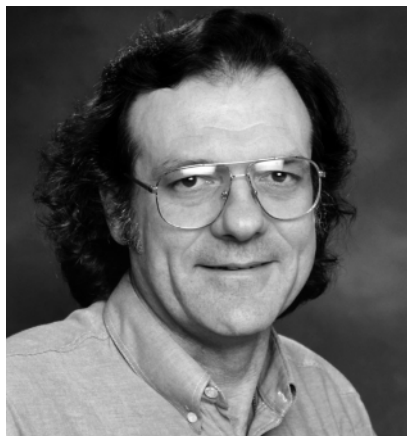




# Green chemistry down under



Green chemistry in Australia had its origins in early February 1998 when Paul Anastas (then at the EPA, Washington DC) and Terry Collins (Carnegie Mellon University) addressed the annual Royal Australian Chemical Institute (RACI) professors and heads of department of chemistry meeting. A great deal of enthusiasm for green chemistry was evident. The next major event was the Department of Chemistry at Monash University, Melbourne, embracing the principles of green chemistry, and ultimately securing a Special Monash University Research Fund (SMURF) as a new research initiative. SMURF is open to all disciplines and interestingly the green chemistry proposal was ranked number one in the Faculty of Science, then ranked number one across the University. Thus non-chemist scientists and non-scientists perceived green chemistry as a most worthwhile endeavour. This gave the Department seed funding for 1999 and a range of new projects started. The same year was an opportunity to apply for an Australian Research Council Special Research Centre. Applications for these are called for every 3 years across all disciplines (excluding medicine) and each university in Australia (38 in total) was allowed to submit 5 applications. Thankfully one of them was for green chemistry which ultimately was funded initially for three years, with additional funding likely for a second 3-year period, and even a third 3-year period, funding being close to \$1m AUS per year. The green chemistry proposal was one of only 11 successful ARCSRC applications and thus was a political winner in securing Federal funds.

The Director of the Centre in the first instance is Roy Jackson (Sir John Monash Distinguished Professor) with Colin Raston as Deputy Director. Monash University has provided a lectureship in green chemistry, which was filled by Janet Scott, who worked in the Centre during 1999 and thus far has made significant advances in projects involved in developing solventless reactions and reaction in ionic liquids with two recent papers in *Green Chemistry*. In addition, Monash University provided additional funding for the Centre as well as embarking on a refurbishment of a significant part of the Department of Chemistry, as a focus for the Centre (offices, meeting room, and laboratories).

The Centre has collaborative projects involving 12 faculty staff in the Department of Chemistry, and increasing with staff in other Departments including Biochemistry and Materials Engineering, and staff with contiguous Divisions of CSIRO (Commonwealth Scientific and Industrial Research Organisation)—Minerals, Molecular Sciences, and Forestry and Forest Products. Key projects include solventless reaction, the replacement of organic

solvents by water, CO<sub>2</sub>, and ionic liquids, the use of aqueous based catalyst systems, the use of microwave energy in chemical reactions, benign mineral processing, new energy efficient materials together with the development of new, appropriate analytical methods. As an ARC funded Centre there is a commitment to basic research with the expectation that the applied arena will be supported at least in part by industry. Even so the distinction between the two is fuzzy since success in green chemistry requires an understanding of processes at a molecular level. Thus far several companies are involved and gratifyingly some have come 'knocking on the door'. In the Australian context this is an exciting development.

An Advisory Committee, with representation from other universities including overseas, the EPA, Industry, and the Plastics and Chemicals Industry Association of Australia has been established. Through this Committee the Centre is committed to create strong collaborative links with research groups overseas, noting that green chemistry is of global concern, and the isolation of Australia. The Centre networks through the Green Chemistry Network, and the Green Chemistry Institute, for which Monash University is the Australian Chapter. The Centre is actively engaged in lobbying Government on key issues relating to Green Chemistry, the environment and where possible striving to get relevant issues into our foreign policy. The Centre is also developing teaching programs in Green Chemistry. The first course was delivered last year and it proved very popular and resulted in a strong interest in research projects at the Honours and PhD levels in the Centre. At present there are over 12 postgraduates and 8 postdoctoral researchers in the Centre. Through community activities there is also a strong interest from the Teachers Association in getting aspects of Green Chemistry into the high school syllabus.

The Victorian EPA and Envirolinx recently ran a highly successful half day workshop on green chemistry in Melbourne, which attracted 50 engineers and process chemists predominantly from the chemical and waste industries, utilities and processing industries. Ron Allison of Nufarm, a large agricultural chemical manufacturer, demonstrated a practical application of green chemistry in the production of 2,4-D herbicide. The Centre is planning a workshop early 2001, and green chemistry will feature in the IUPAC World Chemical Congress to be held in Brisbane, 2–6 July, 2000.

The RACI is also committed to green chemistry with the establishment of the Green Chemistry Challenge Award for excellence in industry and government/university research, and teaching. The inaugural recipient in 1999 was Chris Strauss (CSIRO Molecular Sciences) in recognition of his research in eliminating the use of organic solvents and/or inorganic waste. The 2000 recipient is Eric Kennedy (University of Newcastle) in recognition of his new technology for converting halogenated wastes to useful chemicals. Another researcher in Australia who has embarked on green chemistry is Adam McCluskey (University of Newcastle) with a paper in *Green Chemistry* (1999, **1**, 167) on water-based organic synthesis.

We believe that green chemistry has a bright future in Australia and look forward to keeping you informed of future developments.

**Colin Raston**  
Monash University, Melbourne, Australia



# Hydrogen activation in supercritical fluids

**A. M. Kluwer of the Institute of Molecular Chemistry at the University of Amsterdam, The Netherlands, describes a successful COST meeting in Mülheim, Germany**

The Max-Planck-Institute für Kohlenforschung in Mülheim was the venue for a two-day symposium on the "Activation of Hydrogen for Catalytic Chemical Synthesis in Supercritical Reaction Media" between 14–16 May 2000. This event was organised as part of the activities of a research network within the COST D 10 program of the European Community and its primary goal was to stimulate research activities, collaborations and exchange of expertise within this COST D 10 group. Therefore, the meeting was initially intended as an informal forum for the associated research groups of Professor Bargon/Dr Woelk (Bonn), Professor Dediou (Strasbourg), Professor Elsevier (Amsterdam), Dr George (Nottingham), Professor Heaton (Liverpool) and Dr Leitner (Mülheim). After some inquiries

by colleagues from various backgrounds, however, there appeared to be a greater interest in this subject. Thus, the originally planned COST meeting grew rapidly to a mini-symposium with over 60 participants. This extension was only possible with the generous support of the Max-Planck-Institute für Kohlenforschung, the Foundation for the Advancement of Research in Inorganic Chemistry (BOAC) and Celanese Chemicals Europe GmbH.

The broad interest was certainly peaked by the excellent scientific program put together by the Chairmen C. J. Elsevier and W. Leitner. It included oral contributions from network members as well as lectures from external experts. As highlighted below, the topics covered preparative and mechanistic aspects of hydrogen activation in supercritical fluids

(SCFs), as well as theoretical calculations of their solvent properties and spectroscopic techniques to investigate reactions in SCFs. The presentations of the members of the COST group demonstrated nicely the mutual stimulation of their research within the network and many of the results originated from collaborations and exchange visits between the individual groups.

## Chemical reactions

After an informal get-together on Sunday evening, the program was opened on Monday by Dr Chr. Kohlpaintner of Celanese Chemicals Europe GmbH, who presented examples from the industrial practice of aqueous two-phase catalysis. By using water-soluble catalysts, he emphasized the possibility to reduce the





amount of waste material (*e.g.*, salts), obtain better product/catalyst separation, and also sometimes higher activity. On basis of the Ruhrchemie/Rhône-Poulenc process for hydroformylation, important issues of industrial applications of “unconventional” solvent systems were discussed.

