metal industry is considered energy-related. These amounts of CO_2 greatly exceed consumption, and even if all organic base chemicals (approx. 400 Mt(C)/annum) were made from CO_2, emissions would only decrease by some 6–7%.

CO_2 could be mitigated by other technologies under debate, such as disposal in oceans or by the production of methanol with solar hydrogen. Methanol is considered a future key chemical that can selectively be converted to bulk chemicals, *i.e.* the lower olefins. However, chemical use of CO_2 could imply increasing emissions and is still expensive, due to CO_2 recovery costs and high hydrogen price.[16]

In conclusion, it can be said that CO_2 mitigation by means of industrial consumption will remain rather modest and mainly temporary, and that investigations should focus on increasing efficiencies and on sustainable energy sources, such as biomass, wind, and solar cells. Intuitively, a global policy to restrict CO_2 emissions is appropriate, although the existence of the greenhouse effect is still under debate.

Acknowledgements

We would like to thank Dr John N. Armor, Air Products and Chemicals, Inc., Allentown (USA), for advice.

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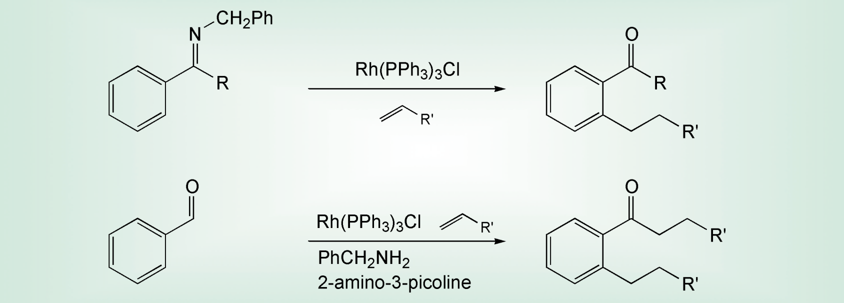
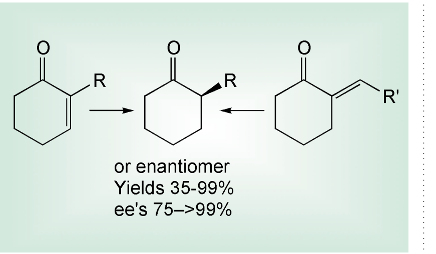
Highlights

Duncan Macquarrie reviews the latest research in green chemistry

Chul-Ho Jun and his group at the Yonsei University in Seoul have discovered an efficient method for the ortho alkylation of aromatic imines (and thus indirectly benzaldehydes). Their work (*Angew. Chem., Int. Ed.*, 2000, **39**, 3440) is based on a Rh catalysis which functions by chelation and activation, leading to efficient alkylation with alkenes at the position ortho to the imine. Linear alkyl groups are introduced in all cases. The chemistry can be extended to insert the alkene to the aldehydic (iminic) C–H bond (right hand example) with the aid of 2-amino-3-picoline.

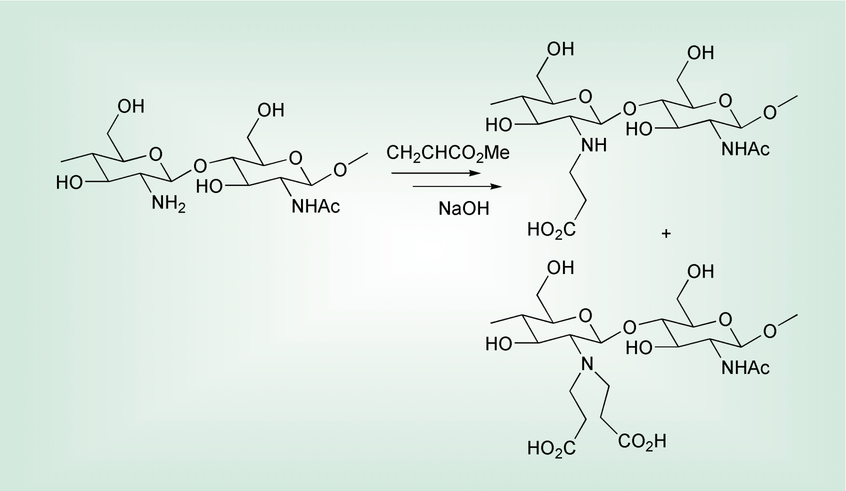


Researchers led by Toshifumi Hirata at Hiroshima University have described an enantioselective reduction methodology based on the use of enzymes (*Chem. Lett.*, 2000, 851). The three enzymes were obtained from *Nicotiana tabacum* and were found to be very effective in the reduction of cyclic enones, giving reduced products in good conversion and excellent ee (⩾95% in all but one case). Both endocyclic and exocyclic double bonds could be reduced.

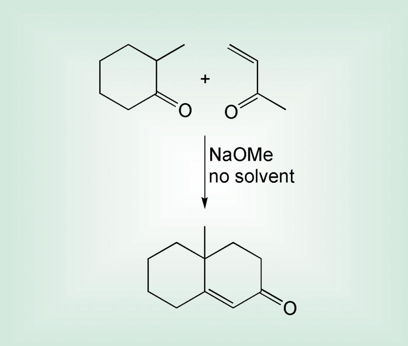


The application of biopolymers such as starch and chitosan in chemistry is growing, as the ability to modify their properties improves. Rene Roy's group at the University of Ottawa have published details of a novel functionalisation of chitosan which renders the polymer water-soluble (*Chem. Lett.*, 2000, 862). This involves a Michael addition of acrylates to the amino groups in the structure, followed by hydrolysis of the ester to acid. High degrees of functionalisation are achieved, and water-soluble polymers are obtained. No indications of applications are given in the paper, although biological studies are in progress. The chemical properties of such a polyacid will also be of interest.

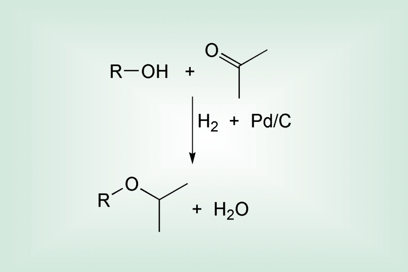
Fumio Toda and co-workers from Ehime University and the Okayama



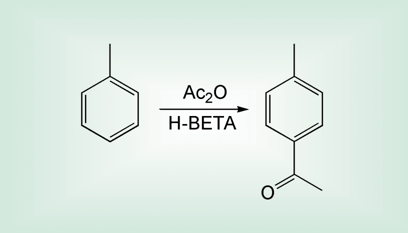
University of Science have published details of a solvent-free Robinson annelation reaction (*Chem. Lett*, 2000, 888). They mixed sodium methoxide, a ketone, and an enone together and kept the mixture at room temperature. Yields were modest, but often better than the corresponding methanol-based process. The work-up involved neutralisation and extraction with ether, but it is likely that a careful distillation could also eliminate the need for ether in the isolation stage.



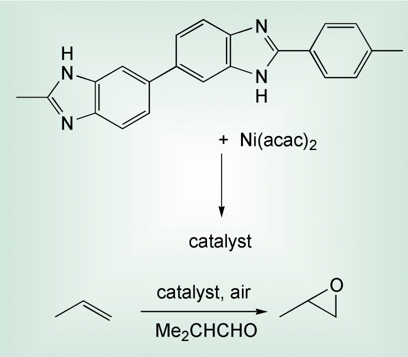
The synthesis of ethers has been studied in attempts to avoid the Williamson synthesis, and the stoichiometric amounts of salts associated with it. A further contribution has come from a team led by Katsumi Kita at the Kao corporation (*Chem. Lett.*, 2000, 926). Their approach is to react an alcohol with a carbonyl compound, and to reduce the adduct with hydrogen and Pd/C. this approach has been used before, but the new procedure requires only atmospheric pressure of hydrogen, and can be run solvent-free. A flow of hydrogen through the reactor appears to remove water efficiently and drive the reaction forward.



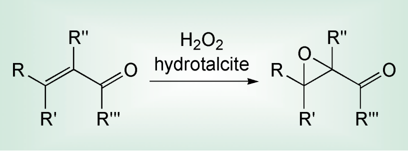
The search for clean Friedel–Crafts acylation technology continues. While aromatic ethers can be effectively acylated using zeolites and anhydrides, less active substrates such as toluene continue to be a problem. A collaborative project between Avelino Corma at the University of Valencia and researchers at Rhodia have published work which goes some way towards solving this problem (*J. Catal.*, 2000, **195,** 161). They have concentrated on the design of a zeolite H-Beta catalyst which gets round the problems of low activity and fast deactivation, to produce a catalyst capable of yields of $>50\%$ in around an hour under reasonable conditions—a significant advance over previous work.



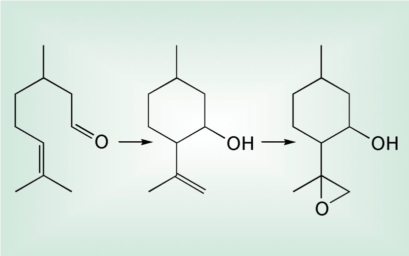
Epoxidations continue to be of great interest. The use of an aldehyde as sacrificial oxidant has many positive aspects, despite the use of an auxiliary aldehyde which is consumed during the reaction. The ability to use air as oxidant, and mild, non-aqueous conditions are often beneficial compared to many protocols, where non-atom efficient oxidants are used, or significant quantities of water are used. The so-called Mukaiyama conditions also require the use of a catalyst. Roeland Nolte of the University of Nijmegen has now published details of a nickel based catalyst where the metal is immobilised on a polybenzimidazole support (*J. Chem. Soc., Perkin Trans. 1*, 2000, 3428). This material is capable of the efficient epoxidation of a number of substrates including limonene, oct-1-ene and styrene. Impressively, the very labile α-pinene oxide could be prepared in 88% yield using these materials. Deactivation was apparent, due to leaching of significant quantities of Ni, but in a catalytically inactive form.



An alternative approach to epoxidation of electron-poor alkenes is the base-catalysed reaction of hydrogen peroxide with enones (see Brunel and Macquarrie, this issue). Kiyotomi Kaneda and co-workers from Osaka University have provided a method using basic hydrotalcite catalysts which works well for a range of enones (*J. Org. Chem.*, 2000, **65,** 6897). Their catalyst is a layered inorganic solid containing Mg and Al as well as hydroxide and carbonate units. This is capable of catalysing the conversion of a wide range of enones to the corresponding epoxides in high yields and reasonable rates, using a small excess of hydrogen peroxide.

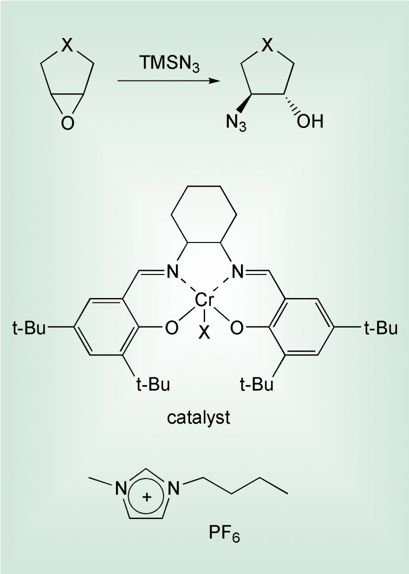


A further epoxidation has been published by Matteo Guidotti's group in Milan (*Chem. Commun.*, 2000, 1789). In this work, they introduce the added twist of an acid-catalysed cyclisation, followed by epoxidation of the resultant double bond. This is achieved by stirring citronellal with a mesoporous titanium silicate to effect ring closure, then adding hydrogen peroxide to epoxidise the double bond in the product. This makes

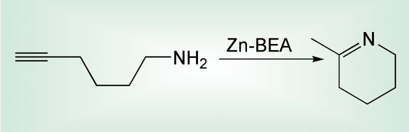


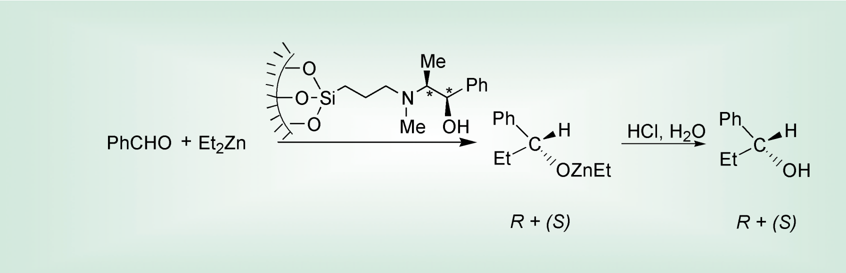
use of the mild acidity of the solid surface, and then the ability of the Ti centres to activate hydrogen peroxide towards epoxidation.

The utility of epoxides as synthetic intermediates is largely related to their ability to undergo specific and selective ring opening. Chung Eui Song's group from the Korea Institute of Science and Technology in Seoul have demonstrated a highly enantioselective method for ring opening of cyclic epoxides with azide using Cr-salen catalysts (*Chem. Commun.*, 2000, 1743). They use the ionic liquid bmim PF$_6^-$ as solvent and a range of cyclic epoxides. Ring opening with TMSN$_3$ in the presence of 3 mol% catalyst gave yields of between 75 and 85%, with ee's up to 97%.



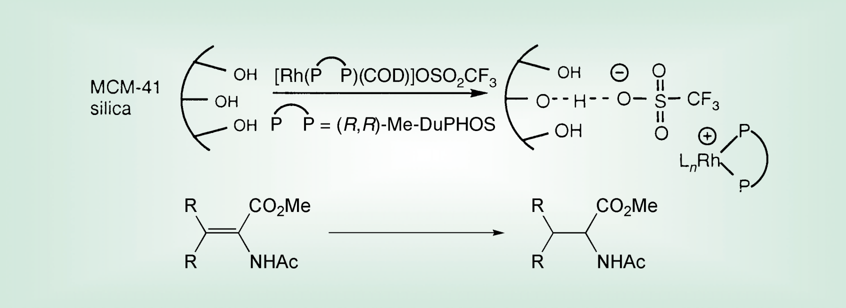
The addition of amines and other nucleophiles to multiple bonds is a clean route to a range of useful compounds. A variety of transition metal salts and complexes are known to catalyse this type of reaction. Thomas Müller and colleagues from the Technische Universität in Munich have now described a heterogeneous catalyst which not only carries out the reaction, but does it faster than the equivalent homogeneous system (*Chem. Commun.*, 2000, 1753). They took a zinc-exchanged BEA zeolite and used it as a catalyst in the intramolecular cyclisation of 6-amino-1-hexyne. Their Zn-BEA catalyst outperformed significantly zinc triflate, and was, interestingly, far better than other Zn-exchanged zeolites and silicas.



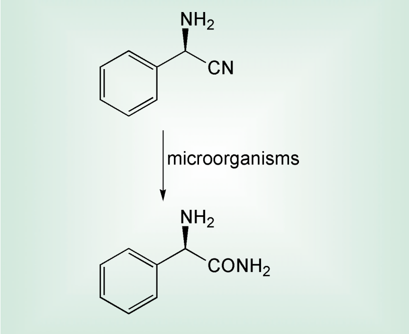


Monique Lasperas and co-workers from the CNRS in Montpellier (see *Green Chem.*, 2000, G48 for a feature on this laboratory) have published findings relating to a mesoporous supported ephedrine catalyst, which can be used for the enantioselective addition of diethylzinc to benzaldehyde (*Chem. Commun.*, 2000, 1773) (see scheme above). This work has led to significant improvements in the efficiency and selectivity of these materials, such that they display the same enantioselectivity as the homogeneous system, and can be easily recovered and reused. The improved activity comes about from a new method for loading the silica surface with a very high density of organic functions, many of which are not catalytically active, but which suppress the catalysis of the reaction by the silica surface, which leads to non-selective reaction.

Richard Broene and co-workers at the Los Alamos National Laboratory and Bowdoin College have described a simple method for the preparation of heterogeneous enantioselective hydrogenation catalysts (*Chem. Commun.*, 2000, 1797). They supported ionic Rh complexes onto MCM-41, and used them in the hydrogenation of enamide esters. Under their conditions, complete conversions and excellent ee's were obtained. The immobilisation works best when a H-bonding active anion is used, presumably to increase interaction with the MCM surface. Reuse was possible, but fouling of the catalyst with reaction products became a problem after four reuses.

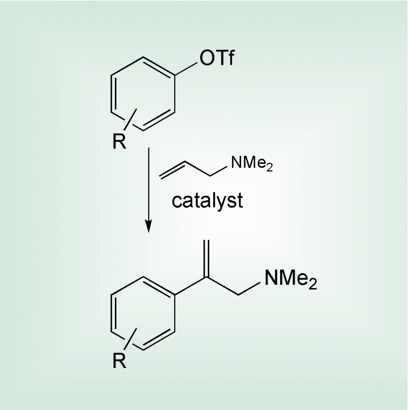


Roger Sheldon's group in Delft have recently published a whole-cell route to D-phenyl glycine amide, a key intermediate in the synthesis of penicillin antibiotics (*Org. Proc. Res. Dev.*, 2000, **4,** 318). This route starts from the unstable D-phenylglycine nitrile (which can undergo retro-Strecker reaction), which is hydrated by nitrile hydratase present in various strains of *Rhodococcus*microorganisms (*R. rhodocrous* being the most efficient). At low temperature conditions, and prolonged reaction times (22 h) a yield of 95.1% could be obtained with an ee of 99.5%. Low levels of the opposite



enantiomer were hydrolysed by amidase enzymes, helping to achieve the very high levels of enantioselectivity achieved.

β-Arylamines are an important class of compounds due to their bioactivity (*e.g.* dopamine) and synthetic methods to them (and the closely related and equally interesting β-exomethylene derivatives) are of great interest. The Heck reaction is one route to the latter, but often insufficient regioselectivities can hamper the use of this method. A group from Uppsala University in Sweden, led by Anders Hallberg has developed an extremely efficient and regioselective route to these compounds (*J. Org. Chem.*, 2000, **65**, 7235). They investigated the coupling of allylamines with aryl triflates, with a palladium acetate / ferrocenyl-diphosphine catalyst system. They managed to achieve reasonable yields of product, with excellent regioselectivites (generally > 99.5%) under thermal heating. With microwave heating, reaction times were 3–5 minutes, but regioselectivity was typically slightly lower, but still very good. In the presence of CO, amides were formed in some cases.



FOCUS ON... Professor James Clark and the York Green Chemistry Group

York is justifiably regarded by many as the home of green chemistry in the UK. The Centre for Clean Technology, under the directorship of Professor James Clark, not only houses the Green Chemistry Research Group but is also the central hub of activity for the RSC Green Chemistry Network and is the editorial focal point for this journal. Continuing this *Focus on...* series Mike Lancaster looks at some of recent work of the York Green Chemistry Group.

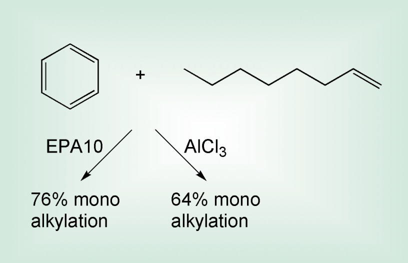
The Green Chemistry Group is one of the largest research groups within the University, consisting of over 30 academics, research fellows and graduate students. James Clark holds one of the ten original Royal Academy of Engineering Clean Technology Fellowships, a scheme which relieves members of academic staff from most of their teaching duties, allowing them to concentrate on research and public understanding activities. The latter area is of particular importance to Professor Clark and through organs such as *Green Chemistry* and the Green Chemistry Network he is striving to make people realise that chemistry can be done with environment awareness. He was the first to recognise that many current processes and products could be improved, but wishes to get across the message that we are making good progress in this direction.

Much of the group's research is focused at solving real industrial problems by application of innovative heterogeneous catalyst technology. Waste minimisation at source is the central theme of much of Clark's thinking[1] and he is quick to point out that the principal current sources of chemical waste come from the more recent fine and speciality chemical sectors. It is in these areas where much of his work is focussed. In

Professor James Clark with his Green Chemistry Research Group at York contrast to the bulk chemicals area many fine & speciality chemical processes use homogeneous catalysts which are often difficult to separate from the product and reuse, a considerable portion of the group's work is aimed at heterogenising these reactions.

Supported acid catalysts

Friedel–Crafts chemistry 'catalysed' by aluminium chloride is widely used in many sectors of the chemical industry. Such catalysts are, however, required in at least stoichiometric amounts and lead to copious amounts of aluminous waste. Working in conjunction with Contract Chemicals, Clark set out to find an environmentally acceptable solution to this problem using supported catalysts. This work resulted in the commercialisation of the Envirocat™ range of catalysts. This collaboration continued over many years and the second generation of Envirocats™ was launched in 1997. The activity and selectivity of these materials compares well with $AlCl_3$ (Scheme 1) and they can be tailored for reactions such as alkylation, acylation and sulfonylation.



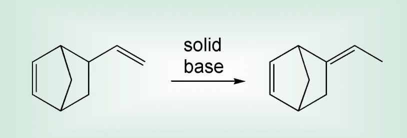
Scheme 1 Alkylation of benzene

This kind of catalyst has important implications for the production of linear alkyl benzenes,[2] precursors to the sulfonates—the world's most widely used laundry detergent, with an annual production of over 2M tpa. Although these surfactants have replaced the older branched sulfonates because of their increased biodegradability, much of the current manufacturing technology is not green, being based either on $AlCl_3$- or HF-catalysed processes which produce large amounts of waste or involve hazardous reagents.

Environmental pollution control through use of supported acid catalysts is one of the main research areas of Dr Karen Wilson, who has recently been appointed to a lectureship after spending a number of years as postdoctoral fellow in the Clark group. Her recent work has centred on supporting the other common Lewis acid—BF_3—on silica.[3] This work has shown that the resulting Bronsted acidity of the catalyst is dependant on how the catalyst is prepared. This dual acidic character has important implications in controlling selectivity for reactions such as the alkylation / etherification of phenol with olefins.

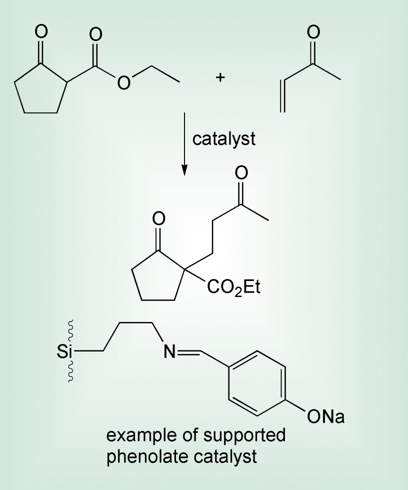
Supported basic catalysts

Heterogeneous acid catalysts have been the focus of much attention for about 40 years, largely due to their use in the petrochemical industry. It is only more recently that heterogeneous base catalysts have found use in industrial processes, such as the Sumitomo process for converting vinyl norbornene to ethylidene norbornene—a key ingredient in EPDM rubbers (Scheme 2). This process overcomes many of the 'green' issues associated with the previous technology—Na/K in liquid ammonia.



Scheme 2 Sumitomo isomerisation process using Na / NaOH on gamma alumina

It is in this more recent and under developed area where Dr Duncan Macquarrie, a Royal Society Research Fellow (and associate editor of Green Chemistry) is concentrating a major part of his research effort. Macquarrie has found that aminopropyl functionalised silica (AMPS) is a versatile catalyst for important synthetic reactions such as the Knoevengel reaction in which the only by-product is water. Modification of AMPS by reaction with hydroxylated benzaldehydes readily gives supported phenolates,[4] as shown in Scheme 3, for example. These materials are efficient and selective catalysts for a wide variety of Michael reactions, the activity largely depending on the steric availability of the phenolate group.

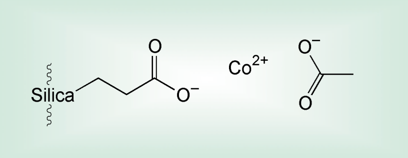


Scheme 3 Example of Michael reaction using supported phenolate catalyst

Clean oxidations

Oxidations for the production of ketones, acids and epoxides often involve use of stoichiometric amounts of toxic high valent metals such as chromium and manganese. Replacement of these environmentally unfriendly and increasingly uneconomic processes by selective, catalytic and Eco-efficient routes is of obvious value to the speciality and pharmaceutical industries.

The Green Chemistry Group has employed its expertise in modifying silica to synthesis a number of supported metal oxidation catalysts. A convenient route to these catalysts involves reaction of a cyanoalkylsilane with mesoporous silica gel, followed by hydrolysis of the nitrile to leave a chemisorbed carboxylic acid. This acid has the capability of strongly binding divalent transition metal ions including Co(II). The metal species are tightly bound and are not removed by common organic solvents. These materials are capable of catalysing the air oxidation of alkyl aromatics (*e.g.* diphenylmethane to benzophenone) and of olefins to epoxides (in the presence of sacrificial aldehydes which act as oxygen transfer agents).



Baeyer–Villiger oxidation of ketones to esters and cyclic ketones to lactones (*e.g.* conversion of cyclohexanone to caprolactone) is also important industrially. This type of reaction centres on the use of peracetic acid or other potentially hazardous peroxides as oxidant. A Ni-based catalyst has been prepared, similar to the above, but based on modified AMPS.[5] This catalyst used in conjunction with benzaldehyde, as sacrificial agent, and oxygen has proved capable of carrying out the cyclohexanone–caprolactone transformation in yields of over 90% at ambient temperature.

Clean routes to organofluorine compounds

Fluoroaromatics are important in the pharmaceutical, fine chemical and advanced materials industries; traditional routes involving halogen exchange, for example, often give rise to harmful waste products. In recent years Clark has become interested in fluorodenitration as a more selective and more environmentally friendly technique for introducing fluorine groups.

Nucleophilic sources of fluoride such as tetramethylammonium bifluoride, which is particularly thermally stable, have proved highly effective in replacing aromatic nitro groups with fluorine. This reagent does not, in general, lead to formation of phenols and ethers which are significant by-products with other 'onium' fluorides.

One particularly interesting example, which once again highlights the group's attention to finding solutions to real industrial issues, is in the formation of 4,4′-difluorobenzophenone (BDF) from 4,4′-dinitrophenylmethane. The synthesis of BDF, used in the manufacture of PEEK thermoplastics for the aerospace and other industries, involves hazardous reagents and generation of toxic by-products. This work,[6] which utilises both the basic and nucleophilic properties of the fluoride ion, has shown that combined fluorodenitration and oxidation can be achieved using tetramethylammonium fluoride (TNAF), in an oxygen atmosphere. The reaction is highly solvent-dependant, with dimethyl acetamide affording the highest yields.

The York Green Chemistry Group has grown considerably in recent years, largely through direct industrial sponsorship and, until recently, initiatives such as the Clean Technology Programme. Whilst there is almost universal acceptance that clean technology and green chemistry are worthy causes, Clark believes there is a current lack of funding opportunities and that there should be a more consistent and longer-term mechanism to maintain and encourage new green chemistry research. Manufacturing molecules is one new future initiative that may prove beneficial. Although Clarke's group has made much progress in cleaning up Friedel–Crafts reactions, he would like to solve the difficult, but highly relevant problem, of carrying out acylations on unactivated substrates with genuine catalysts, under moderate conditions; green chemistry solutions to this problem are currently limited to activated substrates. The scope and activity of the Green Chemistry Group continues to expand and now attracts a number of students and postdoctoral workers from all over the world—proof, if any were needed, that green chemistry solutions to industrial problems are of truly global interest and importance.

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Green chemistry in Estonia

Sirli Sipp and Mihkel Koel of the Institute of Chemistry at Tallinn Technical University in Estonia describe their country's progress in the spreading the 'gospel' of green chemistry

Estonia in a small country in Northern Europe with an area of 45,215 sq km and a population of about 1.5 million. Its educational centres are in the capital Tallinn in the north and in Tartu in the south. The Tallinn Technical University is the main source of engineering education, including chemical engineering. The Estonian *alma mater* is in Tartu – the University of Tartu was established by the Swedes in 1632, and has been a very important academic centre through different periods of Estonian history. Most of the industry in Estonia is located in the north of the country, consisting of power plants, oil-shale mining and chemistry, and textile factories, as well as construction materials and metal processing plants.

Environmental protection has a relatively long history in Estonia, going back to the last century. In 1853 the Estonian Naturalists' Society was established. Classical ideas of wildlife conservation, influenced by the pioneering work done in Germany, spread to Estonia, leading to the foundation of the first Nature Reserve area for sea-birds in 1910. Although the first Nature Protection Law of the Republic was passed in 1935, the Soviet occupation truncated any development in the field until 1957, when the first legislation on nature protection after the beginning of the Soviet occupation was embodied in law once again.

Fifty years of development under conditions of unbalanced economic relations in the closed society of the former Soviet Union resulted in the irrational use of natural resources in Estonia. The nature preservation system has gradually improved since then. In 1990 the Law on Nature Protection of Estonia was passed and in 1997 the National Environmental Strategy for Estonia was approved by Parliament. This strategy covers all aspects of life in society, and its principles can be formulated in the Priority goals of the National Environmental Strategy for the next ten years:

- Stimulation of environmental awareness and environmentally friendly consumption patterns
- Promotion of clean technologies
- Reduction of environmental impacts of the energy sector
- Improvement of air quality including reduction of transport emissions
- Improvement of waste management, reduction of waste generation,

stimulation of recycling
- Clean-up of past pollution
- Sustainable use of groundwater resources
- Surface water protection and rational use of water bodies
- Preservation of landscape and biodiversity
- Modification of built environment in line with human needs and environmental health requirements

These priority goals form a good philosophical basis for green chemistry activities.

Education on sustainable development

According to Article 53 of the Constitution of the Republic of Estonia every person is obliged to preserve the natural environment and to compensate for the damage they cause to the environment. Universal education on this matter is one of the important goals on the transition to sustainability as a long-term strategic issue for society. Unfortunately, the emphasis put on education in sustainable development and green chemistry in the academic sector has so far been insufficient.

The promotion of research activities in chemical aspects of clean technology has not reached the expected level even in those universities that have departments directly working on environmental chemistry: Tallinn Technical University (www.ttu.ee), Tartu University (www.ut.ee) and the Estonian Agricultural University (www.eau.ee). The amount of technical knowledge that is needed to support sustainable development in new alternative solvents and in syntheses that are less polluting requires rapid improvement. The growing popularity amongst students of graduate courses on new materials and dense fluids chemistry can definitely be considered as the first success in green chemistry activities in Estonia.

The bigger step towards a "greener" teaching system has been made by establishing the Green Chemistry Institute of Estonia in Tallinn Technical University in December 1999. The web page describing the principles of and news in "green chemistry" to the students, researchers and public in Estonia will open at the end of October.

Professor Mihkel Koel from the Chemistry Institute at Tallinn Technical University has skilfully performed an assignment in supervising and encouraging several students in actively taking part in sustainable chemistry advancement worldwide. For example: Ms. Maia Sokolova and Ms. Sirli Sipp are the first young chemists from Estonia who have attended the Summer School in Green Chemistry, which has been held in Venice, Italy, annually since 1998. The success of the young scientists is remarkable: Ms. Sokolova's poster won second place in Venice and Ms. Sipp was named as the Joseph Breen Memorial Fellow for 2000 and was sponsored by American Chemical Society's International Endowment Fund for participation in the Green Chemistry and Engineering Conference in Washington, DC, USA. Both Maia and Sirli are helping Professor Koel to raise the awareness of Estonian students in the field of new technologies and solvents in environmental chemistry.

Some recent results

Use of supercritical CO_2

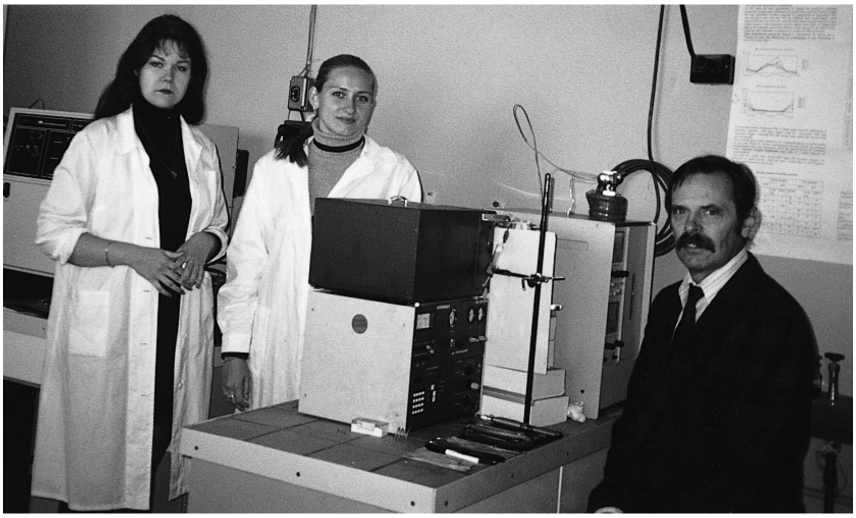
Supercritical extraction (SFE) is a very suitable method for geochemical studies of fossil fuels though less applicable for large scale processing at the moment.[1] From studies in the laboratory of Professor Koel, it was estimated that the yields of the Soxhlet and SFE carbon dioxide extracts from the Estonian oil shale Kukersite are very similar. Carbon dioxide modified with methanol extracts compounds that conventionally are extracted from Kukersite with chloroform after treatment with hydrochloric acid and benzene/methanol mixture. Moderate increases in the temperature of the SFE leads to increases in the extract yield. However, by 200 °C partial heterolytic cracking of the kerogen of Kukersite occurs. Geochemical parameters calculated on the basis of chemical composition are similar in both SFE and Soxhlet extracts of Kukersite. There is a strong predominance in the relative distribution of *n*-alkanes, *n*-alkanones, *n*-alkylbenzenes and *n*-alkylcyclohexanes indicating the immaturity of overburden material (OM) of Kukersite is characteristic of both SFE and Soxhlet extracts.

Another promising application of supercritical CO_2 studied in this laboratory is extraction of local medicinal herbs. Collaboration with the Department of Pharmacy of Tartu University has two aims: characterization of plants and the search for practical applications of extracts.

Use of ionic liquids

Room temperature liquid salts or ionic liquids are materials with environmentally friendly properties. There is now an intensive search for better applications for these materials, including work in Professor Koel's laboratory. In one project gas chromatography and capillary electrophoresis are used to describe the physical and chemical properties of alkylimidazolium ionic liquids. Another project involves the study of possible applications of ionic liquids in oil shale chemistry.[2]

The conversion of oil shale into value-added products is a challenging goal of chemistry and chemical engineering. There is an urgent need for the development of efficient processes that are capable of providing useful products such as alternative synthetic



Professor Mihkel Koel and colleagues at the Chemistry Institute at Tallinn Technical University fuels or high-quality chemical feed stocks. The first step is the development of efficient means to characterise the various components of the shales. Two different types of ionic liquids have been examined for their ability to extract organic compounds, particularly oxygenated compounds from the Estonian oil shale named kerogen in the Tallinn Technical University. 1-Butyl-3-methylimidazolium hexafluorophosphate and chloroaluminate were synthesised and applied to kerogen extraction at various temperatures. In addition, the effect of the Lewis acidity of the chloroaluminate salt was examined. At room temperature there was no evidence of extraction from the kerogen using either ionic liquid. However, these extractions are favoured at elevated temperatures up to the thermal degradation temperature of kerogen (above 400 ºC). At 175 °C the extraction yield of soluble products was increased 10 times over that obtained using conventional organic solvents such as hexane and ethylene chloride. Significant differences were observed in the extraction behaviours between different types of Estonian oil shale because of the unique chemical composition and structure of their organic components.

