC_6H_{11} + H_2O + HCl$ (cat) $\rightarrow R'_2C(OH)CH(R)CHO + $ **H$_2$NC$_6$H$_{11}$**	i-Pr$_2$NH LiCl C$_6$H$_{11}$NH$_2$	101 $+42.5$ $+99$ $=242.5$
Reaction through silyl enol ether with regeneration of enolate	$RCOCH_3 + i\text{-}Pr_2NLi \rightarrow RC(OLi)=CH_2 + $ **i-Pr$_2$NH** $RC(OLi)=CH_2 + (CH_3)_3SiCl \rightarrow RC[OSi(CH_3)_3]=CH_2 + $ **LiCl** $RC[OSi(CH_3)_3]=CH_2 + CH_3Li \rightarrow RC(OLi)=CH_2 + $ **(CH$_3$)$_4$Si** $RC(OLi)=CH_2 + R'_2CO \rightarrow RCOCH_2C(OLi)R'_2$ $RCOCH_2C(OLi)R'_2 + HCl \rightarrow RCOCH_2C(OH)R'_2 + $ **LiCl**	i-Pr$_2$NH LiCl (CH$_3$)$_4$Si	101 $+42.5$ $+88$ $+42.5$ $=274$
	For generation of silyl enol ethers under thermodynamic control $RCOCH_3 + Et_3N + (CH_3)_3SiCl \rightarrow RC[OSi(CH_3)_3]=CH_2 + $ **Et$_3$NH Cl**	Et$_3$NH Cl (CH$_3$)$_4$Si LiCl	123.5 $+88$ $+42.5$ $=254$
Mukaiyama aldol reaction	$RCOCH_3 + i\text{-}Pr_2NLi \rightarrow RC(OLi)=CH_2 + $ **i-Pr$_2$NH** $RC(OLi)=CH_2 + (CH_3)_3SiCl \rightarrow RC[OSi(CH_3)_3]=CH_2 + $ **LiCl** $RC[OSi(CH_3)_3]=CH_2 + R'_2CO + TiCl_4 \rightarrow RCOCH_2C(OTiCl_3)R'_2 + $ **(CH$_3$)$_3$SiCl** $RCOCH_2C(OTiCl_3)R'_2 + H_2O \rightarrow RCOCH_2C(OH)R'_2 + $ **Ti(OH)$_4$** $+ 3HCl$ $3HCl + 3NaOH \rightarrow $ **3NaCl** $+ 3H_2O$	i-Pr$_2$NH LiCl (CH$_3$)$_3$SiCl Ti(OH)$_4$ 3NaCl	101 $+42.5$ $+108.5$ $+116$ $+175.5$ $=543.5$
Boron enol ether aldol reaction	$RCOCH_3 + (C_4H_9)_2BOSO_2CF_3 + (C_2H_5)_3N \rightarrow RC(OBBu_2)=CH_2 + $ **(C$_2$H$_5$)$_3$NH OSO$_2$CF$_3$** $RC(OBBu_2)=CH_2 + R'_2CO \rightarrow RCOCH_2C(OBBu_2)R'_2$ $RCOCH_2C(OBBu_2)R'_2 + H_2O_2 \rightarrow RCOCH_2C(OH)R'_2 + $ **2C$_4$H$_9$OH** $+ $ **B(OH)$_3$** $+ H_2O$	(C$_2$H$_5$)$_3$NH OSO$_2$CF$_3$ 2C$_4$H$_9$OH B(OH)$_3$	251 $+148$ $+62$ $=461$

For the aldol reactions with aldehydes as donors, quantitative generation of the anions of their imines, usually their cyclohexylimine, with a lithium dialkylamide and addition to the acceptor aldehyde or ketone is achieved (Scheme 10). The resulting hydroxy imine is afterwards hydrolysed to the corresponding hydroxy aldehyde. This aldol reaction is known as the Wittig aldol reaction.

Cyclohexylamine is a severe human skin irritant, a suspected carcinogen and is included in the EPA "Extreme Hazardous Substances List". Due to its high water solubility it is most probably discarded along with water effluents.[10] Other waste products are the same as in the direct enolate reaction (Table 1).

Silyl enol ether aldol reactions

Silyl enol ethers as intermediates in the aldol reaction may improve regioselectivity and stereoselectivity of the enolate additions and offer the alternative possibility of carrying out the aldol addition under the Lewis acid promoted conditions known as the Mukaiyama reaction.[13,14]

Silyl enol ethers are prepared by stoichiometric deprotonation of the ketone and silylation of the enolate, most frequently with trimethylchlorosilane. When the derivative of the less substituted enolate of asymmetric ketones is to be prepared, silylation of the enolate generated under kinetic conditions is carried out. However, deprotonation can also be promoted by a tertiary amine in the presence of the silylating agent when the thermodynamic silyl enol ether is sought (Scheme 11). The resulting silyl enol ethers obtained by one or other procedure can be resolved and purified by distillation or chromatography and thus the right regio- and stereo-isomers can be isolated.

Once purified, silyl enol ethers can be used for the aldol addition to any acceptor by generating unequivocally the enolate *in situ*. This can be done either with methyllithium, or with fluoride ion. The behaviour of the enolate may differ according to the reagent used, as the counterion in the first case is a lithium ion, whereas in the second it is a tetraalkylammonium ion. When silyl enol ethers are employed, regioselectivities and stereoselectivities mentioned above for lithium enolates are improved, but stereoselectivities may differ in their trends when fluoride is used as nucleophile for generation of the enolate.

In regard to safety and environment protection, it may be added here that trimethylchlorosilane is a side product in the bulk production of the basic monomers of silicones. Trimethylchlorosilane is found in the list of very dangerous substances and is highly flammable (f.p. -27 °C), toxic, irritant and corroding in contact with skin, eyes and mucous membranes.[10]

Methyllithium in hexane (self ignition) and a variety of tetraalkylammonium fluorides are commercially available. As for concomitants, tetramethylsilane is very volatile (b.p. 26.6 °C) and most likely to be released to the atmosphere. Other waste products are usually discarded to water effluents (Table 1).

As referred to above, the silyl enol ether can react with an aldehyde or a ketone in the presence of a Lewis acid, most frequently titanium tetrachloride, in a nonbasic solvent, namely methylene dichloride or toluene, according to the named Mukaiyama aldol reaction (Scheme 12). The undesirable retro aldol process, present in the catalytic aldol reactions
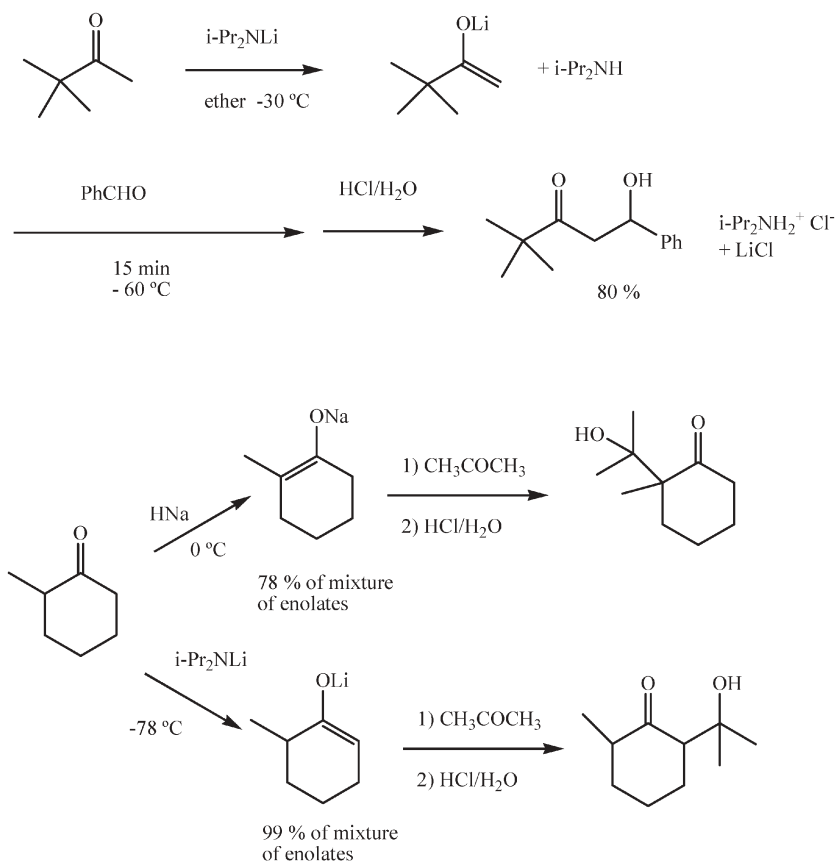
Scheme 8
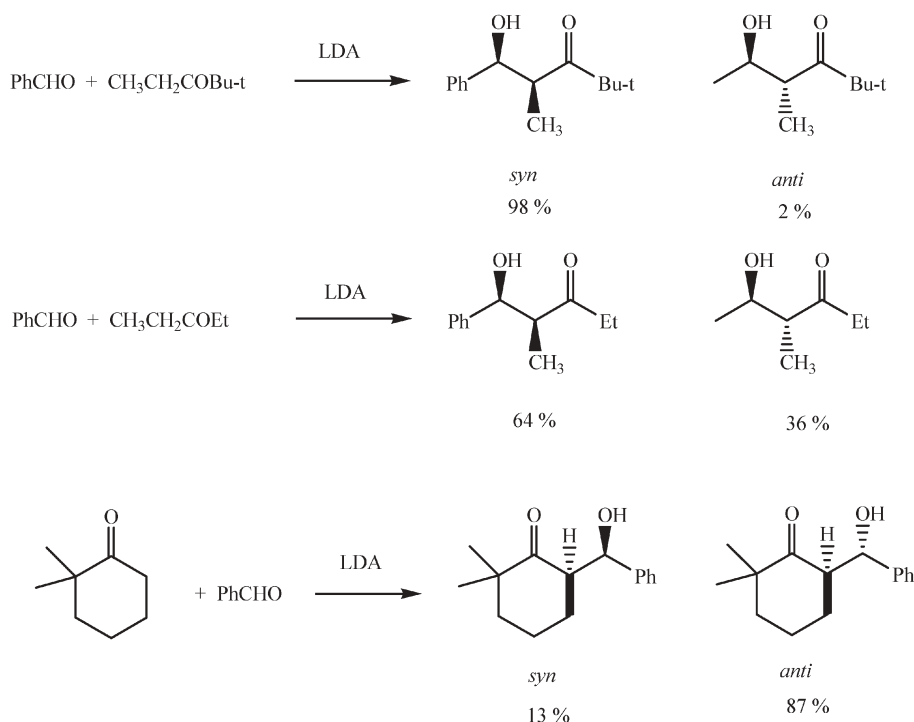
Scheme 9

is inhibited here by formation of a stable titanium chelate, which is hydrolysed by water on work-up and excellent yields are thus obtained. Although high stereoselectivities are rarely obtained by the Mukaiyama aldol reaction, many recent asymmetric reactions are based on Lewis acid catalysed silyl enol ether aldol additions.

Titanium tetrachloride is an intermediate in the preparation of titanium dioxide and of titanium metal, resulting from chlorination of rutile. It is an irritant, corroding and toxic in contact with skin, eyes and mucous membranes and may ignite spontaneously in air.[10] Molar waste for the Mukaiyama aldol reaction is very high (Table 1) and use of methylene dichloride as solvent is a further cause of concern.

Boron enolate aldol reactions

Boron enolates are generated by reaction of a ketone with dialkylboron trifluoromethyl sulfonates (triflates) or chlorides in the presence of a tertiary amine. Interestingly, they react with carbonylic compounds, without need for a catalyst, in methylene dichloride, THF or pentane as solvent. The resulting ketol boron ester is oxidatively hydrolysed with aqueous
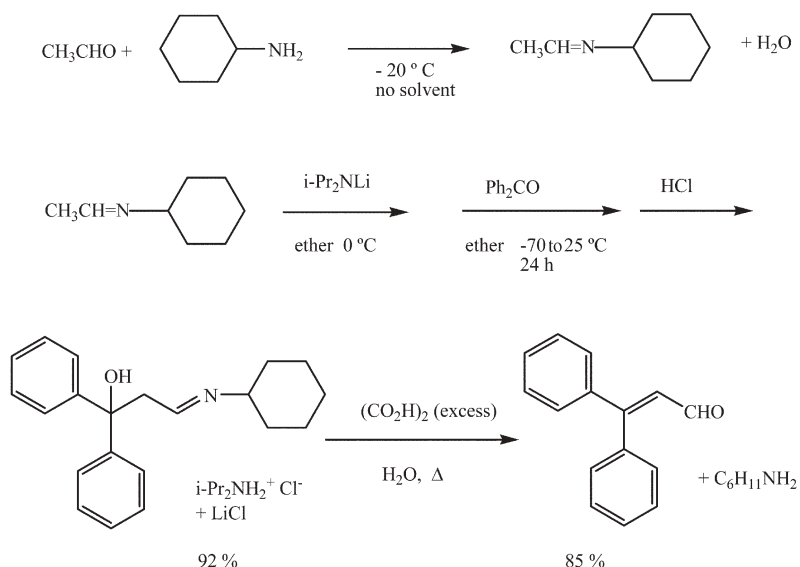
Scheme 10
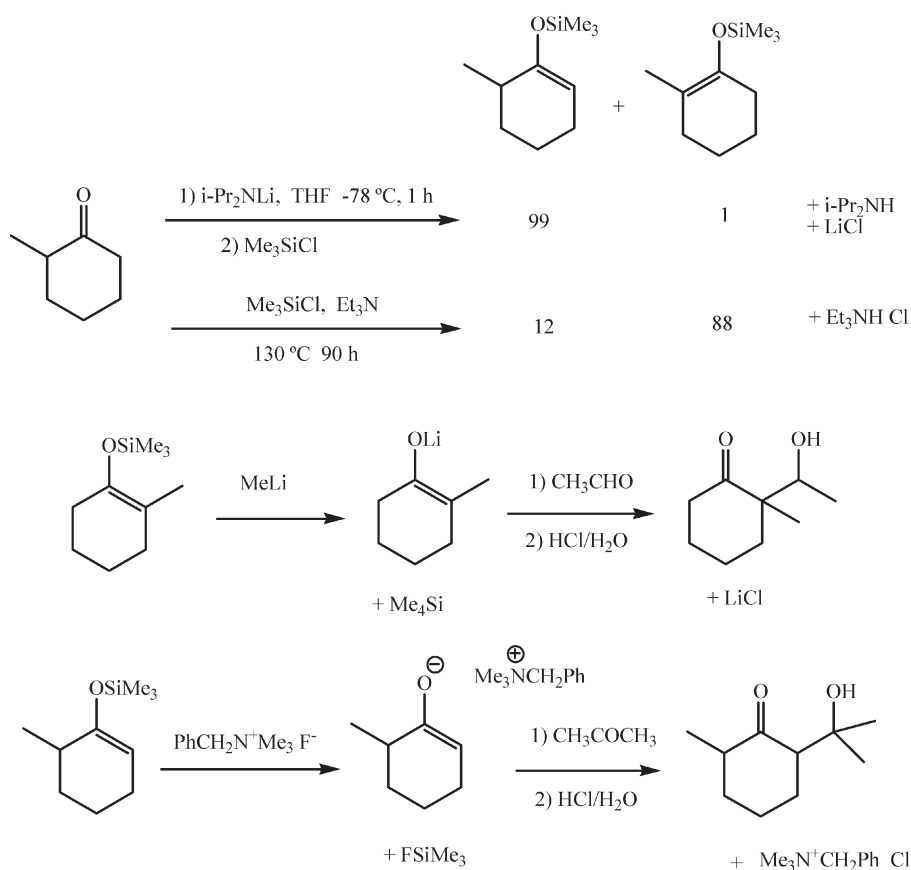
Scheme 11
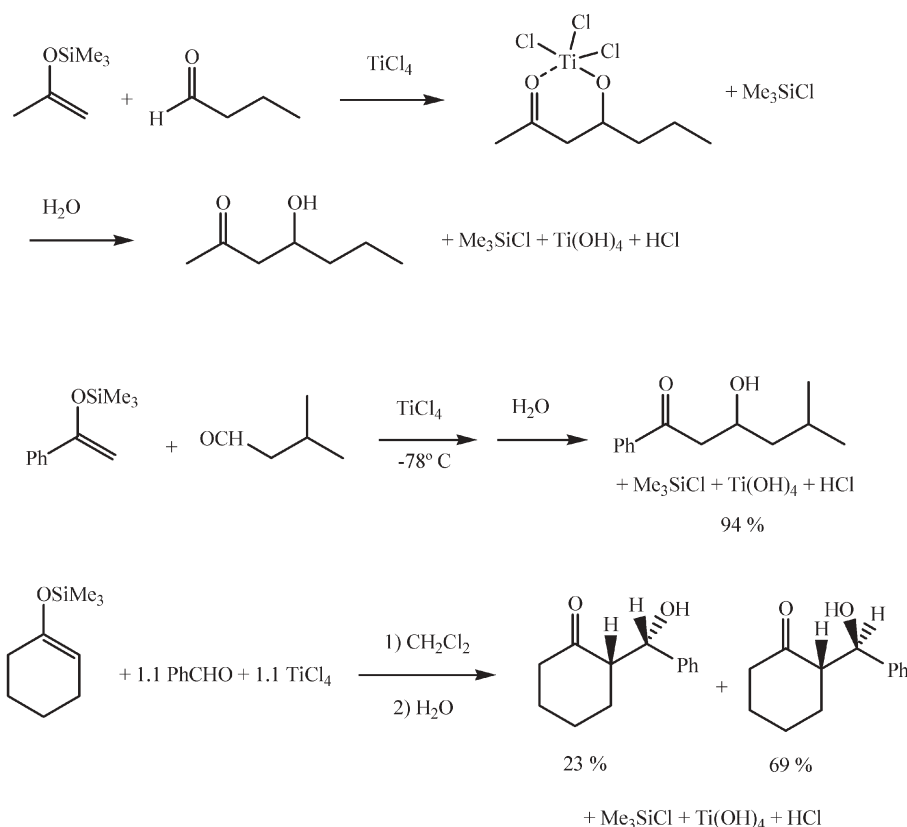
Scheme 12