The topics of this opening lecture were nicely reflected in the closing lecture by Dr R. Karge from Hoffmann LaRoche, who gave a detailed account on possible opportunities and problems associated with the industrial use of supercritical fluids with examples ranging from natural product extraction to hydrogenations in fine chemicals synthesis. The two presentations from industry thus framed the contributions directed towards the fundamental aspects of chemical reactions in SCFs.

The opening lecture was followed by a presentation by Dr W. Leitner of the MPI providing an overview of homogeneous catalysis in compressed carbon dioxide. He started with a historical overview of the use of supercritical carbon dioxide in chemical synthesis and extractions. The major breakthrough came with the development of natural product extraction using  $\text{scCO}_2$  by K. Zosel at the host institute in Mülheim in the early 1960s. The use of supercritical fluids, as an environmentally friendly alternative for organic solvents for homogeneous metal complex catalysed reactions, has only been recently recognized but the number of examples has been growing fast. Leitner presented numerous examples of transition metal catalyzed reactions (*e.g.*, enantioselective hydrogenation, hydroformylation and ruthenium-catalyzed metathesis reactions) that were successfully adjusted to  $\text{scCO}_2$  as a solvent in his research group.

A. M. Kluwer (University of Amsterdam) introduced selective palladium(0) catalyzed hydrogenations of alkynes to (*Z*)-alkenes in supercritical fluids. He showed that it has been possible to synthesize apolar palladium complexes comprising of a dinitrogen ligand and an electron poor alkene which are soluble in  $\text{scCO}_2$ . These complexes have been tested for the hydrogenation of alkynes to (*Z*)-alkenes using various substrates. Product selectivities between 90 to 95% could be obtained and in some cases higher conversions were reported for supercritical media as compared to conventional solvents.

Highly regio- and enantio-selective rhodium-catalysed asymmetric hydroformylation in  $\text{scCO}_2$  was the topic

of G. Franció's (MPI) lecture. The new perfluoroalkyl-substituted (*R,S*)-*R*-BINAPHOS allowed rhodium catalyzed hydroformylation to be carried out in compressed carbon dioxide as a solvent. The catalytic activity and the level of enantiocontrol was similar to the parent (*R,S*)-BINAPHOS/rhodium system but, at the same time, unprecedented high regioselectivity for the branched aldehydes was observed.

Fluorinated catalysts for hydroformylation were also the theme of B. Heaton, who presented recent results in this area obtained by him and J.-L. Xiao at the Leverhulme Centre for Catalysis at Liverpool.

An elegant aqueous/supercritical fluid biphasic system was described by P. Jessop (University of California) for the complex or colloid catalyzed arene hydrogenation. This two-phase system comprising of an aqueous buffer and supercritical ethane gave high conversions, and in some cases high selectivity, for the hydrogenation of arenes and substituted arenes. This is the first successful example of an unsupported colloid-catalysed hydrogenation of a substrate in the supercritical fluid. In the Jessop group, it was also found that the addition of *subcritical* carbon dioxide can have an accelerating effect on a solventless reaction with solid reactants. One of the examples that was presented was the hydrogenation of 2-vinylnaphthalene to 2-ethylnaphthalene which would not proceed without the presence of carbon dioxide. It was noted that the  $\text{CO}_2$  is not dense enough to dissolve any of the reagents except the hydrogen gas and that the carbon dioxide is not needed chemically for this reaction to proceed. The dramatic rate increase is caused, at least partly, by the lowering of the melting point of the vinyl naphthalene by the  $\text{CO}_2$ .

### Theory

Fluorination is known to be an efficient way of increasing the solubility of many compounds in supercritical carbon dioxide. A. Dedieu (CNRS, Strasbourg) presented the latest results obtained in his group on the fundamental interactions between  $\text{CO}_2$  and perfluoroalkyl-substituted benzenes on a molecular level. Calculations performed at the MP2/6-31+G\* level revealed an increased interaction of the carbon dioxide with fluoroalkyl-substituted benzenes compared to benzene. It is hoped that further analysis of the calculations can

help to understand and analyse such weak interaction.

Professor H. Huber (University of Basel) described in a very stimulating talk the state of the art in combining quantum chemistry and molecular dynamics to simulation and analysis of bulk properties and solvent effects of liquid and supercritical carbon dioxide.

### Spectroscopy

The importance of spectroscopy as a powerful tool for the investigation of hydrogen activation in chemical synthesis was stressed during this meeting. Recent advances in IR spectroscopy of SCFs were presented by Mike George (University of Nottingham). C. J. Elsevier (University of Amsterdam) showed that supercritical media possesses beneficial features for NMR spectroscopy of solute molecules. Owing to their low bulk viscosity of these media, the longitudinal relaxation times of quadrupole nuclei increase significantly and hence their line widths will be considerably reduced compared to those in common solvents like benzene and acetone.

The use of toroid cavity detectors (TCD) for high-pressure NMR investigations was described by K. Woelk (University of Bonn). The unique cylindrical geometry and the confinement of the radio-frequency magnetic field to within the cavity predestined its simultaneous use as an NMR detector and high-pressure/temperature autoclave for *in situ* NMR studies. Spectroscopic results from catalytic hydrogenation reactions conducted with these probes in either conventional solvents or in supercritical fluids were presented by H. Niessen from the same group.

The program ended on Tuesday with a visit to the high pressure laboratories of the MPI including some of the original equipment used by K. Zosel. The smooth and efficient local organisation, which was mainly in the hands of Dr K. Beck, was very important for the open and stimulating atmosphere throughout the meeting. There was ample time for scientific discussion with every contribution, which could be continued in an informal atmosphere during the boat trip on the river Ruhr on Sunday afternoon and the conference dinner on Monday. In conclusion, this COST D10 meeting was a fruitful and exciting event and provided an ideal opportunity for the exchange of new ideas, existing know-how and theoretical background in this rapidly growing area of research.



# NEWS

## Producing resources to support education for sustainable development in schools

The Council for Environmental Education (CEE) and the Environment Agency are holding a series of seminars on 'Strategic Approaches to Supporting Education for Sustainable Development' (ESD). The first seminar in the series focused on the changing climate within schools as the transition is made from environmental education to education for sustainable development and its position within the National Curriculum.

The overwhelming message was that there is a lack of clarity as to what is required from both teachers and resource producers alike. To resolve this, the DfEE (Department for Education and Employment) have recently announced that new guidance notes will be issued, but these will not be issued until early 2001.

CEE have an extensive database, available to members, of environmental educational resources produced over the last 10 years. Reviewing the 1500 resources on the database, Libby Grundy, Director of CEE, highlighted the almost complete lack of resources for the post 16 and special needs sectors. Most resources that have been produced fall in the Geography sector, with over 100 resources devoted to 'school grounds' alone! Resources for science teaching in this area come a poor second, with energy conservation dominating the field.

As Nick Jones, Education Officer at CEE, pointed out aspects of sustainable development are statutory in Geography, Science and Citizenship with a further five subjects, Design & Technology, History, Art & Design, Physical Education and ICT expected to promote the concepts. This cross curriculum aspect of ESD partly accounts for the lack of understanding of what is required, according to Bill Scott (Centre for Research in Education and the Environment, University of Bath). He called for the need for a focus of responsibility in schools and greater guidance as to what is required in terms of course content.

Most educationalists believe the focus of ESD to be in Geography where the focus

of teaching lies with conservation projects connected with school grounds. In the revised National Curriculum the contribution of Science to ESD is 'through developing pupils' skills in decision making on the basis of sound science, the exploration of values and ethics relating to the applications of science & technology and developing pupils' knowledge and understanding of some key concepts such as diversity and interdependence'. There is an obvious need for clarity and greater guidance and until this is forthcoming we are not likely to see much sustainable chemistry taught. Hopefully the situation will improve when the new guidelines are produced and that this will lead to a new impetus for producers of science resources. Without more involvement of science in ESD there is some danger that science is seen as the cause of environmental problems and Geography portrayed as the cure!