These are only a few examples of studies related to green chemistry. The search for new materials and the development of new processes cannot ignore their environmental impact. Despite the limited resources of this small country the ideas of sustainable development are spreading and the principles of green chemistry are increasingly being introduced into the chemistry curriculum in Estonian Universities.

The environmental policy of the Republic of Estonia has contributed to the development of green chemistry. It is implemented through executive action programs following the elaboration of environmental strategy trends. The application of resource and pollution changes has provided a solid basis for integrating the principles of environmental protection into economic activities. Investments, financed from the national budget, by different enterprises, local municipalities and various funds, have been made to help address environmental problems; foreign assistance has also been significant.

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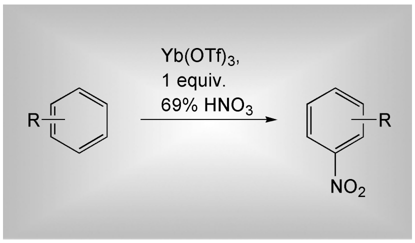
UK Green Chemistry Awards

Winners of the first UK Green Chemistry Awards were announced in September. The Green Chemistry Network on behalf of the sponsors (the Salters' Company, the Jerwood Charitable Foundation and the Royal Society of Chemistry) administer these awards with financial support from the Department of Trade and Industry. The awards are designed to recognise outstanding achievements in the development of green chemical technology and to encourage more R&D in the area, from both the academic and industrial communities.

The Young Academic Category

The winner of the **The Jerwood Salters' Environment Award** in this category went to **Dr Chris Braddock** of Imperial College, London for his work on "Novel Recyclable Catalysts For Atom Economic Aromatic Nitration" (see *Green Chemistry*, 1999, **1**(4), G97-98). Aromatic nitration is practised across the chemical industry and is a key reaction for products such as dyes, pharmaceuticals, plastics, and fine chemicals. However, the conventional reaction employing excess amounts of concentrated nitric and sulfuric acids produces large amounts of 'spent acid' waste which requires treatment and disposal. Lewis acids are known to catalyse the reaction, overcoming the need for sulfuric acid, but because of their water sensitivity they are also required in stoichiometric amounts. Braddock's novel approach to solving this problem involved the use of lanthanide catalysts (*e.g.* ytterbium triflate) and molar amounts of nitric acid. These lanthanide catalysts are unusual in that they are strong Lewis acids but are very stable in the presence of water, and are therefore only required in true catalytic amounts (down to 1 mole %). Braddock has also demonstrated that that the catalysts can be recovered and recycled, opening the way for a waste free nitration process.



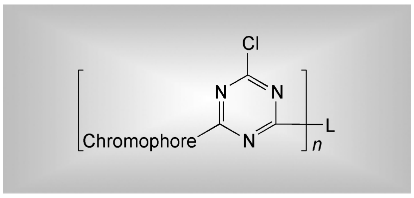
The mechanism of the reaction has been extensively probed and a strong correlation between charge to size ratio of the lanthanide centre and catalytic activity has been found. Extrapolation of these results led to the prediction that Group IV metal triflates of hafnium and zirconium would be excellent nitration catalysts. This prediction was correct and these catalysts proved to be very active for industrially important nitration of electron deficient aromatics such as *o*-nitrotoluene.

Further studies showed that, for optimum catalytic activity, the counter ion should be the conjugate base of a very strong acid, this acting as a phase-transfer catalyst for the nitronium ion. Accordingly synthetic routes to ytterbium and scandium tris(trifluoromethanesulfonyl)methides were developed; these catalysts enabled the quantitative conversion of *o*-nitrotoluene into dinitrotoluene to be achieved.

The Industrial Category

The winner in this category was **BASF plc.**, Cheadle Hulme, Cheshire, for their work on "Super-Efficient Dyes for the Coloration of Cotton; the Procion XL+ Range. Globally around 80,000 tpa of reactive dyes are used to colour cotton by exhaust technology. This dyeing process uses 4×10^8 tpa of fresh water, which is ultimately discarded, in a contaminated state. This contamination includes 24,000 tpa dye and 2.8×10^6 tpa of salt. Most aqueous effluent is discarded via local watercourses. Whilst the dyehouses remove some colour a significant amount of colour, together with salt and other additives find their way to the treatment works and often further. The environmental impact of the dye industry is therefore appreciable and has a wide impact.

BASF designed the Procion XL+ high strength dyes to utilise their carbon frameworks more efficiently to deliver colour. These dyes are based on monochlorotriazine reactive groups attached to carefully designed chromophores.



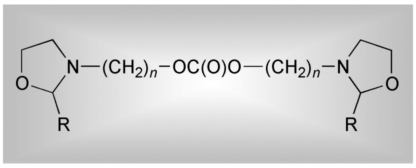
The key benefits of these new dyes include;

- Reduction in energy use by 50%
- Reduction in water consumption of 40%
- Reduction in salt use by up to 33%
- Higher dye fixation, resulting reduced effluent BOD, COD and TDS
- Doubles productivity by reducing dye-processing time

The Small & Medium Enterprise Category

The winners were **Industrial Copolymers Limited** of Preston for their nomination entitled “Oxazolidine Diluents: Reacting for the Environment”. The automotive paint market is one of the major contributors to solvent emissions to atmosphere. The EU introduced legislation in 1999 to restrict emissions to 70% of 1990 levels, which will affect 400,000 firms and impact on 10 million jobs. In the main automotive finishes consist of 2-component solvent-based polyurethane coatings. In order to comply with legislation there are possible routes to reduce solvents, replacing them with water-based alternatives and employing high-solids coatings. Both of these approaches have some technical disadvantages, the former requiring investment in new equipment and at the same time generating contaminated aqueous waste, whilst the latter has limitations in spray applications imposed by the higher viscosity.

Industrial Copolymers have developed a reactive diluent, Incozol LV, based on bisoxazolidine to overcome all these problems.



Incozol LV can be used to replace organic solvent in the polyol component of the finish at levels of up to 30% which leads to a significant reduction in VOC enabling the finisher to exceed legislative requirements.

The bisoxazolidine is reacted into the polyurethane coating via a mechanism that initially involves hydrolysis by trace amounts of water in the finish or in the atmosphere The amino alcohol generated then reacts with the isocyanate to form urea couplings incorporating the Incozol LV into the backbone. Extensive testing has shown that the cure and coating properties of the finish are not adversely altered by the presence of the reactive diluent.

More detailed papers from all the award winners will appear in the next issue of *Green Chemistry*. Papers describing the technology behind these awards will also be presented at the Green Chemistry Sustainable Products & Processes Conference to be held in Swansea (3–6 April 2001).

Global carbon dioxide emission and consumption

Frank Smalberg, Jacob Moulijn and Herman van Bekkum from Delft University of Technology in The Netherlands provide some new estimates of global CO_2 emission and the extent of CO_2 mitigation through industrial consumption

Introduction

Mankind has always had an immense hunger for energy, the consequences of which did not seem too important for many years. It was not until the 1950s that atmospheric CO_2 was suspected of being the possible cause of the temperature rise that had already been noticed between 1880 and 1940. In 1896, Svante Arrhenius wrote an article on the influence of atmospheric ‘carbonic anhydride’ on the surface temperature in the *Philosophical Magazine*. Unfortunately, unambiguous evidence is still lacking and opinions diverge. Policymakers, however, have acknowledged the potential dangers of the increasing CO_2 concentrations in the atmosphere, which led to the well-known Kyoto Protocol in 1997. The intense discussion on CO_2 emission has many participants and is based on different data and assumptions.

Various plausible reactions and promising products that might help in reducing the CO_2 emission have been analysed.[1] But what are the CO_2 streams on earth? Does it make sense to investigate chemical conversion in view of an unbalance between emission and potential use? The purpose of this article is to provide clear and objective background information, helpful in the CO_2 discussion. Nevertheless, the figures mentioned in this article are still estimates and should be handled with care.

Carbon cycle

What is the effect of combustion of fossil fuels in a global perspective? To answer this question, one has to look at the carbon cycle (Fig. 1), which shows that the flow rate of carbon in the earth’s ecosystem in 10^9 tons per annum [10^9 t(C) = 1 Gt(C)]. During the period 1980–1989, approximately 5.5 Gt(C)/annum, corresponding to 20 Gt/a CO_2, was emitted as a result of the combustion of fossil fuels. Together with changes in land use, the extra—often called anthropogenic—emission rose to 7.1 Gt(C)/annum, which is a relatively small increase, compared to the carbon content of the atmosphere (750 Gt(C)) and to the CO_2 flow caused by respiration and decay of biomass (60 Gt(C)/annum). In particular, the oceans contain an enormous amount of carbon (40,000 Gt(C)). Unfortunately, the earth’s ecosystem is not capable of absorbing the additional CO_2, which has led to the current CO_2 concentration of 370 ppm, compared to the pre-industrial level of 280 ppm at the beginning of the 19th century. This increase has been calculated to represent an average accumulation of 3.3 Gt(C)/annum in the atmosphere. The remaining 3.8 Gt(C)/annum is presumably absorbed by the oceans and forests.

The carbon cycle gives a good impression of the relative magnitude of human activities. The absolute figures of the cycle, however, have led to much discussion and should be handled with great care.

Energy consumption and related emissions

The anthropogenic CO_2 emissions are strongly related to the consumption of energy. In 1996, the three fossil energy sources, coal, oil and gas, were responsible for an emission of 6.2 Gt(C).[3] Their supply in Mtoe (million tons oil equivalent = 41.87 × 10^{15} J) and the corresponding emissions are shown in Fig. 2. Note that biomass is considered to be a sustainable energy source and therefore the net production of CO_2 is zero. Furthermore, natural gas has the lowest CO_2 production per Mtoe, which makes it more CO_2-friendly for use in power plants than coal.

Who is producing the CO_2? Several methods exist to estimate the amounts. For example, the production of CO_2 in the transport sector can be estimated by multiplying the fuels consumed by the corresponding emission coefficients. Methods, however, can be based on different definitions, and categories may cover different sources. Fig. 3 shows the

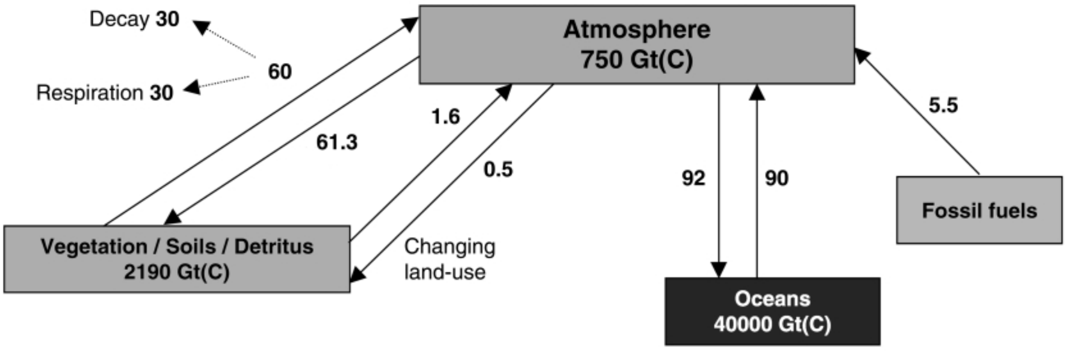


Fig. 1. Carbon cycle with flow rates in Gt(C)/annum² (All numbers are average values over the period 1980–1989)

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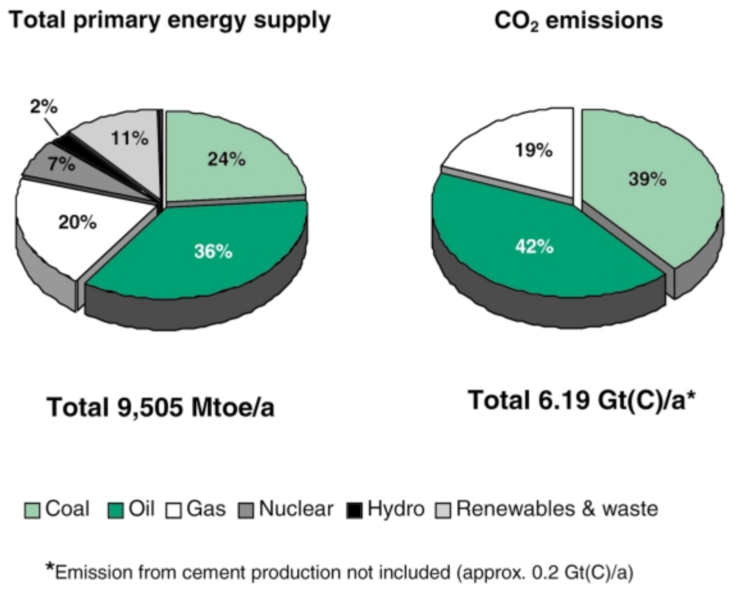

*Emission from cement production not included (approx. 0.2 Gt(C)/a)

Fig. 2. Energy supply and related emissions in 1996.[3]

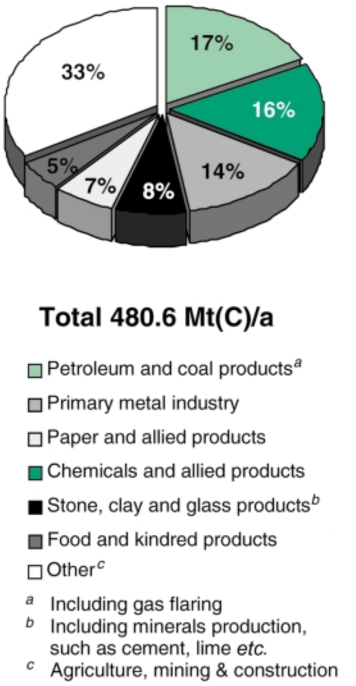

Fig. 4. Distribution of US industry CO_2 emissions in 1994.[4]

distribution of CO_2 emissions in 1996 as estimated from IEA statistics. Two methods have been used: in the left diagram, energy transformation in power plants is considered as a separate sector (other transformation emissions are ascribed to industry). One could argue, however, that the power plants are only intermediates, and therefore the right diagram shows the distribution across the sectors of end-users. Not surprisingly, industry is by far the largest producer of CO_2 when the latter method is used [3.0 Gt(C)/annum].

Industry

Industry is a complex sector with many different players and many CO_2 sources. Unfortunately, global figures on the distribution of emissions in this sector are scarce. To give an impression, Fig. 4 shows the US industry emissions in 1994. Since the US are the world's largest CO_2 producers (approx. 25% of the global emissions), these figures are quite relevant. Note that here the industrial sector includes agriculture, whereas this is not the case in the IEA statistics.

Besides the distribution over the industrial sub-sectors, it would be interesting to know which part of the industrial emission is energy-related and which part is not. The purpose of this section is to estimate the amount of non-energy-related CO_2 produced by industry, although not providing a comprehensive review of all sources. CO_2 is considered non-energy-related when formed in a chemical reaction with no primary intention to fulfil a need for energy, *e.g.* reducing carbon monoxide and carbon in steel manufacture. Obviously, a specific process producing non-energy-related CO_2 will also produce energy-related CO_2.

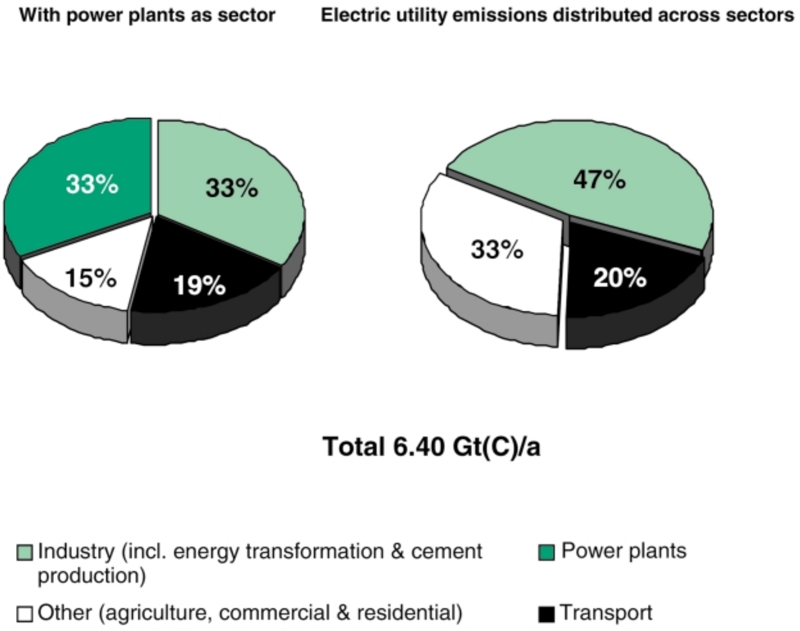

Fig. 3. Distribution of emissions in 1996.[3]

Table 1 shows information on the largest sources of non-energy-related CO_2, dominated by the minerals, metal, petroleum and chemical industries. The corresponding CO_2 streams are calculated by multiplying the global production by an emission coefficient obtained from the IPCC Guidelines for National Greenhouse Gas Inventories 1996[5] or, if not available, by an estimated coefficient.

The production of cement is the largest CO_2 source in the minerals industry, followed by the production of lime. In both cases CO_2, immobilised in calcium carbonate, is set free. Other smaller sources are the manufacture of soda ash, the production of carbides and the use of limestone, *e.g.* in glass manufacture. In the metal industry, the production of pig iron is the main source of CO_2, formed during the reduction of iron oxide ore with coke and carbon monoxide. The carbon-containing iron is then used in the production of steel while scrap is added; the CO_2 production in the latter step is significantly smaller. The production of aluminium forms the second largest source, followed by other metals, such as chromium, lead, nickel and zinc.

Table 1 Largest producers of non-energy-related CO_2 in 1996

Industry	Production	Emission coefficient	
	(Mt/a)	($kgCO_2$/kg)	(kgC/kg)
Minerals[a][6]			
Cement	1488	0.5	0.14
Lime	121	0.8	0.22
Other[c]	30	0.5	0.14
Metals[a][6]			
Iron	528	1.6	0.44
Aluminum	21	1.8	0.49
Other[d]	15	1.6	0.44
Bulk chemicals[b]			
Ammonia[7]	125	1.2	0.33
Hydrogen (refineries and others)[9]	19	8.3	2.26
Ethylene oxide[8]	12	0.67	0.18
Ethanol[10]	25	0.96	0.26

[a] Emission coefficients from IPCC Guidelines[5]. [b] Estimated emission coefficients (*cf.* text). [c] Including limestone use, soda ash manufacture, carbides *etc*. [d] Including chromium, lead, nickel, zinc *etc*.

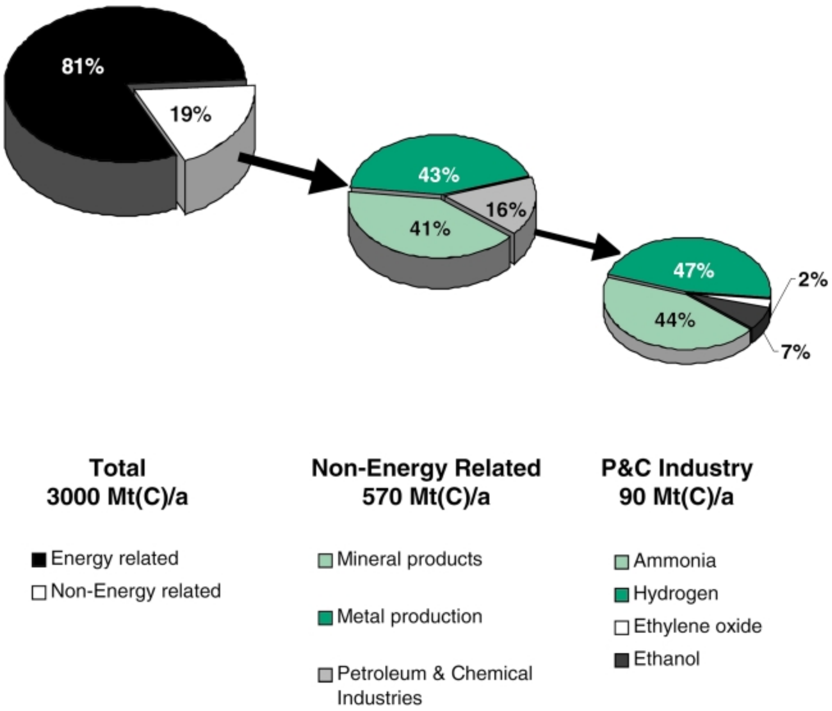

Fig. 5. Distribution of global industrial CO_2 emissions in 1996

The production of synthesis gas plays an important role in the CO_2 production of the chemical industry. 49% of the hydrogen produced is used in the synthesis of ammonia, 37% in the refining of petroleum (hydrocracking and hydrotreating), 8% in methanol synthesis, and 6% is used for other purposes.[9] The quantities of hydrogen can be estimated since the global production of ammonia is accurately known. The CO_2 emission coefficients, however, depend on the feedstock used in the H_2 process: natural gas is generally used in the synthesis of ammonia, heavy residues ($CH_{1.3}$) are often used in refineries. The production of ethanol and ethylene oxide are other significant sources of CO_2; the latter is generally produced with 75% selectivity. The above assumptions led to the coefficients listed in Table 1. Note that the CO_2 related to the production of (bio)ethanol is included, although the fermentation is based on renewable feedstocks.

As a result, Fig. 5 shows that over 80% of all industrial CO_2 is energy-related. Furthermore, the production of mineral products and metals accounts for 84% of the remaining 570 Gt(C)/annum. The petroleum and chemical industries produce significantly less, but these streams are more concentrated and pure, which makes them excellent sources for commercial CO_2 consumption.

Consumption

Table 2 shows the bulk consumers of CO_2, with by far the largest in 1996 being urea production. CO_2 is also used as an additive in methanol synthesis (20 Mt/annum). A CO/CO_2 ratio of 3 is required to convert all hydrogen formed in steam reforming of natural gas. It is estimated that 25% of this maximum amount of CO_2 is actually added.

Enhanced Oil Recovery (EOR) is also a large consumer of CO_2. The gas is used to flood wells in order to increase the extent of oil recovery. This method is used in the US and Turkey, since large natural CO_2 wells are present in these countries. EOR is often mentioned as a promising CO_2 mitigation option, because 50% of the CO_2 remains in the well after extraction. However, the maximum quantity of oil that is globally produced by EOR is less than 10%. Accordingly, the amount of CO_2 that could be sequestered in the wells is approximately 70 Mt/annum, which is only a modest contribution to the mitigation (with 2.7×10^{10} barrels/annum,[13] 50 kg CO_2/barrel[14] and 50% sequestration).

Table 2 Consumption of CO_2 in 1996

Process	Quantity (Mt/a)	CO_2 Equivalent (Mt/a)	Carbon Equivalent (Mt (C)/a)
Urea[11]	90	65	18
Methanol[11]	20	2	0.5
Enhanced Oil Recovery[12]	20	20	5.5
Solid CO_2[11]	2	2	0.5
Liquid CO_2[15]	9	9	2.5
Food industry		3.6	
Beverage carbonation		2.3	
Other[a]		3.4	
Total		98	27

[a] Including welding, use in aerosols, foundry, firefighting, medical, rubber and plastics.

Solid CO_2 is mainly used for refrigeration purposes, while liquid CO_2 has found wide applications in the food industry, such as refrigeration, food packaging, water treatment and supercritical extraction. It is also used for beverage carbonation, welding, fire extinguishers *etc.*

The amount of CO_2 consumed totals 27 Mt(C)/annum, which is only 0.4% of the global anthropogenic emission caused by fossil fuel combustion. Moreover, it should be noted that CO_2 is only sequestered permanently with EOR, while the other consumers are only temporary ‘stations’ for CO_2 on its way to the atmosphere. For instance urea, when applied as fertiliser, is bacterially converted to CO_2 and ammonia. The latter compound either directly serves plant growth or does so after it has been bacterially converted to nitrate. The direct intake of urea by the plant is very small. Obviously, chemical use of urea in for example organic resins, leads to longer periods of immobilisation.

Conclusion

In 1996, energy purposes accounted for 91% of the anthropogenic CO_2 emission of 6.4 Gt(C)/annum, increasing to 95% when the use of cokes in the primary metal industry is considered energy-related. These amounts of CO_2 greatly exceed consumption, and even if all organic base chemicals (approx. 400 Mt(C)/annum) were made from CO_2, emissions would only decrease by some 6–7%.

CO_2 could be mitigated by other technologies under debate, such as disposal in oceans or by the production of methanol with solar hydrogen. Methanol is considered a future key chemical that can selectively be converted to bulk chemicals, *i.e.* the lower olefins. However, chemical use of CO_2 could imply increasing emissions and is still expensive, due to CO_2 recovery costs and high hydrogen price.[16]

In conclusion, it can be said that CO_2 mitigation by means of industrial consumption will remain rather modest and mainly temporary, and that investigations should focus on increasing efficiencies and on sustainable energy sources, such as biomass, wind, and solar cells. Intuitively, a global policy to restrict CO_2 emissions is appropriate, although the existence of the greenhouse effect is still under debate.

Acknowledgements

We would like to thank Dr John N. Armor, Air Products and Chemicals, Inc., Allentown (USA), for advice.

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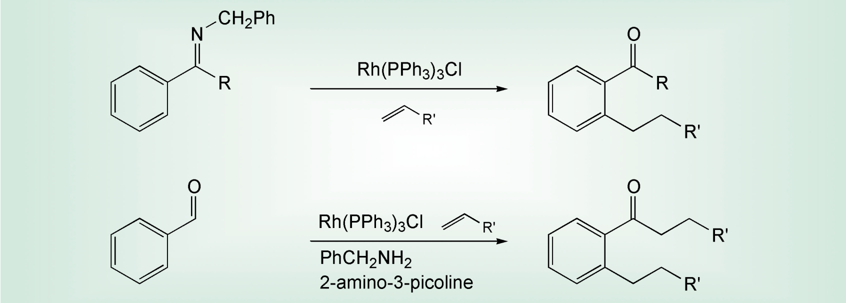
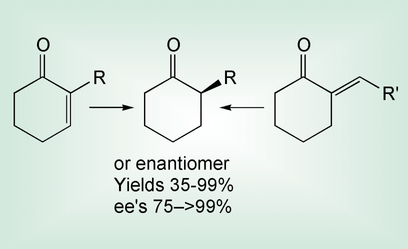
Highlights

Duncan Macquarrie reviews the latest research in green chemistry

Chul-Ho Jun and his group at the Yonsei University in Seoul have discovered an efficient method for the ortho alkylation of aromatic imines (and thus indirectly benzaldehydes). Their work (*Angew. Chem., Int. Ed.*, 2000, **39**, 3440) is based on a Rh catalysis which functions by chelation and activation, leading to efficient alkylation with alkenes at the position ortho to the imine. Linear alkyl groups are introduced in all cases. The chemistry can be extended to insert the alkene to the aldehydic (iminic) C–H bond (right hand example) with the aid of 2-amino-3-picoline.



Researchers led by Toshifumi Hirata at Hiroshima University have described an enantioselective reduction methodology based on the use of enzymes (*Chem. Lett.*, 2000, 851). The three enzymes were obtained from *Nicotiana tabacum* and were found to be very effective in the reduction of cyclic enones, giving reduced products in good conversion and excellent ee (⩾95% in all but one case). Both endocyclic and exocyclic double bonds could be reduced.



The application of biopolymers such as starch and chitosan in chemistry is growing, as the ability to modify their properties improves. Rene Roy's group at the University of Ottawa have published details of a novel functionalisation of chitosan which renders the polymer water-soluble (*Chem. Lett.*, 2000, 862). This involves a Michael addition of acrylates to the amino groups in the structure, followed by hydrolysis of the ester to acid. High degrees of functionalisation are achieved, and water-soluble polymers are obtained. No indications of applications are given in the paper, although biological studies are in progress. The chemical properties of such a polyacid will also be of interest.

Fumio Toda and co-workers from Ehime University and the Okayama

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Environmentally benign oxidation using a palladium catalyst system

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A clean and environmentally benign process to convert benzylic and allylic alcohols into the corresponding carbonyl compounds using a catalytic amount of palladium on activated charcoal under an ethylene atmosphere is developed. The combination of $Pd(OAc)_2$ and vinyl acetate is an excellent system. The efficient conversion is based on hydrogen transfer between allylic and benzylic alcohols and simple olefins such as ethylene and vinyl acetate. In the oxidation of D-glucal to the corresponding enone (1,5-anhydrohex-1-en-3-ulose), the palladium catalyst is proven to be reused without a decrease of catalytic activity. This extremely simple process is not only economically advantageous but it is also environmentally friendly in comparison to conventional methods using chromium or manganese salts.

Introduction

Oxidation of alcohols is one of the most fundamental transformations in organic synthesis.[1] For this purpose, stoichiometric oxidizing agents such as chromium and manganese salts have been used. However, these metal salts are usually toxic and hazardous and they often cause environmental problems. Therefore catalytic processes using oxygen or aqueous H_2O_2 as oxidizing agents with less toxic metal complexes is desirable from the environmental viewpoint. Recently, Markó *et al.* reported an efficient catalytic system consisting of CuCl/phenanthroline/K_2CO_3/$DBADH_2$(1,2-bis(*tert*-butoxycarbonyl)hydrazine)[2a] and TPAP(tetrapropylammonium perruthenate)/MS 4A[2b] using oxygen or air as oxidant. Noyori and co-workers developed organic solvent- and halide-free oxidation of alcohols with aqueous H_2O_2 using Na_2WO_4 and a phase-transfer catalyst (PTC) system.[2c] With regard to a Pd^{II} catalyst process, Uemura *et al.* reported the $Pd(OAc)_2$-catalyzed oxidation of alcohols by molecular oxygen in the presence of MS 3A.[2d] A similar type of palladium-catalyzed oxidation of alcohols was also reported by Peterson and Larock.[2e] Their processes included the oxidation of alcohols by Pd^{II}, which was reduced to Pd^0 when the oxidation was completed. The resulting Pd^0 was successfully reoxidized to Pd^{II} by oxygen. On the other hand, hydrogen transfer reactions using transition metal catalysts have also been examined intensively.[3] Here we report the hydrogen transfer reaction of some benzylic and allylic alcohols with a catalytic amount of $Pd(OAc)_2$ or Pd/C in the presence of vinyl acetate or under an ethylene atmosphere.[4,5]

Results and discussion

Oxidation of simple benzylic and allylic alcohols

A variety of benzylic and allylic alcohols were converted into the corresponding carbonyl compounds under the following conditions; 20–50 wt% of 10% Pd/C, in the presence of 3 equiv. of vinyl acetate or under an ethylene atmosphere in acetonitrile at 50–80 °C. The obtained results are summarized in Table 1. In many cases, the combination of Pd/C and ethylene exhibited the most efficient conversion, though the best combination proved to be dependent on the substrate. Secondary benzylic and allylic alcohols such as benzhydrol **1**, *sec*-phenethyl alcohol **3**, 2-hydroxy-2-phenylacetophenone (benzoin) **5**, 1-(2-pyridyl)-ethanol **7** and 3,5,5-trimethyl-2-cyclohexen-1-ol **9** were converted to the corresponding ketones (**2**, **4**, **6**, **8** and **10**) in high yields (75–86%) under the conditions as indicated in Table 1. Primary benzylic and allylic alcohols such as benzyl alcohol **11**, cinnamyl alcohol **13**, geraniol **15** and nerol **17** were less reactive, that is, benzaldehyde **12** and α,β-unsaturated aldehydes (**14**, **16** and **18**) were obtained in 43, 64, 36 and 21% yields, respectively. These moderate to low yields were due to low conversion. The formation of undesired side-products was not observed. It is noteworthy that in the reaction of **15** and **17**, isomerization was not observed under the reaction conditions. Simple primary and secondary alcohols such as *n*-octyl alcohol, cyclohexanol and *l*-menthol were inert under these reaction conditions. On the more positive side, this limitation of oxidation substrate gave an interesting selectivity in the oxidation of steroidal alcohol. The reaction of **19** with Pd/C under ethylene atmosphere gave 19-nortestosterone **20** in 84% yield and ketone **21** in 5% yield. The formation of **21** was *via* the rearrangement of the double bond in **19**. In the present catalytic system, only the allylic alcohol was oxidized. This is in contrast with the equimolar reaction. That is, Czernecki reported that both hydroxy groups in **19** were oxidized by treatment with a stoichiometric amount of $Pd(OAc)_2$.[6] The reaction of **19** with 9 equiv. of activated MnO_2 gave **20** in 68% yield. The product distribution of the reaction of **22** with 5 mol% of $Pd(OAc)_2$

Green Context

Oxidation of alcohols to aldehydes and ketones in a selective manner is a major area of organic chemistry which is still dominated by toxic reagents such as chromates and other transition metal stoichiometric reagents. Some catalytic methods do exist, and a new version is described in this paper. The authors have found that the use of palladium catalyst and an unsaturated compound lead to clean and selective oxidation of hydroxy groups on sugars and steroids as well as simpler systems. ***DJM***

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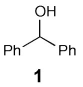
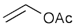
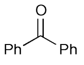
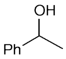
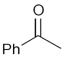
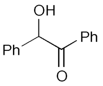
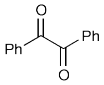
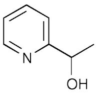
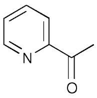
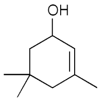
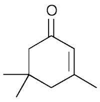
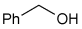
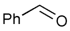
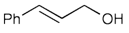
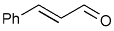
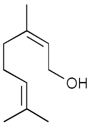
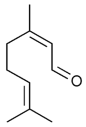
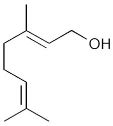
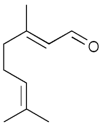
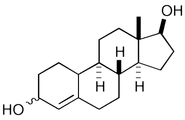
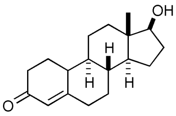
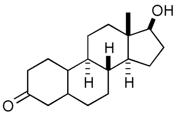
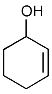
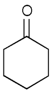
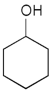
under an ethylene atmosphere was 68% phenol **23**, 28% cyclohexanone **24** and 4% cyclohexanol **25**. The formation of 2-cyclohexen-1-one was not observed when the reaction was completed. When Pd/C was used instead of Pd(OAc)$_2$, the product distribution was changed (**23**:**24**:**25** = 40:33:27).