hydrogen peroxide (9–10 equivalents at pH 7) or with MoO_5–pyridine–HMPA to afford the ketol.[14]

The main advantage offered by the boron mediated aldol reaction is the improved stereocontrol usually achieved. The stereochemical outcome can be predicted through the same Zimmermann–Traxler model applied for lithium enolates, but now the stereoselectivity of the addition is superior. In accordance with that model, *Z*-boron enolates lead to *syn* (*erythro*) ketols, on addition to aldehydes, whereas the *anti* (*threo*) diastereoisomers are obtained from the *E*-boron enolates. The right choice of reagents allows the right geometry of the boron enolate to be attained. Thus, small ligands and a good leaving group on the boron and a bulky amine usually lead to the *Z*-boron enolate of simple ethyl ketones, whereas sterically demanding boron ligands, a less reactive leaving group and small amines usually promote the *E*-boron enolate (Scheme 13). A good control of the diastereoselectivity of the boron enolate aldol addition enables satisfactory enantio-selectivities to be achieved by use of easily attainable chiral boron reagents. Enantioselective aldol additions can thus be obtained without an increase in the amount of waste associated with the use of chiral auxiliaries.

A number of dialkylboron triflates are commercially available in dichloromethane, hexane, or ether solution. Other triflates and the chlorides can be prepared from the dialkylboranes and trifluoromethanesulfonic acid. On the other hand, the starting dialkylboranes must be prepared beforehand by hydroboration. Boron enolates are most sensitive to Lewis acids and to moisture. They must be freshly prepared and their aldol reactions must be carried out under strict anhydrous conditions. No adequate toxicity record is available, but dibutylboron triflate is extremely flammable and dangerous in contact with the skin, according to a commercial catalogue. The actual figures for molar waste depend on the alkyl groups of the boron reagent and on the tertiary amine used (Table 1).

In conclusion, this section has shown that stoichiometric aldol reactions substantially improve the aldol reaction as a general synthetic method, especially in selectivities which cannot be attained by the general base or acid catalytic method. However this improvement is accompanied by a significant increase in molar waste and in hazards associated with toxicity, flammability or susceptibility to contribute to environmental pollution.
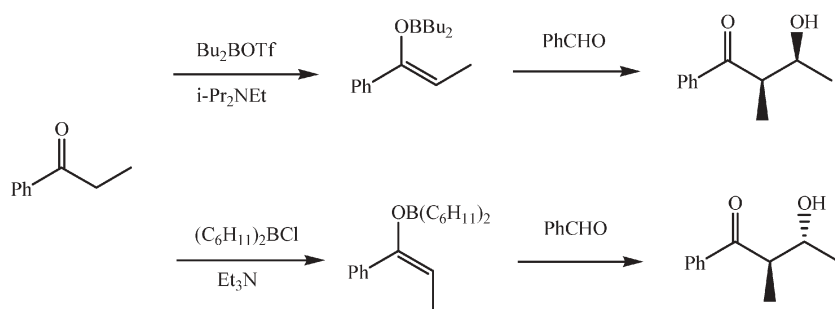
Scheme 13

Recent and greener aldol reactions

Introduction

Some of the recent contributions to the green methodology of the aldol reaction, along with their advantages and limitations are introduced here. It should be said at the outset that these contributions may or may not be the result of green thinking, but in a number of instances they may open up routes for highly efficient, environmentally friendly C–C bond forming processes. Except for the aqueous Mukaiyama reaction, recently published methods are catalytic. This is promising in the context of methods meant to be green, but some of the constraints found above for the early catalytic aldol reactions are met again. Thus, many of these recent contributions can be applied only to a limited number of ketones as donors and aldehydes as acceptors. However, a few of the recent findings excel in the achievement of the control of the stereochemistry of aldolizations.

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 14).[15,16] Microwave activation has proved convenient for Claisen–Schmidt and related reactions carried out with or without solvent, either directly or by use of acetals.[17–19]

Catalytic aldol reactions in water

Aldol addition of a limited number of ketones to nitrobenzaldehydes has recently been reported to occur in water with a catalytic amount of sodium carbonate, to afford excellent yields of ketols.[20] The microwave accelerating effect has also been shown for sodium hydroxide catalysed aldol condensations of aromatic aldehydes with acetone or acetophenone in aqueous medium.[21]

Water at 250 °C (near-critical water, NCW) seems promising as a solvent for organic synthetic reactions, due to its solubility

(ref 16)

(ref 17)
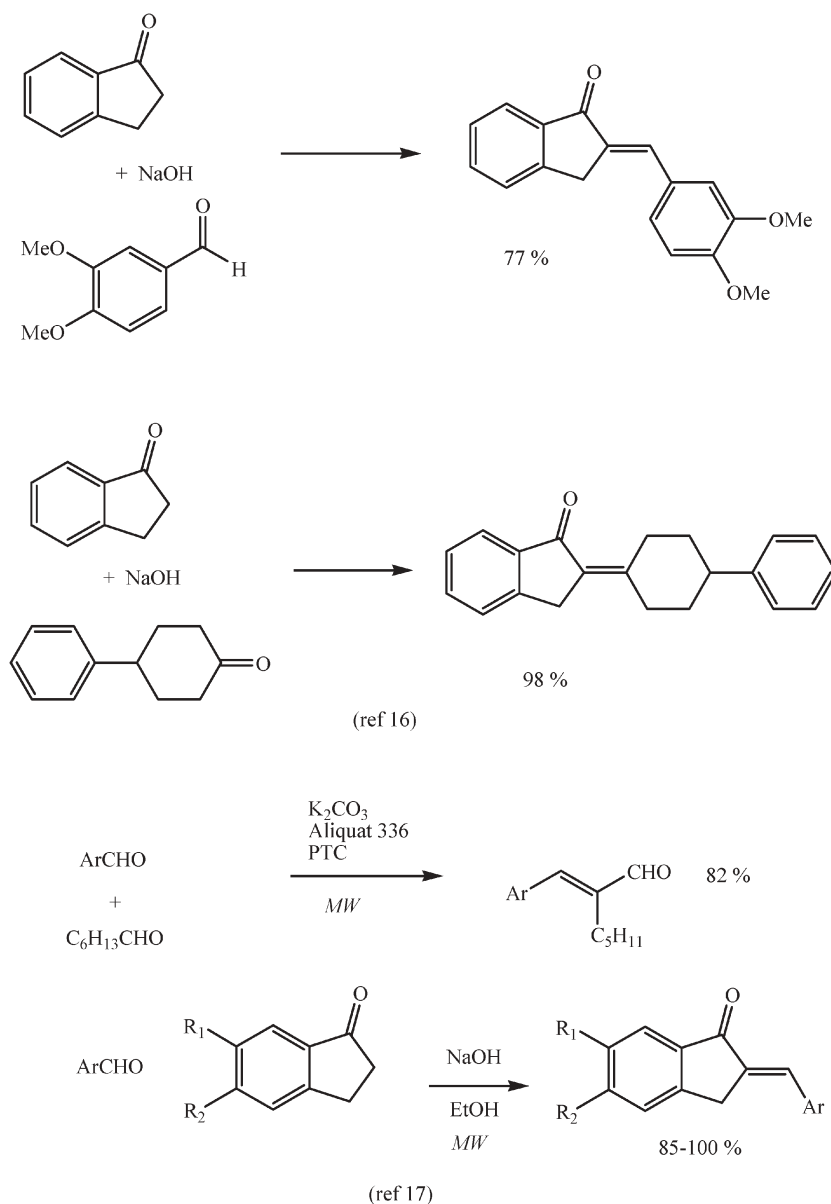
Scheme 14

properties, comparable to those of polar organic solvents at room temperature and to its high dissociation constant. The latter property allows acid or base catalysed reactions to be carried out in NCW without need of added catalysts. Aldol reactions carried out under these conditions lead to rather low conversion yields (below 40%) of the condensation products. Oligomerization competes when alkyl aldehydes are used. On the other hand, butanone leads to regioisomeric mixtures.[22] The Claisen–Schmidt condensation of benzaldehyde with acetone or acetophenone can be very selective and suitable for a large scale continuous process when carried out in water at 200 °C, especially because of the easy separation of products from the unreacted starting compounds.[23]

Reactions in supercritical fluids

No record has been found of aldol reactions in supercritical fluids, although a related asymmetric Mukaiyama reaction of the silyl enol ether of an ester of thioacetic acid in supercritical fluoroform has been described.[24]

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][PF$_6$] 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][BF$_4$] than in water.[25]

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 15).[26,27] Although high yields are described for the aldol condensation of citral with excess butanone, regioselectivities found are still poor.[28]

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 16). 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.[29]

Synthetic chiral catalysts

The turn of the century has witnessed a strong interest for new synthetic chiral catalysts for aldol reactions.[30–33] The general perspective of these asymmetric aldol reactions is beyond the scope of the present study and only two significant lines of work are mentioned here. Good yields and enantioselectivities for asymmetric aldol additions have been described by Trost and coworkers for aryl and alkyl aldehydes and excess of acetone, acetophenone or other aryl methyl ketones with a bimetallic chiral zinc catalyst.[34,35] According to Shibasaki and coworkers, good results are obtained for a wider range of ketones with a lanthanum potassium bimetallic trisbinaphtoxide as catalyst,[36] whereas α-hydroxyacetophenones react diastereoselectively and enantioselectively in the presence of a complex of diethylzinc and a linked BINOL (Scheme 17).[37] Small amounts of catalyst are used (3% to 10%) in all these cases and it may be assumed that catalysts are easily recovered and reused. Although diethylzinc is consumed in any case in two of these procedures, the estimated molar waste is small

96 %; ratio: 2.3 to 1
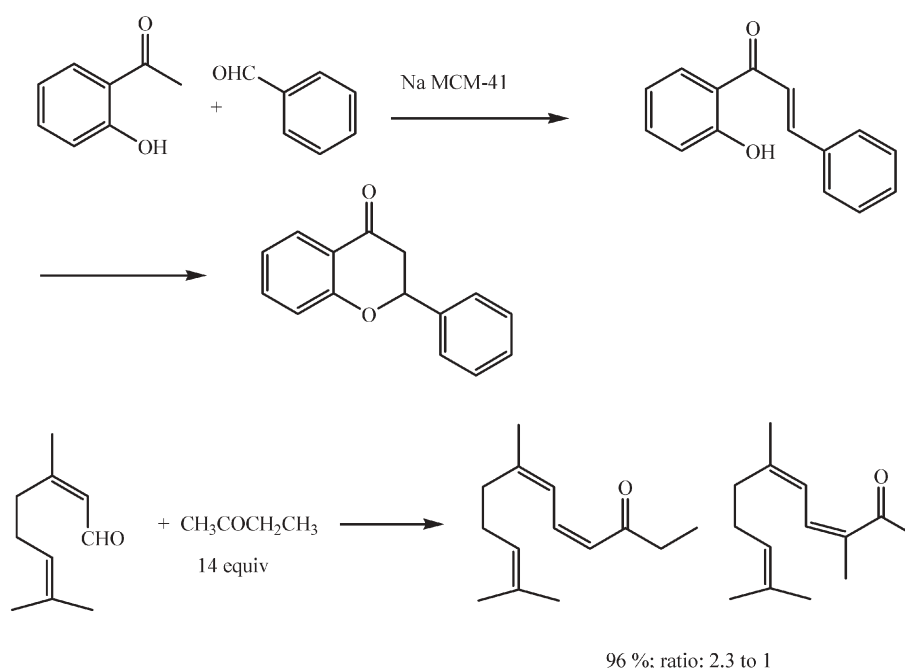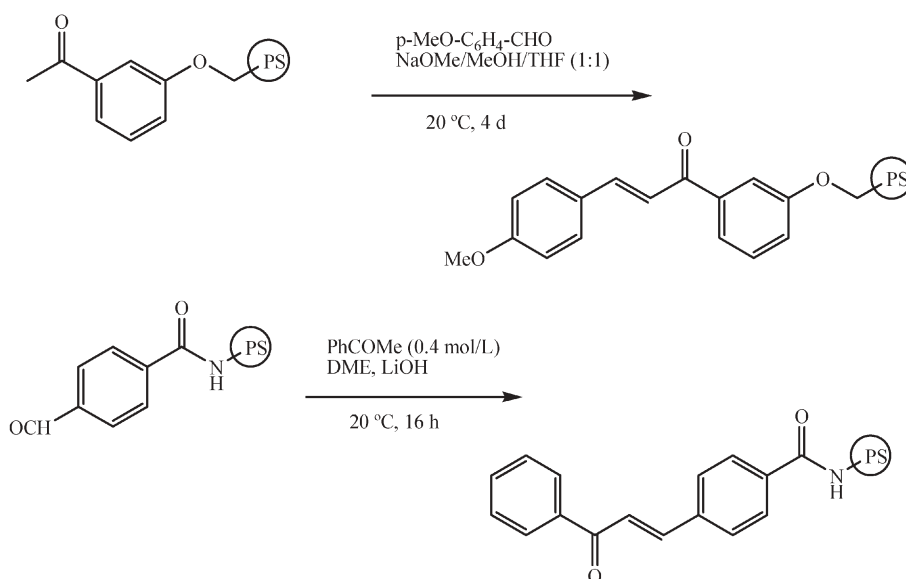
Scheme 15

Scheme 16
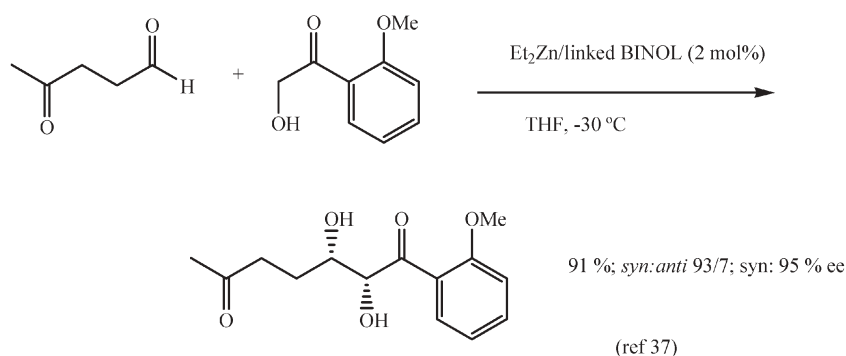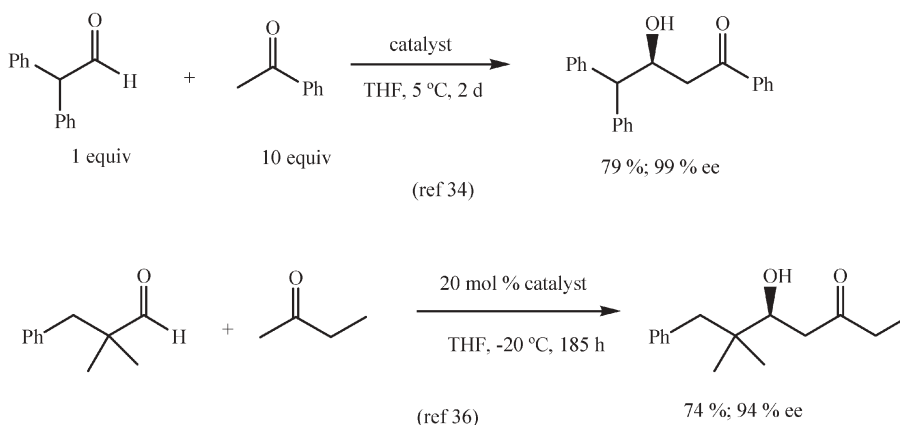
Scheme 17

(zinc chloride: 13.6 g mol^{-1}) and thus, these reactions show a high atom economy, especially if the catalysts are recovered.