## New NSF Science and Technology Center

The National Science Foundation (NSF) has funded a new Science and Technology Center dedicated to studying Environmentally Responsible Solvents and Processes. The key mission of the Center is to establish the fundamental understanding necessary to enable liquid and supercritical CO<sub>2</sub> to replace aqueous and organic solvents in a large number of key industrial processes (in later years other supercritical fluids may be investigated). If successful, the Center should have significant impact on reducing pollution and energy usage in the U.S. and elsewhere. The Center involves the University of North Carolina-Chapel Hill (lead institution), NC State University, NC A&T University of the University of Texas (Austin).

The Center is developing a very extensive website, which has recently become operational. It has many hyperlinks to websites related to development of sustainable technology. They are interested in establishing as many mutual hyperlinks as possible with appropriate websites to facilitate students' learning about "green chemistry". They currently have a hyperlink to the RSC's Green Chemistry Network website. The

Center is planning to support about 45 graduate students and postdoctoral fellows annually. Students are encouraged to visit their website to learn about possible positions:  
<http://www.nsfstc.unc.edu/>.

For further information contact: Dr. Everett Baucom, Deputy Director, NSF Science and Technology Center for Environmentally Responsible Solvents and Processes, 300 Venable Hall, University of North Carolina-Chapel Hill, Chapel Hill, NC 27599-3290, USA.

## Aluminium chloride in decline

It is rare to go to any green chemistry meeting without at least one speaker putting forward a green alternative to the use aluminium chloride in Friedel-Crafts alkylation and acylation. Evidence that green chemistry is working can be found from the rapid decline in anhydrous aluminium chloride (AAA) production in recent years. The UK's only producer, Elementis recently closed its production facility in Durham whilst in the US the number of producers has fallen from 6 to 3 in the last 15 years. Today AAA sales are only around 1000,000 tpa with processes such as styrene and ibuprofen manufacture being recent converts to green technology.

## More efficient *p*-xylene production

IFP have unveiled a new efficient catalyst for converting ethyl benzene to *p*-xylene. The new zeolite based catalyst, called Oparis gives yields of 93% compared to 88% achieved with the conventional mordenite catalyst. Pilot studies have shown that loss of aromatics due to transalkylation have been cut by 50% whilst activity has been increased by 25%. The higher reactivity will result in significant opex and capex savings.

## Cargill Dow start to build new PLA plant

Building work has started, at Cargill Dow's Blair site, on the world's first



large-scale facility for manufacturing plastics from corn. The plant should be operational in early 2002 and is expected to consume 14 million bushels of corn per year. The plant will produce polylactide (PLA), sold under the name NatureWorks PLA, which can be used to manufacture a wide range of biodegradable consumer goods from food packaging and furnishings such as cups to textiles. Production capacity will be 300 million pounds of PLA a year. The company plans to build a similar facility in Europe at some time in the future.

## Biopesticide for Australian Sugar

The first biopesticide for sugar cane, called BioCane, has recently been launched in Australia. The product is based on a naturally occurring fungus that has been cultured on broken rice grains to provide a medium for distribution. BioCane granules are claimed to be particularly effective against grayback canegrub, which cost the industry A\$10 million pa.

## Economic instruments "Not too difficult!" says UK Sustainable Development Round Table

The UK Government must be bolder in moving the economy in more sustainable directions, its key independent environment advisers have urged.

The Round Table makes the following recommendations:

- The Government should initiate processes of updating the Sustainable Development Strategy and integrate these more closely with the Budget and spending planning processes.
- Economic and policy analysis should identify where and to what extent economic instruments including taxes would be the most efficient and effective means of delivering the targets.
- The Treasury should always give sympathetic consideration to using at least some environmental taxes to provide incentives for relevant environmental improvements when it introduces a new sustainable development tax proposal.
- The Government should consider, before introducing any sustainable development economic instrument, its possible impact on the competitiveness of UK firms (including the UK as a whole).
- Where there is real evidence of likely damage to competitiveness, the Government should adopt measures which give firms some flexibility in how to respond.
- The Government should consider, before introducing a sustainable development economic instrument, what equity problems arise (undertaking research into its net impact on identified potentially vulnerable groups in terms not only of costs but also of benefits) and what measures might be taken to overcome them. Further research should be undertaken, after the introduction of a new economic instrument, to assess its actual impact on relevant groups.
- Economics instruments should be assessed for effectiveness in delivering

sustainable development objectives. Where the instrument by itself is likely to be less than fully effective, associated measures aimed at increasing the effectiveness of delivery of the objective should be introduced.

- The Government should take a pro-active approach to establishing the public perception of the policy 'baseline' against which proposals for economic instruments should be judged.
- Effective processes should be considered and adopted, based on the practical experience gained from past exercises in the consideration of environmental taxes.
- The Government should establish an independent, standing advisory body on sustainable development economic instruments, reporting to HM Treasury.
- The Government, and the proposed advisory body, should give further consideration to whether powers to introduce economic instruments to tackle issues of sustainable development might appropriately be given to the devolved administrations or to local government.
- The UK Government should initiate further discussion between groups of countries about the way in which appropriate economic instruments introduced in each country might contribute to the joint solution of common problems of sustainable development.

UK Round Table in Sustainable Development publication "*Not too difficult! – economic instruments to promote sustainable development within a modernised economy*" (see: <http://www.open.gov.uk/roundtbl/hometb.htm> or telephone: +44 207 944 4964 for further information).

# Green chemistry in New Zealand

## Kathleen Crisley from the University of Canterbury describes the areas of green chemistry research being investigated in New Zealand

In 1999, the University of Canterbury in Christchurch launched a campus-wide initiative known as *Green Products and Processes*. This research group

acknowledges the fact that effective research into "sustainability" requires a wide range of specialist skills, each contributing to the study of pertinent

sustainability issues. The initiative encourages interdisciplinary and industry collaborations by involving dedicated project management and organisational



inputs to programme and team development.

Green Products and Processes team members are involved in the following research areas that are particularly relevant to the green chemistry movement:

### Natural products and clean synthesis

We have a research team who are involved in the identification and production of new pharmaceutical agents and enzyme inhibitors that are derived from New Zealand's indigenous estuarine fungi. The team is combining the biochemical and microbial characterisation of the source material with novel process engineering techniques for separation and purification and, where necessary or appropriate, the total synthesis of the new compounds.

The identification and development of enzymatically catalysed processes are also being undertaken for the development of cleaner production techniques for a range of chemical and food products. Such products include high performance machine oils, edible oils and food supplements.

### Ionic solvents

Ionic solvents are the subject of a new research programme *for which international collaborations are actively being sought.*

Ionic liquids are a family of inorganic solvents that exhibit a high degree of catalytic activity. Such liquids also exhibit no significant vapour pressure and high solvating power for a wide range of compounds. They are interesting because their structure can be readily adapted to achieve desired physical and catalytic properties of interest to chemists and to engineers. The prime purpose of the proposed research programme is to study the thermophysical properties of these liquids as well as liquid-liquid equilibria and partitioning with organic solvents to develop tailored ionic liquids for specific separation processes.

We are also studying novel methods of dispersing ionic liquid media for the enhanced separation and recovery of biological products, which is a cross-over between this research programme and the natural products research programme described earlier.

An important aspect of the ionic solvents project is the strengthening of international collaborative links with inorganic chemistry groups in the UK and the USA who will provide support with respect to the synthesis and to modification of the solvent chemistry. Current links exist with the Group headed by Professor Ken Seddon at Queens University, Belfast, Dr Tom Welton, Imperial College, London, and Professor Robin Rogers, Center for Green Manufacturing at the University of Alabama. These linkages will facilitate an iterative research process between chemists, biologists and chemical engineers to understand the relationship between chemical structure and performance of these liquids.