Application to the synthesis of 1,5-anhydrohex-1-en-3-uloses–reuse of palladium catalyst

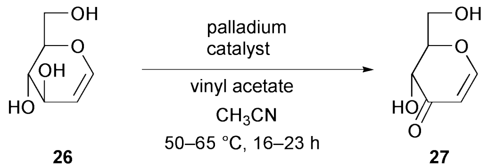
Hexenuloses have played an important role in carbohydrate synthesis. Among these, 1,5-anhydrohex-1-en-3-ulose derivatives are of particular interest, because the 1,4-addition allows the carbon–carbon bond formation at the anomeric center which leads to the formation of 2-deoxy-*C*-glycosides.[7] One general method for incorporating the α,β-unsaturated moiety is the oxidation of allylic alcohols. Actually, some stoichiometric oxidants such as chromium, manganese and palladium salts have been widely used for this purpose.[6,8] However, they are sometimes toxic and the use of these reagents induces hazardous problems. The use of expensive palladium compounds cannot become a truly useful synthetic method. Therefore, the development of catalytic process has been strongly desired from the environmental point of view. We

Table 1 Conversion of benzylic and allylic alcohols into carbonyl compounds[a]

Entry	Substrate	Palladium compound[c]	Olefonic compound	T/°C (t/day)	Product	Yield[b] (%)
1	 **1**	Pd/C[c]	 $H_2C{=}CH_2$	80 (2.5) 50 (4)	 **2**	83 86
2	 **3**	PdC[c]	$H_2C{=}CH_2$	50 (2)	 **4**	78
3	 **5**	Pd/C	$H_2C{=}CH_2$	50 (3.5)	 **6**	86
4	 **7**	Pd/C	$H_2C{=}CH_2$	50 (3)	 **8**	82
5	 **9**	Pd/C	$H_2C{=}CH_2$	50 (4)	 **10**	75
6	 **11**	Pd/C	$H_2C{=}CH_2$	50 (4)	 **12**	43[d]
7	 **13**	Pd/C	$H_2C{=}CH_2$	50 (4)	 **14**	64[d]
8	 **15**	Pd/C	$H_2C{=}CH_2$	50 (4)	 **16**	36[d]
9	 **17**	Pd/C	$H_2C{=}CH_2$	50 (4)	 **18**	21[d]
10	 **19**	Pd/C	$H_2C{=}CH_2$	50 (4.5)	 **20** (84)  **21** (5)	
11	 **22**	Pd(OAc)$_2$	$H_2C{=}CH_2$	50 (1.2)	PhOH **23** (68)  **24** (28)  **25** (4)	

[a] All reactions were carried out in acetonitrile using 50 wt% of 10% Pd/C unless otherwise stated. [b] Isolated yield unless otherwise stated. [c] 20 wt% of 10% Pd/C was used. [d] Determined by ^{1}H NMR (400 MHz) with *s*-trioxane as internal standard.

Table 2 Reuse of palladium catalyst in the oxidation of D-glucal



26 27

Palladium catalyst	Mol%[a]	Yield of product **27** (%)	Recovery of Pd precipitate[b]
$Pd(OAc)_2$	5	82[c]	98
Pd precipitate (run 1)	10[a]	95[d]	96
Pd precipitate (run 2)	10[a]	83[d]	95
Pd precipitate (run 3)	10[a]	95[d]	—
Pd black[e]	10[a]	84[d]	—

[a] Wt%. [b] Calculated as palladium black after centrifugal separation. [c] Isolated yield after recrystallization. [d] Isolated yield after silica-gel column chromatography. [e] Reaction time 94 h.

recently reported the hydrogen transfer reaction of D-glucal by a catalytic amount of palladium compound in the presence of vinyl acetate or under an ethylene atmosphere, which led to the catalytic and efficient synthesis of 1,5-anhydrohex-1-en-3-uloses.[9] Here we disclose the reuse of palladium catalyst. We found that the remaining palladium precipitate could be repeatly recovered from the heterogeneous reaction mixture by centrifugal separation and that it could be repeatedly reused. The results are summarized in Table 2. It should be noted that neither extractive work-up nor chromatographic purification was necessary (see Experimental section). The composition of this palladium precipitate was found (powder X-ray diffraction) to be the same as palladium black.

In summary, we have developed an efficient, catalytic system that transforms benzylic and allylic alcohols into the corresponding carbonyl compounds. Furthermore, reuse of the palladium catalyst was realized which was shown by the oxidation of D-glucal to the corresponding enone. The present system essentially includes hydrogen transfer reaction between alcohols and simple olefins such as ethylene and vinyl acetate. The generation of ethane and ethyl acetate was confirmed by GLC analysis after the reaction was completed. The reactions would be initiated by dehydrogenation of alcohols, and olefins serve as efficient hydrogen acceptors, which facilitates the whole hydrogen transfer reaction by the aid of palladium catalyst. This extremely simple process is not only economically advantageous but it is also environmentally friendly.

Experimental

General

^1H and ^{13}C NMR were recorded on a Bruker Avance 400S (400 and 100.6 MHz, respectively) using TMS as internal standard unless otherwise stated. IR spectra were measured on a Nicolet Impact 410 instrument. Gas–liquid phase chromatography (GLC) was performed on a Hitachi G-5000 instrument. The generation of ethane was detected by a Hewlett-Packard 5890 Sereies II, Porapak R column (He carrier gas: 30 mL min^{-1}; FID: 300 °C, column: 40 °C; retention time (t_R) of ethylene, 2.4 min; t_R of ethane, 3.3 min). Preparative column chromatography was carried out on a Fuji-Davison BW-820 or Wacogel 300. Thin layer chromatography (TLC): foil plates, silica gel 60 F_{254} (Merck; layer thickness 0.2 mm). Acetonitrile was distilled from P_4O_{10}. Pd/C and $Pd(OAc)_2$ were purchased from Wako.

General procedure for the oxidation of simple benzylic and allylic alcohols

A dry Schlenk tube containing a Teflon-coated stirring bar under an ethylene atmosphere was charged with alcohols (2.4–25 mmol) and acetonitrile (1.5–8 mL). To this mixture was added 5 or 10% Pd/C (20–50 wt% per alcohol) and the mixture was stirred vigorously at 50–80 °C for 2–4 d under an ethylene atmosphere using a balloon. The conditions were indicated in Table 1. After confirmation of completion of the reactions by TLC and/or GLC, the palladium precipitate was filtered off. After removal of the solvent, the products were purified by distillation or silica-gel column chromatography. All spectral data of the products were identical with those of commercially available authentic samples.

Application to the synthesis of 1,5-anhydrohex-1-en-3-uloses–reuse of the palladium catalyst

A mixture of palladium acetate (752 mg, 3.35 mmol), D-glucal **26** (9.83 g, 67.3 mmol), vinyl acetate (19 mL, 205.3 mmol), and CH_3CN (40 mL) was stirred at 65 °C for 23 h. The black palladium solid was separated by centrifugation and the solution was then concentrated. Purification by recrystallization from a mixture of acetone and ethyl acetate afforded 1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose (**27**) (7.92 g, 82%) as colorless needles. R_f 0.39 (ethyl acetate); mp 89 °C (lit.,[8] 87–88 °C); $[\alpha]_D^{23}$ +291.6 (c 1, H_2O) (lit.,[8] $[\alpha]_D^{20}$ +297.5 (c 1, H_2O); ν(KBr)/cm^{-1} 3350, 1660, 1605, 1420, 1280, 1120, 1040, 850; $\delta_H(CDCl_3)$ 2.03 (dd, $J_{OH(6)\text{–}H6}$ = 6.3, $J_{OH(6)\text{-}H6'}$ = 7.3 Hz, 1 H, OH(6)), 3.60 (d, $J_{OH(4)\text{-}H4}$ = 1.5 Hz, 1 H, OH(4)), 4.02 (ddd, $J_{H6'\text{-}H5}$ = 4.5, $J_{H6'\text{-}H6}$ = 12.5, $J_{H6'\text{-}OH(6)}$ = 7.3 Hz, 1 H, H6′), 4.11 (ddd, $J_{H6\text{-}H5}$ = 2.6, $J_{H6\text{-}H6'}$ = 12.5, $J_{H6\text{-}OH(6)}$ = 6.3 Hz, 1 H, H6), 4.19 (ddd, $J_{H5\text{-}H6}$ = 2.6, $J_{H5\text{-}H6'}$ = 4.5, $J_{H5\text{-}H4}$ = 11.6 Hz, 1 H, H5), 4.36 (dd, $J_{H4\text{-}H5}$ = 11.6, $J_{H4\text{-}OH(4)}$ = 1.5 Hz, 1 H, H4), 5.50 (d, $J_{H2\text{-}H1}$ = 5.8 Hz, 1 H, H2), 7.42 (d, $J_{H1\text{-}H2}$ = 5.8 Hz, 1 H, H1); δ_C ($CDCl_3$) 61.7 (C6), 67.9 (C4), 83.0 (C5), 103.6 (C2), 164.0 (C1), 194.0 (C3). Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 49.76; H, 5.66%. The palladium precipitate (349 mg) was recovered after centrifugation followed by washing with methanol and dried *in vacuo*. This palladium compound was used in the oxidation of D-glucal (run 1). Thus, continuous use of palladium was realized (Table 2).

Acknowledgements

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The first high yield green route to a pharmaceutical in a room temperature ionic liquid

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The synthesis of the pharmaceutical Pravadoline is achieved in high yield without the production of noxious waste products; the ionic liquid can be recycled and reused in this methodology.

Many processes associated with the pharmaceutical industry result in the production of large quantities of waste. Sheldon has developed a means of quantifying this, known as the *E*-factor,[1] which is defined as the ratio (by weight) of by-products to the desired product formed. Values for the *E*-factor as high at 25 to 100 are not uncommon in the pharmaceutical industry, and examples where *E* is greater that 1000 are known. Hence any technology that can reduce the *E*-factor is highly desirable.[2] We present here the synthesis of the pharmaceutical Pravadoline[3] in an ionic liquid, which significantly reduces the production of waste products. There has been considerable interest in developing new non-steroidal antiinflamatory drugs (NSAIDs). Pravadoline **4b** is a one of a group of (aminoalkyl)indoles that was initially investigated and found to be effective.[4] More recently, Pravadoline and more importantly some of its analogues[5] have been used as a probe for neurochemical receptors, since it has been found to be an agonist of the cannabinoid receptor.[6] Our interest in this molecule, as well as its analogues, is that it is synthesised by a sequence of regioselective nucleophilic displacement reactions[7] and Friedel–Crafts reactions.[8] These are two classes of reaction that work highly efficiently in ionic liquids and can be extended to many other industrial processes.

Room temperature ionic liquids have been used to great effect as solvents for a number of reactions. Recently, this topic has been reviewed by Holbrey and Seddon[9] and Welton.[10] Ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate[11] ([bmim][PF_6]) have a particularly valuable set of properties, being immiscible with water and alkanes, but readily dissolving many metal catalysts and reagents.[12] Such multiphasic ionic liquid systems[13] have been used to enable simple extraction and isolation of products.[14] Here we report a high yielding, low waste, total synthesis of Pravadoline **4b** carried out entirely in the ionic liquid [bmim][PF_6].[11]

Products and by-products can be separated from the ionic liquid by distillation or by solvent extraction with either an aqueous phase or an organic phase (Fig. 1). A recently reported example of product separation from an ionic liquid is the use of supercritical CO_2 as an extraction solvent for compounds dissolved in [bmim][PF_6].[14]

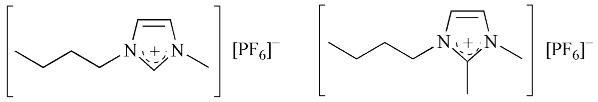

Fig. 1 The ionic liquids [bmim][PF_6][11] and [bdmim][PF_6].[15]

The synthesis of Pravadoline is shown in Fig. 2, and is derived from the commercially available starting materials **1, 2** and 4-methoxybenzoyl chloride. The molecule can be assembled in two separate ways, but it was decided to carry out the *N*-alkylation reaction as the first step, as this would lead to fewer problems in the subsequent Friedel–Crafts reaction.

Based on previous work, the regioselective alkylations in room temperature ionic liquids,[6] it was decided to treat 2-methylindole with the commercially available 1-(*N*-morpho-

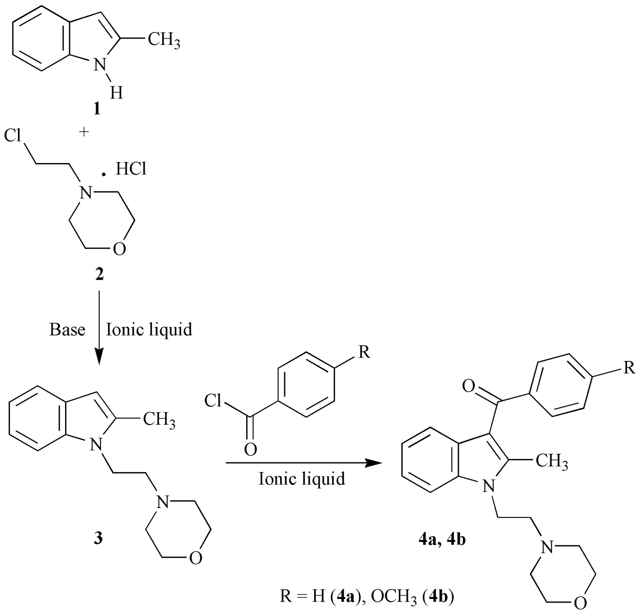

Fig. 2 Synthesis of Pravadoline **4** (R = OCH_3).

Green Context

The use of ionic liquids as solvents has attracted much interest recently, partly due to their polar nature, their phase behavior and their lack of vapour pressure. This article describes the synthesis of Pravadoline in ionic liquids, a synthesis which is shown to work very well in some of these solvents. Crucially, attention is paid to the recovery and reuse of the ionic liquid after reaction, which is readily achieved in the cases described here. ***DJM***

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lino)-2-chloroethane hydrochloride in the ionic liquid [bmim][PF_6], with solid potassium hydroxide as the base. The reaction proceeds smoothly at room temperature to give the 1-(2-(*N*-morpholino)ethyl)-2-methylindole **3** in 95% yield in [bmim][PF_6] and 99% in 1-butyl-2,3-dimethylimidazolium hexafluorophosphate ([bdmim][PF_6]).[15] No dialkylated indoles or other indole by-products were observed by GC or ^{1}H NMR analysis.

The product was extracted from the ionic liquid with toluene, which was distilled from the product and recycled. The ionic liquid was recovered by washing it with water to remove potassium chloride, followed by heating to 100 °C under vacuum. As for the choice of ionic liquids for this step, 2-*H*-imidazolium and 2-methylimidazolium salts gave the best yields. It is interesting to note that this reaction does not work well using *N*-alkylpyridinium-based ionic liquids.[13]

Conventionally, this reaction has been carried out in a dipolar aprotic solvent such as DMF[4] or DMSO,[16] using sodium hydride or sodium hydroxide respectively as bases. Both these conventional processes suffer from the disadvantage that the solvent is difficult to separate from the product, is usually lost to the environment, is noxious (in the case of DMSO), and has an unpleasant odour. This contrasts with the ionic liquid process, where the product is easily separated, the solvent is recycled, and the only chemically generated waste is an aqueous solution of potassium chloride. Other advantages are that the ionic liquid reaction does not need heating and improves the yield from 91%[4] to better that 95% in the ionic liquid.

Indoles are known to be fairly reactive in the Friedel–Crafts reaction, and the use of strong Brønsted or Lewis acids is known to polymerise indoles. For example, indole readily dimerises to 3′-indoyl-2,3-dihydroindole in the presence of a catalytic quantity of acid.[17] Another potential problem in a conventional Friedel–Crafts reaction is that the morpholino group will coordinate to commonly used Lewis acids.[18] The result is large amounts of metal halide must be used for the reaction to be successful. With these considerations in mind, the Friedel–Crafts reaction of 1-(2-(*N*-morpholino)ethyl)-2-methylindole **3** with benzoyl chloride or 4-methoxybenzoyl chloride was attempted in the ionic liquid [emim]Cl–$AlCl_3$ ($X = 0.67$†),[2] or [bmim][PF_6]. It should be noted that the reaction carried out in the chloroaluminate(III) ionic liquid (see Table 1) was similar to carrying out a conventional Friedel–Crafts reaction and gave yields similar to those in original syntheses of analogues of Pravadoline (40–89%).[4] The chloroaluminate(III) ionic liquid process suffers from the same disadvantages as conventional Friedel–Crafts reactions in that large quantities acidic waste are formed. The reaction in [bmim][PF_6] does not require a Lewis acid, and therefore acidic aqueous wastes are not produced. Furthermore, the lower acidity of the reaction leads to fewer by-products and therefore higher yields.

Based on work carried out by Earle *et al.*,[17] indoles were known to undergo Friedel–Crafts reactions under basic or neutral conditions. In the case of Pravadoline synthesis, the 1-(2-(*N*-morpholino)ethyl)-2-methylindole **3** acts as a base in the reaction.

Table 1 The Friedel–Crafts reaction in ionic liquids

Ionic liquid	R	T/°C	t/min	Yield (%)
[emim]Cl–$AlCl_3$ ($X = 0.67$)	H	0	5	70
[emim]Cl–$AlCl_3$ ($X = 0.67$)	OCH_3	0	5	70
[bmim][PF_6]	H	150	2	90
[bmim][PF_6]	OCH_3	150	2	95

The reaction of benzoyl chloride or 4-methoxybenzoyl chloride with **3** in [bmim][PF_6] was found to give the expected products in 90 and 95% yields respectively, simply by heating at 150 °C for 2 minutes in the ionic liquid. The product was isolated by neutralising with aqueous potassium carbonate solution and extraction of the product with toluene. The ionic liquid [bmim][PF_6] was recovered and reused in the reactions after separation and drying under vacuum.

In conclusion, we have developed a complete synthesis of Pravadoline in 90–94% overall isolated yield, with both steps carried out in the same ionic liquid, [bmim][PF_6]. The Friedel–Crafts reaction was found to work without the need for Lewis acids, and without all the associated waste aluminium disposal problems of a conventional Friedel–Crafts reaction.

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Notes and references

† The composition of a tetrachloroaluminate(III) ionic liquid is best described by the apparent mole fraction of $AlCl_3$ $\{X(AlCl_3)\}$ present. Ionic liquids with $X(AlCl_3) < 0.5$ contain an excess of Cl^- ions over $[Al_2Cl_7]^-$ ions, and are called 'basic'; those with $X(AlCl_3) > 0.5$ contain an excess of $[Al_2Cl_7]^-$ ions over Cl^-, and are called 'acidic'; melts with $X(AlCl_3) = 0.5$ are called 'neutral'.

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Direct biocatalytic synthesis of functionalized catechols: a green alternative to traditional methods with high effective mass yield

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Several catechols have been prepared directly from aromatic precursors by treatment with the recombinant organism *Escherichia coli* JM109 (pDTG602), which expresses both toluene dioxygenase (TDO) and dihydrocatechol dehydrogenase (DHCD), the first two enzymes in the natural biodegradation pathway of aromatics by *Pseudomonas* species. The yields and the ease of preparation of these compounds are compared with traditional chemical methods. For three of the products, the *E* value and EMY (effective mass yield, is defined as the percentage of the mass of desired product relative to the mass of all non-benign materials in its synthesis, see ref. 9) are calculated and compared with those obtained by traditional methods to indicate the green component of the preparation. Potential for direct introduction of the catechol unit to various natural product synthons is discussed.

Introduction

The catechol unit, free or alkylated, is a common component of numerous natural products. Among the targets currently pursued by our group several highly oxygenated compounds deserve a mention: morphine (**1**),[1] narciclasine (**2**),[2] pancratistatin (**3**),[3] combretastatins A-1 (**4**)[4] and B-1 (**5**)[4] (Fig. 1).

In most synthetic approaches the protected catechol unit of the target is present in the starting material or is introduced at the beginning of the synthesis by oxidation.[5] However, there arise occasions where synthesis would be simplified if the catechol could be introduced later in the synthesis by mild and selective procedures. In connection with an approach to morphine,[1b,6] we required a large amount of bromoguaiacol (**10**), whose non-enzymatic preparation and demethylation to 3-bromocatechol (**8**) are shown in Scheme 1.

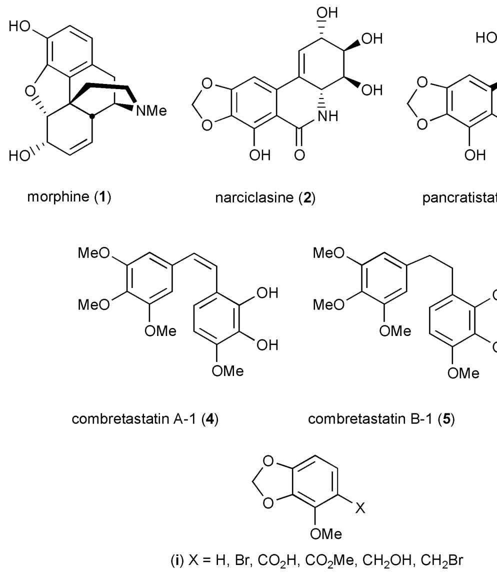

Fig. 1 Highly oxygenated natural products containing a catechol subunit.

3-Bromocatechol is also available by a simple dihydrozylation of bromobenzene with *Escherichia coli* JM109 (pDTG602), an organism developed by David T. Gibson.[7] As this process and subsequent methylation of **8** to **10** are experimentally superior to conventional synthetic methods, we explored the possibility of direct synthesis of several catechols useful as potential synthons in approaches to the targets mentioned above. The enzymatic route offers clear advantages in environmentally benign manufacturing of such compounds.

Here we report the preparation of several functionalized catechols by direct biooxidation of the corresponding substituted aromatic substrates and compare the effectiveness of this method with traditional procedures for several of the products. The *E* values[8] and EMY[9] are reported for these routes. The potential for direct introduction of the catechol unit to more complex substrates that are recognized by TDO and DHCD is indicated as one of the future directions of this research.

Green Context

Oxyfunctionalisation of aromatics leads to a wide range of useful synthetic intermediates. However, traditional catalysis has had limited (but nonetheless significant) success in this area. This paper describes the use of whole-cell organisms to oxygenate aromatics directly to catechols and discusses the use of such products in synthetic applications. An *E. coli* strain which expresses two enzymes capable of aromatic degradations is shown to be useful in this respect. Chemical yields, effective mass yields and *E*-factors compare very favourably to traditional routes. ***DJM***

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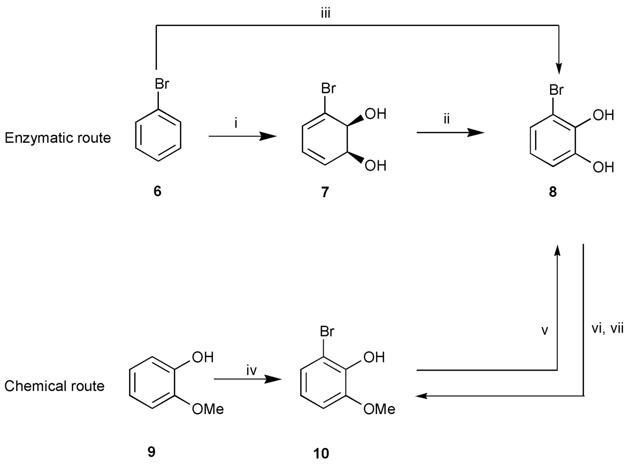
Results and discussion

Syntheses of simple catechols have been reviewed.[5] For the most part, methods involve the cleavage of mono- or di-alkylated catechols by strong protic or Lewis acids under relatively harsh conditions.[10] Other methods of catechol synthesis require strong oxidants[12] or cleavage of mono- and di-acetates.[11] Despite the great potential that catechols offer as synthetic intermediates, their preparation is usually arduous, non-selective and low-yielding.[13] Only three enzymatic methods of catechol synthesis have been reported.[14] Our synthesis of Amaryllidaceae alkaloids would be greatly simplified by an efficient preparation of the oxygenated aromatic fragment.[15]

Our goal was to explore the practical preparation of (especially) 3-bromocatechol (**8**) and other catechols by treatment with whole-cell *E. coli* JM109 (pDTG602), an organism developed by D. T. Gibson. The procedure for growing the cells was identical to that reported for *E. coli* JM109 (pDTG601), which expresses toluene dioxygenase.[16,17] Single colonies of cells are grown for 12 h in a shake flask containing 300 mL of preculture solution. The inoculum is then transferred to a 12-L fermentor (8-L working volume), induced with isopropyl thiogalactopyranoside (IPTG), and the culture grown for 24 h to an optical density (OD) of *ca.* 50. Substrates are generally added over a period of 4 h, with the progress of the biooxidation monitored by UV or TLC. In the case of 3-bromocatechol (**8**), the substrate (bromobenzene) was added at a rate of 0.3 g min^{-1} until 12 g had been added, at which point foaming (indicative of cell death) began, and the process was halted. The product was isolated by centrifugation, followed by extraction and distillation. The results for several catechols are shown in Table 1.



Scheme 1 Enzymatic and non-enzymatic preparation of 3-bromocatechol **8**. *Reagents:* i, *E. coli* JM109 (pDTG601); ii, [O]; iii, *E. coli* JM109 (pDTG602); iv, Br_2, Bu^tNH_2; v, BBr_3; vi, K_2CO_3, MeI; vii, TMSI.

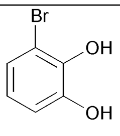
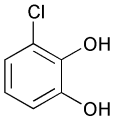
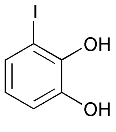
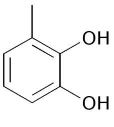
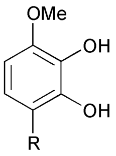
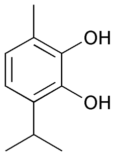
A comparison of the efficiency of biocatalytic *vs.* traditional synthesis of three catchols is shown in Table 2. The overall chemical yields are indicated as reported in the literature. The *E* value is calculated by dividing the weight of all materials used in synthesis by the weight of product. EMY is calculated by expressing the weight of product as a percentage of all non-benign mass used in the manufacturing. Solvents used for extractions are not taken into account in either calculation as they are recycled during manufacturing. It is obvious that the EMY are more informative of the efficiency of the process than the overall yields, because the latter do not provide any information about the process itself. It is also evident that biooxidation in a single step is far more efficient than traditional preparation, even though the yield is limited by the concentration of product at 1–2 g L^{-1}, beyond which it is toxic to the organism.[14b,c]

Table 2 Comparison of efficiency of the preparation of 3-bromocatechol (**8**), 3-iodocatechol (**12**) and 3-methylcatechol (**13**) by traditional and enzymatic methods

	Non-enzymatic			Enzymatic		
Catechol	Overall yield	*E* value	EMY	Overall yield	*E* value	EMY
8	35%[a] 52%[b]	47.5[a] 36.3[b]	2.1%[a] 2.8%[b]	63%	1.25	75.0%
12	No chemical synthesis			34%	2.0	38%
13	1%[c]	63.5[c]	1.6%[c]	45%	2.25	60.6%

[a] Ref. 13*l* (repetition of procedure from ref. 13*k*). [b] Ref. 13*j*. [c] Ref. 13*h*.

Table 1 Catechols prepared by biooxidation of corresponding arenes with *E. coli* JM109 (pDTG602)

	[Yield (g L^{-1})][a]		[Yield (g L^{-1})][a]		[Yield (g L^{-1})][a]
 **8**	[1.0]	 **11**	[0.5]	 **12**	[0.5]
 **13**	[2.0]	 **14**	R = H[b] R = Me [0.65]	 **16**	[0.4]

[a] Yields are not optimized. [b] This experiment was done on shake-flask scale only.

Conclusions

Functionalized catechols can be prepared directly from mono- or di-substituted aromatic precursors by biooxidation on a preparative scale. These are important starting materials for synthetic routes to many natural products and are often unattainable by traditional methods, *e.g.* iodocatechol (**12**). Halogenated catechols are useful for the introduction of this unit into intermediates that rely on Heck cyclization[1a] or tethered radical[1b] cyclization for C–C bond formation. In the near future we intend to screen a broad range of substrates for the recombinant organism and establish substitution limits for recognition by the enzymes. We will report on these findings in due course.

Acknowledgements

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Calcined Mg–Al hydrotalcite as an efficient catalyst for the synthesis of guaiacol

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The use of calcined Mg–Al hydrotalcite as an efficient catalyst for the selective *O*-alkylation of catechol with dimethyl carbonate (DMC) to guaiacol in a continuous fixed bed flow reactor is described. A maximum guaiacol yield of 80% is obtained at 573 K under optimized conditions with a stable catalytic activity. A concerted mechanism involving acid–base pair sites in which a nucleophilic attack at the methyl carbon atom of DMC by the oxygen atom of the H-bonded phenolic compound or phenolate anion is proposed.

Introduction

Currently, new synthetic routes aiming at waste minimization by replacing corrosive and toxic reagents is receiving increasing interest for the production of valuable chemical intermediates in view of environmental concern. Guaiacol, which is an important synthetic intermediate in the production of flavourings, fragrances and pharmaceuticals is conventionally synthesized by methylation of catechol with corrosive reagents like dimethyl sulfate and dimethyl iodide in the presence of stoichiometric quantities of sodium hydroxide as a homogeneous catalyst.[1–3] To avoid the disadvantages of homogeneous catalytic process, vapour phase methylation of catechol with methanol or dimethyl carbonate over metal oxides and zeolites has been explored.[4–6] Dimethyl carbonate is found to be an efficient methylating agent compared to methanol, since the alkylation reaction can be carried out at relatively lower temperatures with improved selectivity of the desired *O*-alkylated products. Recently Fu and co-workers found that modification of alumina with suitable alkali metal compounds can be used for the synthesis of guaiacol, veratrole or catechol carbonate under optimised conditions by the alkyation of catechol with DMC.[7–9]

Calcined Mg–Al hydrotalcites are reported to be very active in various base catalyzed organic transformations.[10–13] They can be viewed as possessing a pair of strong basic sites (O^{2-} ions) and Lewis acid sites (co-ordinatively unsaturated Al^{3+} ions). Here, we tried to explore the basic properties of these materials in the selective synthesis of guaiacol by the methylation of catechol with DMC in a fixed bed continuous flow silica reactor. The reaction parameters were optimized to achieve maximum guaiacol yield.

Results and discussion

The Mg–Al mixed double hydroxides showed the typical XRD patterns of the hydrotalcite structure with intense sharp and symmetric peaks for (003), (006), (110) and (113) planes. The typical IR, TG and DTA patterns also substantiated the formation of layered double hydroxides (LDHs). The important physico-chemical characteristics of LDHs are presented in Table 1. A detailed account of the physico-chemical characteristics of hydrotalcites has been reported elsewhere.[14]

Table 1 Physico-chemical characteristics of Mg–Al hydrotalcites

Catalysts	Mg^{II}/Al^{III} Atomic ratio[a]	Unit cell parameters *a*	Unit cell parameters *b*	Specific surface area/m^2 g^{-1} [b]
Mg-Al3	2.75	3.062	23.331	126
Mg-Al4	3.75	3.073	23.599	179
Mg-Al5	4.79	3.088	23.915	139

[a] ICPES. [b] Calcined at 723 K for 6 h.

The results on the methylation of catechol with DMC as an alkylating agent at 548 K with various DMC–catechol molar ratios ranging from 2 to 6 over calcined Mg–Al hydrotalcite (Mg/Al ratio = 4) is depicted in Fig. 1. Guaiacol and veratrole were obtained as the major products along with small amounts of catechol carbonate and *C*-alkylated products (3-methyl catechol and 4-methyl catechol). A change in molar ratio from 2 to 3 resulted in an appreciable increase in catechol conversion (52 to 69%). However, when the molar ratio was further increased catechol conversion remained almost constant. At higher DMC–catechol molar ratios guaiacol selectivity decreased markedly with a concomitant increase in the selectivity of veratrole. Hence a catechol to DMC ratio of 1:3 was maintained for various investigations.

The effect of temperature on catechol conversion and product selectivity over Mg-A14 catalyst is presented in Table 2. Conversion reached a maximum at 573 K and then it decreased possibly due to the self decomposition of DMC. The selectivities of guaiacol and veratrole were not much influenced by temperature, however, at higher temperature the yield of *C*-

Green Context

Solid catalysts with basic sites and with both acidic and basic sites are beginning to attract considerable attention. This paper describes the use, in a continuous reactor, of a Mg–Al hydrotalcite for the methylation of catechol to form guaiacol. The method also involves the use of dimethyl carbonate as a non-salt forming alkylating agent. The combination of these techniques provides a solvent free route to the product in high selectivity and good throughput.
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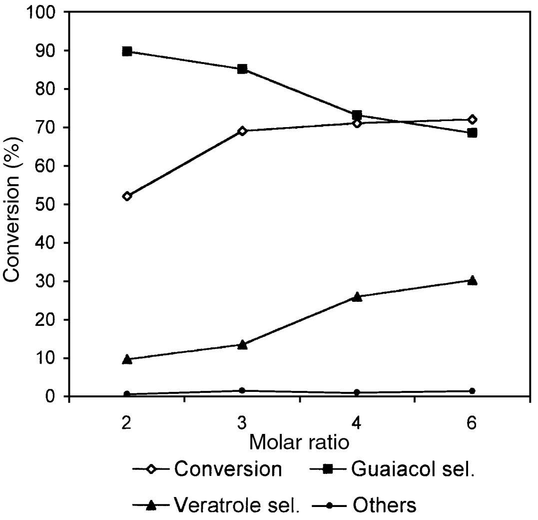


Fig. 1 Effect of DMC–catechol molar ratio on catechol conversion and product selectivity. Reaction conditions: catalyst = MgAl4 (Mg : Al = 4), 548 K, TOS = 2 h, WHSV = 1 h^{-1}.

Table 2 Effect of temperature on the product selectivity in the alkylation of catechol with DMC[a]

Product selectivity (%)	*T*/K 523	548	573	598	623
Guaiacol	86.3	85.1	84.0	79.1	78.3
Veratrole	12.6	13.5	12.1	13.4	10.8
Others[b]	1.1	1.4	3.9	7.5	10.9
Conversion (%)	40.0	69.0	96.0	94.0	80.0

[a] Reaction conditions: 523–623 K, catalyst = MgAl4 (Mg : Al = 4), DMC–catechol molar ratio = 3, WHSV = 1 h^{-1}, time on stream = 2 h. [b] Other products include catechol carbonate and polymethylated products.

alkylated and polymethylated products increased sharply. At 573 K, the guaiacol selectivity was 84% at a catechol conversion of 96% (yield = 80%).

Product selectivity is often influenced by change in contact time of the reactants on catalyst surface. The effect of contact time on the conversion of catechol and product selectivity at 573 K over Mg-A14 catalyst is depicted in Fig. 2. When the contact time was increased by changing WHSV (weight hourly space velocity expressed in terms of gram of feed per gram of catalyst per h) from 2 to 0.66 h^{-1}, the selectivity of veratrole was increased considerably with a concomitant decrease in selectivity of guaiacol. This indicates that veratrole is formed by the subsequent *O*-alkylation of guaiacol. Catechol was completely converted at 573 K with a total *O*-selectivity (guaiacol = 76.1%) of 94.4%, when WHSV was changed to 0.66 h^{-1}. Even at higher contact times the formation of catechol carbonate and *C*-alkylated products was not appreciable.