Biocatalysed aldol reactions

Aldolase enzymes and antibodies may catalyse aldol reactions.[38] Aldolases are donor specific, diastereoselective and enantioselective, but not specific to the acceptor. They are limited thus to their specific donors, but a variety of aldehyde acceptors can be used. Plant aldolases do not require presence

of metals in the active site and catalyse the aldol reaction through an imine (Schiff base) intermediate. Aldolases found in bacteria and fungi are usually Zn-dependent. Some typical donors are shown in Table 2. One of the relevant features of enzyme catalysed aldol additions is that the stereochemical outcome is entirely determined by the enzyme, and any possible enantiomer can be prepared by the right choice of the enzyme (Scheme 18).[38] Synthesis of highly functionalised compounds is feasible through biocatalytic aldol reactions (Scheme 19). The specificity in the recognition of donors is certainly a serious

Table 2 Donors, acceptors and products of enzyme catalysed aldol reactions[a]

Donor	Acceptor	Product

[a] Reference 38.

limitation of biocatalytic procedures. For this reason it is especially interesting that mutant non-donor specific aldolases have been found by Wong (Scheme 20).[39]

Recent findings by Gouverneur and coworkers show that the regioselectivity of the aldol addition of alkyl and hetero-substituted ketones to aldehydes can be reversed by the right choice of antibody as catalyst (Scheme 21).[40]

Biomimetic catalyst aldol reactions

One of the most interesting recent contributions to the aldol reaction is the use of proline as catalyst. Intramolecular aldol condensations promoted by proline (with enantioselective dehydration) have been known since the early 1970s and referred to as the Hajos–Eder–Sauer–Wiechert reaction, an enantioselective Robinson annulation. However, catalysis of intermolecular aldol conversions by L-proline has been recognized only recently. The first report of excellent yields and enantioselectivities for additions of excess acetone to a
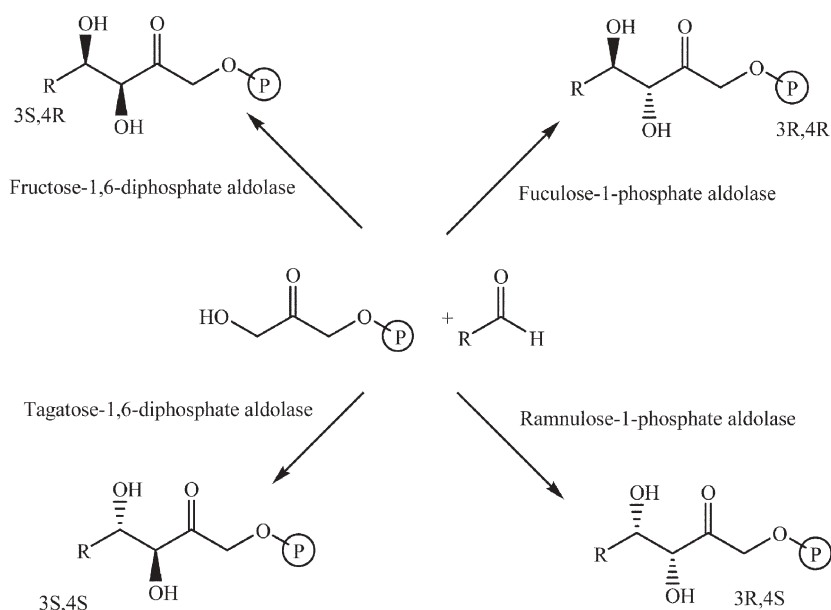
Scheme 18
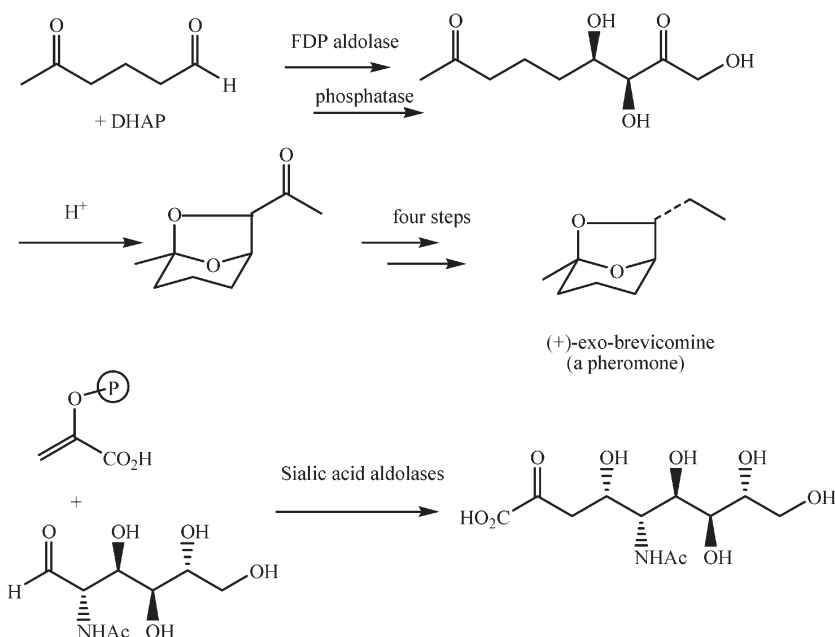
Scheme 19
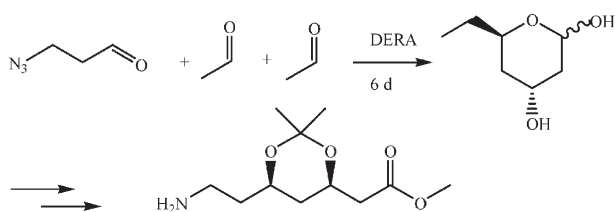
DERA = 2-deoxyribose-5-phosphate aldolase

Scheme 20

limited number of aryl and α-branched alkyl aldehydes in DMSO at room temperature fostered a continuous stream of contributions, with results up to 2002 already reviewed,[41–44] and the mechanism intensively studied.[45] Some relevant results are presented in Tables 3 and 4. The significant point here is that proline raises the expectation of providing green procedures for aldol reactions and, what is especially interesting, combined with high diastereoselectivities and enantioselectivities. Although used in relatively high amounts as catalyst (20–25%), proline is inexpensive, easily available in both its *R*- and *S*-enantiomeric forms, essentially non-toxic, water soluble and easily separated from products for reuse while maintaining enantioselectivity and yield. Proline as catalyst can be regarded as a biomimetic of type I aldolase enzymes and antibodies, as the conversion occurs through the enamine of the donor and the stereochemical outcome is in agreement with a cyclic transition state similar to that depicted by the Zimmermann–Traxler model, where the carbonyl group of the acceptor aldehyde is proton bound to the carboxyl group of proline.[41,42]

The scope of the catalysis by proline has been expanded steadily and the addition to α-unbranched aldehydes has been successfully carried out in acetone or acetone–chloroform.[42] Cross reaction of aldehydes has also been achieved.[46,47] Butanone reacts conveniently through its methyl group, cyclohexanone and cyclopentanone have also been successfully used, but larger ketones, namely 3-pentanone or acetophenone do not react.[42,48] Interestingly, proline promoted aldol additions of free or protected hydroxyacetone as donor occur with excellent regioselectivity, diastereoselectivity and

enantioselectivity to give α,β-dihydroxy ketones.[42,49,50] The potential of proline as catalyst is shown by the trimerization of propionaldehyde to give cyclic hemiacetals in 53% yield as anomeric mixtures of two diastereoisomers (Scheme 22),[51] or by the self-aldolization of alkyl or silyl protected hydroxy-acetaldehyde to give erythrose, as a first step for a simple synthesis of hexoses (see Table 4).[52]
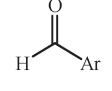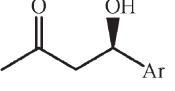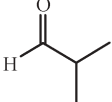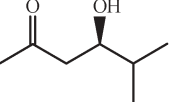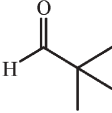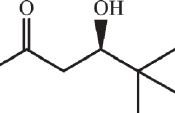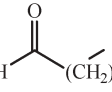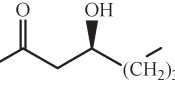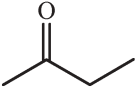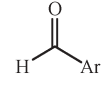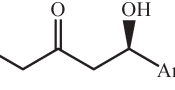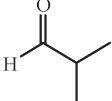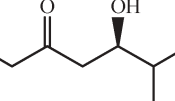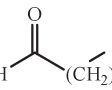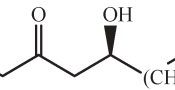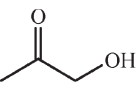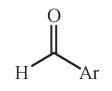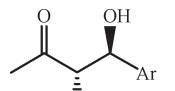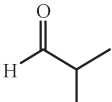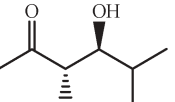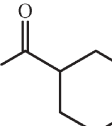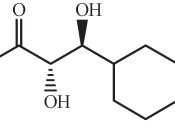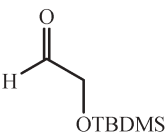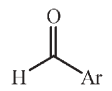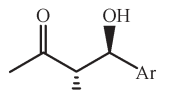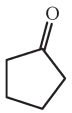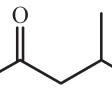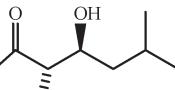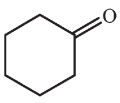
Not surprisingly, the outcome of the first results fostered much interest in finding related biomimetic catalysts that could overcome some of the limitations of proline. Thus, pyrrolidine and acetic acid jointly catalyse the cross aldol reaction of α-branched alkyl aldehydes as donors, when proline is not effective, to give quaternary carbon aldols of otherwise difficult access.[53] Several acyclic and cyclic amino acids and their derivatives have been assayed and 5,5-dimethylthiazolidinium-4-carboxylic acid compares well with proline.[48] Other modifications involve some synthetic peptides that have been prepared and evaluated as catalysts.[54] The amide resulting from proline and enantiomerically pure 1,2-diphenylethanolamine has proved very efficient in the aldol addition of acetone to cyclohexylcarboxaldehyde (Scheme 23) and is in line with a new strategy of catalysis in which a carbonyl group is activated by a double proton bond.[55,56]

One of the drawbacks of the first proline catalysed aldol reactions is the need for aprotic solvents, namely DMSO, DMF or chloroform. The possibility 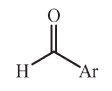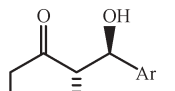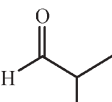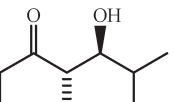of carrying out the reaction in water must then be taken as an interesting improvement and it has been reported that acetone adds to *p*-nitrobenzaldehyde in excellent yield in a phosphate buffered aqueous solution containing sodium dodecyl sulfate (SDS) in the presence of proline. Water inverts the regiochemical trend found for the addition of butanone in DMSO and the product resulting from attack by the methylene group predominates. However, aldol additions in water are poorly stereoselective and proline can be substituted on some occasions by pyrrolidine, by (*S*)-1-(2-pyrrolydinylmethyl)pyrrolidine, or by nornicotine.[57–60] A simple and interesting modification of proline, that allows its use in water, consists of the Zn–proline complex, which is easily prepared from zinc acetate and two equivalents of proline. This complex is water soluble and water stable. Addition of excess acetone to *p*-nitrobenzaldehyde in water affords excellent
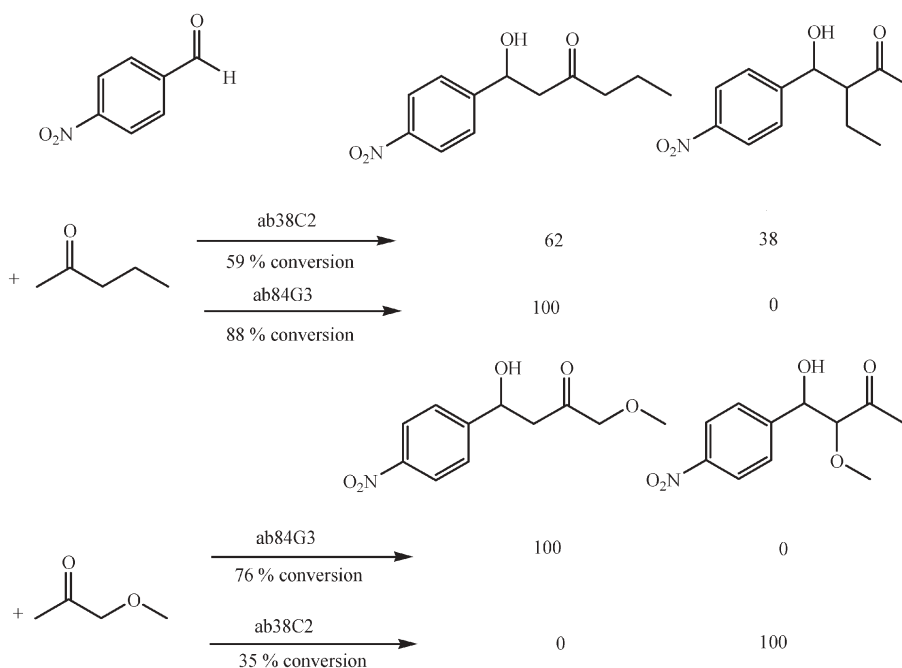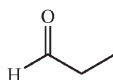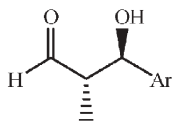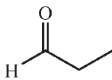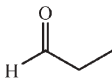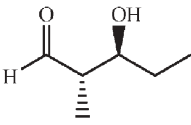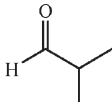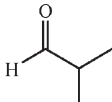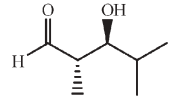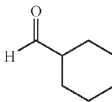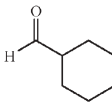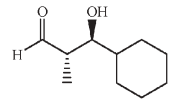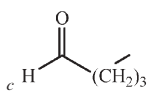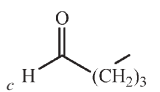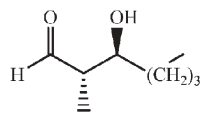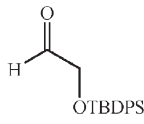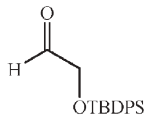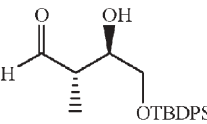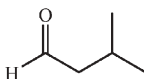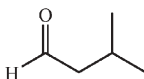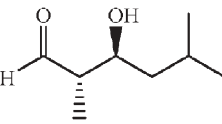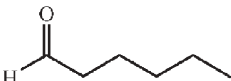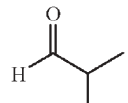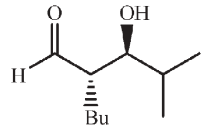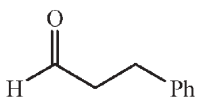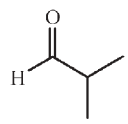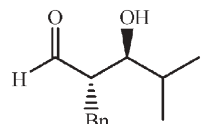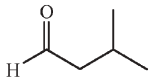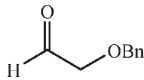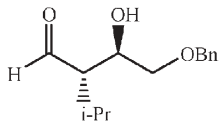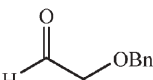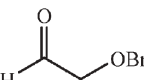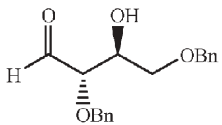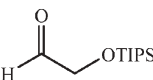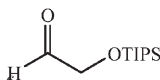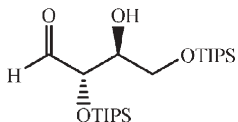
Scheme 21