The Green Products and Processes Group is actively seeking collaborations with offshore colleagues. To inquire about the possibilities for collaboration, contact Kathleen Crisley, Project Manager, Green Products & Processes, University of Canterbury, Private Bag 4800, Christchurch, New Zealand. Tel. +64-3-364-2217; Fax +64-3-364-2063; e-mail: k.crisley@research.canterbury.ac.nz

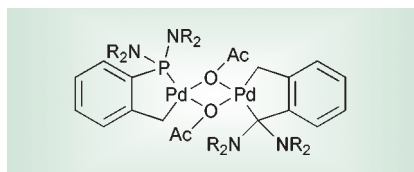


Key green chemistry staff at the University of Canterbury. TOP ROW: Professor Laurence Weatherley, Head of the Chemical and Process Engineering Department and leader of the Green Products & Processes Group; Professor Murray Munro, co-leader of the Marine Chemistry research project; Professor Ken Marsh, co-leader (with Laurence Weatherley) of the new ionic solvents research initiative. BOTTOM ROW: Dr John Blunt, Reader in Chemistry and Head of the Department of Chemistry and co-leader of the Marine Chemistry research project; Associate Professor Tony Cole, Head of the Plant and Microbial Sciences Department.

# Perspectives

## The Heck reaction – remarkable improvements to turnover numbers and frequencies

The Heck reaction remains one of the most useful and versatile C–C bond forming reactions known. Recently effort has been expended in making heterogeneous versions of the Pd catalysts (see, for example, *Green Chem.*, 2000, **2**, 53) and in the development of Pd catalysts with very high efficiencies. The group led by Jean Michel Brunel in Marseille has now reported that a new class of phosphapalladacycles (generally the best type of catalyst) display enormous turnover numbers and turnover frequencies (*Angew. Chem., Int. Ed.*, 2000, **39**, 1946).

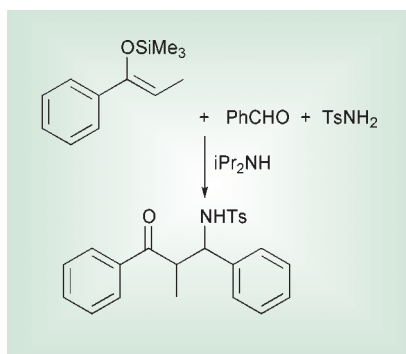


The catalysts structure is as shown in the scheme, and the novelty lies in the use of the bisalkylaminophosphane unit in place of the more usual bisaryl or bisalkyl unit. In test reactions with iodobenzene and norbornene, turnover numbers of up to *ca.*  $10^{10}$  were achieved, with  $> 10^8$  being regularly found. These numbers are substantially higher than any seen before, and allow the Heck reaction to be done with vanishingly small quantities of catalyst.

## New catalytic method for the Mannich reaction

The Mannich reaction is an efficient method for the coupling of three components in one step. This is typically achieved using Lewis acid catalysts such as  $\text{AlCl}_3$  and boron species, leading to acidic spent catalyst waste. Recently, lanthanides have been employed as water stable Lewis acids for the transformation, an approach which may lead to cleaner processes. A new method has also been developed by researchers in Ibaraki led

by Akira Hosomi, which uses base catalysis to carry out the transformation (*Angew. Chem., Int. Ed.*, 2000, **39**, 1958).

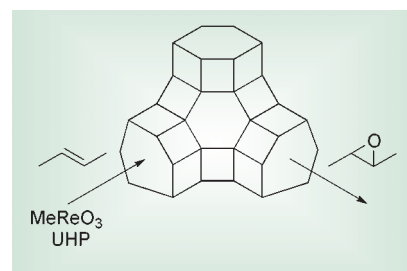


Reactions are run at low temperature and give high yields. A range of substituents can be employed in the reaction. Anti : syn ratios are also generally high, often  $> 90 : 10$ . Such a method may broaden the scope of the reaction to acid-labile reagents and gives a valuable alternative to undesirable catalysts such as aluminium trichloride.

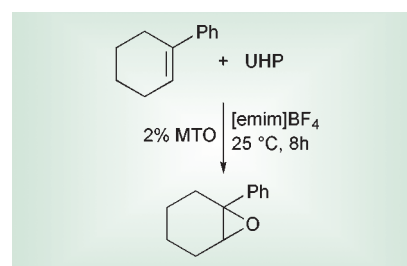
## Two novel catalytic systems for the epoxidation of alkenes

One of the most intensively researched areas of chemistry is the search for novel epoxidation methods. Many exist, but few are genuinely environmentally acceptable. A recent contribution to this area has come from Oliver Weichold and his colleagues at the university of Würzburg (*J. Org. Chem.*, 2000, **65**, 2897). Their system is based on the well known combination of methyl rhenium trioxide (MTO) and hydrogen peroxide. This couple can be used to carry out a number of oxidations, but often suffers from lack of selectivity, and typically requires mild base buffers to control side reactions. If hydrogen peroxide is replaced with the urea–hydrogen peroxide complex (UHP) then these problems can be ameliorated. However, this generates urea as by-product as well as the water from the peroxide. Weichold and co-workers have got round this hurdle by employing a NaY zeolite to act as a host for the oxidations. The NaY provides a suitable

environment for the reaction to take place without the incursion of significant side-reactions, and without the use of soluble basic buffer or significant amounts of urea. For example the epoxidation of a range of alkenes was shown to proceed in excellent conversions and almost complete selectivity.



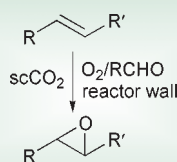
As indicated above, the use of hydrogen peroxide and its complexes as oxidants is an active area of research, as the oxidant is both clean and cheap. The drive to replace high volatility solvents with more easily handled materials such as ionic liquids is likewise a vigorously active field. Gregory Owens and Mahdi Abu-Omar of the Department of Chemistry and Biochemistry at UCLA have now combined the two areas with a new protocol for the epoxidation of alkenes (*Chem. Commun.*, 2000, 1165). They used the catalyst methyl trioxorhenium for the transformation. Cyclic, styrenic and allylic alkenes were oxidised in a few hours at room temperature in excellent conversions and selectivities, but linear alkenes suffered from lower conversion (but still excellent selectivity). The solvent used was a cationic imidazolium tetrafluoroborate, which is easily synthesised and is stable under the reaction conditions. Products can be extracted with organic solvents, leaving the catalyst in the ionic liquid layer.





## Oxidations in supercritical carbon dioxide

A further epoxidation method, this time using oxygen and aldehydes as the oxygen transfer couple has been demonstrated by Frank Loecker and Walter Leitner of the Max Planck Institute in Mülheim (*Chem., Eur. J.*, 2000, **6**, 2011). They have discovered that the epoxidation of alkenes using aldehydes and oxygen can be carried out without the addition of catalysts. Typically, this type of oxidation, which uses an aldehyde as oxygen carrier *via* peroxyacid-type intermediates, requires transition metal catalysts such as iron or nickel to take place. In an interesting twist to this chemistry, they have found that the interior stainless steel walls of their reactor provide the catalytic sites



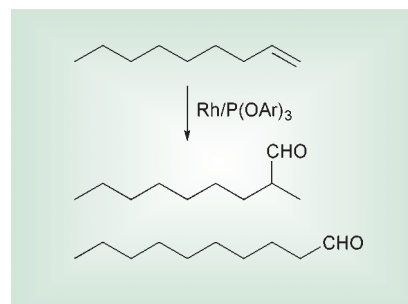
required, without the requirement of any further catalyst, making the reactor the ultimate heterogeneous catalyst! Excellent conversions were achieved for several epoxidations. Whether this process has any implications for the lifetime of the vessel was not discussed.

## New routes for the functionalisation of hydrocarbons

Many attempts are being made to revamp hydroformylation chemistry. This reaction type represents an extremely valuable route to aldehydes from alkenes, but the traditional approaches have significant drawbacks, especially for higher olefins. These include the separation of the expensive rhodium catalyst or forcing conditions and poor selectivity if the cheaper cobalt is used. The ratio of linear to branched aldehyde is often another difficult parameter to control.