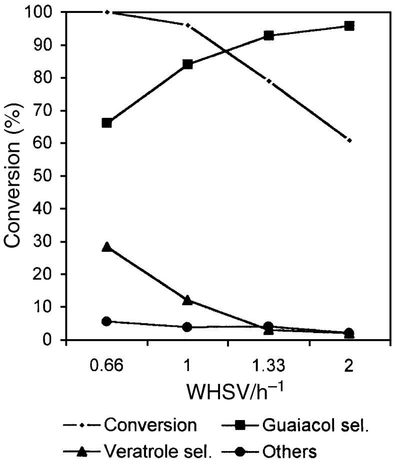


Fig. 2 Effect of WHSV on catechol conversion and product selectivity. Reaction conditions: catalyst = MgAl4 (Mg : Al = 4), 573 K, DMC : catechol = 3, TOS = 2 h.

A comparative study of methylation of catechol with DMC and methanol at 598 K is presented in Table 3. Both the catechol conversion and selectivity of *O*-alkylated products were adversely affected when methanol was employed as the methylating agent. This illustrates that DMC is an efficient methylating agent compared to methanol in the *O*-methylation of catechol.

Table 3 Comparison of methylation of catechol with methanol and DMC as alkylating agents[a]

Methylating agent	Catechol conversion (%)	Product selectivity (%) Guaiacol	Veratrole	*C*-alkylated	Others[b]
DMC	94	79.1	13.4	5.3	2.2
Methanol	14	42.3	15.2	31.6	10.9

[a] Reaction conditions: 598 K, catalyst = MgAl4 (Mg : Al = 4), DMC (methanol) : catechol = 3, WHSV = 1 h^{-1}, TOS = 2 h. [b] Other products include catechol carbonate and polymethylated products.

The activity of three different catalysts with different Mg–Al ratio at 573 K in terms of longevity over a period of 5 h is presented in Fig. 3. It can be seen that calcined Mg–Al hydrotalcite displays a stable activity during the time period investigate. The analysis of gaseous products revealed the presence of carbon oxide and small amounts of dimethyl ether. These results indicate that the basic sites active for the methylation of catechol are weak in strength, since the stronger basic sites present will be more accessible to the poisoning by acidic carbon dioxide formed during the reaction leading to catalyst deactivation. Owing to the difference in the ionic radii of Mg^{II} and Al^{III} ions, as well as to the high surface area and porosity values, calcined hydrotalcites possess a higher proportion of active sites.

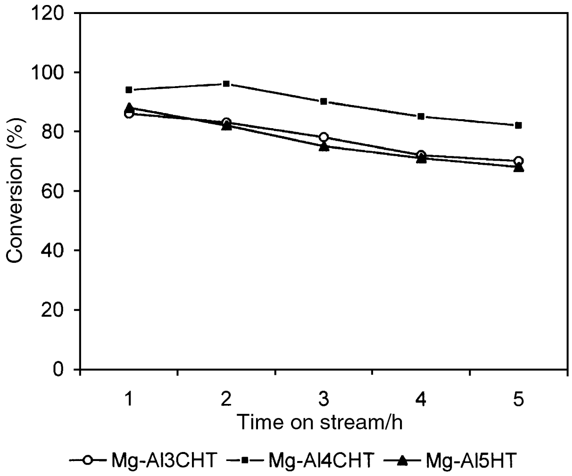
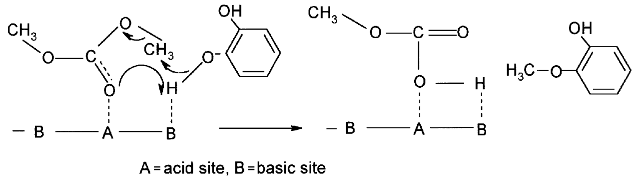


Fig. 3 Conversion of catechol over different catalysts as a function of time. Reaction conditions: 573 K, DMC : catechol = 3, WHSV = 1 h^{-1}.

Based on the recent report by Beutel on the spectroscopic investigation of phenol alkylation with DMC over basic zeolites, it is proposed that catechol is activated by H-bonding to a basic oxygen atom, while DMC is adsorbed on the adjacent Lewis acid site *via* its carbonyl oxygen atom.[15] A concerted mechanism in which a nucleophilic attack at the methyl carbon atom of DMC by the oxygen atom of the H-bonded phenolic compound or phenolate anion is possible as shown in Scheme 1. The residual methyl hydrogen carbonate residue may decompose to form CO_2.



Scheme 1 Plausible mechanism of the *O*-methylation of catechol with DMC over acid–base pair sites.

Experimental

The hydrotalcites with various Mg–Al atomic ratios were prepared by a sequential precipitation method.[14] Two separate solutions, one containing $Mg(NO_3)_2{\cdot}6H_2O$ and $Al(NO_3)_3{\cdot}9H_2O$ in de-ionized water and another containing NaOH in de-ionized water were prepared. The metal nitrate solution was added to the second solution maintaining the pH at 9–9.5. The resulting precipitate was digested at 338 K for 30 min with stirring and washed with distilled water many times until the pH of the filtrate became 7. The catalyst was filtered off and dried at 383 K and calcined in air at 723 K for 6 h and stored in sealed ampoules. For convenience catalysts were designated as Mg-Al3, Mg-A14 and Mg-A15 having Mg–Al atomic ratios of 3, 4 and 5 respectively.

The characterization of LDHs and calcined-layered double hydroxides (CLDHs) were carried out using XRD, thermogravimetry and BET surface-area measurements. The ICPES (inductively coupled plasma emission spectrometry) method was adopted to estimate the ratios of the M^{II} and M^{III} ions in LDHs.

The methylation of catechol with DMC was carried out in the temperature range 523–623 K, in a fixed bed down flow silica reactor. 2 g of the catalyst (as pellets 10–20 mesh) was loaded in the middle of the reactor fitted with a thermocouple for temperature measurements. The catalyst was activated in a stream of air at 723 K for 6 h and brought down to the reaction temperature under nitrogen flow. The reaction mixture consisting of catechol and DMC was introduced at the top of the reactor by means of an infusion pump. The products were collected in a water-cooled condenser and analyzed by a gas chromatograph fitted with a capillary column (HP-1) and flame ionization detector. The mass balance noted each time was found to be in the range 90–94%. The identity of the products was established by the comparison of retention times of authentic samples and also by GC-MS and GC-IR. The yield of guaiacol is calculated as selectivity × converson/100.

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Selective methylation of anisole to 2,6-xylenol over rare earth promoted SnO_2 catalysts

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Rare earth promoted SnO_2 catalysts are found to be active in the selective conversion of anisole to 2,6-xylenol in the presence of methanol. A maximum 2,6-xylenol selectivity of 82% was achieved at 400 °C under optimized conditions at an anisole conversion of 65%. The dealkylation of anisole to phenol and other side reactions such as the formation of polymethylated products is not favoured over these catalysts systems. The activity of these catalysts in the selective formation of 2,6-xylenol is ascribed to the presence of weak Lewis acid sites and comparatively stronger basic sites. The secondary reactions are suppressed over rare earth promoted SnO_2 catalysts due to the unavailability of strong acid sites.

Introduction

There is currently a significant world wide interest in the use of solid acid and base catalysts to promote various organic reactions of industrial importance, since such systems often give value-added products with improved selectivity without creating major burdens to the environment. The selective synthesis of alkyl phenols especially *o*-cresol and 2,6-xylenol is receiving increasing interest in recent years because of their importance as intermediates for the synthesis of a variety of resins, herbicides, insecticides and other chemicals.[1] The synthesis of 2,6-xylenol by the alkylation of phenol with methanol has been attempted over different metal oxide catalysts.[2–6] It is known that anisole can undergo intramolecular rearrangement reaction to *o*-cresol or intermolecular rearrangement between two molecules to methylanisole and phenol. Also, dealkylation reactions can prevail depending upon the reaction conditions or acid–base properties of the catalyst. Apart from the acid–base properties of the catalysts, the product selectivity is often influenced by the operating conditions and the nature of alkylating agent. Bautista and co-workers found that dealkylation to phenol is predominant over $AlPO_4$–Al_2O_3 catalysts in the alkylation of anisole with methanol.[7] Here we report, for the first time, the selective synthesis of 2,6-xylenol by the reaction of anisole and methanol over solid base catalysts comprising of tin oxide and rare earth elements (La, Ce and Sm) as promoters.

In previous papers, we have demonstrated that modification of SnO_2 with rare earth oxides like La_2O_3, Sm_2O_3 and CeO_2 leads to the formation of weak acid sites and comparatively stronger basic sites which are suitable for the selective methylation of phenol to *o*-cresol and 2,6-xylenol.[8–10]

Results and discussion

The addition of rare earth oxide to tin oxide resulted in a broadening of the XRD peaks. This indicated that the addition of a second oxide influenced the crystallization of the major component, SnO_2, by preventing the aggregation of smaller particles. Moreover, no reflections due to the rare earth oxide phase were detected, which suggests that the rare earth oxide was either amorphous or that the crystallite size was below the detection limits of the X-ray technique. The specific surface area of lanthanum-modified SnO_2 (TL) was higher (108.8

Green Context

The formation of alkylated phenols is a major area of chemistry and clean processes are required. The conversion of anisole to 2,6-xylenol is an important target, and heterogeneous catalysts may provide the answer. Typical strong acid catalysts promote a range of undesirable side reactions, but the catalysts here show that the combination of some weakly acidic centres, along with stronger basic sites, can lead to very good selectivity and a clean process.
DJM

Table 1 Physicochemical characteristics of mixed oxides (SnO_2–RO[a]), calcined at 823 K

Catalyst	SnO_2[b] Mol%	RO[b]	Surface area/m^2 g^{-1}	Pore volume/cm^3 g^{-1}	Acidity[c]/mmol g^{-1} W	M	S	Basicity/mmol g^{-1} W	M	S
TL	89.11	10.79	108.80	0.28	0.12	0.05	—	0.07	0.13	0.46
TS	89.20	10.80	105.70	0.31	0.15	0.08	—	0.08	0.11	0.39
TC	89.18	10.82	107.80	0.30	0.12	0.06	—	0.08	0.14	0.41
SnO_2	100	—	36.10	0.45	0.23	0.01	—	0.03	0.09	0.19

[a] Rare earth oxide; [b] From EDX analysis; [c] W, M and S stands for weak, medium and strong acidic or basic sites.

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m^2 g^{-1}) compared to that of pure SnO_2 (36 m^2 g^{-1}). The important physico-chemical characteristics of the tin rare earth-mixed oxides are summarized in Table 1. A detailed account of the characterization of such materials has been reported elsewhere.[11,12]

The effect of anisole to methanol molar ratio on the product selectivity was investigated at 380 °C taking several anisole to methanol molar ratios over the TL82 catalyst to select an optimum feed mix. The major product formed was 2,6-xylenol along with small quantities of phenol, methylanisole, cresol and trimethylphenol. Results are presented in the form of Fig. 1. We have selected a molar ratio of 1 : 6 for further study, as the conversion and selectivity were better.

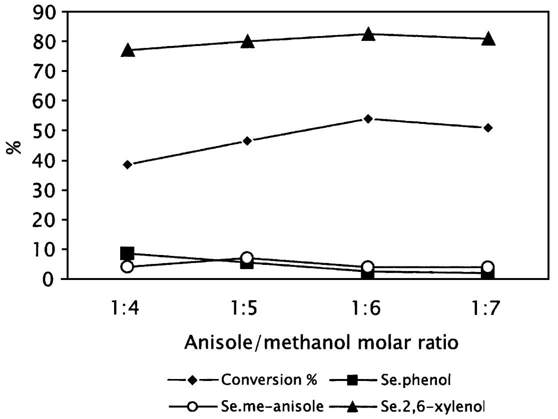

Fig. 1 Effect of anisole/methanol molar ratio on the conversion of anisole with methanol. *Reaction conditions*: 380 °C, catalyst = TL82, time on stream = 1 h, feed rate = 4 ml h^{-1}.

The anisole conversion and selectivity to 2,6-xylenol as a function of temperature is summarized in Table 2. The anisole conversion increased with temperature and attained a maximum of 83% at 420 °C. Thereafter, the decomposition of methanol was appreciable. Maximum 2,6-xylenol selectivity was attained at 380 °C but at higher temperatures it decreased due to the formation of increasing amounts of trimethylphenol (TMP), phenol and cresol. The selectivity of methylanisole decreased with increase in temperature and was not observed above 380 °C. The reaction of methylanisole alone at different temperature was performed and the results are presented in Table 3. As the temperature is increased the conversion to xylenol also increased.

The effect of feed rate on the product selectivity is depicted in Fig. 2. The flow rate of the feed was changed from 4 to 10 ml h^{-1}. It can be seen that the selectivity of methylanisole increases with increase in feed rate with a concomitant decrease in the selectivity of 2,6-xylenol. This suggests that methylanisole is the possible intermediate in the formation of 2,6-xylenol over SnO_2–La_2O_3 catalysts. The isomerisation of methylanisole to 2,6-xylenol further supports this reaction pathway (Table 3). Hence, conversion of anisole to 2,6-xylenol in the presence of methanol must be taking place in two consecutive reactions *via.* (*a*) the formation of methylanisole from anisole and (*b*) isomerisation of methylanisole to 2,6-xylenol. When anisole alone was passed over the catalyst under similar conditions phenol and *o*-cresol were detected as major products but the conversion was low (Table 4).

The SnO_2 based catalysts modified with three different rare earth elements *viz.* La, Ce and Sm were compared under optimized conditions and the results are included in Table 5. It

Table 2 Alkylation of anisole with methanol—effect of temperature on the product distribution[a]

Product distribution/wt%	T/°C 350	380	400	420
Anisole	56.80	46.1	34.80	16.38
Phenol	0.20	1.1	2.60	4.61
Methylanisole	9.82	2.09	nil	nil
Cresol	3.61	3.6	3.71	5.52
2,6-Xylenol	27.61	44.61	53.79	63.29
TMP	1.80	2.5	5.1	10.2
Conversion(%)	43.20	53.9	65.2	83.62
Sel. 2,6-xylenol(%)	63.91	82.9	82.5	75.68

[a] *Reaction conditions*: 350–420 °C, anisole/methanol molar ratio = 1:6, catalyst = TL82, time on stream = 1 h, feed rate = 4 ml h^{-1}.

Table 3 Self-reaction of methylanisole over TL82 catalyst[a]

Reaction temperature/°C	Conversion(%)	2,6-Xylenol selectivity(%)
350	43.6	95.4
380	49.3	92.2
400	56.3	89.1
420	62.5	84.5

[a] *Reaction conditions*: 350–420 °C, catalyst = TL82, time on stream = 1 h, feed rate = 4 ml h^{-1}.

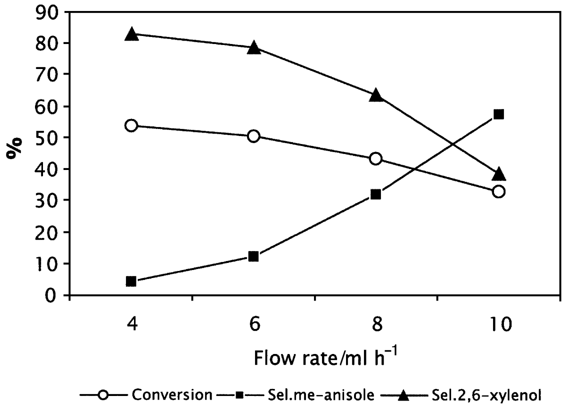

Fig. 2 Effect of feed rate on the conversion of anisole with methanol. *Reaction conditions*: 380 °C, catalyst = TL82, time on stream = 1 h, anisole/methanol molar ratio = 1:6.

Table 4 Self-reaction of anisole over TL82[a]

Reaction temperature/°C	Conversion (%)	Sel. phenol (%)	Sel. *o*-cresol (%)	Sel. 2,6-xylenol (%)
350	12.2	76.4	22.2	—
380	18.4	80.1	16.5	2.2
400	22.6	78.2	13.6	3.4

[a] *Reaction conditions*: 350–400 °C, catalyst = TL82, time on stream = 1 h, feed rate = 4 ml h^{-1}.

Table 5 Alkylation of anisole with methanol over different catalysts[a]

Product distribution(%)	SnO_2	La_2O_3	TL82	TC82	TS82
Anisole	84.7	87.5	46.1	46.8	47.8
Phenol	1.8	1.1	1.1	1.3	1.4
Methylanisole	7.6	8.7	2.1	1.8	1.8
o-Cresol	2.3	1.2	3.6	3.7	3.4
2,6-Xylenol	3.6	1.5	44.6	43.8	42.8
TMP	—	—	2.5	2.7	2.8
Conversion(%)	15.3	12.5	53.9	53.2	52.2
Sel. 2,6-xylenol(%)	23.5	12.0	82.9	82.3	81.9

[a] *Reaction conditions*: 380 °C, anisole : methanol molar ratio = 1 : 6, time on stream = 1 h, feed rate = 4 ml h^{-1}.

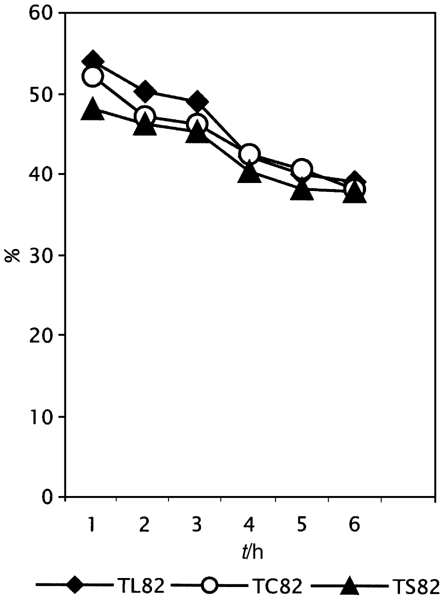

Fig. 3 Effect of time on stream (TOS) on the conversion of anisole with methanol over different catalysts. *Reaction conditions*: 380 °C, feed rate = 4 ml h^{-1}, anisole/methanol molar ratio = 1:6.

can be seen that 2,6-xylenol is the main product in all cases. The selectivity pattern was similar over all the catalysts. However, the single oxide catalysts (SnO_2 and La_2O_3) displayed poor catalytic activity. The higher selectivity of 2,6-xylenol over rare earth promoted tin oxide catalysts is ascribed to the existence of weak acid sites and comparatively stronger basic sites. The undesired side reactions such as the delalkylation to phenol and formation of polymethylated products are suppressed over these catalysts due to the unavailability of strong acid sites. Conversion of anisole as a function of time (TOS) was investigated over TL82, TC82 and TS82 and results are depicted in Fig. 3 An initial deactivation was observed over all the three catalysts and thereafter attained a stable activity.

Experimental

The rare earth promoted SnO_2 catalysts were prepared by co-precipitation method from the required quantities of tin(IV) chloride solution and rare earth nitrate solution using aqueous ammonia as the precipitating agent (1 part of water and 1 part of 25% aqueous ammonia solution). The final pH of the solution was 9. The precipitate was washed several times with deionised water to remove anions and finally filtered, dried at 383 K and calcined in air at 823 K for 3 h. The rare earth nitrates and tin(IV) chloride were obtained from Indian Rare Earths Ltd. and Ranbaxy India Ltd. respectively.

The chemical composition of the catalysts was determined by energy dispersive X-ray analysis (Stereoscan 440, Cambridge UK). The different oxide phases were detected by X-ray diffraction using Ni filtered Cu-Kα radiation (λ = 1.5404 Å). An Omnbisorb 100 CX unit (Supplied by COULTER Corporation USA) was used for the measurement of N_2 adsorption to determine surface areas. The acidity and basicity of the catalysts were measured by butylamine and acetic acid adsorption, respectively. The catalysts were kept in a desicator saturated with butylamine/acetic acid vapor at room temperature for 48 h. The weight loss of the adsorbed sample was then measured by a TGA operating from 313–873 K at a rate of 20 °C min^{-1}. The weight losses between 423–573, 574–723 and 724–873 K are considered to correspond to weak, medium and strong acid sites, respectively.[10] The catalysts used in the present study are designated as follows for convenience: TL = SnO_2–La_2O_3, TS = SnO_2–Sm_2O_3, TC = SnO_2–CeO_2.

Alkylation reactions were carried out in the vapor phase in a fixed bed down flow silica reactor. 3 g of the catalyst (as pellets 10–20 mesh) was loaded in the middle of the reactor fitted with a thermocouple for temperature measurements. The catalyst was activated in a stream of air at 723 K for 6 h and brought down to the reaction temperature under nitrogen flow. The reaction mixture (anisole and methanol) was introduced at the top of the reactor by means of an infusion pump. The products were collected in a water-cooled condenser and analyzed by a gas chromatograph fitted with a capillary column (HP-1) and flame ionization detector. Mass balance was noted each time (> 95%). The identity of the products was established by the comparison of retention times of authentic samples and also by GC-MS and GC-IR.

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Clean and efficient condensation reactions of aldehydes and amines in a water suspension medium

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Condensation reactions of aldehydes and amines occur efficiently in a water suspension medium, and the reaction products are collected easily by filtration.

Introduction

Aliphatic and aromatic aldehydes condense with aliphatic and aromatic primary amines to yield *N*-substituted imines (Shiff bases), which have long found great use as analytical, medicinal, polymer and liquid crystalline materials.[1] The preparation of imines has been carried out by refluxing the mixture of amines and the carbonyl compounds in organic solvent under azeotropic conditions in order to separate the water formed.[2] In recent years, environmentally benign synthetic methods have received considerable attention and some solvent-free protocols have been developed.[3] Kaupp *et al.* reported the solid-state synthesis of various kinds of benzylideneaniline derivatives by grinding together the solid anilines and solid benzaldehydes.[4] Varma *et al.* reported clay catalyzed synthesis of imines and enamines under solvent-free conditions using microwave irradiation.[5] We have now found that the condensation reaction of benzaldehydes **1** and anilines **2** to benzylideneanilines **3** occurred efficiently in a water suspension medium[6] without using any acid catalyst and the products were isolated simply by filtration. Efficient condensation reaction of aldehydes (**1**) and *N*,*N*′-disubstituted ethylenediamines (**4**) to tetrahydroimidazoles (**5**) in a water suspension medium is also reported.

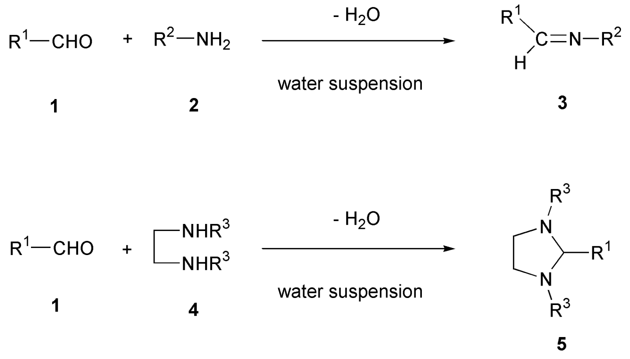
Results and discussion

The preparation of *p*-chlorobenzylideneaniline is representative of the general procedure employed. For example, a mixture of benzaldehyde (0.25 g, 2.35 mmol) and *p*-chloroaniline (0.30 g, 2.35 mmol) was stirred in a small amount of water (5 ml) at room temperature for 30 min. The crystalline powder formed was collected by filtration, washed with water and dried in a desiccator to give *p*-chlorobenzylideneaniline (**3c**, 0.50 g, 99% yield). Results for the reactions between various amines and aldehydes are summarized in Table 1. In contrast, the conventional method in organic solvent is less convenient. A 1 : 1 mixture of benzaldehydes and anilines is refluxed in benzene containing a small amount of benzenesulfonic acid as catalyst for several hours under azeotropic conditions using Dean–Stark apparatus. After the solvent is removed under reduced pressure, the residue is recrystallized from solvent to give the corresponding benzylideneaniline in 47–95% yields.[2] Our new method has advantage because neither acid catalyst nor aromatic solvent for azeotropic water separation are needed, and the product can be isolated simply by filtration. It is also very interesting that the condensation reactions occur very efficiently even in the presence of water.

Condensation reaction of aldehydes and *N*,*N*′-disubstituted ethylenediamines in a water suspension medium was also found

Table 1 Synthesis of benzylideneanilines **3** in a water suspension medium

3	R¹	R²	Reaction time/h	Yield(%)	Mp/°C
a	Ph	Ph	3	98	50–53
b	Ph	*p*-MeC$_6$H$_4$	1	86	52
c	Ph	*p*-ClC$_6$H$_4$	0.5	99	58–61
d	Ph	*p*-BrC$_6$H$_4$	0.5	98	62–65
e	Ph	*p*-MeOC$_6$H$_4$	3	86	66–69
f	*p*-MeC$_6$H$_4$	Ph	1	88	88
g	*p*-ClC$_6$H$_4$	Ph	2	97	58–61
h	*p*-BrC$_6$H$_4$	Ph	1	86	71–74
i	*p*-PhC$_6$H$_4$	Ph	0.5	92	155–158
j	*p*-HOC$_6$H$_4$	Ph	0.5	94	50–53
k	*p*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$	0.5	87	110–113
l	*m*-HOC$_6$H$_4$	*p*-BrC$_6$H$_4$	0.5	94	111–114



Scheme 1

Green Context

The formation of imines and similar condensation products are usually carried out using an acid catalyst and an aromatic to azeotrope off the water formed and drive the equilibrium towards the product. This article describes a remarkably efficient and counter-intuitive approach to this chemistry. Using water as solvent allows the formation of imines without the need for catalysis, or the azeotropic removal of water. Yields are high and reactions are fast, and products can be isolated by filtration. The use of diamines leads to tetrahydroimidazoles in high yields. ***DJM***

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Table 2 Synthesis of tetrahydroimidazoles **5** in a water suspension medium

5	R^1	R^3	Reaction time/h	Yield(%)	Mp/°C
a	Ph	Ph	0.5	92	80–83
b	p-MeC_6H_4	Ph	1.5	95	153–156
c	Ph	p-MeC_6H_4	3	90	oil[a]
d	p-MeC_6H_4	p-MeC_6H_4	4	88	oil[a]
e	p-ClC_6H_4	p-MeC_6H_4	4	86	oil[a]

[a] The products were isolated by extraction with diethyl ether.

to produce tetrahydroimidazole derivatives **5** very efficiently. For example, a mixture of benzaldehyde (0.50 g, 4.71 mmol) and *N*,*N*′-diphenylethylenediamine (1.00 g, 4.71 mmol) was stirred in a small amount of water (3 ml) at room temperature for 30 min. The crystalline powder formed was collected by filtration, washed with water and dried in a desecrator to give 1,2,3-triphenyltetrahydroimidazole (**5a**, 1.30 g, 92% yield). The results for the synthesis of other tetrahydroimidazoles are summarized in Table 2. This method is more convenient and efficient than the previous reported method in organic solvent.[7]

In conclusion, we have developed a simple and green procedure for the synthesis of various kinds of imines and tetrahydroimidasoles that requires neither acid catalyst nor azeotropic conditions using a large excess of aromatic solvents such as benzene.

Experimental

Typical procedure for the preparation of benzylideneanilines

A mixture of liquid benzaldehyde (0.25 g, 2.35 mmol) and powdered crystalline *p*-chloroaniline (0.30 g, 2.35 mmol) was stirred in a small amount of water (5 ml) at room temperature for 30 min. The crystalline powder formed was collected by filtration, washed with water and dried in a deseccator to give *p*-chlorobenzylideneaniline (**3c**, 0.50 g, 99% yield). The crude crystals thus obtained were recrystallized from EtOH to give pure **3c** as yellow prisms (mp 58–61 °C).

Typical procedure for the preparation of tetrahydroimidazoles

A mixture of liquid benzaldehyde (0.50 g, 4.71 mmol) and powdered crystalline *N*,*N*′-diphenylethylenediamine (1.00 g, 4.71 mmol) was stirred in a small amount of water (3 ml) at room temperature for 30 min. The crystalline powder formed was collected by filtration, washed with water and dried in a desiccator to give 1,2,3-triphenyltetrahydroimidazole (1.30 g, 92% yield). The crude crystals thus obtained were recrystallized from toluene to give pure **5a** as colorless needles (mp 80–83 °C).

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One-pot synthesis of tetrasubstituted imidazoles catalyzed by zeolite HY and silica gel under microwave irradiation

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Four-component condensation of benzil, aromatic aldehydes, primary amines and ammonium acetate catalyzed by zeolite HY and silica gel without any solvent under microwave irradiation leads to tetrasubstituted imidazoles in high yields and purity.

Introduction

Compounds with imidazole ring systems have many pharmaceutical activities[1] and important roles in biochemical processes. It seems that the highly substituted imidazoles could have novel therapeutic activities.[2] There are many methods for the synthesis of highly substituted imidazoles: (*a*) condensation of diones, aldehydes, primary amines and ammonia;[3] (*b*) *N*-alkylation of trisubstituted imidazoles;[4] (*c*) condensation of benzoin or benzoin acetate with aldehydes, primary amines and ammonia in the presence of copper acetate;[5] (*d*) cyclization of sulfonamides with mesoionic 1,3-oxazolium-5-olates;[6] (*e*) four-component condensations of diones, aldehydes, primary amines, and ammonium acetate in HOAc under reflux conditions;[7] (*f*) condensation of β-carbonyl-*N*-acyl-*N*-alkylamines with ammonium acetate in refluxing HOAc;[8] and (*g*) conversion of *N*-(2-oxo)amides with ammonium triflouroacetate under neutral conditions.[9]

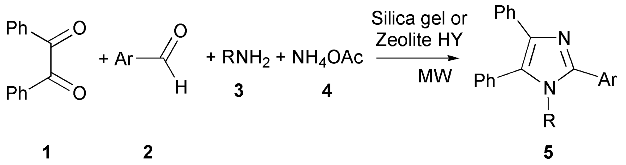
Syntheses of highly substituted imidazole rings are limited and generally cannot be carried out under neutral conditions.[10] In four-component condensation methods (*a*, *c* and *e*) imidazoles could be obtained with varying levels of purity. In addition, highly functionalized synthesis of polar imidazoles in solution require laborious work-up and purifications.[11] In recent years, Mjalli and co-workers reported the synthesis of tetrasubstituted imidazoles using Wang's resin in refluxing HOAc.[12]

Recently, combinations of the supported reagents and microwave irradiation were used to carry out a wide range of reactions in solvent-free conditions.[13] Following our previous work on the synthesis of triarylimidazoles,[14] here we report the four-component condensation of benzil, benzaldehyde derivatives, primary amines and ammonium acetate catalyzed by zeolite HY and silica gel under microwave irradiation as an efficient and facile one-pot synthesis of tetrasubstituted imidazoles (Scheme 1). The reaction conditions and yields are shown in Table 1.

Results and discussion

Silica gel and zeolites as catalysts have received considerable attention in recent years,[15] due to their characteristic properties, such as thermal stability and acidity character. Zeolite HY has a $pK_a = -8.2$.

In a classic approach, these cyclocondensations proceed with low yields after many hours in refluxing HOAc. Other methods also need special and complex reagents. In contrast, under solvent-free conditions, the reactions are completed within 6 min with high yields that are higher or comparable to classical methods. The previously reported products were characterized on the basis of their IR spectra, ^1H NMR spectroscopic data and the melting points.



Scheme 1

Table 1 Solvent-free synthesis of tetrasubstituted imidazoles **5a–q** under microwave irradiation[a]

			Yield(%)[b]	
Product **5**	Ar	R	Silica gel	Zeolite HY
a	Ph	Me	60	42
b	4-$CH_3C_6H_4$	Me	91	59
c	4-BrC_6H_4	Me	80	67
d	Ph	Et	74	56
e	4-$CH_3C_6H_4$	Et	70	77
f	4-BrC_6H_4	Et	62	82
g	Ph	*iso*-C_3H_7	81	71
h	Ph	CH_2=$CHCH_2$	85	57
i	4-BrC_6H_4	CH_2=$CHCH_2$	84	80
j	Ph	*iso*-C_4H_9	80	54
k	4-$CH_3C_6H_4$	*iso*-C_4H_9	85	54
l	Ph	C_6H_{11}	80	79
m	4-$CH_3C_6H_4$	C_6H_{11}	87	84
n	Ph	Ph	79	67
o	4-$CH_3C_6H_4$	Ph	74	83
p	Ph	$PhCH_2$	87	83
q	4-$CH_3C_6H_4$	$PhCH_2$	90	85

[a] All experiments were irradiated with microwaves for 6 minutes. [b] All isolated yields.

Green Context

Imidazoles are versatile intermediates in the manufacture of pharmacologically active products but current methods of synthesis can lead to relatively large amounts of waste. In this paper a number of green chemistry-related improvements to the synthesis of tetrasubstituted imidazoles are reported. The number of steps is reduced to one through a very efficient four-component condensation, solvents are avoided and reusable solid catalysts are employed. ***JHC***

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Four-component condensations of benzil, benzaldehyle derivatives, primary amines and ammonium acetate in the absence of silica gel or zeolite HY and the neat conditions under microwave irradiation furnished the products, but the products and reactants adhered to the reaction vessel walls, and the reactions were irreproducible. Cyclocondensation with benzil, benzaldehyde, methylamine and ammonium acetate in HOAc as the solvent in the absence of silica gel or zeolite HY under microwave irradiation, gave product **5a**. However, this method had a difficult work-up.

In the synthesis of tetrasubstituted imidazoles, yields with zeolite HY were lower than silica gel, because the acidic Brönsted sites were occupied with electron pairs of amine nitrogen atoms and the use of excess zeolite HY is necessary. This condensation took place on the surface of zeolite HY and not in channels. Acidic sites on the surface of zeolite HY can catalyze this condensation because the size of channels in zeolite HY is around 7 Å.

Conclusions

We have showed here an efficient and facile one-pot synthesis of tetrasubstituted imidazole derivatives with a simple set-up and work-up, high yields and short reaction times making the method environmentally friendly.

Experimental

All reported yields are isolated yields. All melting points are uncorrected and were measured on an Electrothermal 9100 melting point apparatus. IR spectra were run on a Shimadzu IR-408 spectrometer and expressed in cm^{-1} (KBr). ^{1}H NMR spectra were recorded on FT-NMR Bruker AC-80 (80 MHz) in $CDCl_3$ with TMS as internal reference. A domestic microwave oven (Moulinex 2735A) at 2450 MHz (100% power, 850 W) was used in all experiments.

General procedure for the synthesis of tetrasubstituted imidazoles

Benzil (421 mg, 2 mmol), aldehyde (2 mmol), ammonium acetate (309 mg, 2 mmol), primary amine (2 mmol) and 2 g silica gel or zeolite HY (prepared from zeolite NH_4Y in an oven at 600 °C for 5 h that afforded zeolite HY) were mixed and then transferred into a beaker (250 cm^3) and irradiated for 6 min. The progress of the reactions were monitored by TLC using CH_2Cl_2 as eluent. The mixture was extracted into CH_2Cl_2 (3×30 cm^3), then filtered and washed with H_2O. The organic phase was removed by a rotary evaporator. Further purification by column chromatography (CH_2Cl_2 as eluent) and recrystalization gave the desired products.