Table 3 Proline catalysed aldol additions of donor ketones[a,b]

Donor	Acceptor	Product	Yield (%)	dr (anti : syn)	ee (%)	Ref.
			62–94		60–85	41
			97		96	41
			81		99	42
			75		73	48
			65		77	48
			80		80	48
			65		58	48
			60–95	3 : 2 to 20 : 1	67–99	49
			62	20 : 1	99	49
			60	20 : 1	99	49
			68–90			50
[c]			55	5 : 2	20	42
			85	1 : 1	85	42
			68	20 : 1	97	43

[a] Reports of aldolizations with yields below 50% have been omitted. [b] DMSO as solvent, unless otherwise stated. [c] Chloroform as solvent.

Table 4 Proline catalysed aldol additions of donor aldehydes[a,b]

Donor	Acceptor	Product	Yield (%)	dr (anti:syn)	ee (%)	Ref.
(propanal)	Ar-CHO		81	3:1	99	46
	propanal		80	4:1	99	46
	isobutyraldehyde		82	24:1	99	46
	cyclohexanecarbaldehyde		87	14:1	99	46
	[c] (CH₂)₃		65		58	48
	OTBDPS aldehyde		84	5:1	99	52
	3-methylbutanal		88	3:1	97	46
(hexanal)	isobutyraldehyde	Bu	80	24:1	98	46
(3-phenylpropanal)	isobutyraldehyde	Bn	75	19:1	91	46
(3-methylbutanal)	OBn aldehyde	i-Pr	64	4:1	94	52
OBn aldehyde	OBn aldehyde	OBn	73	4:1	98	52
OTIPS aldehyde	OTIPS aldehyde	OTIPS	92	4:1	95	52

[a] Reports of aldolizations with yields below 50% have been omitted. [b] DMF as solvent, unless otherwise stated. [c] DMSO as solvent.

yields, though only moderate enantioselectivities are observed. Interestingly, zinc complexes of other amino acids, namely lysine and arginine are also efficient catalysts.[60]

Other solvents have been studied with the common purpose of avoiding DMSO or DMF. Thus, a polyfluorous proline derivative has also been prepared and used as catalyst in benzene trifluoride solvent, with results similar to those obtained with proline in DMSO, although with a much simpler isolation procedure, according to the authors.[61] Ionic liquids have proved convenient media as solvents for proline promoted
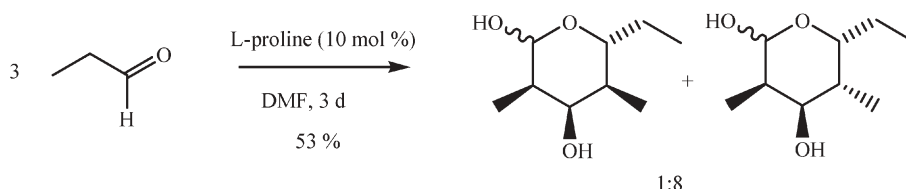
Scheme 22
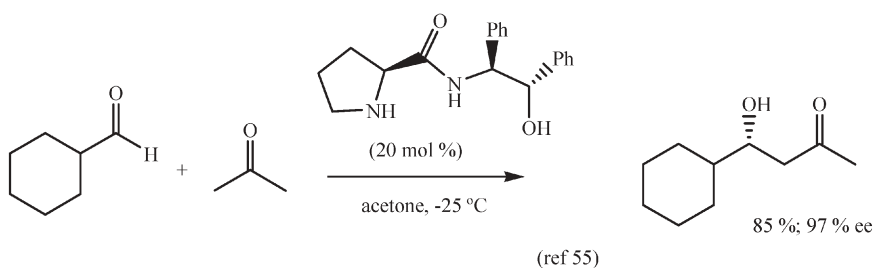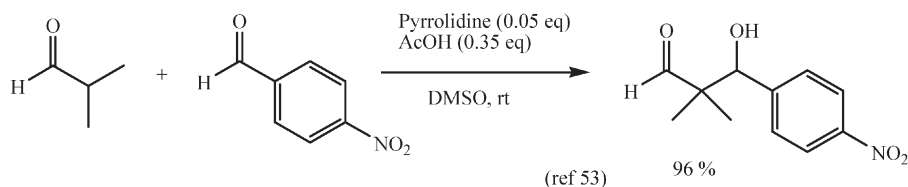
Scheme 23

aldol reactions, with good enantioselectivities being obtained, but with no remarkable advantages over DMSO or DMF.[62,63] As another form of avoiding use of DMSO, the reaction of acetone and several aldehydes has been carried out under pressure, with the ketone as solvent. Good yields of the corresponding ketols are obtained for benzaldehydes, but enantioselectivities seem to decrease at high pressure.[64]

Immobilization of proline for easier separation of products has been carried out by linkage of proline through the carboxyl group to a polystyrene resin. The resin thus functionalised promotes enantioselective aldolizations and can be reused with no loss of activity.[65] Grafting in mesoporous MCM-41 gives poorer yields and enantioselectivities.[66]

Silyl enol ether aldol reactions in water

Aldol reactions of silyl enol ethers promoted by typical Lewis acids must be carried out under strict anhydrous conditions. However, the development of Lewis acids tolerant to water has allowed successful stereoselective aldol reactions of silyl enol ethers in water. Certain metal trifluoromethylsulfonates (triflates) are water soluble and water tolerant, air-stable and easy to handle, such as $Pb(OTf)_2$, $La(OTf)_3$, $Ce(OTf)_3$, or $Ga(OTf)_3$, and others. For instance, a 20 mol% solution of gallium triflate with a semi-crown ligand promotes the

Mukaiyama reaction of the silyl enol ether of propiophenone with aryl and alkyl aldehydes in a water–ethanol (9 : 1) solvent system to give good to excellent yields of the ketols and promising diastereoselectivity (*syn* : *anti* 80 : 20) and enantioselectivity (ee for *syn* ketol 80%).[67,68]

Moderate to good yields of aldol adducts can also be obtained in water by use of silyl enol ethers in the presence of a surfactant copper salt, namely copper dodecylsulfate, and a carboxylic acid. The addition is diastereoselective and, in the presence of a chiral bis-oxazoline, enantioselective (Scheme 24).[69]

Another interesting catalyst for water aldol reactions of silyl enol ethers is diphenylborinic acid, which in the presence of benzoic acid and SDS promotes additions to aldehydes to give *syn*-substituted β-hydroxy ketones in high diastereoisomeric excesses.[68]

Catalytic aldol reactions of α,β-unsaturated ketones under reduction conditions

Recent promising findings by Krische and coworkers show that *in situ* catalytic generation of metallic enolates occurs when α,β-unsaturated ketones or aldehydes are subject to reduction by molecular hydrogen in the presence of a cationic rhodium catalyst capable of causing heterolytic activation of molecular
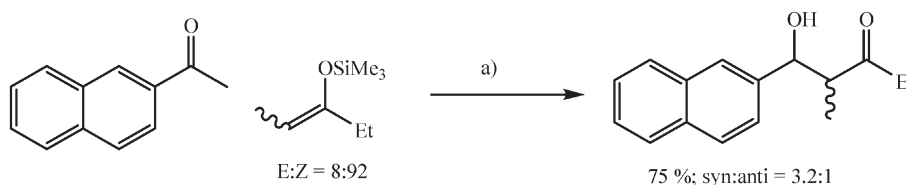
a) 20 %mol $Cu(OSO_3C_{12}H_{25})_2$; 10 % mol $C_{11}H_{23}CO_2H$; 24 % mol chiral bisoxazoline

Scheme 24

hydrogen. The enolates thus generated add efficiently to the carbonyl group of aldehydes or ketones present in the reaction medium, affording the corresponding aldols or ketols. With some constraints, the procedure can be conveniently applied to both inter- and intra-molecular conversions (Scheme 25).[70–73] The significance of the reaction resides in its ability to ensure a regioselective course in the preparation of aldols and ketols of difficult access when starting from simple aldehydes or ketones and using basic or acid catalysis. Further development is expected to expand the scope of the procedure and to achieve both diastereoselectivity and enantioselectivity.

Catalytic aldol reactions of allylic alcohols

Motherwell and coworkers described in 1999 that rhodium catalysed isomerization of allylic lithium alkoxides allowed regioselective generation of the metal enolates of ketones or aldehydes and that these enolates added as expected to aldehydes and ketones in an aldol fashion.[74] However, although allowing regioselective preparation of aldols and ketols, the method needed a waste producing stoichiometric deprotonation of allylic alcohols with butyllithium. Fortunately, Greé and coworkers found that the aldol process can occur satisfactorily with metal enolates catalytically generated directly from allylic alcohols with iron pentacarbonyl or better with rhodium or ruthenium complexes.[75–77]

Later on Li and coworkers found that the reaction could conveniently be carried out in water and in ionic liquids with ruthenium dichloride triphenylphosphine complex (Scheme 26).[78,79]

Conclusion

It has been shown that the general catalytic aldol reaction can be regarded as substantially waste free and safe, but subject to a number of limitations as a method of broad general preparative application. Recently developed catalytic systems have added the achievement of good to excellent stereoselectivities. Stoichiometric procedures expand the scope of the aldol reaction as a general synthetic method and offer the possibility of directing their selectivity trends but at the price of a significant increase in both molar waste and hazard. The recent introduction of water-compatible Lewis acids for the Mukaiyama aldol reaction partly overcomes the safety and environmental drawbacks of silyl enol ether based stoichiometric procedures.

Viewing the present scene, consideration of the sustainability of the reaction would indicate application of catalytic procedures whenever possible, before going to stoichiometric procedures and the direct use of preformed enolates before attempting silyl or boron enol ether mediated stoichiometric reactions.

Biocatalysis and biomimetic catalysis, though not exclusively, seem at present the most promising lines to follow for the development of green aldol reactions. Compatibility of biomimetic catalysts with safe protic solvents or with systems from which products can be easily separated whilst retaining the catalyst would be welcome, especially if conversion yields and selectivities are maintained or improved. However, the search for clean and safe methods in keeping with the achievement of the stoichiometric reactions should also be fostered.

150 mol %   100 mol %   92 %
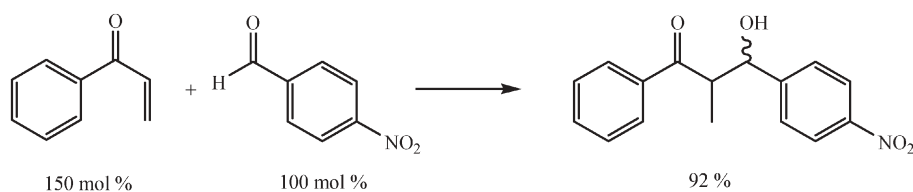
Rh(COD)$_2$ OTf (5 mol %); H$_2$ (1 atm); KOAc (50 mol %); DCE, 25 °C

72 % (16 % 1,4-Reduction)
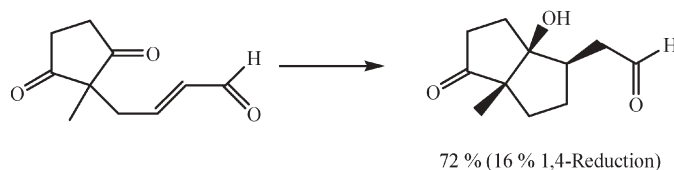
Rh(COD)$_2$ OTf (10 mol %); (2-furyl)$_3$P (24 mol%); H$_2$ (1 atm); KOAc (100 mol %); THF, 40 °C

Scheme 25

1 mmol   2.5 mmol   73 %; syn:anti 79/21
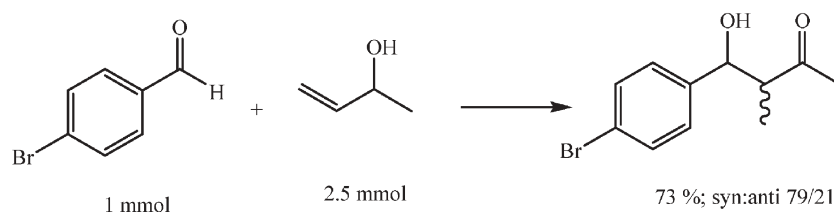
RuCl$_2$(PPh$_3$)$_3$ (0.03 mmol); H$_2$-Toluene (4:1); 5 h; 110 °C

Scheme 26

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PAPER

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Polycrystalline TiO₂ impregnated with cardanol-based porphyrins for the photocatalytic degradation of 4-nitrophenol

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Hydrogenated cardanol (3-n-pentadecylphenol), a renewable organic resource obtained by vacuum distillation of roasted "cashew nut shell liquid" (CNSL), a by-product of the cashew industry, has been used to synthesize novel lipophilic porphyrins. Polycrystalline TiO₂ impregnated with these novel "cardanol-based" porphyrins as sensitizers has been investigated in the photodegradation of 4-nitrophenol (4-NP) in aqueous suspension. The results indicated that the presence of the sensitizer enhances the photoactivity of polycrystalline bare TiO₂ in the process. The activating effect was higher in the case of the Cu-complex.

Introduction

Cardanol is an industrial grade yellow oil obtained by vacuum distillation of "Cashew Nut Shell Liquid" (CNSL), the international name of the alkyl phenolic oil contained in the spongy mesocarp of the cashew nut shell (*Anacardium occidentale* L.). CNSL derives from the most diffused roasted mechanical processes of the cashew industry, represents nearly 25% of the total nut weight and its worldwide production (Africa, Asia, and South America being the main producer areas) is estimated to be about 300 000 tons per year. In addition, CNSL represents a powerful phenolic pollutant of the cashew agro industry.

Therefore, the use of CNSL and its products could represent a strategy to minimise the environmental impact of this low-cost, and largely available natural product.

CNSL is a mixture of anacardic acid, cardanol, and traces of cardol and 2-methylcardol. The alkyl side chain (R) of each of them may be saturated, monolefinic (8-ene), diolefinic (8,11-diene) and triolefinic (8,11,14-triene) with an average of two double bonds per molecule.[1,2]

Due to the decarboxylation of anacardic acid during the distillation process, cardanol is the main component of distilled CNSL. So, CNSL and its components are now considered very attractive renewable bio-sources used under different formulations to develop, for example, new eco-friendly functional materials.[3–5]

3-n-pentadecylphenol 1 (hydrogenated cardanol) is easily obtained by hydrogenation of the double bond(s) in the side-chain of technical grade distilled cardanol (Scheme 1).