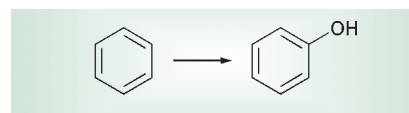
Murielle Sellin and David Cole-Hamilton of the University of St Andrews have now published an interesting method based on supercritical fluids (*J. Chem. Soc., Dalton Trans.*,

2000, 1681). Their process deliberately utilises catalysts which are insoluble in the reaction medium, so that the product-containing solution can be swept from the vessel into a second reactor, where it is depressurised to isolate the product. Their catalyst system is based on Rh complexes of triarylphosphites, and their reaction conditions can be chosen such that selectivity to the more valuable linear isomer is highly favoured. No rhodium could be detected in the product and the catalytic system could be re-used several times.

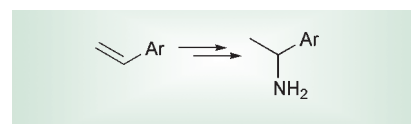


## Benzene hydroxylation

The hydroxylation of aromatic feedstocks is a second important goal in the functionalisation of hydrocarbon feedstocks. This allows the direct formation of valuable raw materials directly from hydrocarbons, and is especially exciting when an oxidant such as hydrogen peroxide is used. The 1980's saw the advent of TS-1, a zeolitic material capable of such reactions under mild conditions. One of the major drawbacks of this material is its very small pore size, which precludes the majority of aromatics from reaching the active sites. Corresponding MCM-type catalysts have been studied and some promising results have been achieved. Another approach, described by Nomiya's group from Kanagawa university in Japan, involves the use of vanadium substituted polyoxomolybdates as catalysts (*J. Mol. Cat., A*, 2000, **156**, 143). They have presented results which demonstrate that these materials are active catalysts for the conversion of benzene to phenol using hydrogen peroxide. Since access to active sites in such polyoxomolybdates is easier, larger molecules should also be amenable to this treatment. Although no results were presented in this article relating to bulkier substrates, such an extension to this system may be of interest.



The formation of amines such as *tert*-butylamine has recently been revolutionised by the advent of the BASF process. This replaces the harsh, corrosive Ritter reaction with a much cleaner direct amination of the alkene with ammonia over zeolites. Extension of this concept to the direct amination has been attempted by the group of Wolfgang Hölderich at the RWTH Aachen (*J. Mol. Cat., A*, 2000, **156**, 255). They found that, using the BASF conditions, the reaction was hindered by thermodynamic difficulties, and that the polymerisation of styrene restricted their choice of operating parameters. Undeterred, they found that the hydration of styrene under

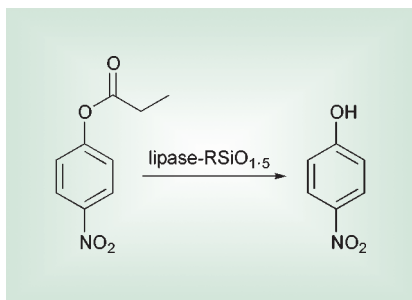


similar conditions, followed by a nucleophilic displacement of the alcohol with ammonia gave the desired product in relatively low yields. More success was found with  $\alpha$ -methyl styrene, where the direct amination proceeded in good yield.

## Entrapped biocatalysts

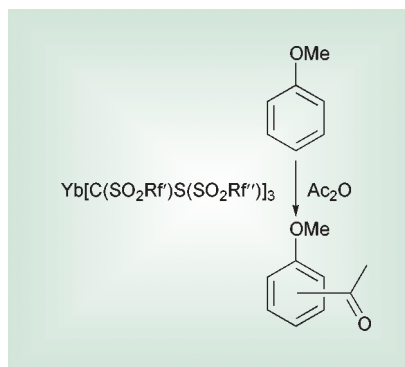
The use of enzymes as catalysts in organic synthesis is a very attractive area of research, with excellent selectivities and mild conditions being commonplace. However, the use of enzymes is often complicated by the sensitivity of enzymes to non-biological conditions. In organic solvents the use of CLICs or powdered enzymes is possible, but can lead to substantial loss of activity. In aqueous solution, the enzyme is typically homogeneous, but this can lead to difficulties in recovery of the enzyme and the product. The group of Manfred Reetz in Mülheim has now developed a system whereby a lipase is entrapped in a hydrophobic silica matrix (*Synthesis*, 2000, 781). The trick here was to have a functionalised silica containing hydrophobic methyl or propyl groups. This led to lipases which were substantially more active than the powdered enzyme in organic solvents. Recovery and reuse of the enzyme-silica composite was demonstrated.





Lanthanides have recently been the subject of intense interest due to their excellent Lewis acid characteristics coupled with their very flexible

coordination chemistry, allowing them to function in Lewis basic solvents such as water, and to behave catalytically in

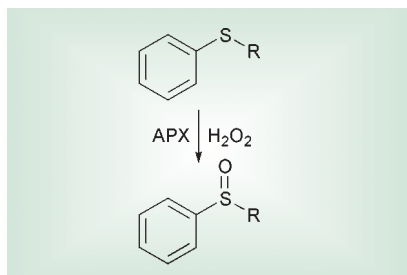


Friedel–Crafts acylations. The group led by Tony Barrett (*Green Chem.*, 1999, **1**, G97) has now published a new method which combines a ytterbium catalysts with fluoruous biphasic conditions, allowing the Friedel–Crafts acylation of anisole and the efficient recycling of catalyst (*Synlett*, 2000, 847). They chose as catalyst the fluoruous Yb catalyst containing three carbanionic ligands, each of which has three perfluorosulfonyl chains, imparting fluoruous phase solubility. This catalyst is active in the acylation of anisole with acetic anhydride, and can be recovered and reused.

# Green Chemistry Network Symposium at the University of Leicester

Following a successful first symposium at York towards the end of 1999 the GCN's 'Young Persons' symposium series moved to Leicester. On this occasion the presentations covered a wide breadth of green chemistry topics including selective synthesis, benign solvents, fluoruous biphasic systems for efficient separations, fuel cells and clean electrochemical synthesis. Abstracts of the talks can be seen on the GCN web site: <http://www.chemsoc.org/gcn>.

Ayhan Celik from Leicester discussed the design of enzymes for carrying out specific, selective chemical transformations, particularly oxidations. The concept was illustrated with the ascorbate peroxidase (APX) catalysed oxidation of aromatic substrates. APX efficiently catalyses the hydrogen peroxide oxidation of aryl alkyl sulfides but with little R:S selectivity. By replacing an active tryptophan site in APX with alanine the R:S selectivity can be as high as 4:1 (for R = Et).



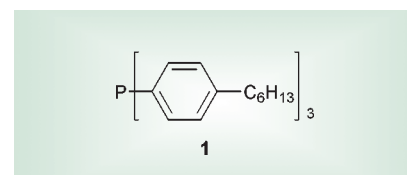
The selectivity theme was continued by Colin Hayman from Loughborough who

discussed stereoselective approaches to Phorbol esters. Phorbol esters are co-carcinogens and an efficient synthesis of these materials is needed to further study their biological properties. The talk focussed on a key intramolecular Diels–Alder reaction introducing stereocontrol, the Diels–Alder reaction being potentially highly green, producing no waste. Approaches to activating the diene and dienophile to speed up the slow reaction were discussed.

The next two presentations from Richard Major and Jie Ke of Nottingham University discussed aspects of supercritical CO<sub>2</sub> technology. Dispersion polymerisation in supercritical fluids is currently a very active research area. AIBN initiated polymerisation of methyl methacrylate. Stabilisers are an essential part of such systems, being required to control particle size and prevent reactor fouling. The Nottingham group have been studying the effects of Krytox 157FSL, an acid terminated perfluoropolyether and have show that particle size can be controlled by both the concentration and MWt of the stabiliser. Since phase behaviour may have a significant influence on the reaction it is important to ensure that so called supercritical reactions actually remain in the supercritical state throughout the reaction. Acoustic measurements have been shown to offer a simple, effective means of monitoring the phase behaviour of reactions. Using hydroformylation of

propene in CO<sub>2</sub> as an example the critical temperature shifts from well below that of CO<sub>2</sub> to well above as the reaction proceeds due to the effect of varying concentration of products and reactants.