1-Methyl-2,4,5-triphenylimidazole (5a)

Mp 143–144 °C (n-hexane), lit.,[16] 143.5–144.5 °C; IR (KBr): *ν* 2950 (CH), 1600 (C=C), 1580 (C=N), 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 3.70 (s, 3 H, CH_3), 7.30–8.10 (m, 15 H, Ph).

1-Methyl-2-(4-methylphenyl)-4,5-diphenylimidazole (5b)

Mp 218–220 °C (n-hexane), lit.,[16] 209–217 °C; IR (KBr): *ν* 1600 (C=C), 1580 (C=N), 1500, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 2.60 (s, 3 H, CH_3), 3.65 (s, 3 H, CH_3), 7.30–7.85 (m, 14 H, Ar).

2-(4-Bromophenyl)-1-methyl-4,5-diphenylimidazole (5c)

Mp 199–200 °C, lit.,[1a] 199–202 °C; IR (KBr): *ν* 2950 (CH), 1600 (C=C), 1575 (C=N), 1500, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 3.45 (s, 3 H, CH_3), 7.00–7.70 (m, 14 H, Ar).

1-Ethyl-2,4,5-triphenylimidazole (5d)

Mp 115–117 °C (n-hexane), lit.,[16] 119.5–120 °C; IR (KBr): *ν* 2950 (CH), 1600 (C=C), 1575 (C=N), 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 1.00 (t, 3 H, *J* 7.1 Hz, CH_3), 4.00 (q, 2 H, *J* 7.1 Hz, CH_2), 7.10–7.90 (m, 15 H, Ph).

1-Ethyl-2-(4-methylphenyl)-4,5-diphenylimidazole (5e)

Mp 122–124 °C (EtOH/H_2O); IR (KBr): *ν* 2980 (CH), 1600 (C=C), 1585 (C=N), 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 0.90 (t, 3 H, *J* 7.1 Hz, CH_3), 2.35 (s, 3 H, CH_3), 3.85 (q, 2 H, *J* 7.1 Hz, CH_2), 7.05–7.85 (m, 14 H, Ar).

2-(4-Bromophenyl)-1-ethyl-4,5-diphenylimidazole (5f)

Mp 128–130 °C (*iso*-PrOH), lit.,[1a] 146–149 °C; IR (KBr): *ν* 2975 (CH), 1600 (C=C), 1575 (C=N), 1500, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 0.95 (t, 3 H, *J* 7.1 Hz, CH_3), 3.90 (q, 2 H, *J* 7.1 Hz, CH_2). 7.00–7.55 (m, 14 H, Ar).

1-Isopropyl-2,4,5-triphenylimidazole (5g)

Mp 181–183 °C (EtOH); IR (KBr): *ν* 2950 (CH), 1595 (C=C), 1575 (C=N), 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 1.40 (d, 6 H, *J* 7.0 Hz, 2CH_3), 4.65 (m, 1 H, CH), 7.10–8.10 (m, 15 H, Ph).

1-(3-Propenyl)-2,4,5-triphenylimidazole (5h)

Mp 104–106 °C (EtOH); IR (KBr): *ν* 2925 (CH), 1600 (C=C), 1575 (C=N), 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 4.40 (d, 2 H, *J* 4.4 Hz, CH_2), 4.80 (d, 1 H, *J* 17.7 Hz, =CH_2), 5.00 (d, 1 H, *J* 13.3 Hz, =CH_2), 5.35–5.90 (m, 1 H, =CH), 6.90–7.80 (m, 15 H, Ph).

2-(4-Bromophenyl)-1-(3-propenyl)-4,5-diphenylimidazole (5i)

Mp 111–112 °C (iso-PrOH), lit.,[1a] 111–114 °C; IR (KBr): *ν* 2850 (CH), 1600 (C=C), 1565 (C=N), 1500, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 4.40 (d, 2 H, *J* 4.4 Hz, CH_2), 4.75 (d, 1 H, *J* 17.7 Hz, =CH_2), 5.05 (d, 1 H, *J* 13.3 Hz, =CH_2), 5.40–5.90 (m, 1 H, =CH), 7.00–7.60 (m, 14 H, Ar).

1-Isobutyl-2,4,5-triphenylimidazole (5j)

Mp 134–135 °C (benzene/ligroin), lit.,[3] 133 °C; IR (KBr): *ν* 2950 (C–H), 1600 (C=C), 1580 (C=N), 1505 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 0.45 (d, 6 H, *J* 6.5 Hz, 2CH_3), 1.20–1.45 (m, 1 H, CH), 3.70 (d, 2 H, *J* 7.5 Hz, CH_2), 6.90–7.80 (m, 15 H, Ph).

1-(Isobutyl)-2-(4-methylphenyl)-4,5-diphenylimidazole (5k)

Mp 150–153 °C (EtOH); IR (KBr): *ν* 2950 (CH), 1600 (C=C), 1580 (C=N), 1500, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$): *δ* 0.30 (d, 6

H, J 6.6 Hz, $2CH_3$), 1.00–1.40 (m, 1 H, CH), 2.20 (s, 3 H, CH_3), 3.60 (d, 2 H, J 7.5 Hz, CH_2), 6.90–7.50 (m, 14 H, Ar).

1-Cyclohexyl-2,4,5-triphenylimidazole (5l)

Mp 167–169 °C (EtOH), lit.,[3] 171 °C; IR (KBr): ν 2850 (CH), 1595 (C=C), 1575 (C=N), 1500, 1480 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.60–1.90 (m, 10 H, CH_2), 3.70–4.05 (m, 1 H, CH), 6.90–7.70 (m, 15 H, Ph).

1-Cyclohexyl-2-(4-methylphenyl)-4,5-diphenylimidazole (5m)

Mp 162–164 °C (EtOH); IR (KBr): ν 2925 (CH), 1600 (C=C), 1575 (C=N), 1500, 1485 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.55–2.10 (m, 10 H, CH_2), 2.35 (s, 3 H, CH_3), 3.60–4.25 (m, 1 H, CH), 6.85–7.50 (m, 14 H, Ar).

1,2,4,5-Tetraphenylimidazole (5n)

Mp 216–218 °C (EtOH), lit.,[4] 221 °C; IR (KBr): ν 1600 (C=C), 1575 (C=N), 1495 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.80–7.60 (m, 20 H, Ph).

2-(4-Methylphenyl)-1,4,5-triphenylimidazole (5o)

Mp 185–188 °C (EtOH); IR (KBr): ν 2925 (CH), 1595 (C=C), 1575 (C=N), 1495 cm^{-1} ^1H NMR ($CDCl_3$): δ 2.15 (s, 3 H, CH_3), 6.80–7.60 (m, 19 H, Ar).

1-Benzyl-2,4,5-triphenylimidazole (5p)

Mp 158–160 °C (EtOH), lit.,[16] 163–164 °C; IR (KBr): ν 2985 (CH), 1600 (C=C), 1580 (C=N), 1500, 1480 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.00 (s, 2 H, CH_2), 6.60–7.65 (m, 20 H, Ph).

1-Benzyl-2-(4-methylphenyl)-4,5-diphenylimidazole (5q)

Mp 165–166 °C (EtOH), lit.,[3] 162 °C; IR (KBr): ν 2925 (CH), 1600 (C=C), 1575 (C=N), 1495, 1485 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.00 (s, 3 H, CH_3), 5.00 (s, 2 H, CH_2), 6.65–7.60 (m, 19 H, Ar).

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Clean oxidation of benzoins on zeolite A using microwave irradiation under solvent-free conditions

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Oxidation of benzoins are efficiently performed with zeolite A without any oxidizing agent under solvent-free conditions and microwave irradiation; the method is clean, fast, facile, efficient, low-cost and environmentally benign and operates selectively only on benzoins.

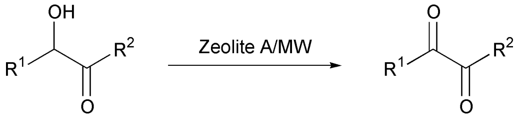
Introduction

Benzils have received a great deal of attention because of their practical applications, *i.e.* as photosensitive agents and synthetic agents in organic and pharmaceutical chemistry.[1] Oxidation of benzoin derivatives with an oxidizing agent is a common method for the preparation of benzils. There are many reagents for this oxidation such as nitric acid,[2] Fehling's solution,[2] thallium nitrate,[3] ytterbium(III) nitrate,[4] ammonium nitrate–copper acetate,[5] clayfen,[6] ammonium chlorochromate–alumina,[7] nickel acetate,[8] iron(III) chloride[9] and bismuth(III) nitrate–copper(II) acetate.[10] Long reaction periods, using toxic metallic compounds and corrosive acids are some disadvantages of these methods. Consequently, it is notable to develop an easy and environmentally benign method for this process.

Recently the combination of supported reagents and microwave irradiation are used to carry out a wide range of reactions in short times, high conversion and selectivity, without solvent.[11] For instance, copper sulfate on alumina[12] and oxone[13] are used as oxidants under microwave irradiation. Owing to environmental concerns, there is increasing need and interest in developing processes that minimize production of toxic waste. We introduce here zeolite A as a suitable catalyst for the oxidation of benzoins by microwave irradiation without using any oxidizing agent (Scheme 1).

Results and discussion

During our previous research work on microwave assisted cyclocondensation of organic compounds,[14] we decided to synthesize the oxazole skeleton through three-component condensation of benzoin, benzaldehyde (or benzoic acid) and water-free ammonium acetate in solvent-free conditions. However, only oxazole was obtained in low yield and the oxidized form of benzoin. Reaction of benzoin acetate with ammonium acetate or formamide gave the same result. In this situation benzoin acetate is oxidized to benzil. Therefore, we assumed it was not a suitable path to obtain oxazole. So we developed the reported method in order to oxidize symmetrical and unsymmetrical benzoin derivatives.



Scheme 1

Symmetrical and unsymmetrical benzoins were oxidized on zeolite A as an efficient catalyst under microwave irradiation with high yields (69–91%) in shorter times than classical methods (Table 1). We did use some other surfaces for this reaction instead of zeolite A such as montmorillonite, silica gel, bentonite and zeolite HX, but the yields were unacceptably low.

Zeolite catalysts with their supercages and channels of defined sizes, have received considerable attention in the last decade for organic transformations, *e.g.* in the synthesis of intermediates and the petrochemical industry. There is an increasing interest in the use of environmentally benign reagents and particularly in solvent-free conditions. Zeolite A has been used in many organic reactions.[15]

The solvent-free conditions were achieved by mixing benzoins thoroughly with zeolite A followed by irradiation in a

Table 1 Clean oxidation of benzoins using zeolite A[a]

				Mp/°C	
Entry	R^1	R^2	Yield(%)	Found	Lit.
a	Ph	C_6H_5	80	92–95	94–96[17]
b	p-ClC_6H_4	p-ClC_6H_4	72	195–198	195–197[8]
c	p-MeC_6H_4	p-MeC_6H_4	75	103–105	101–104[17]
d	p-$MeOC_6H_4$	p-$MeOC_6H_4$	91	133–135	132–134[17]
e	p-$MeOC_6H_4$	Ph	81	65–67	62–63[6]
f	2-furyl	2-furyl	69	164–166	162–164[7]

[a] Reaction time of all experiments was 6 minutes.

Green Context

Oxidations remain one of the great challenges for green chemistry. Industry still runs many oxidations with toxic metal reagents and even catalytic oxidations often present problems due to such factors as acidic solvents and use of promoters. In this paper a remarkably simple oxidation procedure is described using only substrate and catalyst. This is a good example of one of the essential principles of green chemistry—to minimise the components. The less you use the less there is to waste! *JHC*

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domestic microwave oven. Secondary benzylic alcohols, *e.g.* 1-phenyl-1-propanol, were also oxidized by this method but only in low yields. In the oxidation of furoin with ceric ammonium nitrate[16] and bismuth(III) nitrate,[10] a competitive cleavage reaction was reported. In contrast, in our method this wasn't observed. Silica gel and ammonium acetate–silica gel could also oxidize benzoin derivatives under microwave irradiation, but the yields were low. It is noteworthy to mention that in the absence of zeolite A or silica gel under microwave irradiation the yield of the reactions were also very low and the reactants and products adhered to the reaction vessel which reduced reaction yields and led to irreproducible results. Meanwhile the catalyst can be reused (zeolite after washing twice with methanol was activated again at 500 °C before reuse). The catalytic efficiency is essentially retained, however, the yields decrease significantly after using the zeolite three or four times. So the recyclability aspect of the materials can be hereby assumed. The optimized irradiation time was either determined by TLC or a gradual yield study by extracting the purified products after certain times. There seemed to be no obvious change in the product amount after 6 minutes for almost all reactants. The reaction product structures were characterized on the basis on IR, ^{1}H NMR and melting points.

This method has some advantages over others, such as good yields, shorter reaction times and can also be considered as an important early example of green chemistry. In this reaction, both the symmetrical and unsymmetrical benzoins are rapidly oxidized to the corresponding benzils in the absence of organic solvent or oxidizing agents and the yields obtained are comparable to those reported before.

Conclusions

The present solid-phase synthesis of benzils with zeolite A in solvent-free conditions under microwave irradiation is facile, clean and environmentally friendly; meanwhile this method has many advantages such as higher yields, shorter reaction times, easy set-up and easy work-up, reusable catalyst and elimination of organic solvent and oxidizing agent.

Experimental

Melting points were measured on an Electrothermal 9100 melting point apparatus and are uncorrected. IR spectra were recorded by a Shimadzu IR-408 spectrometer on KBr (cm^{-1}). ^{1}H-NMR spectra were determined in $CDCl_3$ in a FT-NMR Bruker AC-80 (80 MHz) and were reported in δ (ppm). We used a domestic microwave oven Moulinex 2735A at 2450 MHz (100% power, 850 W).

Benzoin (2 mmol) and zeolite A (2 g) were mixed thoroughly in a mortar and the mixture was transferred to a beaker and irradiated for 6 minutes. The progress of the reaction was monitored by TLC using CH_2Cl_2 as solvent. The mixture was extracted into methylene chloride and then filtered. The solvent was removed under reduced pressure to afford pure benzil (340 mg, 80%). Further purification was carried out by column chromatography (CH_2Cl_2 : light petroleum, 80 : 20, *v/v*) and crystallization in EtOH.

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Aspects of allylic alcohol oxidation—a bimetallic heterogeneous selective oxidation catalyst

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Here we report the use of a bimetallic Pt,Bi/graphite catalyst for the efficient aerobic selective oxidation of primary allylic alcohols. The influence of the allylic bond location, substrate conformation, and of reaction parameters in modifying aldehyde yield are discussed.

Introduction

The selective oxidation of hydrocarbons by heterogeneously catalysed routes presents major challenges for current chemical technologies.[1,2] Both the US Council for Chemical Research Vision 2020 report[3] and the European NICE group[4] have identified such green catalysis for fine chemical synthesis as the chemical industry's top priority.

The current use of stoichiometric inorganic oxidants such as potassium dichromate in multistep fine chemicals syntheses, though dying out, remains widespread.[5,6] Their associated waste production and often poor atom efficiency has been well documented, and catalytic oxidation routes are now demanded.[7] In response many homogeneously catalysed liquid phase oxidations, usually employing soluble metal salts, have been commercialised. These utilise a range of oxidants, predominantly hydrogen peroxide or peroxyacids. Such processes generally offer high product yields, but suffer the traditional disadvantages associated with separation/recycling, and batch *vs.* fixed-bed operation in comparison with their heterogeneous counterparts.

Attention has thus shifted towards the development of micro/mesoporous materials and supported reagents as catalysts for such oxidation chemistry.[8] Despite successes, current materials such as TS-1 and Ti-substituted MCM-41 also possess drawbacks. Diffusion-limitations inhibit efficient mass/heat transfer to and from reaction sites and thus selectivity control, while restrictive pore size distributions limit the range of both substrate and oxidant (*e.g.* H_2O_2 *vs.* bulky TBHP) amenable for in-pore catalysis. Many promising solid acids and supported homogeneous catalyst analogues also exhibit poor hydrothermal stability, requiring lengthy high temperature re-activation procedures, poor solvent tolerance, and are prone to leaching of toxic metals.

Alternative supported transition metal catalysts overcome many of these limitations, operating over wide temperature, pressure and solvent regimes. Platinum group metals (PGMs) readily activate dioxygen, and hence facilitate aerobic liquid phase oxidation in place of the expensive and hazardous oxidants used in current homogeneous processes.[9,10] Their major shortfall is a poor selectivity towards partial over total oxidation pathways. Bimetallic catalysts, incorporating a second metal component, can offer enhanced selectivity and reduced deactivation.[11] Recent studies have demonstrated the efficacy of Pt- and Pd-derived bimetallics for the aerobic partial oxidation of carbohydrates (*e.g.* glucose and L-sorbose), and of primary and secondary alcohols to the corresponding aldehydes, ketones and carboxylic acids. Electrocatalytic measurements have shed some insight into the nature of the active phase, and mechanisms of catalyst deactivation within aqueous systems.[12] For example, Bi is believed to disrupt Pt ensembles through surface decoration and/or alloying, thus hindering sterically demanding decomposition pathways[13] which lead to combustion. However very little is known about adsorbate–substrate interactions, and in particular of generic characteristics of either catalysts or substrates requisite for high product yields. For practical fine chemicals application, such catalysts must be effective with a broad range of substrates, often possessing functional groups themselves susceptible to oxidation.

This paper examines the oxidation of allylic alcohols over carbon supported PGM catalysts [eqn. (1)].

$$\mathrm{RCH{=}CHCH_2OH} \xrightarrow[\text{Pt or Pd}]{O_2} \mathrm{RHC{=}CHCHO} + \mathrm{H_2O} \qquad (1)$$

Cinnamyl alcohol and its derivatives find widespread use in the the fragrance, pharmaceutical and agrochemicals industries. Cinnamaldehyde is currently synthesised *via* benzaldehyde condensation using activated methylenes. Here we identify some of the key molecular features influencing oxidation over a versatile Pt,Bi/graphite catalyst.

Experimental

A range of standard commercial PGM catalysts (Pd, Pt and Pt/Bi) supported on activated carbon and graphite supplied by Johnson Matthey were used in these experiments. Following impregnation catalysts were reduced, washed, filtered and dried. Catalyst loadings are given in wt%. No futher activation treatments were required prior to reaction. Simultaneous screens were performed in a CAMLAB Microtherm 56 sample incubator/shaker. Sample vials containing 1.5 ml of 5 mmol cinnamyl alcohol (Aldrich 99%) in ethanol and 10 mg of

Green Context

The selective catalytic oxidation of simple organic molecules remains one of the major challenges for green chemistry. In particular, the use of oxygen as primary oxidant will allow the development of cheap and sustainable processes. This contribution describes the use of a bimetallic Pt,Bi catalyst supported on graphite as an efficient catalyst for allylic oxidations. Good conversions and selectivity were obtained.
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catalyst were heated to 40 or 60 °C while shaken, open to the atmosphere, at 720 rpm for 15 h. Control vials with only catalyst + solvent or solvent + substrate were also included.

All other experiments were performed in a glass Buchi batch reactor under air (E & G 99.9%). A 100 mg catalyst charge was placed in the reactor with 5 mmol substrate (cinnamyl alcohol, 3-phenyl-1-propan-1-ol, *trans*-hex-2-en-1-ol, hex-5-en-1-ol, crotyl alcohol or butan-1-ol, Aldrich >98%) in 60 ml solvent, and samples heated and stirred at 1000 rpm for 15 h. A constant air pressure was maintained inside the reactor, with oxygen uptake followed *in situ* by a pressure transducer attached to an external reservoir. An inert internal standard, tetradecane (Aldrich 99%), was included in all experiments to compensate for solvent losses during depressurisation. Product % yields were calculated from yield = conversion × selectivity, and regularly checked against the absolute aldehyde yield to ensure closure of the carbon mass balance (better than 5% in all cases).

Analysis was performed using a Perkin-Elmer 8500 GC and a 30 m × 0.25 mm HP5 capillary column and a Finnegan GC-MS fitted with a 30 m × 0.25 mm CP-Sil5 column. Quoted conversions and selectivities are ±3%. Surface areas were determined by N_2 adsorption and H_2 chemisorption.

Results and discussion

A range of mono- and bi-metallic PGM catalysts were simultaneously screened for the aerobic selective oxidation of cinnamyl alcohol to cinnamaldehyde at 40 °C. Their performance is shown in Fig. 1(*a*). A selection of promising catalysts from the first screen were subsequently re-tested at 60 °C, Fig. 1(*b*). In all cases the only products were cinnamaldehyde and cinnamic acid.

Both carbon and graphite supports exhibited very low activity, and additional runs under controlled atmosphere batch conditions confirm the supports are essentially inert. Monometallic and bimetallic catalysts show a similar poor performance at 40 °C with the best conversion only approaching 20% over a 5 wt% Pt, 3 wt% Bi/graphite, although selectivity to cinnamaldehyde was high in all cases. Increasing the reaction temperature increased conversion over the monometallic Pd samples and the bimetallic Pt,Bi/graphite catalyst as commonly observed for oxidation chemistry. However unlike corresponding gas phase selective oxidation catalysis, wherein high temperatures favour side products and combustion, aldehyde selectivity remained high resulting in good yields up to 52% (the carbon mass balance was >95%). Combustion only became significant above 80 °C at which temperature around 20% of cinnamyl alcohol formed gaseous products. The strong temperature dependence presumably reflects α-C–H bond activation, which is the likely rate-determining step.[10] Catalyst performance is also not a simple function of either total surface area (graphite *ca.* 10 $m^2\,g^{-1}$ *vs.* carbon *ca.* 650 $m^2\,g^{-1}$) or metal dispersion (graphite *ca.* 0.04 *vs.* carbon *ca.* 0.96). The striking difference between the Pt,Bi/graphite and Pt,Bi/carbon catalysts may reflect a combination of particle morphology, support acidity and/or platinum oxidation state. Highly dispersed Pt particles are generally more susceptible to over oxidation,[14] widely cited as the cause of reversible catalyst deactivation.[10]

The preliminary screens identified Pt,Bi/graphite as a promising candidate for cinnamyl alcohol oxidation. In order to explore the generic properties of this catalyst, the oxidation of a range of alcohol substrates was studied under reaction conditions of 4 bar, 60 °C in the Buchi batch reactor: crotyl alcohol (*trans*-but-2-en-1-ol) was chosen to determine the importance of the phenyl ring; 3-phenylpropanol and butan-1-ol were examined to ascertain the importance of the alkene moiety; *trans*-hex-2-en-1-ol and hex-5-en-1-ol were selected to assess the influence of the double bond position within the chain. The (unoptimised) results are shown in Table 1.

Good yields of the respective aldehydes were obtained for all the allylic alcohols, although hexenol oxidation is clearly influenced by the allyl function position. This finding is extremely encouraging in our goal of identifying catalysts applicable for the oxidation of a broad range of allylic alcohols, independent of substrate size or structure. In contrast the same Pt,Bi/graphite catalyst gave extemely poor conversion, albeit selectively, to the corresponding non-olefinic alcohols, indicating the C=C double bond is important in controlling oxidation. The significantly lower conversions of 3-phenylpropanol (butan-1-ol) compared with cinnamyl (crotyl) alcohol suggests the C = C bond may help anchor the hydroxy group close to the catalyst surface facilitating oxidative dehydrogenation to the aldehyde.[10] In this respect the presence of a distant aryl group, though itself expected to strongly chemisorb on bare platinum,

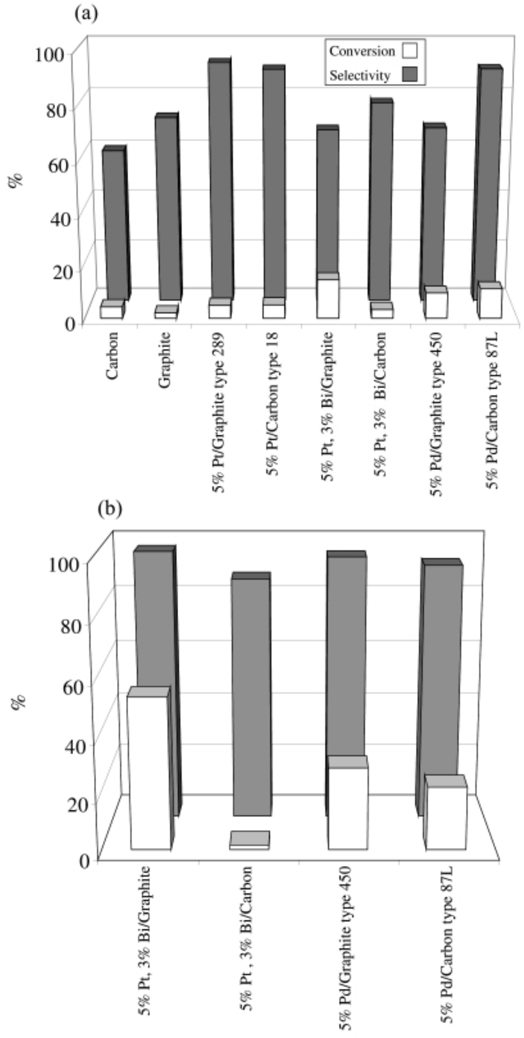

Fig. 1 Cinnamyl alcohol oxidation over PGM catalysts at (*a*) 40 °C and (*b*) 60 °C.

Table 1 Aerobic selective oxidation of alcohols over a 5% Pt, 3% Bi/graphite catalyst.

Alcohol	Conversion(%)	Yield(%)
cinnamyl alcohol	54	51
crotyl alcohol	42	42
3-phenylpropan-1-ol	3	3
butan-1-ol	10	0
trans-hex-2-en-1-ol	61	57
hex-5-en-1-ol	14	14

does not bring the alcohol into close proximity with the surface. The comparison of hex-5-en-1-ol with *trans*-hex-2-en-1-ol supports that increasing the separation of anchoring group and OH function results in a poor conversion. Conjugation between the olefin and carbonyl functions may also be important in stabilising the aldehyde product, thus reducing competitive hydrogenation back to the alcohol and further oxidation to the acid.[10]

To better understand the respective roles of substrate and oxidant the effect of air pressure on several substrates was also examined. Conversion and selectivity remain essentially independent of applied pressure between 1.3 and 7.5 bar, Fig. 2. Coincident *in situ* oxygen uptake data (not shown here) support that aldehyde formation is zero-order in dioxygen under these mild conditions, consistent with an oxidative dehydrogenation mechanism.[10,15] Indeed the only influence of oxygen was on the extent of cinnamyl alcohol hydrogenation/disproportionation to 3-phenylpropanol. This minor pathway ($<3\%$ selectivity) was only observed at atmospheric pressure, presumably reflecting the lower surface oxygen concentration, and thus the accumulation of adsorbed hydrogen.[10] A similar side reaction has been observed over palladium/soot catalysts[16] and was likewise a function of oxygen concentration. The main role of gas-phase oxygen in aldehyde formation probably lies in the clean-off of carbonaceous residues which are believed to cause irreversible catalyst deactivation.[9,10, 17]

The influence of substrate concentration on the oxidation rate was also assessed. Rate data were obtained from experiments in which the reaction mixture was periodically sampled by withdrawing small (0.1 ml) aliquots. Under all reaction conditions a short (*ca.* 5 min) induction period was observed, followed by a linear region during which the rate remains constant, followed by a much slower deactivation period, Fig. 3. Initial reaction rates determined by GC are independent of substrate concentration between 2 and 100 mmoles for both cinnamyl and crotyl alcohols at $0.0018 \pm 5 \times 10^{-4}$ and $0.0128 \pm 5 \times 10^{-4}$ mmol min^{-1} respectively. This observation is again consistent with zero-order kinetics. Turnover numbers based on the available metal sites (titrated by H_2) are very high, ranging between 60 (cinnamyl)–600 (crotyl) h^{-1}, and easily outperform the vast majority of alternative homogeneous and heterogenous catalyst systems.[2] The faster oxidation of crotyl alcohol over its aromatic cinnamyl counterpart may reflect the ability of smaller substrates to access additional Pt sites within the graphite interstices, and not an intrinsic rate difference. It thus remains unclear whether the aromatic moeity plays any direct role in facilitating/hindering the surface reaction.

Although catalyst deactivation is comparatively rapid, activity tailing off within *ca.* 4 h of reaction, recycling experiments revealed that Pt,Bi/graphite was almost completely reactivated following simple air exposure and ambient drying. Fig. 4 shows the results of a series of such recyles in which 500 mg of catalyst was operated for 20 h, and then repeatedly filtered and dried under ambient conditions prior to re-use. Cinnamyl alcohol conversion remains high, despite recent *in situ* XAFS evidence for irreversible Pt particle sintering during reaction.[18] Selectivity also remains high, though cinnamic acid production increases slightly with recycling, possibly reflecting the larger ensembles now available for simultaneous cinnamaldehyde binding and oxygen insertion. Ongoing mechanistic studies suggest the catalyst surface oxidation state plays a crucial role. *Ex situ* air exposure may serve to generate a surface oxide layer, which is more active towards C–H scission than metallic Pt. However we can discount over-oxidation leading to bulk platinum oxide formation, previously posulated as the origin of deactivation. The kinetic data in Fig. 2 suggest that reoxidation of the catalyst surface *via* dissolved oxygen does not occur on the timescale of our experiments. This presumably reflects poor oxygen transport from the gas to liquid and liquid to solid phases.

Cinnamyl alcohol oxidation was also examined as a function of stirrer speed and catalyst mass to confirm that reaction was not mass-transport limited. Neither the initial oxidation rate (Fig. 5) nor the selectivity towards cinnamaldehyde changed over the mixing range of 100–1000 rpm. In contrast, varying the catalyst charge from 20 to 200 mg increased the reaction rate *ca.* 10-fold, as anticipated (Fig. 6), without altering selectivity. The reactions catalysed by our Pt,Bi/graphite catalyst are thus consistent with the rate law below [eqn. (2)], analogous to that

$$-\frac{d[\text{Alcohol}]}{dt} = k_{\text{Pt,Bi/graphite}}\,\omega^0\,Pt_s^1\,[\text{Alcohol}]^0\,[P_{O_2}]^0 \qquad (2)$$

describing propan-2-ol oxidation over Pt/C, where ω represents the stirring speed, Pt_s the number of surface Pt sites, and P_{O2} the oxygen partial pressure maintained during reaction.

In conclusion allylic alcohol oxidation thus appears to be a surface reaction rate limited process over Pt,Bi/graphite[15] in which the catalyst surface is saturated with adsorbed substrate over the concentration range examined. Oxidation is a strong

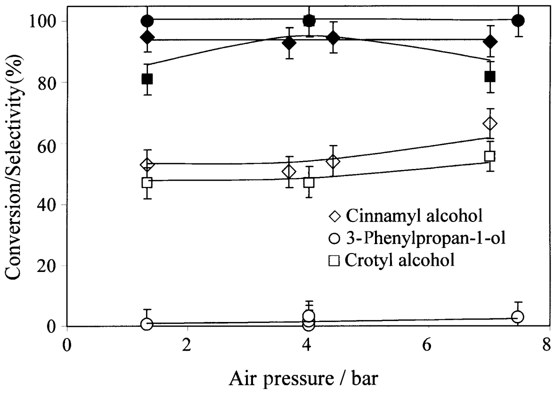

Fig. 2 Effect of air pressure on alcohol conversion (◇○□) and selectivity (◆●■) over a 5% Pt, 3% Bi/graphite catalyst at 60 °C.

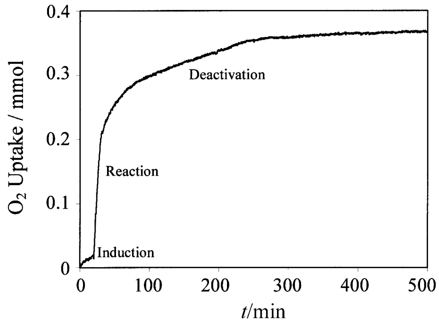

Fig. 3 *In situ* oxygen uptake during cinnamyl alcohol oxidation over a 5% Pt, 3% Bi/graphite catalyst at 60 °C and 4 bar.

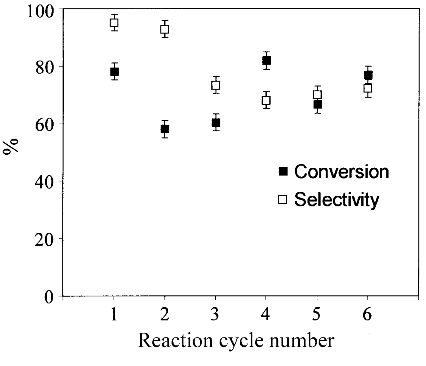

Fig. 4 Recycle experiments using a 5% Pt, 3% Bi/graphite catalyst (500 mg) operated at 60 °C and 4 bar. Catalyst was dried in air prior to repeated reaction with 5 mmol cinnamyl alcohol.

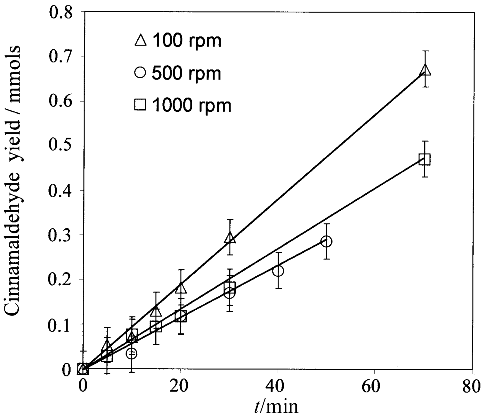

Fig. 5 Effect of stirrer speed on the rate of cinnamyl alcohol oxidation over a 5% Pt, 3% Bi/graphite catalyst at 60 °C and 4 bar.

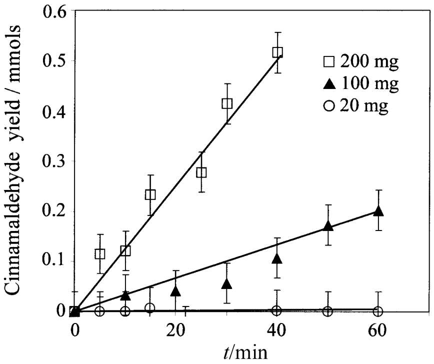

Fig. 6 Effect of catalyst charge on the rate of cinnamyl alcohol oxidation over a 5% Pt, 3% Bi/graphite catalyst at 60 °C and 4 bar.

function of reaction temperature but is insensitive to other experimental conditions and high aldehyde yields (between 42–57%) have been obtained. *Ex situ* air-exposure helps regenerating catalyst activity. The allylic bond is important in promoting oxidation, possibly by anchoring the α-C–H bond close to the surface thus assisting dehydrogenation.