Thus, hydrogenated cardanol 1 was used for the synthesis of novel cardanol-based porphyrins.

Recently, we have carried out studies on photocatalytic degradation of 4-nitrophenol (4-NP) in aqueous suspension by using polycrystalline TiO₂ impregnated with functionalised porphyrins or phthalocyanines.[6,7] It was found that TiO₂

anacardic acid

cardanol

cardol

2-methylcardol

R=
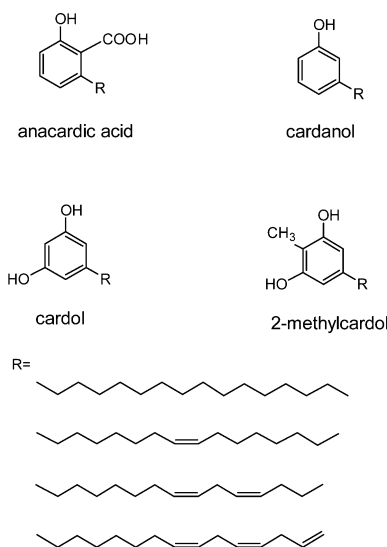
(anatase) samples impregnated with copper-porphyrin or copper-phthalocyanine complexes were more efficient photocatalysts compared with bare TiO₂. In particular, Cu-porphyrin showed a higher photocatalytic activity than that of Cu-phthalocyanine. The photocatalytic activities of samples impregnated with metal-free porphyrin and metal-free phthalocyanine were always lower than those observed by using the samples impregnated with the corresponding Cu complexes.

Moreover, we have evidenced that the introduction of a cardanol moiety in the porphyrin structures was important in order to improve the solubility in organic solvents, and, as a consequence, the hydrophobicity (hence insolubility in water and very low affinity with the aqueous phase), as well as to make their stability on the TiO₂ surface sufficient to support the photocatalytic process.[7,8]
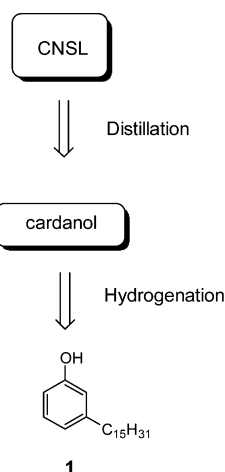
Scheme 1

Experimental

Materials

All the starting materials were purchased from Aldrich Chemical Co. and used as received. TiO$_2$ (anatase phase, specific surface area 8 m^2 g^{-1}) was kindly provided by Tioxide Huntsman. Cardanol and 3-*n*-pentadecylphenol (**1**) were kindly supplied by Oltremare Spa (Bologna, Italy). Silica gel (Merck) was used in the chromatographic separations. Solvents were dried and distilled under an atmosphere of dry nitrogen.

Physical methods and analysis

FT-IR spectra were recorded on a JASCO FT-IR 430 spectrometer. UV-Vis spectra were recorded on a Cary 100 scan UV-Visible spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 at room temperature and chemical shifts are reported relative to tetramethylsilane.

Mass spectrometry analyses were carried out by using an LC mass spectrometer 1100 Series (Agilent) equipped with an electrospray (ESI) interface. The samples, dissolved in dichloromethane and acidified by addition of formic acid, were injected into the mass spectrometer by an auto sampler spraying a THF–H$_2$O 1 : 1 solution at a flow rate of 0.5 mL min^{-1}. Positive ions were extracted *via* a heated capillary to a skimmer lens arrangement at reduced pressure and transferred by an octapole to the main analytical quadrupole assembly. The instrumental conditions were as follows: drying gas (nitrogen) 7 L min^{-1}, nebulizer pressure 60 psi, drying gas temperature 300 °C, capillary voltage 4000 V, mass range 500–2500 amu.

For the photoreactivity experiments a Pyrex batch photoreactor of cylindrical shape containing 0.5 L of aqueous suspension was used. The photoreactor was provided with a jacket for cooling water circulation and ports in its upper section for the inlet and outlet of gases, for sampling and for pH and temperature measurements. A 125 W medium pressure Hg lamp (Helios Italquartz, Italy) was immersed within the photoreactor; the photon flux emitted by the lamp was $\Phi_i = 13.5$ mW cm^{-2}. This value was measured by using a radiometer "UVX Digital" leaned against the external wall of the photoreactor containing only pure water. O$_2$ was bubbled into the suspensions for *ca.* 0.5 h before switching on the lamp and throughout the course of the photoreactivity experiments. The amount of catalyst used for all of the experiments was 0.8 g L^{-1}, and the initial 4-nitrophenol (BDH) concentration was 20 mg L^{-1}. The initial pH of the suspension was adjusted to 4.0 by addition of 1 M H$_2$SO$_4$ (Carlo Erba RPE), and the temperature inside the reactor was held at *ca.* 27 °C by a continuous circulation of water in the jacket around the

photoreactor. The photoreactivity runs lasted 6.0 h. Samples of 5 mL volume were withdrawn from the suspensions every 30 or 60 min and the catalysts were separated from the solution by filtration through 0.45 µm cellulose acetate membranes (HA, Millipore). The quantitative determination of 4-nitrophenol was performed by measuring its absorption at 315 nm with a Shimadzu UV-2401 PC spectrophotometer. Non purgeable organic carbon (NPOC) determinations were carried out by using a Shimadzu total organic carbon analyzer 5000-A.

Results and discussion

Synthesis of porphyrins H$_2$Pp and CuPp from 3-*n*-pentadecylphenol (1)

According to previously reported conditions,[8] 3-*n*-pentadecylphenol **1** was reacted with 1,2-dibromoethane **2** in the presence of KOH at 70 °C for 6 h to give **3** in 77% yield. Under solvent-free conditions, the unreacted 1,2-dibromoethane **2** was recovered quantitatively by vacuum distillation. The reaction of the 2-bromoethoxy derivative **3** with 4-hydroxybenzaldehyde **4** in the presence of potassium carbonate in acetone under reflux for 24 h affords the 4-substituted benzaldehyde **5** (Scheme 2).

Aldehyde **5** was reacted with pyrrole **6** in chloroform in the presence of catalytic amounts of BF$_3$·OEt$_2$ at room temperature for 30 h. The subsequent oxidation *in situ* with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for 64 h gave rise to the *meso* substituted porphyrin H$_2$Pp in 14% overall yields (Scheme 3).

H$_2$Pp was characterized by FT-IR, UV-Vis, ^{1}H and ^{13}C NMR, LC-MS using an electrospray ionization (ESI—working in positive ion mode) interface. The UV-Vis spectrum of H$_2$Pp shows a Soret band at 421 nm and Q bands at 518, 555, 593,
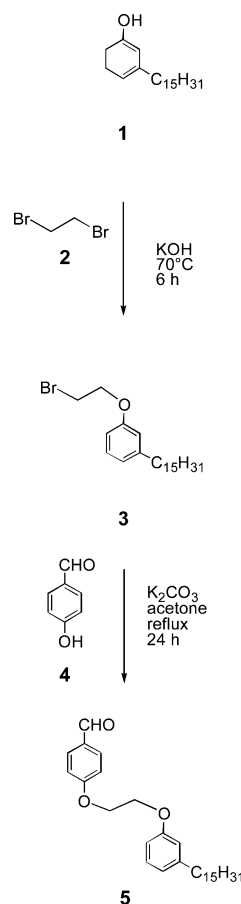
Scheme 2

Scheme 3
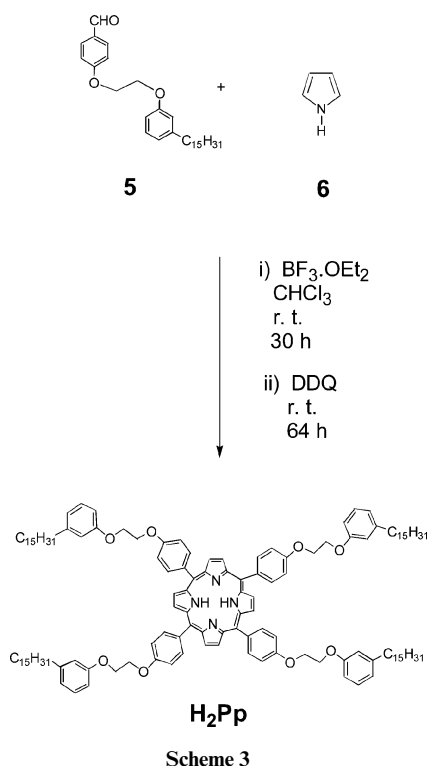
649 nm. The mass spectrum of H$_2$Pp shows the expected molecular ion peak at m/z 2001 (M+H)$^+$.

The ^{1}H NMR and FT-IR spectra of H$_2$Pp were also consistent with the proposed structure. In particular, the ^{1}H NMR spectrum of this compound exhibited one typical singlet centered at 8.89 ppm attributable to the 8 protons at the β position of the pyrrole moiety, the aromatic protons in the range 8.20–6.80 ppm, a multiplet in the range 4.75–4.50 ppm for the O–CH$_2$–CH$_2$–O system, the aliphatic protons in the range 2.70–0.85 ppm and the NH protons as a broad singlet centered at −2.73 ppm. The IR spectrum of H$_2$Pp showed a weak band at 3300 cm^{-1} characteristic of the NH vibration.

Successively, H$_2$Pp was reacted with CuCl$_2$ **7** in chloroform at room temperature for 16 h producing the corresponding Cu complex in nearly quantitative yield (Scheme 4).

Scheme 4
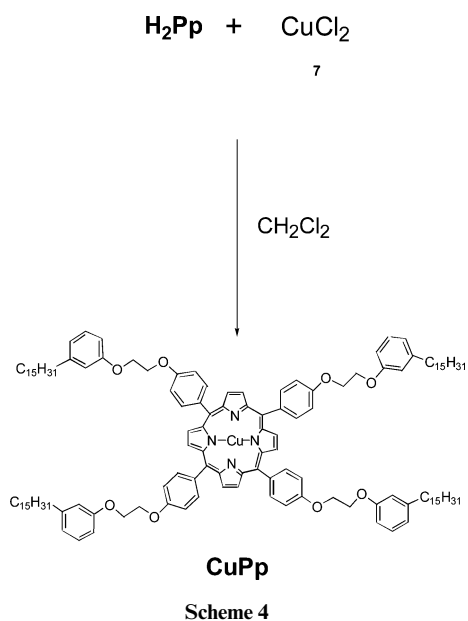
Preparation of TiO$_2$–CuPp and TiO$_2$–H$_2$Pp samples

The TiO$_2$ (anatase) porphyrin-loaded samples used as photocatalysts for the photoreactivity experiments were prepared by impregnating TiO$_2$ (Tioxide, anatase phase, specific surface area 8 m^2 g^{-1}) with various amounts of CuPp (5.55, 6.65, 11.10 µmol g^{-1} TiO$_2$) or H$_2$Pp (6.65, 11.10 µmol g^{-1} TiO$_2$). The sensitizers were dissolved in 10 ml of CHCl$_3$ (or CH$_2$Cl$_2$) and 2 g of finely ground TiO$_2$ were added to this solution. The mixture was stirred for 3–4 h and the solvent was removed and collected by vacuum distillation. The porphyrin impregnated TiO$_2$ samples were dried and used for the photocatalytic experiments.

The code used for the samples is as follows: the figure indicates the µmol of sensitizer used for the impregnation of 1 g of TiO$_2$, (A) the crystalline phase anatase, CuPp the copper porphyrin and H$_2$Pp the metal-free porphyrin. For instance 6.65-TiO$_2$(A)–H$_2$Pp represents the sample prepared by using 6.65 µmol of metal-free porphyrin to impregnate 1 g of TiO$_2$ (anatase).

Photostability experiments and recovery of the catalysts

Preliminary investigation was carried out in order to detect possible decomposition or chemical modification of H$_2$Pp and CuPp supported onto TiO$_2$ under the same conditions used for the photocatalytic experiments. NPOC determinations were carried out *ad hoc* in aqueous suspension of stirred photocatalysts in the absence of 4-NP to check the photochemical stability of the impregnated catalysts under irradiating conditions. No significant release of organic degradation compounds was observed even after long irradiation times (5–7 h). Moreover the supported sensitizers can be recovered quantitatively (and unchanged) from the TiO$_2$ surface by extraction with chlorinated solvents (CHCl$_3$ or CH$_2$Cl$_2$) after the photocatalytic experiments. The absence of structural modifications was confirmed by analytical and spectral data (TLC, UV-Vis,^{1}H NMR, LC-MS).

Photocatalytic degradation of 4-nitrophenol

Phenolic compounds are a class of very dangerous pollutants and 4-NP, chosen as a probe molecule to carry out the photodegradation experiments, is one of the most refractory pollutants in industrial wastewater. Its high stability and solubility in water are the main reasons why the degradation of this compound to non dangerous levels is a very difficult task.

The apparent kinetics of disappearance of 4-NP were followed by determining the concentration of the substrate at various time intervals. No analysis of intermediates was performed because this was outside the scope of this work and, besides, 4-NP heterogeneous photocatalytic degradation has already been studied exhaustively.[9,10] Dihydroxy nitrobenzene isomers were found initially as intermediate products, but these compounds absorb mainly in the visible range and do not interfere at 315 nm where the analysis of the probe molecule was performed.

Fig. 1 shows the evolution of 4-NP concentration *versus* irradiation time for selected runs performed using bare TiO$_2$ and some TiO$_2$ samples impregnated with metal-free and Cu(II)-porphyrin. An improvement in the photoreactivity with respect to that shown by the bare support was observed for all of the samples loaded with Cu(II)-porphyrin and in particular, the most photoactive appeared to be the 6.65-TiO$_2$(A)–CuPp sample.

The samples impregnated with the metal-free porphyrin were only slightly more photoactive than the bare TiO$_2$. This finding indicates that the porphyrinic macrocycle is photocatalytically active even in the absence of the metal. In Table 1 the initial reaction rates (zero order kinetics) for 4-NP disappearance per

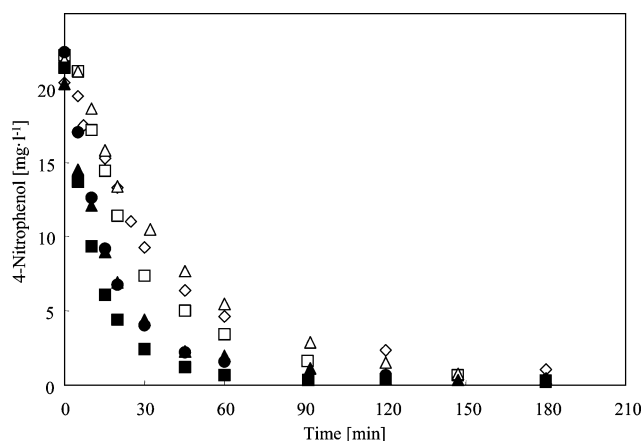**Fig. 1** 4-Nitrophenol concentration *versus* irradiation time in the presence of ($\diamond$) bare TiO_2; ($\square$) 6.65-TiO_2(A)–H_2Pp; ($\triangle$) 11.10-TiO_2(A)–H_2Pp; ($\bullet$) 5.55-TiO_2(A)–CuPp; ($\blacksquare$) 6.65-TiO_2(A)–CuPp; ($\blacktriangle$) 11.10-TiO_2(A)–CuPp.

Table 1 List of the samples used together with the BET specific surface areas and the initial photoreaction rates per used mass (r_0) and per unit surface area (r'_0) of the samples, determined by using the 0.5 L batch photoreactor

Samples	BET specific surface areas (S.S.A.)/ $m^2 g^{-1}$	$r_0 \times 10^{10}/$ mol $L^{-1} s^{-1}$	$r'_0 \times 10^{10}/$ mol $L^{-1} s^{-1} m^{-2}$
TiO_2(A)	8	467	146
6.65-TiO_2(A)–H_2Pp	8	677	212
11.10-TiO_2(A)–H_2Pp	8	533	166
5.55-TiO_2(A)–CuPp	8	937	293
6.65-TiO_2(A)–CuPp	8	994	311
11.10-TiO_2(A)–CuPp	8	775	242

used mass of the sample (r_0) and per square meter of powder (r'_0) are reported, along with the specific surface areas of the photocatalysts.