The next two presentations discussed green aspects of fluoruous biphasic systems which exploit the temperature dependant miscibility of highly fluorinated solvents and normal organic solvents. Adrian Dobbs (Open University) discussed 'greening' of the Wittig reaction. Although very versatile the Wittig reaction is not widely used in industry, one reason for this is the difficulty of removing triphenyl phosphine oxide residues from the product. However by using phosphines such as **1** containing a perfluoro alkyl



group the resulting phosphine oxide can be readily extracted into a perfluorinated hydrocarbon solvent and recycled.

Alison Stuart from Leicester discussed some catalytic applications of fluoruous soluble phosphorous ligands, with particular reference to hydroformylation. Hydroformylation of terminal with catalysts such as HRh(CO)L<sub>3</sub> where L is triphenyl phosphine give aldehydes with a normal : iso chain ratio of around 2.5. Since



it is the normal aldehyde which is usually required reactions which produce more of the desired product are both greener and more efficient. By replacing triphenyl phosphine with a series of fluorinated phosphine ligands the normal : iso ratio has been increased to over 6.

Fuel cells are of current topical interest and offer tremendous potential as a more efficient and cleaner method of energy generation than conventional methods. Robert Cunningham (Keele) described work on the direct internal fuel reforming in solid oxide fuel cells. SOFCs have several advantages over other fuel cell systems, not least because they operate at high temperatures and can therefore use a variety of fuels including natural gas. There are several problems however mainly concerned with carbon deposition on the anode and sintering of the anode during the high temperature operation.

The Keele group has developed a unique test system based on thin walled yttria-stabilised zirconia (electrolyte) tubular reactors for studying anode performance. By modifying the nickel/zirconia anode significant lowering of the carbon deposition rate can be obtained, incorporation of Mo into the anode is proving especially beneficial. Stephanie Livermore (Keele) continued the SOFC theme concentrating on cells that run at intermediate temperatures (600 °C). Ceria-gadolinia based cells have high ionic conductivity and therefore can operate at lower temperatures than the cells discussed above. This gives the potential advantage of producing less carbon deposits.

The Keynote speech 'How Green is Electrochemistry?' was given by Professor Keith Scott (Newcastle). The usefulness of electrochemical techniques

in areas as diverse as fuel cells, organic synthesis and waste remediation were discussed. Some of the synthetic applications highlighted includes naphthalene oxidation, synthesis of 3-bromothiophene (avoiding zinc acetate waste) and hydrogenation of vegetable oil. By way of an excellent conclusion Scott highlighted the relevance and potential areas of application to all the 12 Principles of Green Chemistry. Potentially, electrochemical reactions are also relatively inexpensive with electrons costing £8/te equivalent, much less expensive than most other redox reagents. However the cost of the electrochemical cells are relatively high, preventing investment in all but 'secure' long-term chemical production. So is electrochemistry green? Well it certainly can be but, like most things, it depends on how it is applied.

## Green Industrial Applications of Ionic Liquids—a NATO advanced research workshop

In the first international meeting dedicated to the study and application of ionic liquids as solvents, forty-one scientists and engineers from academia, industry, and government research laboratories met in Heraklion on the island of Crete from 12–16 April 2000 to discuss the current and future status of the application of ionic liquids to new green industrial technologies. They were joined by six industry observers and four student/staff helpers. The full program, scientific abstract, attendee list, and group picture can be accessed *via* the website create for this ARW at <http://bama.ua.edu/~rdrogers/NATO>.

The workshop began with a plenary lecture on green chemistry by Professor John Warner (University of Massachusetts-Boston) followed by three-and-a-half days of intensive lectures and discussion on the current status of ionic liquid research and application. Topics covered included industrial needs in green chemistry, current industrial applications of ionic liquids, separations, electrochemistry, novel chemistries in ionic liquids, green catalysis, and the status of East–West collaborations.

The last day-and-a-half were devoted to roundtable discussions meant to distill the workshop's content into major

recommendations of the ionic liquid research community. The three roundtables included: a) outlining industrial priorities, needs, and challenges in green chemistry, b) drafting ionic liquids research priorities to meet the green needs of the chemical industry, and c) developing protocols to enhance East–West collaborations in ionic liquids research.

The major outcomes of the workshop included the following:

- Ionic liquids are intrinsically interesting and worthy of study for advancing science (ionic vs. molecular solvents) with the expectation that something useful may be derived from their study.
- Combined with green chemistry, a new paradigm in thinking about synthesis in general, ionic liquids provide an opportunity for science/engineering/business to work together from the beginning of the field's development.
- Readily available, well characterized ionic liquids, free of intellectual property, are needed to encourage development of applications.
- Toxicity, biodegradation, bio-accumulation, safety, health, and environment (SHE) impact data are needed immediately.

- Ionic liquid research should include cost/benefit, economic, and life-cycle analyses.
- Regulatory road blocks to ionic liquid implementation should be tackled now.
- A public (free), verified, web-based database of physical, thermodynamic, and related data (*i.e.*, not process specific) is needed, and work should start immediately on identifying the best methods to accomplish this.
- There is an urgent need to increase the number, but especially the areas of expertise of ionic liquids researchers. A model of open collaboration needs to be encouraged.
- International collaboration and communication/education regarding the results are needed.
- A brochure should be developed to advance the understanding of ionic liquids and their applications.
- A NATO Advanced Study Institute should be held dedicated to all facets of the study and application of ionic liquids from scientific, engineering, and business perspectives. This meeting should occur no earlier than Spring 2002.

Further information on this research workshop can be obtained at the Green Chemistry website at <http://www.rsc.org/greenchem>



# Clean, efficient syntheses of cyclotrimeratrylene (CTV) and tris-(*O*-allyl)CTV in an ionic liquid

Janet L. Scott, Douglas R. MacFarlane, Colin L. Raston\* and Ching Mei Teoh

Department of Chemistry, Monash University, Clayton, Melbourne, 3800, Victoria, Australia.

E-Mail: colin.raston@sci.monash.edu.au

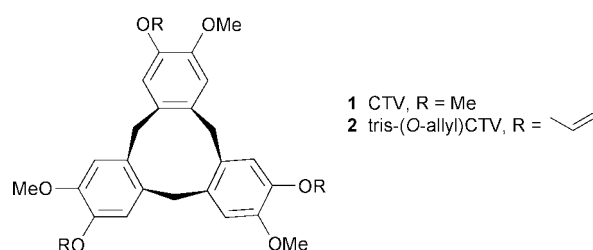
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Cyclic cyclotrimeratrylene (CTV) type supramolecular host compounds are traditionally synthesized under harsh dehydrating conditions and require the use of large quantities of organic solvent in the reaction workup. We now report both solvent-free and ionic liquid reaction media in efficient 'green' syntheses of CTVs under mild conditions. The ionic liquid tributylhexylammonium bis(trifluoromethylsulfonyl)amide ( $N_{6444}$  Imide) provides a safe, non-volatile reaction medium that is readily recycled. This methodology obviates the need for the use of large quantities of organic solvent and strong dehydrating acids yet provides pure crystalline product in high yields. Unlike most traditional synthetic routes to these compounds extensive recrystallisation or chromatographic steps are avoided and the molten salt reaction medium is readily recovered. Interestingly, condensation also occurs under ambient conditions on grinding of solid benzyl alcohol monomers with a suitable solid acid to afford the corresponding CTV. Ionic liquids have, as yet, been little explored as reaction media or solvents yet these offer significant advantages over volatile (and often toxic) organic solvents. Human exposure to potentially harmful vapours is obviated and recycling of the ionic liquid reaction medium significantly reduces waste generated. The procedures described here serve to extend the use of ionic liquids as reaction media.