Acknowledgements

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The preparation and use of novel immobilised guanidine catalysts in base-catalysed epoxidation and condensation reactions

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Novel guanidine bases supported on silicas and Micelle Templated Silicas (MTS) have been prepared, and investigated in the base catalysed epoxidation of electron deficient alkenes with excellent conversions and selectivities both with respect to the alkene and the primary oxidant. They are also efficient catalysts for the condensation of malonic acid with heptanal.

The development of silica supported catalysts has recently received a substantial amount of attention, partly because of the increasing importance of such heterogeneous catalysts in the drive towards green chemistry,[1] but also because of the great strides made in the synthesis of MTS and their applications in catalysis.[2,3] Not only does this latter concept provide a wide range of silica supports with very well defined pore sizes and high surface areas, but the possibility of a one-pot, atom efficient process for the preparation of organically modified MTS materials has also led to several novel catalysts, including base catalysts.[4,5] Applications of these base catalysts include the Knoevenagel reaction,[5–8] Michael addition,[9] aldol reaction[10] and selective ring opening of epoxides to form monoglycerides.[11,12,13] Two papers discuss the use of a supported guanidine (1,5,9-triazabicyclononane)—one paper describes its use in the formation of monoglycerides,[13] the other discusses the use of supported guanidines in the base-catalysed epoxidation of α,β-unsaturated ketones, a reaction which is of importance in the synthesis of natural products,[7] While selectivities in this latter reaction were high with respect to the organic reactant, the reported conversions were relatively low and the selectivity towards hydrogen peroxide was also relatively low (*ca.* 20%). Nonetheless, this represents a useful extension to the homogeneous methodology, especially in terms of the isolation of the very reactive products. A further paper describes the encapsulation of a guanidine inside a zeolite Y structure, using 'ship-in-a-bottle' methodology,[14] and its application to the aldol condensation.

We now report on a series of catalysts based on the attachment of 1,1,3,3-tetramethylguanidine to different silicas, their activity in the base catalysed epoxidation of alkenones, and the influence of the nature of the catalyst on the conversion and selectivity to both alkene and oxidant. Optimum catalysts give excellent degrees of conversion, as well as high selectivity towards both the alkene and the oxidant. These basic catalysts were also used in the condensation of malonic acid and heptanal, in order to obtain 3-nonenoic acid, which is a precursor of γ-nonanoic lactone, a flavour component of coconut.

Results and discussion

Preparation of catalysts

Three strategies were evaluated for the preparation of catalysts. These were the stepwise grafting of guanidine units onto chloropropyl-substituted silicas (Method 1, Scheme 1); the preparation of a silyl-substituted guanidine derivative followed by subsequent grafting onto the silica surface (Method 2, Scheme 2); and the one-step templated sol–gel preparation of guanidine-MTS materials and chloropropyl-MTS materials which were subsequently functionalised as in Method 1 (Method 3, Scheme 3).

Two silicas were used as supports for the grafting reaction—a chromatographic silica (Merck Kieselgel 60) and a MTS prepared by a previously published method.[3] These methods led to catalysts whose properties are detailed in Table 1. Some of the catalysts have exposed silica surface, while others have had the silica surface covered with trimethylsilyl groups to remove

Green Context

Bases are widely used in chemical synthesis but the traditional use of soluble bases such as metal hydroxides and alkoxides generally leads to the production of salt waste through a neutralisation step in the work-up. Consequently there is considerable interest in the use of solid bases that remain physically separate from the organic phase and can be easily recovered and reused. Guanidines are versatile strong bases and are also candidates for immobilisation. Previous work has demonstrated that supported guanidines can be prepared but their successful application in organic synthesis has been limited. Here we see the generation of novel forms of supported guanidines that have very promising activity in important epoxidation and condensation reactions. *JHC*

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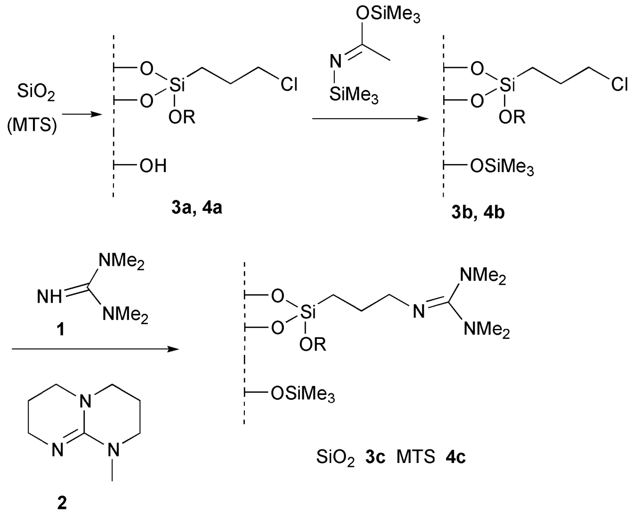
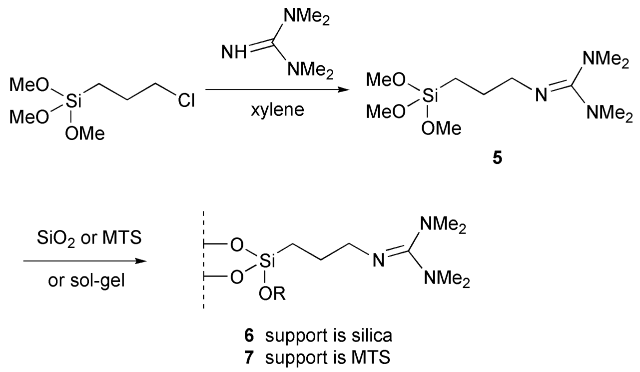
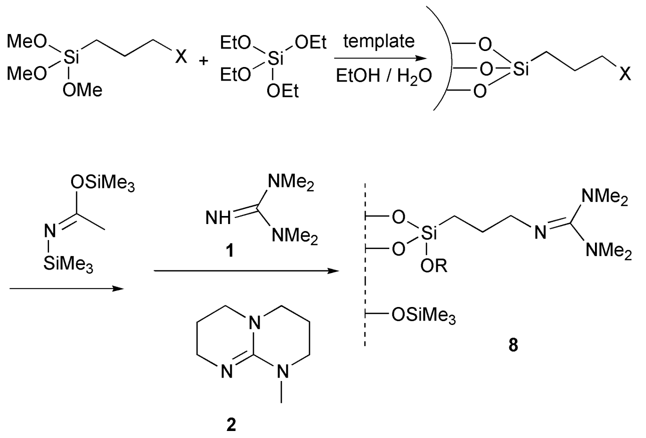


Scheme 1 Preparation of catalysts by stepwise functionalisation of chloropropyl silicas.



Scheme 2 The preparation and grafting of guanidine-silane **5**.



Scheme 3 Templated sol–gel synthesis of guanidine-MTS **8**.

Table 1 Physical characteristics of the catalysts

Material	SSA/m^2 g^{-1}	Pore diameter/nm	Loading in TMG unit/mmol g^{-1}
Kieselgel 60	424	6 (broad)	—
6	244	10 (broad)	1.1
MTS	972	3.0	—
7	221	1.9	1.7
4a	912	2.8	—
4b	741	2.4	—
4c	807	2.5	0.4
8	1281	2.4	1.4

a significant proportion of the surface silanol groups and to make the surface more hydrophobic.

The first route involved the chloropropylation of the preformed supports, Kieselgel 60 and a standard MTS. For the MTS route two different grafting methods were used. The first involved the standard grafting procedure of reflux in toluene with removal of the methanol liberated. Subsequent trimethylsilylation of the surfaces was achieved with *N*,*O*-bis(trimethylsilyl)acetamide, a powerful silylating agent.[15] Finally, the materials were treated with 1,1,3,3-tetramethylguanidine (TMG **1**) and 1-methyl-1,5,9-triazabicyclo[4,4,0]decane **2** (a stronger base) to give the final catalysts **3c** and **4c**. Physical characteristics of the catalysts are given in Table 1. It is clear from the results that the reductions in surface area and pore size are consistent with in-pore functionalisation in both the grafting reaction and the subsequent transformations. It should be noted that the interpretation of the isotherms is complicated by the possibility that some of the materials may give anomalous results, as has occasionally been noted for these materials. Thus the extremely high surface area for the 9:1 chloropropyl material may be due to enhanced adsorption in the mesopores which would give such unusually high surface areas.

As an alternative to this three-step route, a direct coupling of a TMG-substituted silane was carried out. The required silane **5** is described in the patent literature[16] and was easily prepared and purified. Subsequent grafting onto both Kieselgel 100 and MTS gave guanidine substituted silicas **6** and **7** respectively). In contrast to the other catalysts prepared, these materials have exposed silica surfaces (Scheme 2).

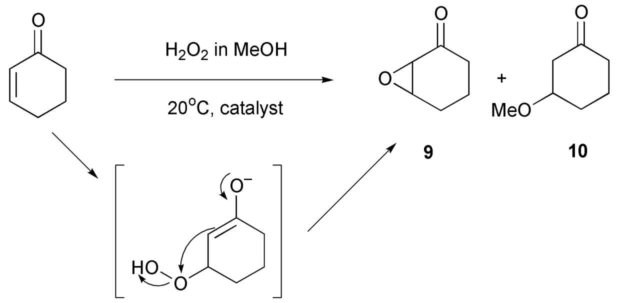
A third approach[17] involved the direct sol–gel synthesis of MTS materials containing chloropropyl and TMG-silane units (Scheme 3). Only one structured material was produced, that from the chloropropylsilane at a ratio of chloropropylsilane:tetraethoxysilane (TEOS) of 1:9. This was converted to a guanidine-containing material **8** by the method described above. Higher chloropropylsilane contents (1:4 and above) resulted in amorphous materials, as did all materials prepared with the TMG-silane. The latter can be explained by the high pK_a of the TMG unit, which causes the silane to exist as the protonated conjugate acid in aqueous environments, and the known reluctance of charged silanes to take part in the co-operative assembly process.[18]

Application of catalysts

The catalysts were then evaluated in the reaction between cyclohexenone and hydrogen peroxide in methanol at 20 °C.

The alkene and catalyst were added to methanol and stirred magnetically while 30% hydrogen peroxide was added dropwise over the period of the reaction. The amount added depends on the selectivity towards hydrogen peroxide (see experimental for details). Reactions were monitored by GC with external standard calibrated to both reagent and product. The results are summarised in Table 2.

As can be seen from Table 2, the best catalysts display excellent conversions and selectivities towards product **9**, with



Scheme 4 Base catalysed epoxidation of enones.

excellent selectivity towards the enone being achieved in the best cases—previous supported guanidines have only achieved 42% conversions, whereas our materials can reach 89%. Similar results were obtained with cyclopentenone. Chalcone failed to react, and could be recovered unchanged. The reasons for this are unclear—the homogeneous 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)/Bu^{t}OOH (a more powerful combination) successfully carries out this transformation.[19] Steric reasons may play a part, as the larger substrate may diffuse more slowly, but catalysts of the pore dimensions of these materials have been used to successfully catalyse the reactions of larger molecules, for example see later. Very importantly in the case of the cycloalkenones, the selectivity towards H_2O_2 is excellent, with the surface-coated catalysts (up to 56% as compared to 21% with other systems).[7] This latter point is very important, even with a relatively non-polluting and cheap reagent, as low utilisation of hydrogen peroxide leads to very high dilutions and poor vessel occupancy. It is thought that decomposition of the hydrogen peroxide takes place on the exposed silica surface of the materials, and that the passivation of this surface reduces this decomposition significantly. Non-passivated surfaces give selectivites towards hydrogen peroxide of 4–10%, leading to extreme dilution, and problems with separation. The addition of MTS to a run using catalyst **8** led to a reduction in H_2O_2 selectivity to 16%, indicating that exposed silica can cause decomposition of hydrogen peroxide in this system. This phenomenon has also been observed in the case of Ti-containing Micelle Templated Silicas (large pore analogues of the Ti–Si zeolite, TS-1)[20,21] where selectivities towards H_2O_2 could be improved dramatically (in one case from 43 to 100%) in a range of reactions, by silylation of the surface.

While the reasons for the changes in selectivity towards the organic reactants are not clear, one possible contribution to the enhancements may be the lower polarity of the surface, allowing more rapid desorption of product, and lower water content in the reaction. Both of these will reduce the level of epoxide ring-opening. The shorter reaction times should also help, as the relatively fragile product is exposed to a hostile environment for a shorter time, even when desorbed from the catalyst.

Small amounts of the methoxy addition product **10** are seen in all reactions. This is present at low levels (2–4%) throughout the reaction, remains constant after the first few minutes, and is the only product seen (at similar levels) in the blank reaction implying that the reaction is both non-catalytic and reversible. Replacing the methanol with isopropanol suppresses this side reaction almost completely, but results in a lower reaction rate and poorer conversion. Reaction stops upon removal of catalyst from a partially completed reaction, indicating that the catalyst remains heterogeneous throughout the reaction. Apart from the methanol addition product, there are many other products, all present in very small quantities, which are visible by GC. These could not be identified unambiguously, but none were formed in $>1\%$. There was no evidence of Baeyer–Villiger lactonisation. Other products expected include diol, and oligomerisation products from the alkenone, neither of which would be visible by our GC method. NMR of the product mixture indicates the presence of many minor components, and IR analysis of recovered catalyst indicates the presence of extra organics on the surface, which may well be strongly adsorbed diols or oligomeric species. Comparative data taken for selected runs at similar levels of conversion indicate that, broadly speaking, selectivities do not change significantly with time. The rate of addition of hydrogen peroxide has been studied for each catalyst, and reflects a balance between non-productive decomposition, epoxidation and subsequent product decomposition. Thus the apparent rates of reaction are complicated by the necessity of controlling the addition rate of hydrogen peroxide, and thus it is difficult to assign any meaningful levels of catalytic activity to each catalyst. Therefore a full analysis of the kinetics of each reaction would be very difficult in this reaction system. It is unlikely that diffusion limitations play a significant role in this reaction, since the catalysts are capable of good reactivity with much larger substrates (see below).

Table 2 Epoxidation results

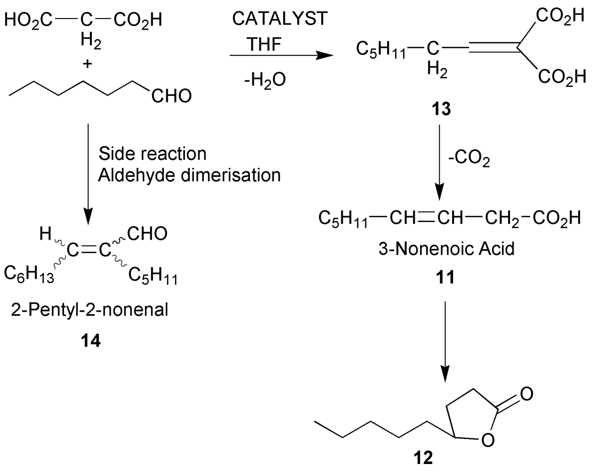
Catalyst	t/h	Conversion of cyclohexenone (%)	Selectivity(%) Enone	Selectivity(%) H_2O_2
Cyclohexenone				
6	4	55	42	4
8	12	85	65	7
7	18(3)	82(22)	85(76)	10(10)
4c	2(1)	40(24)	89(84)	46(50)
8	2	65	89	56
8[a]	2	34	93	52
8[b]	8(2)	51(20)	78(81)	6(19)
Silica	8	3	—	—[c]
Cyclopentenone				
4c	2	43	85	48
8	2	60	87	54
Chalcone				
4c	18	0	—	—
8	18	0	—	—

Numbers in parenthesis indicate data at similar levels of conversion. [a] Using isopropanol as solvent. [b] Run with 0.2 g silica added. [c] Hydrogen peroxide decomposed during this run, but no product was observed except for the formation of 3% of the product derived from the Michael addition of methanol.

Reuse of recovered catalyst indicates a significantly poorer performance, possibly due to adsorption of small quantities of byproducts such as diols at the active site. The exact reasons for this reduced behaviour are the subject of current investigations, but IR data indicates that there are still guanidine units at the surface (C = Nstr. at 1623 cm^{-1}) along with unidentified organic impurities.

The second reaction investigated is the condensation of malonic acid with heptanal to give 3-nonenoic acid **11**, an important step in the production of γ-nonanoic lactone **12**, an important component of coconut oil (Scheme 5).

The reaction involves the condensation and dehydration/decarboxylation of the intermediate adduct to give the β,γ-unsaturated carboxylic acid, which then undergoes acid-catalysed ring closure to the lactone. The first step is typically carried out using triethylamine or triethanolamine as solvent/base at elevated temperatures. This procedure, the so-called



Scheme 5 The course of the Knoevenagel condensation of heptanal with malonic acid.

Linstead variation of the Knoevenagel condensation, leads to the β,γ-unsaturated product, as opposed to the more typical α,β-unsaturated product. This route is the only direct, clean route available for the synthesis of this group of compounds.[22,23] Recent advances in this area of chemistry have included work by Ragoussis[24] who prepared these materials using piperidinium acetate as catalyst (rather than bulk solvent/catalyst) in refluxing xylene. Good yields could be achieved (75% in the case discussed here) but at the expense of requiring 3 equiv. of malonic acid. The high temperatures used in this work cause the decomposition of this reagent, leading to significant waste. Kumar *et al.*[25] have used microwave irradiation to produce high yields of product (84%) in short times on silica, but large quantities of silica were necessary to achieve this (*ca.* 2.5 g per gram of product).

With our materials (*e.g.* catalysts **4c** and **7**), we found that the reaction proceeds very smoothly in THF at reflux with a 1 : 1 ratio of reactants. According to the catalyst, we found different results (Table 3).

One can observe that the design of the catalyst influences mainly the conversion of heptanal. The great differences in terms of loading, pore size and specific surface area between the two catalysts (see Table 4) can explain the specific behaviour of each catalyst. Thus, the better activity with catalyst **4c** could be due to better accessibility of the catalytic sites in the larger pores (2.4 nm) of **4c** compared with the narrower pores (1.9 nm) of catalyst **7**. The turnover numbers for the two catalysts at different times during the reaction are given in Table 4.

The selectivities to 3-nonenoic acid are quite moderate in both cases. The side reaction involving the aldehyde *via* an aldol condensation to form 2-pentyl-2-nonenal **14** is not a consistent explanation of the moderate selectivities because the dimer of the aldehyde is formed only in small amounts. Actually, the crude reaction mixture contains the precursor of 3-nonenoic acid : 2-decene-2-dioic acid **13**, which is not detectable by our GC method using FID, but which has been identified after isolation. Thus, we explain our results by the reaction conditions which are too mild to allow complete decarboxylation of the precursor of the 3-nonenoic acid to the final product.

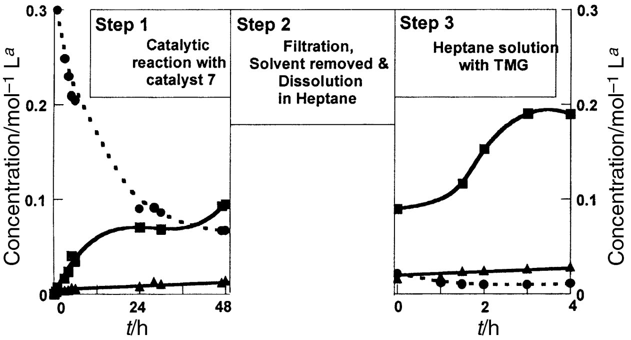


Fig. 1 Catalytic condensation between malonic acid and heptanal with catalyst **7** and decarboxylation improvement by post-treatment with TMG. ●: Heptanal ■: 3-nonenoic Acid ▲: 2-pentyl-2-Nonenal. ^{a} Determined by GC using dodecane as standard. No dicarboxylic acids are detected by GC equipment with FID.

Table 3 Catalytic Knoevenagel condensation experimental data

Catalyst	*t*/h	Conversion of heptanal(%)	Selectivity(%)	
			3-Nonenoic acid	2-Pentyl-2-nonenal
4c	0.3^a	20^a	11^a	5^a
	1	40	21	10
	6	68	39	13
	13.1^a	78^a	47^a	15^a
	24	86	50	13
	48	95	58	14
7	1	3	11	1
	3.3^a	20^a	29^a	1^a
	6	34	34	3
	7.1^a	40^a	35^a	3^a
	19.2^a	68^a	38^a	4^a
	24	70	33	3
	48	78	40	5

^{a} Intrapolated data.

Table 4 TON of each catalyst in the catalytic Knoevenagel condensation

t/h	TON	
	Catalyst **4c**	Catalyst **7**
1	66	1
6	113	13
24	143	27
48	158	31

Indeed, post-treatment of the crude mixture resulting from catalytic condensation with catalyst **7** with a small amount of 1,1,3,3-tetramethylguanidine in order to make easier decarboxylation results in an increase of the amount of 3-nonenoic acid, the quantity of heptanal still remaining the same (Fig. 1).

These results are in agreement with an incomplete decarboxylation of the diacid and with Corey's assumption concerning the mechanism of α,β- and β,γ-unsaturated malonic acid derivatives.[26]

In comparison with literature results, these results are promising. However, reuse of recovered catalysts indicates a significantly decrease of their activities. Current investigations are in progress in order to increase stabilities of our materials.

In conclusion, we have demonstrated that highly efficient basic catalysts can be prepared by attaching guanidine units to the surface of various silicas. The resultant materials are excellent catalysts for the epoxidation of electron deficient alkenes, and show significant promise in the condensation of malonic acid with aldehydes.

Experimental

All solvents used were analytical grade, and were not purified further unless specified. Reagents were purchased from Aldrich, and were used as received. The silica utilised was Kieselgel 60, an amorphous silica with a broad pore size distribution centred around 6 nm. The MTS used was prepared following a published route,[3] and was calcined to remove template shortly before use. The chloropropyl-MTS was prepared by the one-step co-condensation route described previously.[4,17] Porosity and surface area measurements were carried out using dinitrogen on a Micromeritics ASAP2100 instrument. ^{13}C MAS-NMR measurements of the modified solids were carried out on a Bruker Model AM 300 spectrometer operating at 75.470 MHz with Fourier transform. The instrument setting were the following: 90° pulse of 4.80 ms; proton decoupling power: 30 G; contact time: 5×10^{-3} s; delay time: 5 s; rotor spinning speed: 5 KHz. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 MHz spectrometer in $CDCl_3$.

Grafting of chloropropyl trimethoxysilane onto supports

This protocol was followed for both silica-supported materials and for MTS-supported materials. The example given is for a MTS material.

The support (2.31 g) was pre-activated by heating to 150 °C under vacuum (1 Torr) in the reaction vessel for 18 h. After cooling and release of the vacuum, dry toluene (50 ml) was added and chloropropyl trimethoxysilane (1.79 g, 9 mmol) was added and the system refluxed for 3 h with continuous distillation of methanol. After cooling and filtration, the resultant solid was washed with toluene (3 × 20 ml) and diethyl ether (2 × 20 ml) and then extracted by Soxhlet apparatus using a 1 : 1 by volume mixture of dichloromethane and diethyl ether.

Trimethylsilylation of the chloropropyl functionalised materials

This protocol was followed for the conversion of all the chloropropyl-functional materials. It is exemplified by using the material described above.

The material from the above reaction (2.00 g) was suspended in dry toluene (75 ml) and heated to reflux. *N*,*O*-Bis-trimethylsilyl acetamide (5.6 ml, 27.5 mmol) was added and the reaction mixture refluxed for 2.5 h. The solution, after cooling, was filtered and washed with toluene (1 × 25 ml). The solid was subjected to Soxhlet extraction with methanol for 6 h, and subsequently dried at 100 °C.

Conversion of the chloropropyl group by reaction with 1,1,3,3-tetramethylguanidine

The trimethylsilyl/chloropropyl material from the previous experiment (1.3 g) was activated at 150 °C for 2 h, suspended in dry toluene (30 ml), 1,1,3,3-tetramethylguanidine (TMG, 1.00 g, 8.7 mmol) and 1-methyl-1,5,9-triazabicyclodecane (TBD, 0.3 ml, 2.0 mmol) were than added and the mixture heated to reflux and held at this temperature for 7 h. The mixture was cooled to room temperature, filtered, and the solid washed thoroughly with toluene (3 × 20 ml), methanol (20 ml) 1 : 1 *v/v* methanol/water (20 ml) methanol (2 × 20 ml) and then extracted in a Soxhlet apparatus containing dichloromethane/diethyl ether (1 : 1) for 18 h. This yielded 1.3 g of product, the physical parameters of which are recorded in Table 1.

Preparation of guanidine silane 5[16]

1,1,3,3-tetramethylguanidine (TMG, 42.31 g, 0.277 mol) and mixed xylenes (2.7 ml) were mixed together and heated to 120 °C. Chloropropyl trimethoxysilane (22.4 g, 0.113 mol) was aded dropwise over 2 h, and the solution allowed to react for two more hours. On cooling, a salt precipitates (TMG·HCl) which is filtered, and the remaining liquid is then distilled under reduced pressure. Two fractions were obtained, the first boiled at 58–65 °C/5 Torr, and was unreacted TMG, the second, at 85–90 °C, was the desired product. Yield 8.09 g, 10%), NMR: ^{1}H, $\mathrm{CDCl_3}$), δ 0.61 (m, 2H, $\mathrm{Si}C\!H_2$); 1.48 (m, 2H, $\mathrm{SiCH_2}C\!H_2$); 2.58 (s, 6H) and 2.63 (s, 6H) 2 × $\mathrm{NMe_2}$; 2.88 (m, 2H, $\mathrm{C}H_2$-$\mathrm{N{=}CNMe_2}$); 3.40 (s, 9H, $\mathrm{C}H_3\mathrm{O}$); ^{13}C, δ 6.98 ($\mathrm{Si}C\mathrm{H_2}$); 26.1 ($\mathrm{SiCH_2}C\mathrm{H_2}$); 39.1 and 39.4 4× $\mathrm{N}C\mathrm{H_3}$; 50.7 ($C\mathrm{H_3O}$); 53.6 ($C\mathrm{H_2N{=}C}$); 160.4 ($\mathrm{N{=}}C\mathrm{(NMe_2)_2}$.

Attachment of guanidine silane **5** to MTS and silica was carried out using the same methodology as for the chloropropyl silane.

NMR (^{13}C, CPMAS), δ (10.5) ($\mathrm{Si}C\mathrm{H_2}$); 24.7 ($\mathrm{SiCH_2}C\mathrm{H_2}$); 40.4 (4× $\mathrm{N}C\mathrm{H_3}$); 47.8 ($C\mathrm{H_3O}$); 51.9 ($C\mathrm{H_2N{=}C}$); 162.2 ($\mathrm{N{=}}C\mathrm{(NMe_2)_2}$.

Epoxidation

To a solution of 2-cyclohexenone (0.96 g, 10 mmol) in methanol (10 ml) containing the catalyst (0.100 g) was added, at 20 °C, hydrogen peroxide (30% *v/v* in water) dropwise. The amount added is determined by the selectivity to hydrogen peroxide as detailed in Table 2. For example, a selectivity towards hydrogen peroxide of 50% means that a total of 2 equiv. was added; a selectivity of 10% indicates that 10 equiv. was needed. The time of additions was 30 min less than the reaction time documented in Table 2. Reaction was followed by GC, using 2-phenylbutan-2-ol in methanol as external standard, and products identified by GC-MS and by comparison with an authentic standard (Aldrich).

Knoevenagel condensation

To a mixture of heptanal (1.14 g, 10 mmol) and malonic acid (1.04 g, 10 mmol) in THF (30 ml) was added the catalyst (150 mg, activated at 100 °C overnight under vacuum) and the mixture was heated to reflux under nitrogen atmosphere. Reaction is followed by GC, using dodecane in THF as external standard. 3-Nonenoic acid and 2-pentyl-2-nonenal are identified by GC-MS and by comparison with authentic compounds. No dicarboxylic acids are detected by GC with flame ionisation.

After two days, the reaction is stopped and the catalyst filtered off and washed with THF. The solvent is removed and the crude mixture recovered. Isolation of products can be achieved by flash chromatography (SDS silica 60 AC.C/70–200 mesh, cyclohexane–diethyl ether–formic acid 90/10/1). 2-Decene-2-dioic acid: NMR: ^{1}H, δ 0.9 (broad peak, 3H, $\mathrm{C}H_3$); 1.2 (broad peak, 8H, $\mathrm{CH_3(C}H_2\mathrm{)_4CH_2}$); 2.9 (m, 2H, $\mathrm{C}H_2\mathrm{CH{=}C}$) and 7.9 (t, 1H, $\mathrm{CH_2C}H\mathrm{{=}C}$). ^{13}C, δ 18.6 ($C\mathrm{H_3}$); 27 ($\mathrm{CH_3}C\mathrm{H_2CH_2}$); 32.9 ($\mathrm{CH_3CH_2}C\mathrm{H_2}$); 33.6 ($\mathrm{C_3H_7}C\mathrm{H_2}$); 34.2 ($\mathrm{C_4H_9}C\mathrm{H_2}$); 35.2 ($\mathrm{C_5H_{11}}C\mathrm{H_2}$); 36 ($\mathrm{C_6H_{13}}C\mathrm{H_2CH{=}C}$); 128.4 ($\mathrm{CH{=}}C$); 164.3 ($\mathrm{CH_2}C\mathrm{H{=}C}$); 171.9 and 172.8 ($C\mathrm{O_2H}$)

Decarboxylation test

The crude mixture from experiment using catalyst **7** is dissolved in heptane (30 ml) and heated at reflux during 2 h, without increasing of the quantity of 3-nonenoic acid. Then TMG (100 μl) was added. Reaction is followed by GC using dodecane in THF as external standard.

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Life cycle assessment and green chemistry: the yin and yang of industrial ecology

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The practice of life cycle assessment has been well documented as a tool for comparing products and processes or comparing various components within a life cycle. This paper addresses the question of how changes can be made once an assessment has been completed, such as identifying the improvements that can be made to address environmental problems and to decrease impacts on human health and the environment. Green chemistry, a fairly recent approach that addresses environmental concerns at a fundamental level, has already demonstrated examples of what we call 'life cycle innovation', that is, improvements at all stages of the product or process life cycle. This paper explores various applications of green chemistry methodologies to all stages of a product or process life cycle.

Introduction

Sustainability is often defined as meeting the needs of current generations without sacrificing the ability to meet the needs of future generations. The ideas of industrial ecology provide a systems-based view of how, where, and why environmental improvements can be made to move towards an environmentally sustainable economy. Life cycle assessment (LCA) is a powerful tool for industrial ecology to facilitate understanding and characterization of the range and scope of environmental impacts at all stages within a product or process (see, for example, refs. 1 and 2). Streamlined life cycle analysis, as recently articulated,[3] can make this approach more easily accessible to the population of potential users. With the results from these assessments, interested parties are empowered with knowledge about where the most important problems lie within a life cycle. The question then becomes how to best address these problems. One method that is generating notable and quantifiable answers to this question is green chemistry.

Background

Introduced in the early 1990s, green chemistry is an approach to addressing the environmental consequences of products or processes at the design stage. A new but straightforward method, green chemistry is defined as the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.[4,5] For the purposes of this definition, the use of the term 'chemistry' is used in its formal definition as applying to the structure and transformation of all matter, making the applicability extremely broad. It should be noted that since the consequences of energy generation and use are directly and inextricably linked to the materials used to generate, capture, store and transport it, energy concerns are inherently addressed by the above definition. Therefore the methods and techniques of green chemistry address these issues at the design stage and at the most fundamental level, *i.e.* the molecular level, dealing with the intrinsic rather than the circumstantial properties of a product or process.

Another important clarification in the above definition is the term 'hazardous'. The hazards addressed in the definition of green chemistry include the full range of threats to human health and the environment. This includes, but is not limited to, toxicity, physical hazards (*e.g.* explosions, fires, *etc.*), global climate change, and resource depletion. All of these hazards can be and are being addressed through green chemistry because they are all derived from the physical, chemical, and structural properties of the molecule or molecular transformations that take place.

The growth in environmental regulations has produced dramatic and beneficial results to the environment over the course of the past generation. However, the costs both to industry and society have made this approach, as a unilateral strategy, unsustainable. During the introduction of pollution prevention as a way of achieving environmental goals, green chemistry was immediately recognized as a tool for decreasing waste and emissions at the source. However, it was not long before green chemistry was also recognized as a powerful tool for sustainable technology and industrial ecology. Green

Green Context

The key feature of this paper is that it demonstrates the essential nature of green chemistry in achieving life cycle innovations. As this article shows green chemistry can facilitate environmental improvements at every stage of the life cycle, and implementation of green chemistry technology can offer environmental benefits that propagate throughout the life cycle. This dual nature of green chemistry provides great potential for improving process environmental impacts both at a particular life cycle stage and also up- and down-stream of a specific improvement.

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chemistry differs from historical approaches to environmental protection in several major ways:

- It addresses hazard rather than exposure
- It is economically driven rather than economically draining
- It is non-regulatory
- It prevents problems before they occur through avoidance approaches
- It considers the full life cycle impacts at the design stage

The examples of industry using green chemistry to move towards sustainable manufacturing are well documented and have been lauded through the Presidential Green Chemistry Challenge Awards, established in 1995 and presented annually at the National Academy of Sciences in Washington, D.C. The design, development, and implementation of green chemistry have manifested across all of the stages of the product life cycle (Fig. 1). Advances in green chemistry provide specific methods and techniques to improve life cycle environmental impacts and to achieve the goals of industrial ecology.

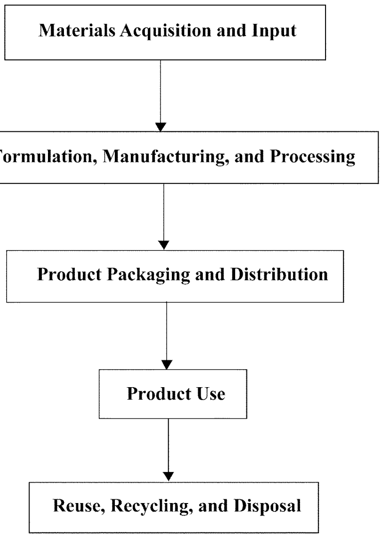


Fig. 1 Elements of a product life cycle.

Discussion: how green chemistry affects all aspects of the life cycle

Green chemistry effects changes in the hazard of a product at the most fundamental level, the molecular level. The types of hazards that are of concern for their impact on human health and the environment can be viewed simply as physical or chemical properties of the substances being used. Simply put, the molecular structure (including, of course, molecular volume and electronic profile) of a chemical substance determines its properties, such as potential health hazards. Chemists can manipulate chemical structure to more closely approach the desired properties. Practitioners of green chemistry focus on modifying these intrinsic properties to reduce or eliminate the hazardous nature of these substances. In the same way that a substance can be designed to be brittle or to be flexible, it is possible to design substances such that they do not possess certain hazardous properties. It is for this reason that green chemistry is capable of accomplishing its goals throughout the life cycle of a product or process; inherent properties do not change merely by moving through the various life cycle stages. When change is effected by addressing environmental issues *via* a circumstantial solution, *e.g.* how materials will be handled by workers or consumers, then by definition those solutions are contextual and therefore cannot transmit throughout the life cycle. Life cycle innovation, therefore, is recognizing that by designing the fundamental properties of the substances used in particular stages of the life cycle, green chemistry has the power to impact the entire life cycle of a product or process.