The data reported in the table are the average of three measurements. The optimum photoreactivity exists probably due to the achievement of an optimum number of Cu-porphyrin species and the number of available photoactive sites.

On the other hand, the photoactivity of bare TiO_2 (anatase) is sufficiently high that the modification of some physico-chemical surface properties, in particular the occupation of sites by CuPp, could partially balance the beneficial effect due to its presence when the amount of CuPp becomes high (compare in Table 1 the initial reaction rate of 11.10-TiO_2(A)–CuPp and 6.65-TiO_2(A)–CuPp samples).

Fig. 2 shows the NPOC results after 5 h of irradiation. 4-NP was completely photodegraded by using all the photocatalysts, but it was scarcely mineralised in the presence of some samples. All the loaded samples, both metal-free and Cu(II)-porhyrins, however, presented some improvement with respect to bare TiO_2 as far as 4-nitrophenol mineralization is concerned. After *ca.* 5 h of irradiation small NPOC values (*ca.* 1–2 mg L^{-1}) were found for these samples, whereas for bare TiO_2 the concentration of NPOC was approximately double this level.

It has been reported that the photosensitization of TiO_2, due to the sole excitation of Fe(III)-phthalocyanine, Cu(II)-phthalocyanine or Cu(II)-porphyrin can be ruled out because photons with $\lambda \geqslant 420$ nm, suitable for photoexciting only the macrocycles, proved to be ineffective for the degradation of some organic molecules in water. It is necessary to photoexcite both components of the system, *i.e.* TiO_2 and the sensitizer, in order to obtain significant improvement of the photodegradation rate. This co-catalytic effect was explained by considering
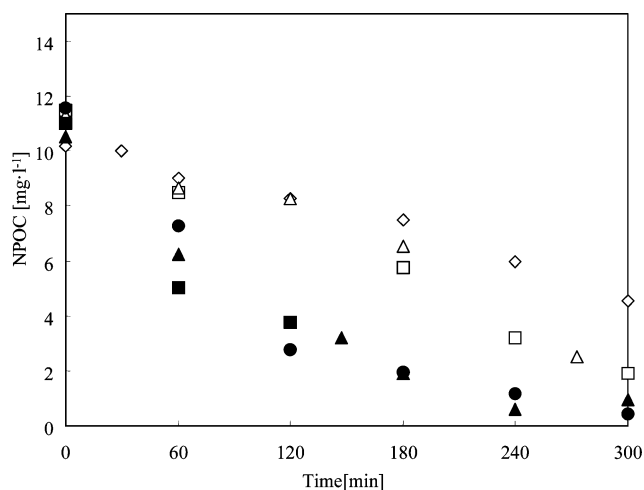
Fig. 2 Non purgeable organic carbon (NPOC) *versus* irradiation time in the presence of ($\diamond$) bare TiO_2; ($\square$) 6.65-TiO_2(A)–H_2Pp; ($\triangle$) 11.10-TiO_2(A)–H_2Pp; ($\bullet$) 5.55-TiO_2(A)–CuPp; ($\blacksquare$) 6.65-TiO_2(A)–CuPp; ($\blacktriangle$) 11.10-TiO_2(A)–CuPp.

a cooperative mechanism of the macrocycle and TiO_2.[6,7,11] It is worth noting that the photoactivity of porphyrins bearing hydrogenated cardanol appears quite similar to that of analogous (*t*-butyl) functionalized porphyrins[6,7] indicating that this low cost product can be successfully used instead of other synthetic chemicals.

As shown in Fig. 3, diffuse reflectance spectra in air of bare TiO_2, 6.65-TiO_2(A)–H_2Pp, 5.55-TiO_2(A)–CuPp, 6.65-TiO_2(A)–CuPp and 11.10-TiO_2(A)–CuPp samples, recorded in the range 250–800 nm, indicate that all the loaded samples reflect light less significantly than the bare support and their absorption throughout the range investigated increases by increasing the amount of supported porphyrins.

The improvement of light absorption in the visible range might in principle favour some reaction steps of the photocatalytic process, but the above finding cannot be simply invoked to explain the beneficial effect on the photoreactivity due to the presence of Cu(II)-porphyrin.

Some hypotheses can be drawn to explain these results by taking into account some physico-chemical and electronic properties both of TiO_2 and CuPp.

It is likely that the use of CuPp improves the spatial separation of photoproduced e^-–h^+ pairs by trapping electrons and/or delocalizing holes. The presence of coordinated Cu(II) is probably essential to trap electrons that would be transferred to adsorbed O_2 by means of favourable kinetic step(s), leading
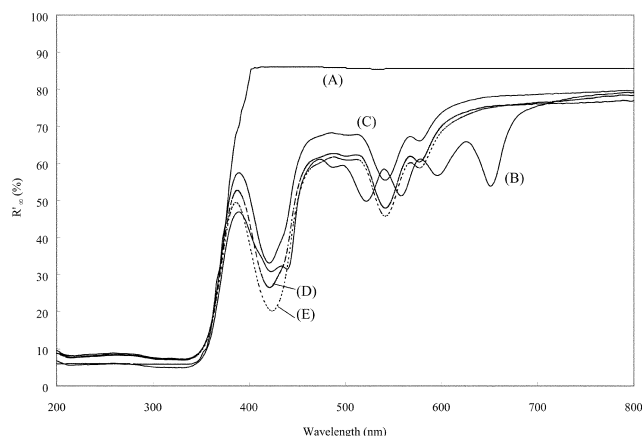
Fig. 3 Diffuse reflectance spectra in air of: (A) bare TiO_2; (B) 6.55-TiO_2(A)–H_2Pp; (C) 5.55-TiO_2(A)–CuPp; (D) 6.55-TiO_2(A)–CuPp; (E) 11.10-TiO_2(A)–CuPp.

to a process that is faster than the direct O_2 reduction. The formation of $O_2^{\cdot-}$ is needed to produce species responsible for the oxidant attack during the photocatalytic reactions.[12–14]

In addition, as the aromatic macrocycle enables a good delocalization of the holes, the so obtained stabilisation of the photoproduced positive charge makes the electrons more available both for O_2 and coordinated Cu(II). Alternatively, holes could be trapped by H_2O and/or $OH_{(surface)}$ giving rise to a well known set of reactions affording the oxidation of 4-NP.[9,10,15] Nevertheless these phenomena should probably work concurrently in order to achieve an improvement of the photoreactivity.

Conclusions

In this paper we have described the synthesis of new metal-free and Cu-substituted *meso*-tetraarylporphyrins containing 3-*n*-pentadecylphenol, a natural renewable material obtained as by-product of the cashew industry.

The novel cardanol-based porphyrins showed high solubility in organic solvents and were used to impregnate TiO_2 in the crystalline phase of anatase. The photocatalytic activity of TiO_2 loaded with these novel porphyrins, investigated through the examination of the probe reaction of photodegradation of 4-NP in aqueous suspension, indicated that the presence of the sensitizer increases the photoactivity and confirms the important role of Cu in this process.

Moreover, these cardanol-based porphyrins represent a new class of dyes having green and real prospects not only for photocatalytic processes, but also for other technological applications, especially when high solubility in organic solvents and processability are required.

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Synthesis of methylethers by reaction of alcohols with dimethylcarbonate

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A new synthetic procedure to methylethers has been developed by the reaction of alcohols with dimethylcarbonate, a non-toxic and environmentally friendly reagent. The methylation of alcohols is catalysed by alumina or hydrotalcite. The methylcarbonate formed in the first step undergoes decarboxylation in the second step, to give the corresponding methylether. The reactivity follows the order: primary > secondary ≫ tertiary alcohols. The reaction can be efficiently performed under both batch and continuous flow conditions.

Introduction

Methylations in synthetic chemistry are typically carried out using methyl halides or dimethyl sulfate. Both reagents are toxic and corrosive chemicals. Moreover the reaction requires a stoichiometric amount of a base as catalyst and produces a stoichiometric amount of inorganic salts that need to be disposed of.

Dimethylcarbonate (DMC) is an environmentally benign substitute for dimethyl sulfate and methyl halides;[1,2] as a methylating agent ($B_{Al}2$ mechanism)[3] it requires temperatures higher than 150 °C.[4,5] CO_2 and methanol are the only by-products formed.

$$YH + CH_3OCOOCH_3 \xrightarrow{K_2CO_3} YCH_3 + CH_3OCOOH$$
$$CH_3COOH \rightarrow CO_2 + CH_3OH \tag{1}$$
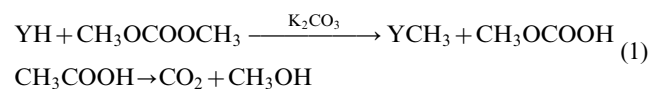
According to eqn. 1 (YH is an acidic compound), in previous papers we reported that N-methylation of aniline,[6] C-methylation of methylene-active compounds[7] and O-methylation of phenol[8] can be carried out with DMC, in the presence of a catalytic amount of weak base. Selectivities up to 99% toward the mono-methylderivatives were observed in the case of methylene-active compounds.[7] However, under similar conditions the reaction of alcohols with DMC gave exclusively methylcarbonates ($B_{Ac}2$ mechanism), also at high temperatures, according to eqn. 2.[9]

$$ROH + CH_3OCOOCH_3 \underset{K_2CO_3}{\rightleftharpoons} ROCOOCH_3 + CH_3OH \tag{2}$$
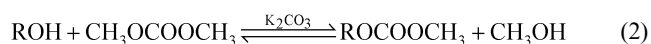
A few patents report the preparation of methylethers with DMC as the reagent, either by a nucleophilic displacement from the alkoxide[10] or by the decarboxylation of methylcarbonates at high temperature (220–300 °C).[11] Where the latter method is concerned, the best performance was obtained with catalytic beds containing Mg–Al oxides or Ru, Rh, Pd, Pt supported on silica or alumina, but the processes described were characterised by low yields or a broad product spectrum. In any case, methylethers were never achieved with a selectivity higher than 50%, with symmetrical carbonates and symmetrical ethers being formed as side products.

We report here the synthesis in good yields of methylethers by the reaction of alcohols with DMC in the presence of basic alumina or hydrotalcite KW 2000 as catalyst. Eqn. 3 describes the process.

$$ROH + CH_3OCOOCH_3 \xrightarrow{Al_2O_3 / KW\ 2000}$$
$$ROCH_3 + CH_3OH + CO_2 \tag{3}$$
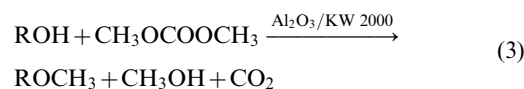
Results and discussion

Preliminary experiments to identify the best catalyst for the reaction were performed using 1-octanol and benzyl alcohol as the substrates.

Further experiments were dedicated to the understanding of the reaction pathway and to the investigation of the behaviour of primary, secondary and tertiary alcohols. Finally, we have shown that the reaction is a general one: it can be extended to other alkylcarbonates and can be performed under continuous flow conditions.

Reaction of 1-octanol with dimethylcarbonate

The reaction of 1-octanol with DMC was carried out in a magnetically stirred stainless steel autoclave at 200 °C. After cooling down, the gaseous components were removed through the side valve and the composition of the product mixture was determined by gas chromatographic analysis. Table 1 reports the effect of several basic catalysts, from classic basic

Table 1 Reaction of 1-octanol with DMC[a] (eqn. 3; R=n–C_8H_{17}–)

Entry	Catalyst	Time/h	Conv.	MOE	MOC
1	K_2CO_3 (1 mol equiv.)	2.5	99	—	100
2	DMAP (0.1 mol equiv.)	6	100	—	100
3	KF/Al_2O_3[b] (1 mol equiv. KF)	1	100	—	100
4	MgO (1 : 1 w/w)	1	78	2	98
5	Acidic Al_2O_3[c] (1 : 1 w/w)	1	98	24	76
6	Basic Al_2O_3[d] (1 : 1 w/w)	1	100	100	—
7	KW 2000[e] (1 : 1 w/w)	1	100	97	3

[a] Reaction conditions: 1-octanol : DMC 1 : 15 w/w; 200 °C; all catalysts were used without any activation. Data given as GC%. MOE: methyloctylether; MOC: methyloctylcarbonate. [b] 3 : 1 w/w Al_2O_3; prepared as reported by Ando et al..[12] [c] Riedel-De Haën, type S acid active for chromatography, less than 0.063 mm. [d] Merck, type 60 basic for chromatography, 70–230 mesh. [e] Kyowa Chemical Industry Co. Tokyo, $Mg_{0.7}Al_{0.3}O_{1.15}$, specific surface area 202 $m^2\ g^{-1}$.

promoters, like potassium carbonate, dimethylaminopyridine (DMAP), alumina-supported KF and MgO, to amphoteric catalysts containing both acidic and basic sites, such as alumina and hydrotalcite. All the catalysts were used without any activation.

The effect of the catalyst structure on the reaction was found to be very significant. In fact, methyloctylcarbonate (MOC) was the major product in the presence of potassium carbonate (entry 1), as is well known from the literature. DMAP (entry 2) and supported KF (entry 3)[12] behaved similarly, promoting the complete conversion of the alcohol in the MOC.

Vice versa, methyloctylether (MOE) was formed in trace amounts (2%) in the presence of MgO (entry 4), in significant amounts (24%) with acidic alumina (entry 5) and with very high selectivity (100% and 97%) in the basic alumina and KW 2000 (a synthetic hydrotalcite with formula $Mg_{0.7}Al_{0.3}O_{1.15}$) promoted reactions (entries 6 and 7, respectively).

No other product was detected.

Reaction of benzyl alcohol with dimethylcarbonate

The catalytic effect of basic alumina and KW 2000 was confirmed in the reaction of benzyl alcohol with DMC under similar conditions.
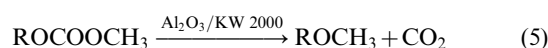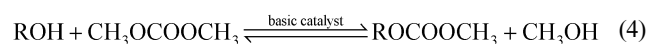
Benzyl alcohol was completely converted into benzylmethylether (BME) at 200 °C, in the presence of 1 : 1 (w/w) basic Al_2O_3 or KW 2000 (Table 2, entries 1 and 2, respectively).

As shown in the table, scale down of basic alumina (entry 3) and KW 2000 (entries 4–5) slightly decreased the substrate conversion, but strongly influenced the methylether selectivity. In the presence of smaller amounts of catalyst, in fact, benzylmethylcarbonate (BMC) was found as a reaction intermediate. Also in this case, BME and BMC were the only products detected.

Identification of the reaction pathway

The presence of benzylmethylcarbonate might suggest a two-step reaction pathway.

Accordingly, the reaction might proceed through a first step (a transesterification reaction between the alcohol and DMC, according to eqn. 4), followed by a second step (decarboxylation of the methylcarbonate into the methylether—eqn. 5).

$$ROH + CH_3OCOOCH_3 \xrightleftharpoons{\text{basic catalyst}} ROCOOCH_3 + CH_3OH \quad (4)$$

$$ROCOOCH_3 \xrightarrow{Al_2O_3 / KW\,2000} ROCH_3 + CO_2 \quad (5)$$

To confirm the above hypothesis, benzylmethylcarbonate alone was reacted in an autoclave at 200 °C, in the presence of basic alumina or KW 2000 as catalyst, using DMC itself as the solvent. The K_2CO_3-catalysed reaction was also carried out for comparison. (Table 3).

As expected, BMC was completely converted in the presence of basic alumina or KW 2000, forming BME with very high selectivity (see entries 1 and 2). Conversely, no reaction was observed when potassium carbonate was the catalyst (entry 3).