## Introduction

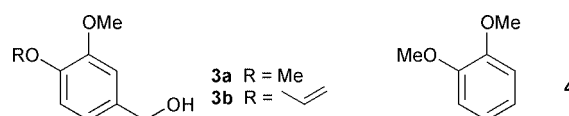
2,3,7,8,12,13-Hexamethoxy-10,15-dihydro-5*H*-tribenzo-*[a,d,g]*cyclononene or cyclotrimeratrylene (CTV) **1** and related molecules such as the tris-(*O*-allyl)CTV analogue **2** are versatile



supramolecular host compounds. CTV itself has been shown to form a range of fascinating supramolecular arrays with guest molecules ranging from volatile solvent molecules<sup>1</sup> to large globular molecules such as carboranes<sup>2</sup> and even  $C_{60}$ .<sup>2a,3</sup> Association of CTV and mesoporous silica leads to a qualitative test for the presence of  $C_{60}$ <sup>4</sup> while further derivatisation of a CTV analogue yields improved binding of the fullerene.<sup>5</sup>

The tris-(*O*-allyl) ether of cyclotrimeratrylene **2** is readily deprotected<sup>6</sup> and resolved into its enantiomers.<sup>7</sup> This triphenol provides a convenient starting material for a range of differently substituted CTV type compounds, which may be optically active.<sup>7,8,9</sup> CTV derivatives have also been used in the synthesis of materials exhibiting liquid crystalline phases<sup>10</sup> and as starting materials in the synthesis of cryptands.<sup>11</sup>

The first reports of the synthesis of CTV type compounds date back to the early part of this century with the report of the acid-catalysed condensation of veratryl alcohol, **3a**, or veratrole, **4**, and formaldehyde.<sup>12</sup> These methods remain little changed, being achieved under acidic, dehydrating conditions involving reaction media such as conc.  $H_2SO_4$ , conc.  $HClO_4$ , 6 M  $HCl$ ,  $HCl/ZnCl_2$  or solvents such as acetic acid or benzene combined with  $H_2SO_4$ ,  $HClO_4$  and  $BF_3$  etherate.<sup>13</sup>



Condensation methods using strong acids have proven unsuitable for the synthesis of CTV analogues from benzyl alcohol derivatives bearing appreciably acid-labile OR groups such as the *O*-allyl derivative **3b** and minor modifications have been reported.<sup>6</sup>

Clearly there is considerable scope for improved syntheses of CTV and CTV analogues and as part of our research in green chemistry, which includes design of more benign synthetic protocols, we have devised two simple, high yielding, yet low waste-producing synthetic routes to CTV and related molecules. We have previously reported atom and energy efficient solvent-

## Green Context

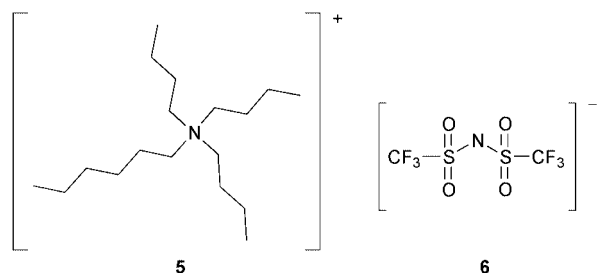
Cyclic cyclotrimeratrylenes have been known for over 80 years but they are now receiving considerable attention as supramolecular host compounds for various species including low molar mass organic solvents through to  $C_{60}$ . Unfortunately, their syntheses does not match their new 'high technology' applications and continues to rely on large volumes of volatile organic solvents and soluble strongly acidic catalysts. In this paper, a major step forward is made towards greening their preparation. Successful syntheses are described using both no solvent (the ideal situation but one that can be impractical for some reactions owing to viscosity issues or heat transfer problems) and using involatile (and totally recyclable) ionic liquids as solvents. Under these environmentally favourable conditions reactions occur under quite mild conditions.

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free Aldol condensation reactions<sup>14</sup> and are now able to extend this methodology to the condensation of solid benzyl alcohol derivatives to form CTV type compounds. While solvent-free syntheses offer huge benefits in terms of reduced waste and ease of hazard management, issues such as handling of partially solid or very viscous reaction mixtures and effective heat transfer in bulk mixtures may make these procedures unsuitable for reactions carried out at elevated temperatures. We have thus also considered the use of an emerging class of compounds known as ionic liquids as 'green chemistry' reaction media.

Solvents are generally high on the list of toxic or otherwise damaging chemicals largely due to the huge volumes used and the difficulty in containing volatile liquids. Ionic liquids are salts which are molten in the temperature range of interest.<sup>15</sup> An increasingly large family of salts is becoming available which are molten at, and sometimes below, room temperature. Those that exhibit high stability to air and moisture are particularly interesting as potential reaction media as the non-volatile nature of these compounds makes them attractive candidates for replacement of volatile or toxic organic solvents in synthetic procedures, at the same time diminishing the risk of fire or explosion.<sup>15</sup>

Many salts prepared from unsymmetrical quaternary ammonium cations such as the tributylhexylammonium ion, **5**, with



the bis(trifluoromethanesulfonyl)amide<sup>†</sup> anion, **6**, (together designated *N*<sub>6444</sub> Imide) prove to have freezing points close to or below room temperature.<sup>16</sup>

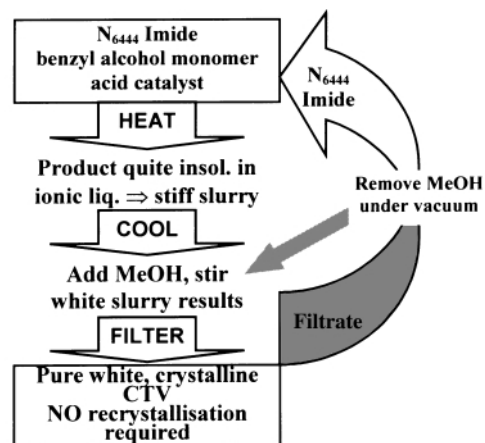
We now demonstrate the utility of this ionic liquid as a reaction medium in the acid catalysed condensation of benzyl alcohol derivatives to form CTV type compounds. Thus we present two alternative synthetic methodologies to the traditional syntheses of CTVs. Both of these methods benefit from vastly reduced waste and occupational hazard inherent in the use of volatile organic solvents and corrosive (and volatile) acids while producing product of high purity in excellent yield. The solvent-free methodology proves to be particularly well suited to analogues of CTV synthesized from solid benzyl alcohol derivatives that are sensitive to strongly acidic conditions while condensation in the ionic liquid *N*<sub>6444</sub> Imide facilitates the condensation of liquid or molten benzyl alcohol monomers to CTVs.

## Results and discussion

The ionic liquid *N*<sub>6444</sub> Imide proves to be an exceptionally good medium for the synthesis of CTV type compounds by condensation of benzyl alcohol monomers in the presence of catalytic amounts of acid. This contrasts strongly with traditional methods that require the use of strongly dehydrating bulk acids or acid/organic solvent combinations. In addition to providing pure crystalline product in high yield the non-volatile nature of the ionic liquid provides unique recycling possibilities and no chlorinated solvents are required for recrystallisation of the product. The procedure used is summarised in Fig. 1.

The ionic liquid reaction medium could be recycled five times before product quality was compromised, presumably due to a buildup of impurities in the recycled reaction medium (<sup>1</sup>H NMR analysis of this material indicates the presence of unrecovered CTV and some CTV related byproducts). No intermediate purification, apart from removal of methanol under vacuum, is required and, indeed, recycling of the reaction medium is required to achieve maximum yield as CTV is not completely insoluble in the ionic liquid/methanol mixture from which it is filtered. As the methanol required during product isolation is removed by distillation this may also be recycled back into the process.