Materials acquisition and input

One characteristic that all tangible products share, whether they are as simple as a piece of paper or as complex as a space shuttle, is that they are all made from chemical substances. Since all materials are chemical substances, they lend themselves to the advances and advantages that have accompanied the developments in green chemistry. One of the most important advantages is versatility in starting materials. While a necessary material may currently be manufactured by starting with chemical substance ‘x’ and using basic synthetic chemistry methodologies, it may also be possible to make the identical material using, say, chemical ‘y’ or ‘z’. A fortuitous effect is that the more complex the material, the more chemical pathways and starting materials are possible from which to make it. Certainly in the case of some complex pharmaceuticals there are literally thousands of theoretical routes to manufacture the product.

For example, Fig. 2 shows the potential for complexity in a chemical transformation. Each node represents a chemical reaction which may participate in transforming starting chemical ‘C’ into the target compound ‘T’. As the number of reaction nodes increases, the total number of potential transformation pathways also increases. As shown in Fig 2, pathways (A) and (B) are two potential routes by which the target compound can be manufactured.

In general, this fundamental chemical fact provides enormous potential for positive impact on the materials impact requirements for product manufacture. Knowing that it is possible to manufacture a product from a variety of materials allows for selection and decision criteria in choice of material input. Therefore, instead of changing the final product and perhaps affecting product performance, one can manufacture the identical product while dramatically improving the environmental profile of the product life cycle.

The primary question then becomes what kind of criteria green chemistry can place on materials inputs to effect a positive environmental impact. Several are listed below with examples:

- The methods used to obtain starting materials, *e.g.* mining, refining, agriculture, should have minimum impact on the natural environment.
- The material inputs over the life cycle should be of little or no toxicity (or at least reduced toxicity by comparison to traditional methods, if they currently exist).

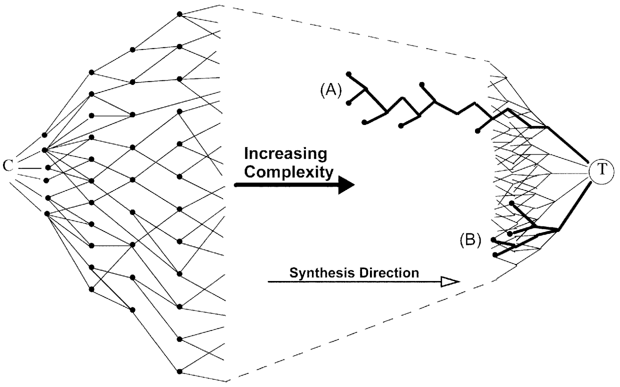


Fig. 2 A synthesis tree diagram which demonstrates increasing complexity as the number of processing compounds and pathways increase (reproduced with permission from ref. 6). The starting compound is indicated by ‘C’, and the target compound is denoted as ‘T’. (A) and (B) show two potential pathways out of many by which the target compound could be synthesized.

- Feedstocks/starting materials should be renewable rather than depleting wherever possible.
- When possible, the starting materials for a process should be the 'waste' from another process.

For example, consider the production of adipic acid, which is used to manufacture Nylon 66. Over 1.9 million metric tonnes of adipic acid are produced annually, and most commercial processes use petroleum-derived benzene as the starting material. Additionally, the last step includes a nitric acid oxidation, resulting in the formation of nitrous oxide as a by-product, which accounts for about 10% of the annual increase in atmospheric nitrous oxide levels.

Recent green chemistry research at Michigan State University has resulted in the development of the Draths–Frost synthesis of adipic acid where microbes are used for environmentally benign synthetic catalysis. Glucose is used as the starting material and is converted to *cis,cis*-muconic acid using a genetically-engineered microbe, and this acid is then hydrogenated to give adipic acid.[7] This synthesis both eliminates the use of benzene as a starting product and the formation of nitrous oxide as a by-product.

The Draths–Frost synthesis uses a renewable feedstock, and the process materials are of little or no toxicity. The criteria for materials input coupled with examples of how this is being achieved by green chemistry practices demonstrate how fundamental science can and is empowering the design of products at the front end of the life cycle.

Product design and manufacture

Manufacturing is the stage in the product life cycle that is generally associated with green chemistry. This is likely due to the fact that so many manufacturing processes use chemicals and chemical techniques. As is well known, the manufacturing process itself can have significant environmental impacts even if the product being made is innocuous. A prime example of this is a pharmaceutical product, where although the product may be a life-saving drug, the manufacturing process can be environmentally damaging. It is not uncommon to have pharmaceutical manufacturing processes that create 100–1000 units of waste for each unit of product. Therefore it is important to review all associated manufacturing processes to see if green chemistry opportunities exist to reduce environmental impacts.

Within a manufacturing process, several green chemistry changes can be implemented to reduce environmental impacts. The following examples are a few of the major areas where green chemistry has been used to improve manufacturing processes from an environmental perspective.

Through green chemistry techniques of designing safer products, materials, and chemicals, the end products that are forwarded to customers can be as innocuous as is scientifically feasible.

Atom economy. The use of chemicals in manufacturing and processing can proceed in ways that can either incorporate the materials into the final product at the molecular level or have the material pass through the process and emerge as waste. The consideration of how much of the reactants end up in the product, *i.e.* the atom economy, has largely been ignored. While the percent yield of a product has been carefully monitored, the amount of waste generated has not been as much of a concern. Examples of processes that generate large amounts of inorganic salts include stoichiometric reductions with metals and metal hydrides and stoichiometric oxidations with permanganate and dichromate.[8]

The concept of atom economy illustrates the methods and benefits of incorporating all of the materials that are used in the process into the final product (see, for example, refs. 8–11). An example of a chemical reaction with 100% atom economy is shown in Fig. 3. Ideally, a manufacturing process would design a process so that all atoms are included in the product structure; the goal is a product with high yield and low waste instead of a high yield with accompanying high waste. To do otherwise results in paying first for material inputs and again for waste disposal costs. Ironically, one typically pays less for the substance as a virgin material. Green chemistry methods have been extensively studied in this use.

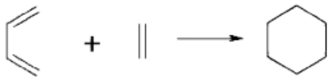


Fig. 3 An example of a chemical reaction with 100% atom economy.

An example from industry of increasing atom economy is the BHC Company's improved process for manufacturing ibuprofen. The new technology has three catalytic steps with about 80% atom economy, and this increases to about 99% atom economy with the recovery of the acetic acid by-product. This process replaces the previous technology with six stoichiometric steps and less than 40% atom economy. Anhydrous hydrogen fluoride is used as both a catalyst and a solvent; this improves the reaction selectivity and also decreases waste. The anhydrous hydrogen fluoride is also recovered and recycled with over 99% efficiency.[12]

Structural manipulation. For product design, one of the most powerful tools used in green chemistry is the manipulation of molecular structure to reduce or eliminate the toxicity of the molecules and their potential to do harm. It is now possible to understand at the molecular level how structure gives a substance the performance characteristics that one needs and also what structural aspects cause toxicity. With this knowledge, scientists are researching green chemistry techniques on products ranging from pesticides to photographic film to ensure that the product performs its function without the hazards and the resultant mitigation that is normally required to deal with hazardous materials. Simply stated, reduced hazard is considered a performance criterion for green chemistry products.

Reduced hazard reagents and solvents. As mentioned earlier, in cases where both a product and also its feedstock are innocuous, the chemical transformation agents (reagents) used may be extremely hazardous. It is important that these reagents be designed or selected such that the full range of hazard to human health and the environment is minimized. This necessity obviously has direct implications for the manufacturing workers who must handle the hazardous substances and for the surrounding community, which may have concerns about the risks associated with hazardous reagent use.

For example, paclitaxel is an anti-cancer compound that is typically produced using methylene chloride as a solvent. The company Hauser, Inc. has developed green chemical processes for extraction and production of paclitaxel at higher quality, yield, and concentration and at a lower cost than with the conventional method, and this process also does not use methylene chloride. The paclitaxel is currently derived from Yew trees, and with this process the annual production of 254 000 pounds of waste has been eliminated. Current research may lead to the future development of green synthetic methodologies for a low-waste synthesis of paclitaxel that do not require the use of Yew trees. One renewable alternative to Yew trees is the hazelnut tree; recent research has found that paclitaxel can be isolated from the hazelnut tree and from the fungi that grow on the trees, although at a lower concentration than the Yew trees.[13]

However, there are also indirect concerns with the reagents and solvents used, which further compel the reduction of the use of toxics. These concerns emerge at the intersection of life cycles, where the manufacturing stage of the product life cycle

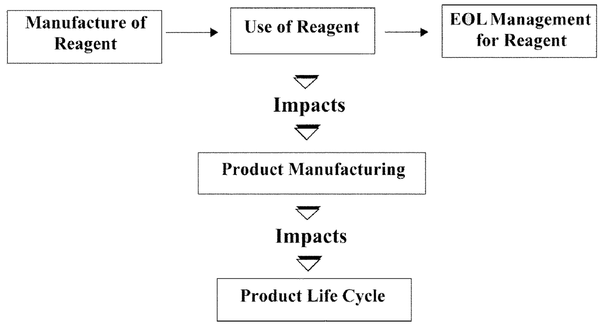


Fig. 4 Selecting an aspect of a chemical manufacturing process, such as the choice of reagent, will have associated upstream and downstream impacts over the life cycle of the reagent. The choice of reagent affects the environmental impacts of the product manufacturing stage, and this in turn will influence the overall environmental impacts of the product life cycle.

intersects with the use stage of the reagent life cycle (Fig. 4). Simply by requiring the use of the hazardous reagent, the product life cycle compels or drives to some degree all of the other stages of the reagent life cycle. Any reduction in the use of the hazardous substance in the manufacturing stage of the product life cycle will have a multiplier effect by impacting all the upstream and downstream stages of the reagent life cycle, including material inputs and manufacture and transport of the reagent.

There are well known examples of products such as paints, coatings, or adhesives where the environmental concerns did not stem from the materials themselves, but rather from the solvents in which they were dissolved. Through the use of green chemistry techniques, alternative solvents (*e.g.* water, supercritical CO_2) or even solventless systems are being developed so that the products can still be used but without the associated hazards.

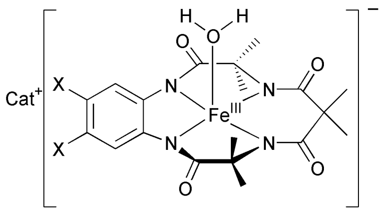
Energy use and efficiency. The manufacturing sector is second only to the transportation sector in the consumption of energy. Green chemistry is directly involved with energy issues throughout all of the environmental consequences of the materials used in the generation, storage, and transport of energy. However, it is also involved because the design and manipulation of manufacturing chemistry can have a dramatic impact on the energy demand of a particular process.

The energy required for a chemical reaction depends upon the bond dissociation energy of the atoms comprising the molecules. For example, breaking a single carbon–carbon bond (C–C) requires 347 kJ mol^{-1}, while breaking a double carbon–carbon bond (C=C) requires as much as 611 kJ mol^{-1}.[14] Thus the choice of starting materials affects the energy required for the chemical reaction. Additionally, the chemistry and chemical pathway chosen may also dictate whether a reaction needs to be conducted at high temperature or high pressure or requires extensive separation and purification, all of which have high process energy requirements.

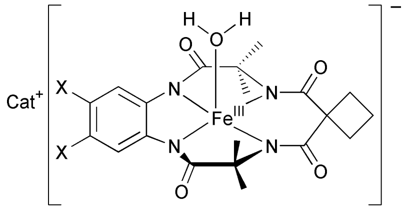
Many manufacturing operations that use chemicals require a great deal of energy in the form of either heat or pressure to drive the chemical process to completion. The use of catalysis has led to environmental benefits in numerous types of manufacturing processes from pharmaceuticals to plastics. Catalytic processes offer several valuable advantages, such as significantly lowering the energy demands of manufacturing operations. This is possible in many applications where the relevant materials can be activated by the catalyst rather than needing to be driven thermally or through pressurization. For example, GE Plastics has developed a catalyst that enables them to synthesize their ULTEM® thermoplastic resin in a more environmentally friendly manner. The new process uses 25% less energy per unit of resin, consumes 50% less catalyst, generates 90% less organic waste, and produces 75% less waste in the manufacture of the catalyst itself.[15]

Product selectivity. In virtually all manufacturing processes using chemicals, there is a constant struggle to produce only the desired products and to minimize or eliminate the formation of by-products and waste impurities. Catalysis has been used in many green chemistry solutions to dramatically improve the chemical selectivity of a process to eliminate the resulting by-product wastes and environmental impacts.

For example, the environmental impacts of chlorine-based paper bleaching have become well known. To reduce the dissipation of persistent chlorinated compounds into the environment, the pulp and paper industry has been moving towards elemental chlorine-free or totally chlorine-free technologies. As an environmentally friendly alternative to chlorine-based bleaching, Professor Terrence Collins at Carnegie Mellon University has developed selective catalysts that enable or improve the use of hydrogen peroxide for low-temperature pulp bleaching. These TAML™ catalysts, shown in Fig. 5, are nontoxic and have easily controlled lifetimes, and the bleaching process performs best at room temperature.[7,16] This technology is more selective than other totally chlorine-free processes and is as selective as the current primary delignification technology based on chlorine dioxide.[16] This bleaching method offers significant environmental benefits over chlorine-based paper bleaching.



$Cat^+ = Li^+, [Me_4N]^+, [Et_4N]^+, [PPh_4]^+$
X = Cl, H, OMe



$Cat^+ = Li^+, [Me_4N]^+, [Et_4N]^+, [PPh_4]^+$
X = Cl, H

Fig. 5 TAML™ catalysts.

Reduced materials use. As discussed earlier, chemicals are often used to transform raw materials into a final product. When a given amount of chemical is needed to produce an equivalent amount of product, it is called stoichiometric transformation; however, the actual yield is almost always lower than the theoretical yield predicted by stoichiometry. Green chemistry innovations have drastically reduced material requirements for making products, often by increasing the efficiency of a current process or by developing an entirely new manufacturing pathway that requires less materials consumption.

For example, the use of microwaves to facilitate organic reactions has been studied by both Dr Ajay Bose of the Stevens Institute of Technology and Dr Rajender Varma of the U.S. Environmental Protection Agency. Microwave irradiation can allow for the use of less or no solvent and can produce fewer by-products, giving a more pure product. This technology has been targeted at industrially significant reactions that use toxic or corrosive chemicals or that generate hazardous waste.[7]

Final product formulation. While materials input and manufacturing processes can have significant environmental impacts, the actual final product will often be what most individuals encounter. For this reason, the initial green chemistry design can lead to innovations that reduce the inherent hazard of a particular product and eliminate significant negative impacts to human health and environment that may have been identified during life cycle assessments.

Often, environmental concerns associated with a product are closely tied to the form and formulation of the product rather than the product itself. For example, a product may be a human health concern if sold as a powder that can be breathed in by users and cause respiratory damage. Since materials and products exist in different phases, *i.e.* solid, liquid or gas, scientists are working to ensure that materials are in their most innocuous form when sold.

Product packaging and distribution

Green chemistry research typically focuses on manufacturing processes. However, green chemistry life cycle innovations can also affect packaging and distribution, an important stage in terms of environmental impact.

Product conception. The conception of a new product offers the opportunity to design and choose its characteristics such that environmental impacts will be minimized. Application of green chemistry concepts can result in a design where less product is required for a given use when compared to similar products currently in use. The initial design of a product will determine how much of it may be required for a given use. A familiar example of this is fabric softener. In recent years, 'concentrated,' liquids have been introduced; the same volume of softener can be used for, as an example, 40 loads of laundry instead of 20 loads. Such improvements to the "efficiency density" of a product will decrease not only the packaging required per load of laundry, but will also have indirect effects, such as decreasing the product transportation costs and resource demands per load of laundry. More subtle benefits can also be realized, such as possibly decreasing the required number of trips to the store.

Energy demands and costs for transportation can be lowered by altering the form of a product, such as having a light powder rather than a heavy liquid formulation. The choice of a powder over a liquid can have additional environmental impacts for the packaging as well. Typically, powders such as laundry soap can be packaged in paperboard containers, which are more easily recycled than the colored plastic jugs containing liquids.

Eliminating packaging through product design. At a minimum, excessive packaging contributes to the consumption of resources and increases the materials waste problem. There are examples of products that have been designed to completely eliminate the need for packaging. For example, in recent years software has moved from excessive packaging to no packaging. When software and manuals are downloaded directly from the internet, the need for packaging is eliminated.

An example of decreasing or eliminating packaging through green chemistry is a production process that incorporates desired properties into a material without separate processing steps. For example, if materials that require a pigmentation or dyeing step to add color can instead be easily designed at the molecular level to be a specific color, the environmental impacts associated with the paint or dye can be eliminated.

Packaging made from the same material as the product. Historically, the plastics industry has had a problem with the transfer of raw polymer resin into reactors due to the need for cleaning and disposing of the polymer packaging. Recent green chemistry advances have designed these bags such that they are made of the same polymer that is contained inside the bag. In this way, the plastics company can merely put the entire 'package' in the reactor, and there is no excess packaging requiring further disposal.

Product use

Ideally, product use would require little or no non-renewable energy and would have no associated hazards or hazardous by-products. However, products often impact the environment through several avenues. The product itself may be potentially hazardous to human and environmental health, such as insecticides or the chemicals used in dry-cleaning. An innocuous product may have harmful by-products, such as phosphate-containing laundry detergents which may cause a nitrification problem in a nearby river. Finally, while a product and its by-products may be harmless, the renewal or reuse of the product may require some consumption of resources. These impacts are being minimized through the application of green chemistry.

Energy consumption. Recently revised indoor air quality standards have doubled ventilation requirements and have increased the need for dehumidifying and cooling outdoor air. Studies of desiccant wheel use in heating, ventilation, and air conditioning systems have shown desiccant wheels to decrease costs and energy use, and they have the potential to replace fluorocarbon refrigerant systems. Most desiccants currently produced are inorganics such as silica gels. However, researchers at Purdue University are investigating the potential for developing starch- and cellulose-based desiccants. These bio-based adsorbents are made from renewable resources and are biodegradable. Additionally, their availability and lower cost could make them a viable alternative for both industrial and residential air conditioning.[7]

Waste generation. Green chemistry can also decrease the amount of hazardous or non-hazardous by-products generated during the use of a chemical product, such as fire extinguishment agents. The aqueous film-forming foams developed by the U.S. Navy in the 1960s for use on volatile hydrocarbon fires release both hydrofluoric acid and fluorocarbons during use, and the fluorosurfactants often lead to ground water contamination. In 1993 PYROCOOL Technologies, Inc. developed Fire Extinguishing Foam (FEF) as a more environmentally-friendly alternative to current fire extinguishing agents. The FEF contains no glycol ethers or fluorosurfactants and is biodegradable. The FEF has also been demonstrated to be effective. An oil tanker fire estimated to require 10 days to extinguish was put out in under 13 minutes using the FEF; as a result the spillage of 78 000 tons of crude oil was prevented.[7]

End of useful life: reuse, recycling and disposal

At the end of its useful life, a chemical or product may be reused, recycled, or disposed of, or all three may occur, depending on the product's components. The application of green chemistry methodologies can directly or indirectly impact the environmental effects of the final stages of product life.

Reuse and recycling. For a material or product whose manufacture is energy intensive, reuse may be the best option for decreasing overall environmental impacts. Reusing products and materials is also often the least expensive option. When reuse of a product is technically or economically infeasible, recycling the materials may be an option. The chemical processes and materials used to manufacture a product are an essential determinant in the ability to recycle materials at end-of-life (EOL).

When materials are recycled after consumer use, the recovered material may either be used as an input to make the same product again, termed ‘closed-loop recycling’, or it may be used to make lower-value products, called ‘open-loop recycling’.[1,2] For example, when a plastic two-liter bottle is recycled, if the recovered plastic is used to make new two-liter soda bottles, this would be closed-loop recycling. If instead the recovered plastic is used to make a product like tennis shoes or a park bench, the recycling would be open-loop. Current recycling of plastics and polymers is not profitable, and the goal of closed-loop recycling is complicated by different colors of plastics and polymers that are used. If a clear bottle is recycled along with colored plastics, it is difficult and expensive to recover the plastic as a potential input for new clear plastic bottles.

A third option is ‘equivalent closed-loop’ recycling, where although a recovered material is not used to make the same product again, it is used in place of virgin material as the input for a similar product. Equivalent open-loop recycling varies from the post-consumer recycling described above in that it replaces virgin plastic of the same value, but to manufacture a product other than the original item. Further chemical research for plastics and polymer recycling is still needed to provide more technically and economically feasible options to facilitate closed-loop and equivalent closed-loop recycling.

A basic concept of industrial ecology is to design or modify an industrial system such that the wastes and by-products of one industry can become the feedstocks for another process or another industry. For process chemicals used in industry, immediate reuse is usually not possible, since at least some minimal processing is often required. However, recycling process chemicals within a facility and them reusing them is often feasible, cost-effective, and environmentally desirable. Such a recycling and reuse process is being used by the Roche Colorado Corporation in producing an antiviral agent. In their patented process, in addition to decreasing the use of toxic chemicals, 100 metric tonnes per year of ammonium hydroxide are recycled and reused.[17] Advances in green chemistry can make it possible for more feasible reuse or recycling and can encourage substitution of non-hazardous materials in products likely to be thrown away.

Disposal. Disposal may be necessary at several stages in a product life cycle. Materials acquisition and manufacturing often require disposal of wastes or other by-products that cannot be economically reused or recycled. Ideally, any product that is likely to be disposed of should be designed to biodegrade harmlessly in the environment or should at least minimize use of toxic materials.

Aside from process wastes, the product may be disposed of at the end of useful life if reuse or recycling of a chemical or material is not feasible. The complexity of materials makes recovery and recycling difficult and often infeasible. Future innovations in chemistry are needed to overcome these technical and economic barriers to recycling.

Highest entropy products made most durable and *vice versa*. A design consideration that affects all EOL options is the residence time that a product, material, or chemical will have during its useful life. Generally, a product that requires the largest input of resources should also be the most durable and the most easily reusable. Products which have a short residence time should be designed such that the minimum amount of resources is expended to initially produce the product, especially if reuse or recycling is not feasible. Careful design of the process chemistry can ensure that resource use is optimized.

The essential nature of green chemistry in achieving life cycle innovations

One essential aspect of green chemistry is that it can facilitate environmental improvements at every stage of the life cycle, as demonstrated in the previous sections of this paper. A second essential aspect is that implementation of a green chemistry technology can offer environmental benefits that propagate throughout the life cycle. As an example of this, consider the

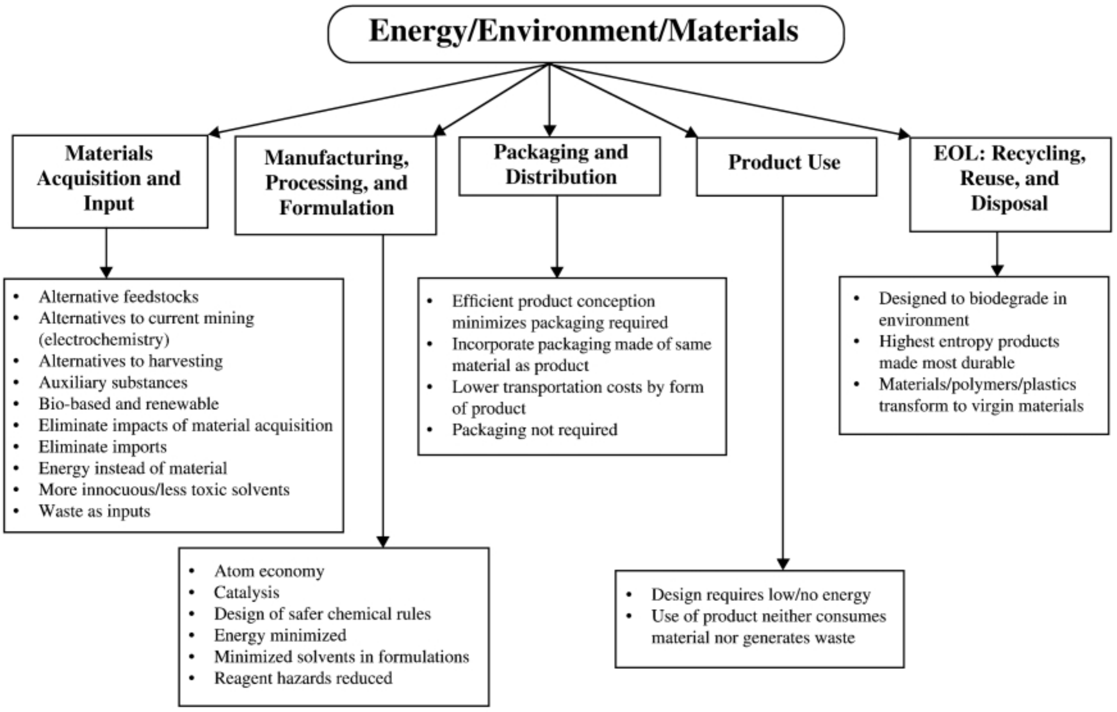


Fig. 6 Summary diagram showing how specific innovations in pollution prevention can be achieved at each stage of the life cycle.

work of Professor Richard Gross *et al.* (*e.g.* see ref. 18) on biodegradable polymers, surfactants, and emulsifiers. Their research on fully biodegradable polyhydroxyalkanoates (PHAs) is an example of a product whose manufacture can offer significantly improved environmental impacts over current polymer production. The biodegradable PHAs are made from inexpensive renewable feedstocks and are processed by fermentation in aqueous media. The biodegradable PHAs can also be tailored to meet or exceed the desired properties of current non-biodegradable products. The vision for these polymers at end-of-life is for them to comprise part of the bio-waste fraction, suitable for composting. Use of biodegradable polymers can help avoid the problem of landfill disposal or expensive, difficult, and typically low-value recycling of currently manufactured polymers.

Conclusions

To illustrate the areas and methods of impact that green chemistry can have and has had at the various stages of the life cycle, the basic principles of green chemistry and the application of these principles are categorized in the various stages of the life cycle where they have the most effect. In this way, one can see a pathway for identifying life cycle innovations through green chemistry. A summary of these potential innovations is described by Fig. 6.

The dual nature of green chemistry research offers a wide variety of demonstrable achievements and future potential for improving process environmental impacts both at a particular life cycle stage and also up- and down-stream of a process improvement. As is described in Fig. 6, advances in green chemistry are essential in providing the specific innovations at all stages of a product or process life cycle by which we can achieve the broad goals of industrial ecology while also maintaining a sustainable economy.

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Lewis acid-catalysed sequential reaction in ionic liquids

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The utility of ionic liquids as a safe recyclable reaction media at 200 °C in the presence of anhydrous scandium trifluoromethanesulfonate for a sequential reaction involving a Claisen rearrangement and cyclizations is discribed.

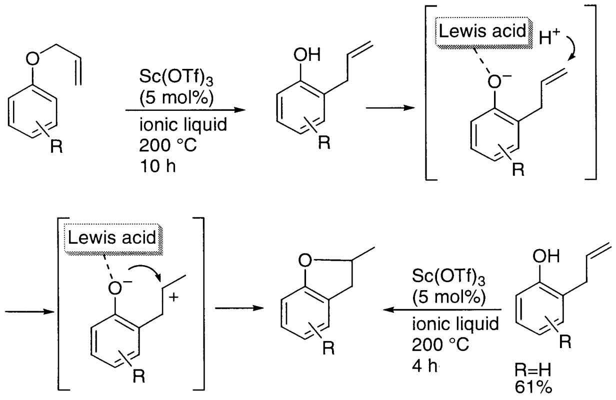
Introduction

Recent studies of ionic liquids as a new alternative reaction media are having an important impact on organic chemistry.[1] To date, the use of ionic liquids as reaction media have been reported for Friedel–Crafts chemistry,[2] alkylation reactions,[3] alkane isomerisation,[4] alkylation of isobutane with butene,[5] Diels–Alder reactions[6] and the Heck reaction.[7] Recently we have reported the use of new ionic liquids (such as 8-ethyl (8-methyl)-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate) in organic syntheses such as the one-pot synthesis of heterocycles, one-pot aza-Diels–Alder reaction[8] and the synthesis of fluorinated alkenes by the Horner–Wadsworth–Emmons reaction.[9]

In our continuous study of ionic liquids as a recyclable media, we describe here the possibility of the reuse of the ionic liquid at 200 °C, proceeding sequential syntheses (domino reactions) involving Claisen rearrangements and cyclization reactions in the presence of a Lewis acid to give 2-methyl-2,3-dihydrobenzo[*b*]furan derivatives.

Results and discussion

As the impact of the Claisen methodology in modern synthetic strategies and its application for the preparation of highly functionalized derivatives are well known,[10] we initially examined the Claisen rearrangement of allyl phenyl ether at 150 °C for 4 h in an ionic liquid (*e.g.* 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **1**). The uncatalysed reaction did not proceed. The addition of a Lewis acid (anhydrous scandium trifluoromethanesulfonate, Wako Pure Chemical Industries, Ltd.) induced the Claisen rearrangement and cyclization reactions. After 4 h at 200 °C, 2-allylphenol, 2-methyl-2,3-dihydrobenzo[*b*]furan and the starting material

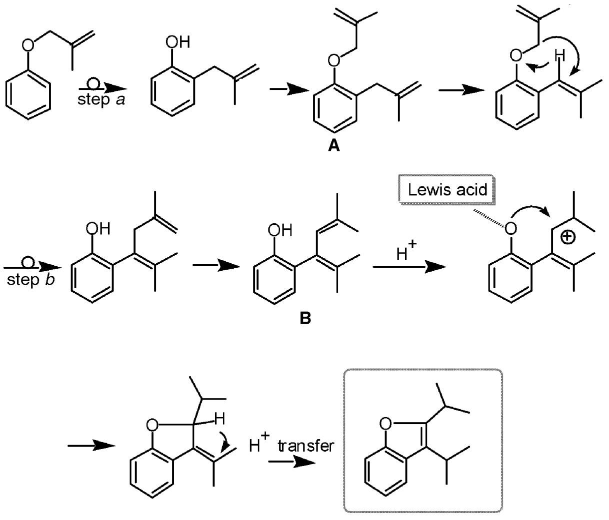


Scheme 1 Sequential reaction in ionic liquids.

Table 1 Lewis acid catalyzed sequential synthesis.

Entry	Substrate	Ionic liquid[a]	Yield (%)
1	allyl phenyl ether	**1** [EtDBU]OTf]	62
2		**2** [MeDBU][OTf]	20
3	allyl *p*-tolyl ether	**1** [EtDBU][OTf]	88
4		**2** [MeDBU][OTf]	40
5		**3** [bmim][BF$_4$]	12
6		**4** [bmim][PF$_6$]	9
7	allyl *o*-tolyl ether	**1** [EtDBU][OTf]	91
8		**2** [MeDBU][OTf]	51

[a] Ionic liquid: 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **1**; 8-methyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **2**; 1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate **3**; 1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate **4**



Scheme 2 Preparation of 2,3-diisopropylbenzo[*b*]furan.

Green Context

Ionic liquids represent a fascinating and potentially very valuable group of new solvents which have the benefit of zero vapour pressure and thus easier handling than many conventional solvents. The work described here relates to sequential reactions carried out in ionic liquids, using Lewis acids. The reactions proceed well, and the authors have also shown that the ionic liquid can be effectively purified after reaction, in an efficient manner. ***DJM***

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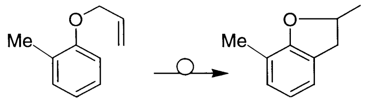
Table 2 Recycling ionic liquids



Cycle	Yield (%)	Recovered(%) ionic liquid and Lewis acid
1	91	> 99
2	95	> 99
3	90	> 99

(1 : 1 : 1) were detected by ^{1}H NMR. When the reaction was carried out at 200 °C for 10 h, the expected rearrangement material, 2-allylphenol, was not produced. The obtained product was 2-methyl-2,3-dihydrobenzo[*b*]furan which was produced from the domino reaction of a Claisen rearrangement and an intramolecular cyclization of 2-allylphenol catalysed by the Lewis acid. To determine the reaction path and 2-allylphenol as a reaction intermediate in this reaction, we examined the cyclization reaction of 2-allylphenol in the system of Sc(OTf)$_3$ and ionic liquid **1** under the same reaction condition. After 4 h of heating, the target material, 2-methyl-2,3-dihydrobenzo[*b*]furan was obtained in 61% yield.[11]

The structure was conformed by ^{1}H and ^{13}C NMR spectroscopy. Signals at δ 1.38 (3 H, d, J 6.60 Hz) and 4.82 (1 H, m) suggest a methyl group and one proton attached (CHCH$_3$), and then δ 2.73 (1 H, dd, J 15.38, 7.69 Hz) and 3.23 (1 H, dd, J 15.38, 8.79 Hz) suggest the two protons attached on the ring. Further, aromatic protons appeared at δ 6.67–7.09.

In the case of 2-methyl-2-propenyl phenyl ether as a starting material, 2,3-diisopropylbenzo[*b*]furan was obtained in 15% yield. The reaction mechanism, not clear until now, followed a Claisen rearrangement (step *a*) as the first step to produce intermediate **A**. Further, **A** was produced *via* step *b*, and then cyclization gave 2,3-diisopropylbenzo[*b*]furan.

In view of 'green chemistry', reuse of the catalyst and solvent are preferable. In the reaction of allyl *o*-tolyl ether, ionic liquid **1** and the Lewis acid were recovered in more than 99% yield after extracting the product with diethyl ether.

Before the use and reuse of ionic liquid **1**, it was purified under dynamic vacuum at 70–80 °C for 1 h, and then its purity and structure checked by ^{1}H and ^{19}F NMR spectroscopy (no other peaks except an ionic liquid **1**).

Successive reuse of the recovered ionic liquid **1** in the same reaction yielded amounts of product as high as in the first cycle (Table 2).

In conclusion, we have found that ionic liquid **1** is a good alternative reaction medium for sequential reactions involving Claisen rearrangements and cyclization reactions at high temperatures. In addition it can be reused and is stable at high temperatures.

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Novel approaches to the recovery of chromium from the chrome-containing wastewaters of the leather industry

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A leather tanning system combining both vegetable tannins and chromium (semi-chrome process) is indispensable for certain types of leathers. However, the effluent generated from such a process presents a problem of separating chromium from vegetable tannins, as the latter tend to precipitate along with chromium. Environmental legislations on the release of chromium into various water bodies demands its recovery and reuse at every possible stage. This investigation describes the development of suitable methods for separation of vegetable tannins followed by recovery of chromium.