Table 2 Reaction of benzyl alcohol with DMC[a] (eqn. 3; R=C₆H₅CH₂–)

Entry	Catalyst	Subst. : cat./w/w	Conv.	BME	BMC
1	Basic Al_2O_3	1	100	100	—
2	KW 2000	1	98	96	—
3	Basic Al_2O_3	4	83	19	63
4	KW 2000	4	96	76	20
5	KW 2000	10	93	33	58

[a] Reaction conditions: benzyl alcohol : DMC 1 : 15 w/w; 200 °C; 3 h. Data given as GC%. BME: benzylmethylether; BMC: benzylmethylcarbonate.

Table 3 Reaction of benzylmethylcarbonate: effect of the catalyst[a] (eqn. 5; R=C₆H₅CH₂–)

Entry	Catalyst	Conv.	BME
1	Basic Al_2O_3 (1 : 1 w/w)	>99	98
2	KW 2000 (1 : 1 w/w)	>99	97
3	K_2CO_3 (1.2 mol equiv.)	2	—

[a] Reaction conditions: BMC : DMC 1 : 15 w/w; 200 °C; 1.5 h. Data given as GC%. BME: benzylmethylether.

Such results, together with those reported in Table 1, clearly show that, while any basic catalyst is able to promote the transesterification of alcohol with DMC, to give the methylcarbonate (step 1, eqn. 4), only the peculiar catalytic activity of alumina and hydrotalcite is effective for its decarboxylation to methylether (step 2, eqn. 5).

Reaction of primary, secondary and tertiary alcohols with dimethylcarbonate

In further experiments, the reactivity of primary, secondary and tertiary alcohols with DMC was investigated. For such reactions, basic alumina was used as the catalyst. The substrates explored and the results obtained are reported in Table 4.

As previously found, 1-octanol (**1**, entry 1) and benzyl alcohol (**3**, entry 3) were quantitatively converted into methyloctylether (**1a**) and benzylmethylether (**3a**), while side reactions occurred in the methylation of secondary and tertiary alcohols.

In particular, the yield of methylethers **2a** and **4a** in the reactions of 2-octanol (**2**, entry 2) and 1-phenylethanol (**4**, entry 4) were decreased by the formation of octenes (10%) and styrene (28%), respectively.

In the reaction of 2-phenyl-2-propanol (**5**, entry 5), the corresponding methylether **5a** was formed only in small amounts, being 2-phenylpropene the major product.

Two possible paths leading to the olefins may be envisaged, (i) the β-elimination of H_2O from the alcohol and (ii) the pyrolysis of the methylcarbonate (Tschugaev's reaction) with elimination of methoxycarbonic acid, which is in turn rapidly decomposed in CO_2 and methanol. In all likelihood, both paths are effective with secondary alcohols while tertiary substrates are too hindered to undergo transesterification. Alkene side-products are probably mainly due to β-elimination.

In conclusion, the methylation of primary alcohols with DMC catalysed by basic Al_2O_3 is a highly selective reaction. Secondary alcohols can be methylated with DMC, although with lower selectivity. The methylation of tertiary alcohols, on the contrary, practically does not occur.

The order of reactivity was therefore: primary > secondary ≫ tertiary alcohol.

Reaction of alcohols with diethylcarbonate

The reaction described (eqns. 4–5) is also a general one with respect to the alkylating agent.

Table 4 Basic Al_2O_3-catalysed reaction of primary, secondary and tertiary alcohols with DMC[a]

Entry	Alcohol	Conv.	Methylether	Other products
1	**1**	100	**1a** (100)	—
2	**2**	83	**2a** (87)	CH₃(CH₂)₄CH=CHCH₃; CH₃(CH₂)₅CH=CH₂ (10)
3	**3**	100	**3a** (100)	
4	**4**	100	**4a** (68)	PhCH=CH₂ (28)
5	**5**	99	**5a** (8)	PhC(CH₃)=CH₂ (88)

[a] Reaction conditions: alcohol : basic Al_2O_3 1 : 1 (w/w); alcohol : DMC 1 : 15 w/w; 200 °C; 1.5 h. Data given as GC%.

Table 5 Reaction of alcohols with DEC[a]

Entry	Alcohol	Conv.	Ethylether	Other products
1	**1**	99	**1b** (100)	—
2	**3**	93	**3b** (77)	PhCH$_2$OCOOCH$_2$CH$_3$ (5)
				PhCH$_2$OCH$_2$Ph (12)

[a] Reaction conditions: alcohol : basic Al$_2$O$_3$ 1 : 1 (w/w); alcohol : DEC 1 : 15 w/w; 200 °C; 1.5 h. Data given as GC%.

If diethylcarbonate (DEC) is used in the place of DMC (Table 5), ethyloctylether (**1b**) and benzylethylether (**3b**) are formed from 1-octanol (**1**, entry 1) and benzyl alcohol (**3**, entry 2), respectively.

Methylation of 1-pentanol under continuous-flow conditions

The possibility of performing the methylation of alcohols with DMC under continuous-flow conditions was investigated.

The reactor employed was a cylindrical column, heated at 180 °C by an external oven, containing basic alumina as the catalytic bed. Continuous feeding of the reagents (DMC and 1-pentanol in 3 : 1 weight ratio) was ensured by sending the liquid mixture of the reagents into the column by a metering pump with 30 ml h^{-1} feeding rate. The reaction was carried out for a period of six hours, collecting the gaseous products at the outlet of the column by a condenser. The product mixture was analysed by gas chromatography at hour intervals.

The results, reported graphically in Fig. 1, showed a steady composition throughout the period of investigation, with 90% selectivity for methylpentylether.

After that time, the reagents were removed from the catalytic bed by flushing with cyclohexane and heating at 180 °C overnight under vacuum.

With such a procedure, dictated by the necessity of stopping the reaction during the night, carbon dioxide released during the reaction and adsorbed on the weakly basic sites was also removed.[13]

The same product composition, was observed the day after, performing the reaction under the same conditions.

Re-iteration of the above procedure showed almost no catalyst deactivation after four cycles.

The selectivity of methylpentylether (■) was around 90% during the entire time of investigation (24 hours).

Conclusion

We have shown that DMC is an efficient substitute for toxic methylating agents, such as dimethylsulfate and methyl halides, in the synthesis of methylethers from alcohols. In the new synthetic procedure, non toxic reagents are used and no by-products are formed but methanol and carbon dioxide.

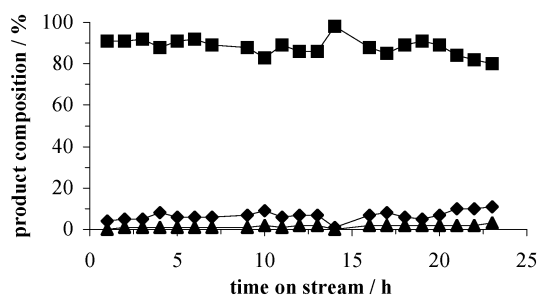The methylation reaction described is of general application

Fig. 1 Continuous-flow methylation of 1-pentanol. Catalytic bed: basic Al$_2$O$_3$ (15 g); DMC : 1-pentanol: 3 : 1 w/w; feeding rate: 30 ml h^{-1}; 180 °C. ■, methylpentylether; ◆, 1-pentanol; ▲, methylpentylcarbonate.

to primary and secondary alcohols, while the selectivity with tertiary alcohols becomes too low.

Dialkylcarbonates other than DMC can be also successfully used: ethylethers are formed in the reaction of alcohols with DEC.

Moreover, the reaction can be performed under both batch and continuous flow conditions maintaining very high selectivity, without catalyst deactivation.

While other nucleophilic substrates (anilines, phenols, methylene-active compounds) are methylated by DMC by a B$_{Al2}$ mechanism,[5] the mechanism operating in the methylation of alcohols is a B$_{Ac2}$. transesterification followed by the decarboxylation of the resulting methylcarbonate.

Weak bases, which are productive catalysts for the transesterification step, are unable to promote the decarboxylation. Elimination of CO$_2$, in fact, seems to require both weakly basic and acidic sites, present in alumina and hydrotalcite.

The interaction of the methylcarbonate with the catalytic sites, as well as the reaction mechanism, are currently under investigation and will be the subject of a separate paper.

Experimental

Methylation of alcohols by dimethylcarbonate: general procedure

In a stainless steel autoclave, the desired amount of the catalyst was added to the alcohol and DMC in 1 : 15 w/w ratio. Air was removed from the autoclave by bubbling with a nitrogen stream for about 5 minutes. The autoclave was then heated at 200 °C by an electric oven at the reaction temperature under magnetic stirring over the period indicated. The reaction temperature was controlled by a thermocouple dipped into the reaction mixture. After cooling down, the gaseous components were removed through the side valve, and the reaction mixture was filtered over Gooch n° 4 to remove the solid catalyst. The reaction products were analysed by gas chromatography, with a CP-SIL 24 CB capillary column (30 m × 0.25 mm ID).

Preparation of benzylmethylcarbonate

In a three-necked flask equipped with a dephlegmator, benzyl alcohol (30 g) DMC (450 g) and basic alumina (30 g) were heated at refluxing conditions (90 °C) under magnetic stirring. Continuous removal of methanol as an azeotropic mixture with DMC (3 : 1 w/w) boiling at 64 °C pushed the equilibrium over to the right. The reaction course was followed by both GC analysis of the reaction mixture and measurement of the refraction index of the distilled azeotropic mixture. At complete conversion of the substrate, the mixture was filtered over Gooch n° 4 to remove the solid catalyst and the filter was washed three times with *ca.* 100 ml of methanol. After removal of methanol and unreacted DMC by evaporation *in vacuo*, benzylmethylether (39 g, 85%) was obtained as a colourless oil.

Decarboxylation of benzylmethylcarbonate to benzylmethylether

In a stainless steel autoclave, the desired amount of the catalyst was added to benzylmethylcarbonate (1 g) and DMC (15 g). The reaction conditions and the work-up procedure were those described above for the methylation of alcohols.

Continuous-flow methylation of 1-pentanol.

A solid bed composed of 15 g basic alumina was heated overnight at 180 °C under vacuum before the reaction. A liquid mixture containing DMC and 1-pentanol in 3 : 1 weight ratio was fed to the head of a tubular reactor (i.d. 2 cm) containing the solid bed acting as catalyst. Complete vaporization of the

components was assured by the excess of DMC, used also as gaseous carrier for the reaction. The reaction mixture was collected with a condenser placed at the column outlet and analysed by GC. After 6 hours, the reagents were removed by flushing with cyclohexane and the bed was heated overnight at 180 °C under vacuum, before reiteration of the procedure (four times).

Acknowledgements

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PAPER

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Synthesis of styrene carbonate from styrene oxide and carbon dioxide in the presence of zinc bromide and ionic liquid under mild conditions

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The synthesis of styrene carbonate (SC) from styrene oxide (SO) and CO_2 has been studied with various catalyst systems including metal halides and ionic liquids. The total conversion of SO and the selectivity for SC strongly depend on the catalyst systems used. The highest SC yield of 93% can be achieved at a low temperature of 80 °C for 1 h with a catalyst system of $ZnBr_2$ and [C_4-mim]Cl at a molar ratio of 1 : 2. A CO_2 pressure of 4 MPa is optimal but elevated pressures have no positive effects on this SC synthesis.

Introduction

Carbon dioxide is one of the greenhouse effect gases but it has gained increasing attention as an abundant and non-toxic building block for organic synthesis in recent years.[1] The coupling reaction of CO_2 and epoxides to produce valuable cyclic carbonates is of great importance in industry. The five-membered cyclic carbonates can find extensive applications as monomers, aprotic polar solvents, and intermediates in the production of biomedical materials such as drugs and pesticides.[2] A number of catalyst systems such as metal halides,[3] organic bases,[4] metal oxide,[5] base modified zeolites,[6] lanthanide oxychloride,[7] metal complexes,[8] ionic liquids,[9] and DMF[10] have been developed for the coupling reaction of CO_2 and epoxides. Most of these catalyst systems were used for the reactions of CO_2 with ethylene oxide (EO) or propylene oxide (PO). Very recently Kim *et al.* have reported highly active catalysts, imidazolium zinc tetrahalides, for these two epoxides under such mild conditions as 100 °C and 3.5 MPa CO_2.[8f,g,9d]

During the course of our study on the fixation of CO_2 to useful chemicals in different green reaction pathways,[5c,11] we have been investigating the coupling of CO_2 and epoxides such as EO, PO, and styrene oxide (SO). The latter is a bulky epoxide and its conversion to styrene carbonate (SC) is lower as compared with those of EO and PO to the corresponding cyclic carbonates, probably due to the low reactivity of the β-carbon atom of SO.[9c] A few different catalyst systems have been reported for the coupling of CO_2 and SO,[4b,4c,5,6d,8a–8d,8i,8j,9c,10] which, however, require high reaction temperature, long reaction time, high CO_2 pressure, and/or toxic organic solvent to obtain high SC yields. For example, Nomura *et al.* reported that organoantimoy compounds showed high TOF values larger than 300 h^{-1} at 120 °C; unfortunately, a polymer of SO was also produced with these catalysts.[8a] Kawanami *et al.* showed an ionic liquid of 1-octyl-3-methylimidazolium salt, [C_8-mim]BF_4, to be a good catalyst;[9c] a moderate yield of 61% and a SC selectivity of 100% were obtained in supercritical CO_2 (14 MPa) at 100 °C for 2 h, in which TOF was about 30 h^{-1}. This reaction system is sensitive to the variation of CO_2 pressure. When the CO_2 pressure was reduced to a subcritical pressure of 7 MPa, the SC yield sharply decreased from 61% to 28%.

Considering reaction mechanisms for the synthesis of cyclic carbonate from epoxide and CO_2 using metal oxide catalysts, it has been proposed that this synthesis requires both Lewis base-activation of CO_2 and Lewis acid-activation of epoxide.[5a,5b] In accordance with this, the combination of organic bases with metal complexes has been found to give satisfactory reaction results.[8c–8e,8h–8j] These bi-functional catalyst systems give higher carbonate yields than those obtained by separately using a single component; however, they still require high reaction temperatures. So, the exploration of more efficient catalysts for green synthesis of cyclic carbonates, in particular SC, under mild reaction conditions still remains a challenging problem.

The present work has been undertaken to study the activity of various catalyst systems that include metal halide and ionic liquid for the coupling of SO and CO_2. This work is a part of our study on direct synthesis of SC from styrene in the presence of ionic liquids. We have recently reported better SC yields, compared with previous achievements reported in the literature, but not satisfactory for practical applications.[12] Our aim is to find effective catalysts for the coupling of SO and CO_2, which is the second step following the initial oxidation of styrene to SO, in the direct synthesis of SC. In the present work, the coupling of SO and CO_2 has been examined using various couples of metal halides and ionic liquids under different reaction conditions. A highly active catalyst system has been found to be a couple consisting of zinc bromide and 1-butyl-3-methylimidazolium chloride, with which SC can be produced in excellent yields under mild conditions; for example, 93% yield at 80 °C for 1 h. The present work has studied the influence of the kinds of metals and ionic liquids and reaction conditions in detail. A possible reaction mechanism is also proposed on the basis of the results obtained.