Introduction

The process of converting putrescible raw hides and skins into a non-biodegradable matrix leather involves a series of steps[1] which can be broadly classified into beamhouse, tanning and post-tanning operations. Beamhouse processes aim at purification of collagen, the leather making constituent of skin, by removal of unwanted material such as hair, flesh and interfibrillary material. Tanning results in the stabilisation of the biological matrix against heat and bacterial attack. Post tanning operations impart desired characteristics such as softness and fullness besides improving the aesthetic appeal of the leather. The leather making process employs copious amounts of water. Nearly 30–35 litres of water is discharged for every kilogram of leather processed.[2]

Chromium tanning, employing the use of basic chromium sulfate (BCS), remains the most popular tanning method due to the hydrothermal stability and strength characteristics it imparts to leather. In the chromium tanning process, chromium in the sectional stream is as high as 1700–2500 mg L^{-1}, compared to the environmental regulatory norms where the permissible concentration of chromium ranges from 0.3–2 mg L^{-1}.[3] For leathers such as suede and nubuck, a semi-chrome tanning process, where vegetable tannins and BCS are used in combination, is indispensable in order to achieve properties such as nap, strength and hydrothermal stability. Of the 0.9 billion kgs of leather processed in India, around 20% of the total leather processed is tanned by the semi-chrome method, generating a voluminous 50–60 million litres of effluent containing both vegetable tannins and chromium.

Tannery wastewater containing chromium when discharged into the environment has adverse effects. Though chromium in its trivalent state is known to be an essential trace element in micro levels,[4] in larger quantities it is a potential soil, surface water, ground water, sediment and air contaminant under specific conditions.[5,6] The biological implications of chromium are known to vary with the oxidation state of the metal ion.[7] Oxoanions like chromates are well established human carcinogens.[8] This mandates technological interventions for combating chromium pollution. Chromium recovery-reuse processes have now been acknowledged as being commercially most attractive.[9] These are based on the principle that chromium(III) present in solution can be precipitated as chromium(III) hydroxide at a pH of 8.5 by the addition of alkali; and further redissolution of the precipitate using sulfuric acid to a pH of 3.0 to form chromium sulfate or other basic salts.

Although chromium(III) hydroxide can be generated from aqueous solutions of Cr^{III} salts with almost any alkali at pH 8–9, magnesium oxide is most extensively used.[10] This is because of high bulk density and good settling of particulate matter. However, MgO can be used only for a batch process. Recently, a semi-continuous method for the recovery of chromium(III) from tannery waste waters using sodium carbonate has been established.[11] However, effluents generated from leathers tanned with a combination of chromium salts and vegetable tannins present a problem in recovering chromium due to the presence of vegetable tannins, which are mostly polyphenolic in nature. There is a possibility of co-precipitation of vegetable tannins along with chromium upon the addition of alkalies such as MgO and $Ca(OH)_2$.[12] When the chromium(III) hydroxide precipitate is redissolved to basic chromium sulfate, the vegetable tannins continue to be an inherent part of the recovered liquor. The presence of vegetable tannins plays a detrimental role in the dyeing of tanned leathers. Similar problems could arise during chromium recovery from post tanning liquors as approximately 300 mg L^{-1} of chromium leaches out from leather at this stage and the spent liquor also contains chemicals based on phenols.

The vegetable tannin mostly used for tanning is wattle, which is of the catechol type. The auto-oxidation of catechol[13,14] is associated with the well-known browning phenomenon.[15] It is known that between a pH of 4 to 8, catechin is auto-oxidised to red catechin tannin.[16] The semi-chrome processing is completed at a pH of 4.2–4.5, hence the auto-oxidation is feasible. The possible mechanisms have been attributed either to enzymic oxidation[17,18] or due to a free radical formation.[19]

Although chromium recovery/reuse methodology has been commercially well accepted for chromium tanning waste

Green Context

Chromium compounds have many useful applications but their use also causes serious environmental concerns. Effective recovery of chromium from processes is vital as long as we use chromium reagents. Here we see how studying and modifying the liquor environment in which the chromium is located can considerably enhance the efficiency of metal recovery. The most effective modification employs hydrogen peroxide which makes a good economic and environmental process. ***JHC***

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liquors emanating from chromium tanned leathers, the usage of the same methodology for spent semi-chrome liquors (vegetable-chromium combination tanning) needs to be developed. The present investigation highlights a suitable approach for the recovery of chromium from spent semi-chrome liquors. In this study, an attempt has been made to recover chromium from semi-chrome liquors through two approaches, *viz*. 1. Direct precipitation of chromium by addition of alkali and its regeneration by re-dissolution with sulfuric acid; and 2. Removal of vegetable tannins followed by precipitation of chromium and subsequent recovery of chromium by redissolving using sulfuric acid. Removal of vegetable tannins can be performed in two ways. They can be reduced to quinol and precipitated using zinc chloride or, they can be completely oxidised to simpler organic acids or carbon dioxide.

Experimental

Spent semi-chrome liquor was obtained form the tanning yard of a commercial tannery. The liquor was filtered through a Whatmann No.1 filter paper. The pH of the spent semi-chrome liquor was noted and analyses were done for the determination of suspended solids (SS), chemical oxygen demand (COD), biochemical oxygen demand (BOD) and total chromium by standard methods.[20]

Semi-chrome liquor (500 ml) was taken and alkali (NaOH) was added to raise the pH of the spent liquor to 8.5 so as to precipitate chromium as chromium(III) hydroxide. A 14 h period was required for complete settling. The supernatant was decanted and the precipitate filtered under vacuum through a Whatmann No.1 filter paper. The chromium(III) hydroxide was re-dissolved to a pH of 2.5 by drop-wise addition of sulfuric acid.

The spent semi-chrome liquor was treated first for the removal of vegetable tannins followed by the recovery of chromium. The removal of vegetable tannins was attempted in two ways. In one set of experiments the semi-chrome liquors were treated with reducing agents followed by precipitation of vegetable tannins using zinc chloride. In another set of experiments, an oxidising agent, hydrogen peroxide, was employed, followed by $ZnCl_2$ treatment.

The various reducing agents employed in this study were sodium sulfite, sodium metabisulfite, hydroxyammonium chloride and sodium dithionite. In all the experiments, 150 ml of the semi-chrome liquor was heated to 60 °C in order to accelerate the reaction rate. About 1–2 g of each reducing agent was weighed accurately. In each case aliquots of the reducing agents were added under constant stirring. The electronic spectrum was recorded 5 min after each addition in the visible range of 450–750 nm using a Shimadzu UV-160A spectrophotometer.

A 0.5 M solution of $ZnCl_2$ was prepared. 50 ml of the sodium sulfite reduced liquor was taken in four beakers and 2.5, 3.75, 5 and 10 ml of the $ZnCl_2$ solution was added respectively. The precipitate was allowed to settle, and the solutions filtered under vacuum. The COD of the filtrate was determined. The optimum amount of $ZnCl_2$ required to achieve maximum precipitation of vegetable tannins was determined by comparing the COD reduction obtained from the four cases. The optimised quantity of $ZnCl_2$ was maintained constant for all the other reducing agents, and the COD was calculated in each case.

Semi-chrome liquor (4 L) was heated to 60 °C. The optimised quantity of the sodium sulfite was added with constant stirring. After the completion of the reduction process, the optimised quantity of zinc chloride was added under constant stirring and further stirred for 15 min. The precipitate was left undisturbed for 12–14 h to aid complete settling. The liquor was filtered through a Whatmann No.1 filter paper. The same procedure was repeated for the other reducing agents. The average time required for the completion of each reduction process was about 3–4 h.

The semi-chrome liquor obtained after treatment for removal of vegetable tannins was subjected to precipitation of chromium as chromium(III) hydroxide by raising its pH to 8.5 using NaOH. The precipitate was allowed to settle for approx. 12 h until a clear supernatant was obtained. After complete settling, the supernatant was decanted and the precipitate was filtered under vacuum using a Whatmann No.1 filter paper. The chromium bearing sludge was redissolved to a pH of 2.6–2.7 using sulfuric acid.

For the experiments carried out to oxidise the vegetable tannins, hydrogen peroxide (50% *w/w*) was used as the oxidant. 7.6 ml of H_2O_2 was added to 50 ml of the semi-chrome liquor under constant stirring. The experiment was carried out at room temperature as well as at 60 °C using the same quantity of peroxide. For the experiment done at 60 °C, the electronic spectrum was recorded in the visible region at 450–750 nm using a Shimadzu UV 160A spectrophotometer at intervals of 1 h, to check for the completion of oxidation of the organic matter. After the completion of the oxidation process, the semi-chrome liquor was left undisturbed and the time required for the complete decomposition of peroxide was determined. Aliquots were drawn at definite intervals of time and the residual peroxide was determined by the iodometric method after the precipitation and subsequent removal of trivalent chromium. After the complete decomposition of H_2O_2, the COD was calculated in both cases. The semi-chrome liquor was then subjected to chromium recovery as described earlier.

Results and discussion

The spent semi-chrome liquor was analysed for SS, BOD, COD and total chromium. The results are presented in Table 1. It is expected that the COD and BOD values for the spent semi-chrome liquor will be higher than the values obtained for spent chromium liquor.[21] This is because of the presence of vegetable tannins, which leach out during the semi-chrome tanning process owing to their water solubility. The amount of chromium present in the semi-chrome liquor is 1080 mg L^{-1} that is about half the amount present in the spent chromium liquor. However, the stipulated limit for the presence of chromium(III) in various water bodies is 2 mg L^{-1}, which makes chromium recovery processes mandatory. The recovery of chromium from semi-chrome liquors can be accomplished in two ways, *viz.* direct precipitation of chromium without removal of vegetable tannins or removal of vegetable tannins keeping chromium in solution followed by chromium precipitation and recovery.

The direct precipitation of chromium from spent semi-chrome liquors did not yield satisfactory results. The settling of chromium(III) hydroxide was observed to be poor and analysis revealed around 780 mg L^{-1} of Cr in the supernatant. This implies that only 28% of the total amount of chromium present in the spent semi-chrome liquor settled as chromium(III) hydroxide. This could be attributed to the interference of vegetable tannins during the settling process. Also, the colour of

Table 1 Characteristics of the spent semi-chrome liquor

Parameter	Values[a]
pH	3.4
Suspended solids	1280
COD	9040
BOD	800
Total chromium	1080

[a] All units except pH in mg L^{-1}.

the recovered chromium liquor without any treatment for the removal of vegetable tannins is brownish green. Hence, this recovered chromium cannot be used for chromium tanning in leather processing.

Among the reducing agents employed, the addition of hydroxyammonium chloride resulted in chromium precipitation due to an increase in pH. The other reducing agents were quantified as in Table 2. The spectral changes observed during the reduction process carried out using sodium sulfite and sodium metabisulfite are presented in Figs. 1 and 2, respectively. The optimal quantity of the reducing agent was ascertained whereby the addition of even a large excess of the reducing agent did not cause any change in the absorption spectra. The reduction process could also be inferred visually by a colour change from brownish green to green, the latter due to trivalent chromium. Sodium metabisulfite proved to be the most effective reducing agent, causing a decrease in COD by 48%, *i.e.*, from 9040 mg L^{-1} of the spent semi-chrome liquor to 4700 mg L^{-1} after treatment of the liquor with zinc chloride for removal of vegetable tannins. Besides, the requirement of sodium metabisulfite was quantitatively the least as compared to other reducing agents, as seen in Table 2.

The reduction process converts the quinone to hydroquinone as shown in Scheme 1. This hydroquinone can be precipitated by means of an ion pair formation with zinc chloride. $ZnCl_2$ was the preferred precipitating agent as the zinc tannate sludge obtained can be used as landfill and also as a fertiliser.[22] The optimal quantity of $ZnCl_2$ was deduced by adding increasing amount of 0.5 M zinc chloride solution to the spent semi-chrome liquor treated with the optimised amount of reducing agent. The percentage reduction of COD for various quantities of zinc chloride addition is shown in Table 3. The increase in the amount of zinc chloride added to the treated spent semi-chrome liquors causes effective removal of vegetable tannins. This is evident from the percentage reduction in COD of the treated liquor up to a certain level of addition of zinc chloride, beyond which further removal of vegetable tannins was not effected. 5 ml of 0.5 M $ZnCl_2$ (0.3407 g of $ZnCl_2$ for 50 ml of semi-chrome liquor) caused the most effective precipitation of vegetable tannins, with a reduction in COD by 44%. The COD reduction data after precipitation of vegetable tannins using various reducing agents are shown in Table 4. It is evident that there is only a marginal difference in the percentage COD reduction between all the screened reducing agents. However, sodium metabisulfite treatment of spent semi-chrome liquor followed by treatment with an optimised quantity of zinc chloride exhibits the highest percentage reduction in COD compared to other reducing agents.

Table 2 Quantities of reducing agents required

Reducing agent	Vol. of semi-chrome liquor[a]/ml	Quantity of reducing agent required/g
Sodium metabisulfite	150	0.21
Sodium sulfite	150	0.33
Sodium dithionite	150	1.36

[a] Semi-chrome liquor having COD of 9040 mg L^{-1}

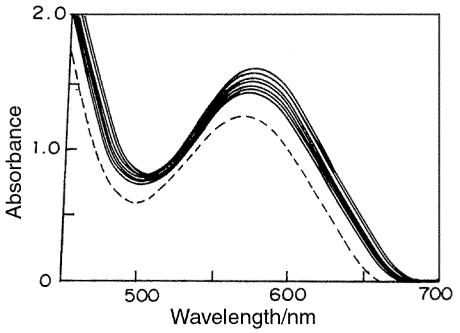


Fig. 1 Visible spectra for the reductive process using sodium sulfite, semi-chrome liquor before treatment (-----) and during reduction (——).

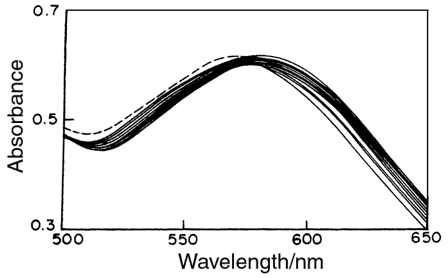
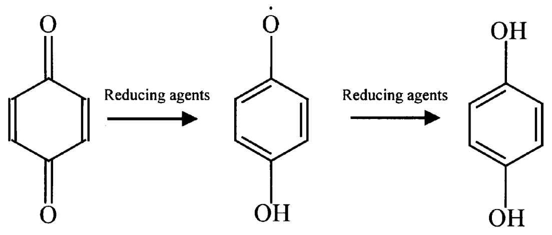


Fig. 2 Visible spectra for the reductive process using sodium metabisulfite, semi-chrome liquor before treatment (----) and during reduction (——).



Scheme 1

In all cases, a reddish brown tinge is observed while redissolving the $Cr(OH)_3$ sludge. This is due to the presence of catechols, which exhibit a reddish tinge on addition of sulfuric acid.[23] This implies incomplete removal of vegetable tannins when reducing agents are used.

The oxidative process involves the use of hydrogen peroxide. Hydrogen peroxide has been shown to be effective in reducing the COD of tannery effluents.[24] The approximate quantity of peroxide required to reduce the COD was calculated according to eqn. (1).

$$2\ H_2O_2 \rightarrow 2\ H_2O + O_2 \qquad (1)$$

From eqn. (1), for 1 mole of O_2, 2 moles of H_2O_2 (68 g) are required. Hence, 2.13 mg of H_2O_2 is required per litre of the sample to bring down the COD by 1 unit, assuming complete

Table 3 % Reduction of COD on precipitation of vegetable tannins with zinc chloride after reduction with sodium sulfite

Vol. of semi-chrome liquor/ml	Vol. of 0.5 M $ZnCl_2$/ml	COD/mg L^{-1}		Reduction(%)
		Untreated	Treated	
50	2.5	9040	7232	20
50	3.75	9040	6056	33
50	5	9040	5062	44
50	10	9040	5785	36

Table 4 COD reduction data after treatment with optimal quantities of reducing agents and zinc chloride

Reducing agent	COD of semi-chrome liquor/mg L^{-1}		Reduction(%)
	Untreated	Treated	
Sodium metabisulfite	9040	4700	48
Sodium sulfite	9040	5014	44
Sodium dithionite	9040	5333	41

utilisation of hydrogen peroxide for the oxidation of the organic matter.

The oxidation process presented a colour change of the semi-chrome liquor from brownish green to brown, indicating the oxidation of vegetable tannins; followed by a transition to green colour of trivalent chromium. The latter implies further oxidation of quinones to simpler colourless organic matter. The spectral changes taking place during the oxidation are as shown in Fig. 3. As seen from the figure, the commencement of the oxidation process upon the addition of hydrogen peroxide results in an increase in absorbance at around 500 nm. This is due to the oxidation of the polyphenolic constituents of vegetable tannins to quinones. As the oxidation proceeds, this absorbance decreases owing to the disappearance of the charge transfer band as a result of the breakdown of organic matter.

Hydrogen peroxide behaves both as an oxidising as well as reducing agent as shown by eqns. (2)–(4).

$$H_2O_2 + 2H^+ + 2\,e^- = 2\,H_2O \qquad E° = 1.77\text{ V} \qquad (2)$$

$$O_2 + 2H^+ + 2e^- = H_2O_2 \qquad E° = 0.68\text{ V} \qquad (3)$$

$$HO_2^- + H_2O + 2e^- = 3\,OH^- \qquad E° = 0.87\text{ V} \qquad (4)$$

In the oxidative process, quinones are formed, followed by aromatic ring cleavage.[25] The formation of simpler organic acids is possible as indicated by a drop in pH by 1 unit. Oxidation of phenol results in complete loss of phenol.[26]

There was subtle difference in COD reduction when peroxide was used at room temperature and at 60 °C, though the time required was drastically reduced at 60 °C. The results are depicted in Table 5. After oxidation, the COD of the spent semi-chrome liquor was analysed to be 3540 mg L^{-1}, which indicates a 60% reduction in COD as compared to the COD of 9040 mg L^{-1} in the untreated liquor. In cases of stronger oxidation, the possibility of organic matter being expelled as CO_2 cannot be ruled out.

The addition of zinc chloride did not cause any precipitation of vegetable tannins, neither was any difference observed in COD before and after $ZnCl_2$ treatment. This indicates a breakdown of the organic matter at the oxidation stage itself. However, liquors treated with $ZnCl_2$ prior to chromium precipitation resulted in excellent settling of the chromium(III) hydroxide sludge, while samples not treated with $ZnCl_2$ showed poor settling characteristics. This observation could be explained based on the fact that $ZnCl_2$ is a good flocculating agent. The residual peroxide was allowed to decompose with time, as residual peroxide can contribute to COD and also results in formation of Cr^{VI} in alkaline conditions at the chromium precipitation stage. It was found that residual H_2O_2 decomposed rapidly with time for the first 40 min. and subsequently it decomposed very slowly. Near total decomposition of the residual H_2O_2 needed 12 h at 25 °C. The time needed to decompose the residual H_2O_2 could be brought down to 10 h by maintaining the solution temperature at 70 °C. However, this reduction in time by 2 h is insignificant when we take into account the energy requirements for the heating process. During chromium recovery, addition of sulfuric acid to the chromium(III) hydroxide sludge did not indicate any reddish tinge, further consolidating the absence of vegetable tannins as catechols.

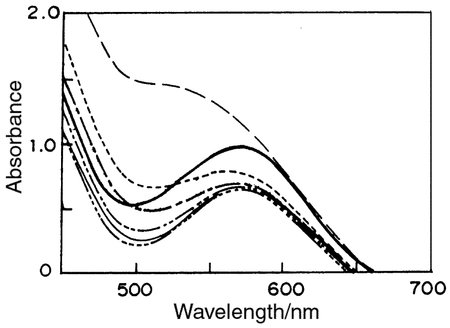


Fig. 3 Visible spectra for the oxidative process using hydrogen peroxide, semi-chrome liquor before treatment (——) and during oxidation immediately (––––), after 1 h (······); 2 h (–·–·–·), 3 h (–··–··–), 4 h (——) and 5 h (———-).

In another set of experiments, ferrous sulfate in varying concentrations was used as catalyst for the decomposition of unreacted H_2O_2 and the reduction in COD noted. The addition of Fe(III) salts as catalysts caused only a fractional decrease in COD and there was subtle difference in time required for the completion of the oxidation reaction. This could possibly be due to presence of large quantities of chromium which, being a transition metal ion, can act as a catalyst for H_2O_2 promoted oxidation.

The recovered chromium is re-used for leather tanning after adjusting the pH to 2.6–2.7 and the basicity to 30–35%. The leathers so obtained had comparable properties to conventional chromium tanned leathers.

The methodology of recovering chromium from semi-chrome wastewaters can be easily enlarged to a commercial scale with slight modification in the existing chromium recovery system for waste chromium solutions. A schematic diagram for the recovery of chromium from semi-chrome wastewaters is given in Fig. 4. The process involves collection of semi-chrome wastewaters in a collection tank (3) passing through a screen (2), followed by treatment for the removal of vegetable tannins in a vegetable tannins precipitation tank (4). The solution free of vegetable tannins is collected in a waste chromium liquor collection tank (5) and precipitated as chromium(III) hydroxide in a chromium precipitation tank (6) and finally treating the chromium(III) hydroxide sludge with sulfuric acid in a redissolution tank (7) to generate basic chromium solution, which can be reused for leather processing. Generally, the recovery of chromium from waste chromium solutions in the leather industry employs a collection tank, chromium precipitation tank and a redissolution tank of the required capacity based on the processing capacity of leather. In the present methodology, inclusion of a vegetable tannin precipitation tank and a waste chromium solution (free of vegetable tannins) collection tank is necessary. Hence, it becomes feasible to integrate this process with available chromium recovery systems in commercial scale applications.

Conclusions

The present investigation suggests suitable methods for the recovery of chromium from spent semi-chrome liquors. While

Table 5 Influence of temperature on time and COD reduction using hydrogen peroxide

Vol. of semi-chrome liquor/ml	Vol. of H_2O_2 added/ml	Temperature/°C	*t*/h	COD/mg ml^{-1} Untreated	COD/mg ml^{-1} Treated	Reduction (%)
50	7.6	35	14–18	9040	3934	56.28
50	7.6	60	5–6	9040	3540	60.66

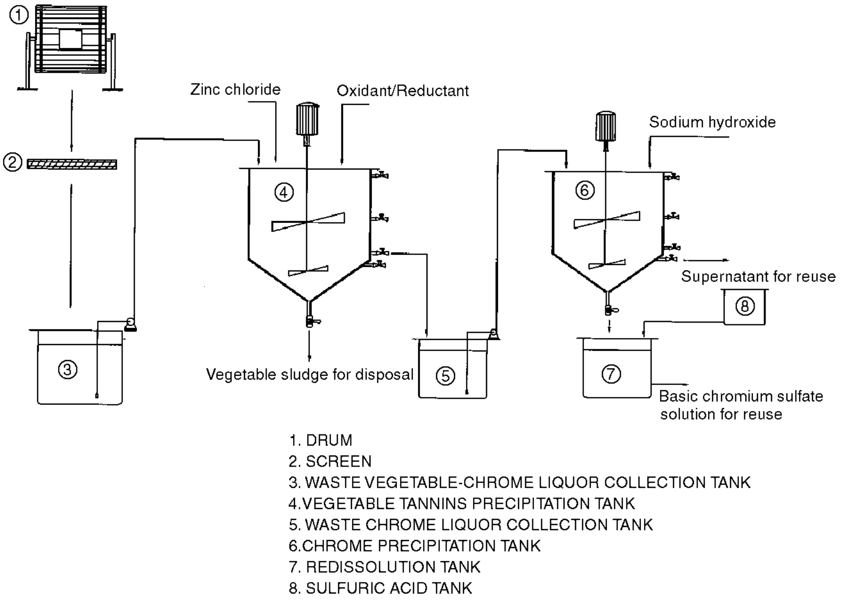


Fig. 4 Schematic diagram for the recovery of chromium from spent semi-chrome liquor.

direct precipitation of chromium does not yield satisfactory results, fairly good separation of chromium is achieved after removal of vegetable tannins by reductive and oxidative methods. Sodium metabisulfite offers maximum reduction in COD among the reducing agents employed. H_2O_2 presents the maximum reduction in COD among all methods. The cost factor of H_2O_2 is not very high, and it does not add to the solid content of the liquors as it gets reduced to water. Though the process is slightly time consuming due to the time required for the complete decomposition of H_2O_2, the use of this oxidising agent offers the best techno-economic and environmentally clean method for the recovery of chromium from semi-chrome liquors.

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Selective Stobbe condensation under solvent-free conditions

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Solvent-free condensation of cyclohexanone (**1**) and diethyl succinate (**2**) in the presence of Bu^{t}OK at room temperature gives cyclohexylidenesuccinic acid (**3**), while heating a mixture of **1**, **2** and Bu^{t}OK at 80 °C gives only cyclohexenylsuccinic acid (**4**).

Introduction

Stobbe condensation is an important C–C bond forming reaction.[1] Stobbe condensation reactions of ketones and diethyl succinate to monoesters of alkylidenesuccinic acid have been carried out under refluxing the alcoholic solution in the presence of a strong base such as sodium hydride or potassium *tert*-butoxide. This reaction, however, yields complex mixtures, both of stereoisomers and of regioisomers in which the double bond can occupy several positions.[2] We have now found that the Stobbe condensation reaction proceeds efficiently in the absence of solvent. Very interestingly, solvent-free Stobbe condensation reaction of cyclohexanone (**1**) and diethyl succinate (**2**) in the presence of Bu^{t}OK at room temperature and at 80 °C gave cyclohexlidenesuccinic acid (**3**) and cyclohexenylsuccinic acid (**4**), respectively.

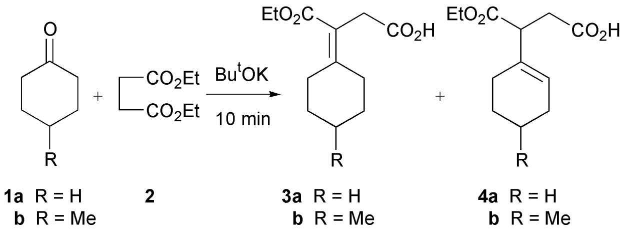
Results and discussion

To a equivalent mixture of **1a** and **2** was added powdered Bu^{t}OK (1.2 equiv.) in a mortar. The mixture was ground at room temperature for 10 min. The reaction was exposed to the air. Then, the reaction mixture was neutralized with dil. HCl and the crystals formed were isolated by filtration to give cyclohexylidenesuccinic acid (**3a**) in 75% yield. In contrast, when the reaction was carried out at 80 °C, cyclohexenylsuccinic acid (**4a**) was obtained in 92% yield. Interestingly, the yield of **4a** was increased as the reaction temperature was raised (Table 1). This method is very useful because both structural isomers (**3a** and **4a**) can be prepared selectively simply by changing the reaction temperature. Similar treatment of **1b** with **2** in the presence of Bu^{t}OK for 10 min at room temperature and at 80 °C gave **3b** and **4b** in 55 and 85% yields, respectively (Table 1).

We also found that paraconic acid derivatives (**5a** and **5b**) can be prepared efficiently in a one-pot reaction. For example, a mixture of **1a**, **2** and Bu^{t}OK was mixed and ground using a mortar and pestle for 10 min and then heated 80 °C in conc. HCl for 1 h to give γ,γ-pentamethyleneparaconic acid (**5a**)[2] in 92% yield. Similarly, **5b** was also obtained in 92% yield from the reaction between **1b** and **2** in a one-pot reaction (Scheme 1).

Solvent-free Stobbe condensation reactions of alkyl phenyl ketones (**6**) and diethyl succinate (**2**) were also found to proceed more efficiently and more selectively than those in solution. For example, a mixture of **6a**, **2** and Bu^{t}OK was mixed and ground using a mortar and pestle for 10 min at room temperature. The reaction mixture was neutralized with dil. HCl and then the crystalline product was isolated by filtration to give only **7a** (E:Z = 10:90) in 93% yield. The E:Z ratio was determined by ^{1}H NMR and the major isomer of **7a** was determined to be Z by comparison of its melting point with an authentic sample.[4] In contrast, the reaction under refluxing in Bu^{t}OH gave a 90:10 mixture of **7a** and **8a**, and the E:Z ratio of **7a** was 65:34.[2]

Table 1 Stobbe condensation of **1** and **2**



Cyclohexanone **1**	Solvent	T/°C	Yield(%)	**3**:**4**[a]
a	Bu^{t}OH	reflux	84	27:73[b]
a	None	rt	75	100:0
a	None	40	88	65:35
a	None	60	81	10:90
a	None	80	92	0:100
b	None	rt	55	95:5
b	None	80	85	0:100

[a] Determined by ^{1}H NMR.

Green Context

The development of solvent free processes is an important area of activity and many studies have been carried out, mostly using solid catalysts and microwave irradiation. Many such reactions proceed well, but use solvents to separate the product and catalyst at the end, making them not truly solvent free. This paper describes the use of solvent free processes in the Stobbe condensation, normally carried out with metal alkoxides in refluxing alcohols. Here, the solvent is omitted and the reaction proceeds smoothly. The base is neutralised, causing the product to crystallise, allowing solvent free isolation and a genuinely solvent free process with only salt waste being formed. Also of interest is the excellent selectivity of the reaction—at room temperature one isomer is exclusively formed; heating the reaction leads to the exclusive formation of a different isomer. ***DJM***

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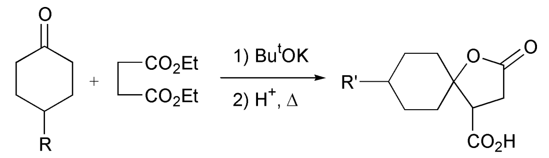
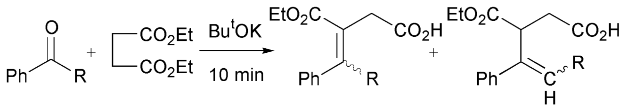


1a R = H
b R = Me
2
5a R = H
b R = Me

Scheme 1

Table 2 Stobbe condensation of **5** and **2**



6a R = Me
b R = Et
2
7a R = Me
b R = Et
8a R = H
b R = Me

Ketone **6**	Solvent	*T*/°C	Yield(%)	**7**:**8**[a]	*E*:*Z* ratio of **7**
a	Bu^tOH	reflux	71	90:10	65:35
a	None	rt	93	100:0	10:90
a	None	80	82	90:10	55:45
a	None	120	82	85:15	55:45
b	Bu^tOH	reflux	18	90:10	25:75
b	None	rt	59	90:10	10:90
b	None	80	87	35:65	45:55
b	None	120	79	30:70	45:55

Similarly, Stobbe condensation reaction of **6b** and **2** in the absence of solvent gave a 90:10 mixture of **7b** and **8b** in 68% yield with high *E/Z* selectivity (Table 2). However, the selective formation of **8** was not completely accomplished when the reaction was carried out even at 120 °C (Table 2).

In conclusion, we have developed a solvent-free procedure[5] for the selective Stobbe condensation reaction. This provides a simple, stereoselective and environmentally friendly organic synthetic method.

Experimental

Solvent-free Stobbe condensation reaction of 1a and 2 in the presence of Bu^tOK at room temperature

To a mixture of **1a** (1.0 g, 10.2 mmol) and **2** (1.78 g, 10.2 mmol) was added powdered Bu^tOK (1.37 g, 12.3 mmol) in a mortar which was well ground with a pestle at room temperature for 10 min. The reaction was exposed to the air. The reaction mixture was neutralized with dil. HCl and then the crystals formed were isolated by filtration to give β-carbethoxy-β-cyclohexylidene-propionic acid **3a** (colorless plates, 1.73 g) in 75% yield after recrystallization from acetone. Data for **3a**: mp 59–61 °C; ν(C=O) 1718, 1700 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.21 (2H, q, *J* 7.2 Hz), 3.42 (2H, s), 2.45 (2H, br s), 2.25 (2H, br s), 1.62 (6H, br s), 1.29 (3H, t, *J* 7.2 Hz).

Solvent-free Stobbe condensation reaction of 1a and 2 in the presence of Bu^tOK at 80 °C

A neat mixture of **1a** (1.0 g, 10.2 mmol), **2** (1.78 g, 10.2 mmol) and powdered Bu^tOK (1.37 g, 12.3 mmol) was heated at 80 °C for 10 min. The reaction has been exposed to the air. The reaction mixture was decomposed by adding dil. HCl and extracted with ether to give β-carbethoxy-β-cyclohexenylpropionic acid **4a** (2.13 g) in 92% yield as an oil. Data for **4a**: bp 150–155 °C (0.5 mmHg); ν(C=O) 1733, 1708 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 5.63 (1H, s), 4.16 (2H, q, *J* 7.1 Hz), 3.38 (1H, dd, *J* 5.1 and 9.9 Hz), 2.97 (1H, dd, *J* 9.9 and 16.8 Hz), 2.50 (1H, dd, *J* 5.1 and 16.8 Hz), 1.52–2.09 (8H, m), 1.27 (3H, t, *J* 7.1 Hz).

One-pot preparation of γ,γ-pentamethyleneparaconic acid (5a)

A mixture of **1a** (1.0 g, 10.2 mmol), **2** (1.78 g, 10.2 mmol) and Bu^tOK (1.37 g, 12.3 mmol) was mixed and ground using a mortar and pestle for 10 min, followed by heating the reaction mixture at 80 °C in conc. HCl (10 ml) for 1 h. After cooling to room temperature, the crystals formed were isolated by filtration to give γ,γ-pentamethyleneparaconic acid **5a**[2] (colorless plates, 1.98 g) in 92% yield after recrystallization from MeOH–toluene (1:1). Data for **5a**: mp 185–186 °C; ν(C=O) 1734, 1717 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.69–2.78 (1H, m), 3.00–3.18 (2H, m), 1.25–1.85 (10H, m).

Solvent-free Stobbe condensation reaction of 6a and 2 in the presence of Bu^tOK at room temperature

To a mixture of **6a** (1.23 g, 10.2 mmol) and **2** (1.78 g, 10.2 mmol) was added powdered Bu^tOK (1.37 g, 12.3 mmol) in a mortar and well ground with pestle at room temperature for 10 min. The reaction was exposed to the air. The reaction mixture was neutralized with dil. HCl and then the crude crystals formed were isolated by filtration to give 2-(1-phenylethylidene)-succinic acid 1-ethylester **7a** (2.35 g) in 93% yield. Recrystallization of crude crystals from acetone gave pure (*Z*)-**7a**[4] (2.1 g, 83%). Data for (*Z*)-**7a**: mp 110–112 °C; ν(C=O) 1720, 1692 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.12–7.35 (5H, m), 3.86 (2H, q, *J* 7.2 Hz), 3.57 (2H, s), 2.17 (3H, s), 0.79 (3H, t, *J* 7.2 Hz). Distillation of the solvent from the mother liquor of (*Z*)-**7a** gave (*E*)-**7a** as a viscous oil (0.2 g, 8%). Data for (*E*)-**7a**; ν(C=O) 1720, 1692 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.12–7.35 (5H, m), 4.27 (2H, q, *J* 7.2 Hz), 3.24 (2H, s), 2.43 (3H, s), 1.31 (3H, t, *J* 7.2 Hz).

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