Results and discussion

Influence of various metal species and ionic liquids

Several catalysts of metal halide or oxide with 1-butyl-3-methylimidazolium chloride ([C_4-mim]Cl) as a co-catalyst were screened for the coupling reaction of SO and CO_2. The reaction results obtained are listed in Table 1, in which the selectivity for SC is 100% in all cases. No activity was observed with $ZnBr_2$ alone (entry 1) and [C_4-mim]Cl gave a very low yield of the desired carbonate (entry 2). However, the combination of zinc

Table 1 Catalytic activities of various metal compounds in the presence of ionic liquid in the synthesis of styrene carbonate from styrene oxide and CO_2

Entry	Metal compound	Ionic liquid	Yield (%)
1	$ZnBr_2$	—	No reaction
2	—	[C₄-mim]Cl	6
3	$ZnBr_2$	[C₄-mim]Cl	93
4[a]	$ZnBr_2$	[C₄-mim]Cl	82
5[b]	$ZnBr_2$	[C₄-mim]Cl	96
6[c]	$ZnBr_2$	[C₄-mim]Cl	89
7	$FeBr_3$	[C₄-mim]Cl	73
8	$FeBr_2$	[C₄-mim]Cl	47
9	$MgBr_2$	[C₄-mim]Cl	39
10	LiBr	[C₄-mim]Cl	17
11	NaBr	[C₄-mim]Cl	7
12	ZnI_2	[C₄-mim]Cl	75
13	$ZnCl_2$	[C₄-mim]Cl	20
14	ZnO	[C₄-mim]Cl	11

SO, 35 mmol; metal compound, 0.4 mmol; [C₄-mim]Cl, 0.8 mmol; CO_2 pressure, 14 MPa; 80 °C, 1 h. [a] [C₄-mim]Cl, 0.4 mmol. [b] [C₄-mim]Cl, 1.6 mmol. [c] For the second run using the same catalysts which were separated after the first run. For the procedures used, see Experimental section.

bromide with [C₄-mim]Cl exhibited a markedly high activity; SC was obtained with a high yield of 93% and no by-products such as polycarbonate or polyester were detected by GC-MS and GC (entry 3). When the $ZnBr_2$: [C₄-min]Cl ratio was changed from 1 : 2 to 1 : 1 (entry 4), the SC yield decreased from 93% to 82%. However, further changing the ratio to 1 : 4 little affected the SC yield (entry 5). The type of metal cations had a strong effect on the carbonate yield (entries 3, 7–11), the order of activity being Zn^{2+} > Fe^{3+} > Fe^{2+} > Mg^{2+} > Li^+ > Na^+, in accordance with the order of Lewis acidity of the metal cations. The counter anion of the salts also significantly affected the catalytic activity (entries 3, 12–14). When ZnI_2, $ZnCl_2$ or ZnO was used instead of $ZnBr_2$, the SC yields were lowered. The notable catalytic activity of zinc bromide with [C₄-mim]Cl may originate from the cooperative action of both the acidic site (Zn) for epoxide activation and basic site (Cl^- in [C₄-mim]Cl and/or Br^- in $ZnBr_2$) for CO_2 activation, as proposed previously for several catalyst systems.[5a,5b,8b,8d,8j] The catalysts were separated and reused for another run (entry 6). The carbonate yield gave no significant loss, indicating that the catalysts can be recyclable.

Table 2 shows the influence of the type of ionic liquid. When an ionic liquid having a longer alkyl chain, [C₈-mim]Cl, was used instead of [C₄-mim]Cl, the transformation of SO to SC was complete under the conditions used. This may result from an increase in the solubility of CO_2 and SO in the ionic liquid phase. A similar promoting effect of a longer alkyl chain was observed for the coupling of propylene oxide and CO_2 using various ionic liquids of 1-alkyl-3-methylimidazolium tetrafluoroborate.[9c] The anions of ionic liquids also have a striking effect on the carbonate yield. The use of [C₄-mim]BF₄ and [C₄-mim]PF₆ resulted in low SO conversions and low SC selectivities. In these cases, a large amount of oligomers of SO

Table 2 Influence of ionic liquids on the SC synthesis using $ZnBr_2$

Ionic liquid	Conversion (%)	Selectivity (%)	Yield (%)
[C₄-mim]Cl	93	100	93
[C₈-mim]Cl	100	100	100
[C₄-mim]BF₄	8	67[a]	5
[C₄-mim]PF₆	14	7[a]	1

SO, 35 mmol; $ZnBr_2$, 0.4 mmol; ionic liquid, 0.8 mmol; CO_2 pressure, 14 MPa; 80 °C, 1 h. [a] The main by-products are oligomers of the substrate, SO and/or the product, SC.

Table 3 Effects of reaction parameters on the SC synthesis with $ZnBr_2$/[C₄-mim]Cl

Entry	Temperature/°C	Time/h	Selectivity	Yield (%)
1	100	1	100	100
2	80	1	100	93
3	80	2	100	100
4	60	3	100	75
5	45	3	100	19

[a] SO, 35 mmol; $ZnBr_2$, 0.4 mmol; [C₄-mim]Cl, 0.8 mmol; CO_2 pressure, 14 MPa.

and/or SC were produced as by-products. These results indicate that the BF_4^- and PF_6^- anions are not favourable components for the cycloaddition of CO_2 to SO.

Influence of reaction parameters

Table 3 shows the effects of reaction variables on the SC synthesis using $ZnBr_2$ and [C₄-mim]Cl. At 100 °C for 1 h, SO was completely transformed to SC under the conditions used. As expected, the SC yield decreased with a decrease in the reaction temperature. It is worth noting, however, that this catalyst system can give a good SC yield even at 60 °C in a longer reaction time of 3 h.

In order to investigate the influence of CO_2 pressure on the activity, the reaction was carried out with a smaller amount of catalyst to obtain yields that were not so high. Fig. 1 illustrates the dependence of SC yield on CO_2 pressure. The SC yield increased with increasing pressure from 1 MPa up to 4 MPa. When the pressure was further raised up to 18 MPa, the SC yield was not improved. This indicates that higher CO_2 pressure is not needed to obtain good SC yields. The pressure dependence observed is not simple and the SC yield shows a minimum around 12 MPa. A similar trend of the pressure dependence was previously reported in the presence of ionic liquid [C₂-mim]BF₄.[9c] The authors suggest that the concentration of the CO_2 reactant in the ionic liquid phase is an important factor and that the initial increase of yield at low pressures is due to an increase in the CO_2 concentration and the decrease of yield at elevated pressures is a dilution effect with an excessively increasing quantity of CO_2. However, they do not give possible reasons for the pressure effect observed in the middle range of CO_2 pressure.

To explain the pressure dependence of Fig. 1 and the features of the reaction, the phase behaviour has been examined under the reaction conditions. The state of the reaction mixture at 80 °C and at different CO_2 pressures is shown in Fig. 2. At low pressures, there are two phases, a CO_2-rich gas phase and a liquid phase including SO, [C₄-mim]Cl and $ZnBr_2$ and CO_2 is also soluble in this liquid phase. However, at an elevated pressure of 18 MPa or higher, the reaction mixture is in a single phase and so the reaction takes place homogeneously in this
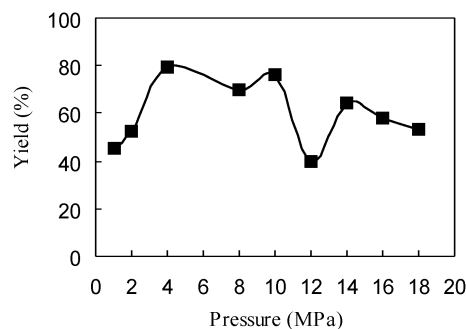
Fig. 1 Pressure dependence of SC yield in the coupling of SO (35 mmol) and CO_2 in the presence of $ZnBr_2$ (0.15 mmol) and [C₄-mim]Cl (0.3 mmol) at 80 °C for 1 h.
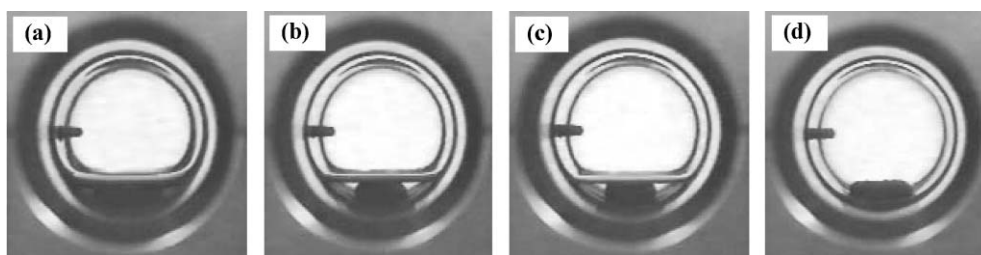
Fig. 2 Photographs of the reactant mixture (styrene oxide, 0.8 ml; $ZnBr_2$, 0.03 mmol; [C_4-mim]Cl, 0.06 mmol) taken at CO_2 pressure of (a) 4 MPa, (b) 12 MPa, (c) 14 MPa and (d) 18 MPa at 80 °C.

phase. At lower pressures, the reaction should also occur homogeneously in either the CO_2-rich gas phase or the liquid phase. The solubility of reacting species (SO, [C_4-mim]Cl and $ZnBr_2$) in the gas phase is likely to increase with increasing CO_2 pressure and, therefore, the dominating reaction phase should shift from the liquid phase to the gas phase with increasing CO_2 pressure.

Since the reaction system is not simple, the overall rate of reaction should depend on several factors including the volume of the phases present, the concentration of the reacting species, the activity of catalytically active species and the reaction kinetics in these phases. The changes of Fig. 1 at low and elevated pressures may also be explained by the increase of CO_2 concentration in the liquid phase and the dilution effect, respectively, as mentioned above. Further study is needed to explain the results clearly and several chemical and physical factors should be considered. An important point should be noted here again that the reaction occurs homogeneously in the liquid phase and/or the CO_2-rich gas phase, which is useful for discussing the reaction mechanism.

Mechanism consideration

Based on the experimental results obtained, the mechanism for the synthesis of SC using $ZnBr_2$/[C_4-mim]Cl catalyst is postulated in Scheme 1, which involves the following steps: first, the epoxide is coordinated with the Lewis acid site Zn to form the adduct of the metal-epoxide complex **1**;[8h,9d] then, the

Cl^- anion of the ionic liquid makes a nucleophilic attack on the less hindered carbon atom of the coordinated epoxide followed by ring opening, producing an oxy anion species **2**;[4b] next, CO_2 is coordinated to the complex through interactions with Br^- and O^-, resulting in the formation of **4**; finally, SC is produced by intramolecular cyclic elimination, leaving the catalytic components.

The influence of the acidity of the cation and the nucleophilicity of the anion of the metal complex may be interpreted by this mechanism. When the Lewis acidity of the metal cation is stronger, the coordination of the epoxide is easier. Furthermore, a more nucleophilic anion is beneficial for its interaction with the carbon atom of CO_2. So, the activity order of $ZnBr_2 > ZnCl_2 > ZnO$ observed is in accordance with the increasing nucleophilicity of anions. However, the activity over $ZnBr_2$ is higher than over ZnI_2 (Table 1, entries 3, 12), which can be explained by the steric hindrance of halide anions. The two conflicting factors: the nucleophilicity and the steric hindrance of the halide anions may make the interaction of Br with the carbon atom of CO_2 stronger than $I\cdots C$ and $Cl\cdots C$, rendering the C atom of CO_2 (complex 3) more positive.

The mechanism can explain that a high SC yield is achieved at a [C_4-mim]Cl/$ZnBr_2$ molar ratio of 2 and a larger ratio of 4 does not improve the activity; two epoxide molecules are coordinated with a $ZnBr_2$ molecule and two ionic liquid molecules interact with the resulting adduct of the metal-epoxide complex. The catalyst systems using [C_4-mim]BF_4 and [C_4-mim]PF_6 show poor activity and selectivity, as observed,
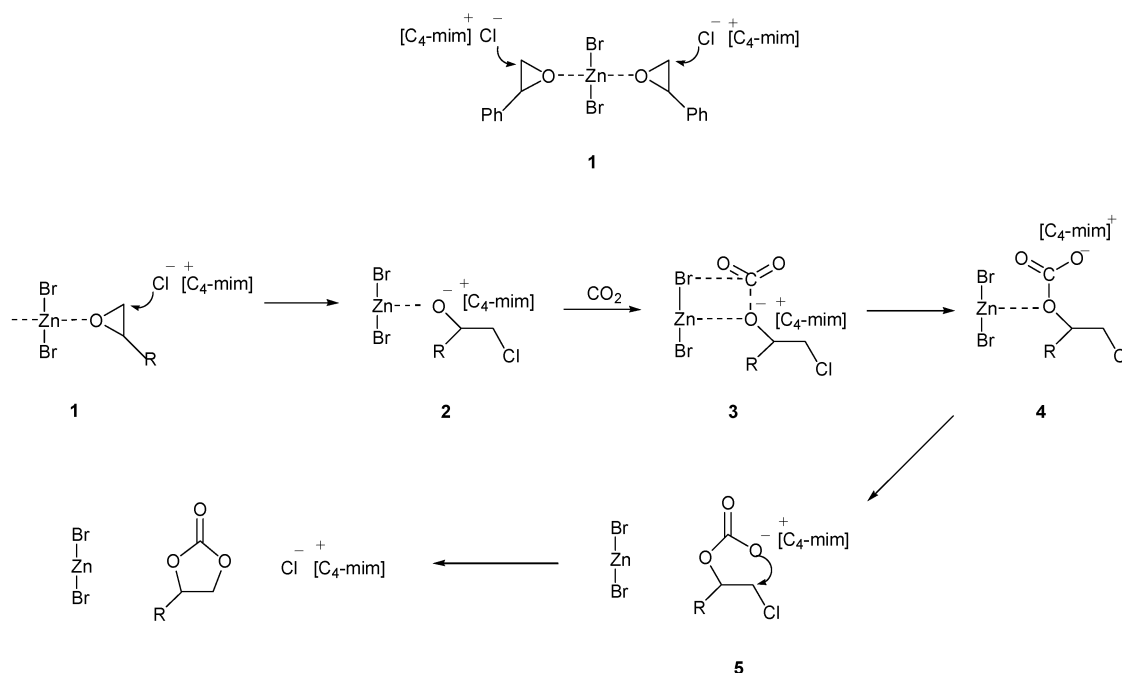
Scheme 1 A proposed mechanism for the synthesis of styrene carbonate from styrene oxide (SO) and CO_2 with $ZnBr_2$/[C_4-mim]Cl catalyst. The successive steps are illustrated for only one of the two SO molecules coordinated with a $ZnBr_2$ molecule.

and this is due to the non-nucleophilic nature of BF_4^- and PF_6^- ions.[9a,13]

Conclusion

This work demonstrates the successful use of both ionic liquid and $ZnBr_2$ as an effective catalyst system for the coupling reaction of styrene oxide and CO_2. An almost quantitative yield of styrene carbonate is obtained with the highest atom economy under mild reaction conditions. Compared with the other literature works on the coupling reaction of styrene oxide and CO_2, the notable features are: (1) the reaction system is simple; (2) organic solvent is not needed; (3) the catalyst is easy to separate and recycle; and (4) high reaction temperature/pressure and prolonged reaction time are avoided. The reaction process is of great potential in industry because of its environmentally benign nature and high throughput of the useful product.

Experimental

The reaction of SO and CO_2 was conducted batchwise in a 50 ml high-pressure stainless steel reactor. Zinc bromide (powder, Wako), ionic liquid (Fluka) and styrene oxide (Wako) were charged into the reactor successively and then the reactor was heated using a water bath. When the desired reaction temperature was attained, the reaction mixture was pressurized with CO_2, while stirring, up to the desired pressure controlled by a back-pressure regulator. After the reaction, the reactor was cooled by ice water to room temperature and depressurized to atmospheric pressure with the back-pressure regulator. Then, ethyl acetate (Wako) was added to the reactor, with which the catalysts were obtained as a solid. The catalysts were separated, filtered off, washed with ethyl acetate twice (10 ml $\times$ 2), and then dried under vacuum. The products extracted with ethyl acetate (25 ml) were analyzed by a gas chromatograph (Shimadzu 390B) with a packed capillary column (GL Science TC-17) using a flame ionization detector. The structure and the purity of the products were further identified using GC-MS (Shimadzu QP-5000) by comparing retention times and fragmentation patterns with authentic samples. The solid catalysts were reused for another reaction under the same conditions to examine the possibility of catalyst recycling.

The phase behaviour of the reaction mixture was visually examined with a 10 ml high-pressure sapphire-windowed view cell at 80 °C at different CO_2 pressures. The detailed procedures are given elsewhere.[14]

Acknowledgements

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