The conditions of each reaction and isolated yields of pure crystalline products are summarised in Table 1. In each case the product isolated is a pure white crystalline material which was confirmed as **1** or **2** by comparison with authentic samples of **1** and **2** by melting point, TLC and <sup>1</sup>H NMR analysis. The molecular structure and conformation of **2** is confirmed by single crystal diffractometry studies<sup>‡</sup> and is illustrated in Fig. 2. Yields reported are for first crop materials only. In the case of the neat (solid or liquid) reactions a significant amount of product is detectable in oils resulting from complete evaporation of crystallisation solvent and second crops could be



**Fig. 1** Schematic indicating procedure followed to achieve recycling of the ionic liquid.

**Table 1** Yields of pure CTV and tris-(*O*-allyl)-CTV under different reaction conditions

Monomer <b>3</b>	Method	Acid	<i>T</i> /°C	Reaction time	Yield <sup>a</sup> (%)
<b>a</b>	<i>N</i> <sub>6444</sub>	H <sub>3</sub> PO <sub>4</sub> (cat)	75–80	4 h	83–89
<b>b</b>	<i>N</i> <sub>6444</sub>	H <sub>3</sub> PO <sub>4</sub> (cat)	70–75	4.5 h	82–83
<b>a</b>	neat liquid	H <sub>3</sub> PO <sub>4</sub> (cat)	R.T.	<sup>b</sup>	—
		H <sub>3</sub> PO <sub>4</sub> (cat)	80–85	5 h	41
		<i>p</i> -TsOH·H <sub>2</sub> O (cat)	75–80	<sup>c</sup>	—
<b>b</b>	melt	H <sub>3</sub> PO <sub>4</sub> (cat)	75–80	4 h	59
		<i>p</i> -TsOH·H <sub>2</sub> O (cat)	75–80	<sup>c</sup>	—
<b>b</b>	solid	<i>p</i> -TsOH·H <sub>2</sub> O (1 equiv.)	R.T.	2 d	54
		<i>p</i> -TsOH·H <sub>2</sub> O (0.05 mol equiv.)	R.T.	10 d	35

<sup>a</sup> Isolated yields of pure crystalline product. <sup>b</sup> Reaction imperceptibly slow. <sup>c</sup> Forms solid grey material around *p*-toluenesulfonic acid crystals and reaction rate slows significantly.

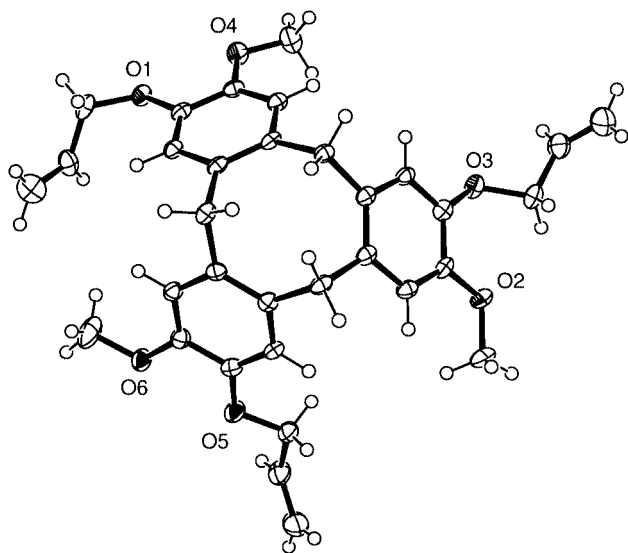


Fig. 2 ORTEP plot of product **2** with ellipsoids shown at the 50% probability level. Oxygen atoms are labelled for clarity.

separated from these oils by chromatography, significantly improving yields. In the light of the high yields of pure product obtained by reaction in ionic liquid, laborious chromatographic procedures requiring relatively large amounts of organic solvents seem unjustified.

*p*-Toluenesulfonic acid was chosen as a suitable acid catalyst for the solvent-free reaction of the solid monomer **3b** as it is a solid at room temperature. Where reaction mixtures were intermittently ground this proved effective but introduction of solid acid catalyst into neat liquid monomers resulted in rapid passivation of the acid catalyst by formation of solid product shells around the acid crystals rendering the catalyst inaccessible. This also occurred in reactions carried out in the ionic liquid as the reaction medium (*p*-toluenesulfonic acid is insoluble in  $N_{6444}$  Imide) and thus a mineral acid readily miscible with  $N_{6444}$  Imide was chosen as a suitable acid catalyst.

It is interesting to compare the results obtained in neat reactions at temperatures comparable to the ionic liquid reactions. In each case reaction is observed to proceed at a rapid rate on addition of the acid catalyst. The reaction mixture becomes progressively more viscous as product forms until the reaction mixture becomes too viscous to achieve effective stirring. On cooling this reaction mixture solidifies. While significant quantities of product are detectable by TLC analysis, a number of impurities are also noted and crystallisation of the pure product is inhibited. In contrast the reactions in ionic liquid proceed to completion with virtually no impurity formation and crystallisation of product proceeds rapidly as ionic liquid is dissolved in methanol, thus the ionic liquid has the added advantage of shutting down competing reactions.

Compared to traditional methods of CTV synthesis using strong acids and vigorously dehydrating conditions,<sup>12,13</sup> the conditions used in both the neat and ionic liquid reactions are mild and are therefore suitable for use with monomers bearing acid labile groups. In addition the hazards associated with the use of solutions of strong acid are significantly reduced (only catalytic amounts required) and organic solvent use is hugely reduced and restricted to product isolation. Organic solvents used in product isolation are not heated above ambient temperature, thus reducing the difficulties associated with containment of vapours and, in the ionic liquid process solvent use is restricted to methanol which is subsequently recovered. Energy expenditure associated with methanol recycling (inherent in the recovery of ionic liquid) is relatively low due to the low boiling point of the solvent and high solvent demand

chromatographic procedures are only required for purification of the ionic liquid reaction medium after a number of cycles.

That the reaction proceeds to high yields under these relatively mild conditions in the ionic liquid is probably a direct reflection of the chemical nature of the ionic liquid. The organic salts of the bis(trifluoromethyl)amide ion have typically been found to be strongly hydrophobic; the salts are usually prepared in good yield by separation from water. This property of the anion is thought to be related to the diffuse and partly protected nature of the negative charge.<sup>16</sup> In the present reactions, the low equilibrium water activity in the ionic liquid assists in driving the reaction to high yields, the excess water being continually lost to vapour. In this respect the interesting and beneficial properties of the ionic liquid as a reaction medium have their origins in some of the chemical and physical properties of this particular ionic liquid. This underscores the need for a wide range of such ionic liquids to be developed and their properties understood in order that the most beneficial green synthetic aspects of their use may be identified.

Given the vigorous dehydrating conditions reported by other authors it is remarkable that the condensation of solid monomer **3b** proceeds under solvent-free conditions at ambient temperature without protection from atmospheric moisture. While recovery of tris-(*O*-allyl)CTV after reaction at room temperature for 10 d was poor, this method provides for condensation of benzyl alcohol monomers bearing acid labile groups under extremely mild conditions and it is possible that such methodology could be optimised to yield novel CTV analogues.

## Experimental

<sup>1</sup>H NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer in CDCl<sub>3</sub> solution with TMS as reference. Melting points were recorded on an Electrothermal digital melting point apparatus and are uncorrected. X-Ray diffraction data were collected on an Enraf Nonius CCD diffractometer at 123 K using graphite monochromated Mo-K $\alpha$  radiation ( $\lambda = 0.71073$  Å). Data were corrected for Lorentz polarisation effects. Structures were solved by direct methods using the program SHELXS-97<sup>17</sup> and refined by full matrix least squares refinement on  $F^2$  using the programs SHELXL-97<sup>18</sup> and Xseed.<sup>19</sup> Non-hydrogen atoms were refined anisotropically and hydrogen atoms inserted at geometrically determined positions with temperature factors fixed at 1.2 times that of the parent atom except for methyl hydrogen atoms where the temperature factors were constrained to equal 1.5 times that of the parent carbon atom.

## Synthetic procedures

Representative experiments of each type are described, details of all relevant experiments are summarised in Table 1.

*Reaction in ionic liquid  $N_{6444}$  Imide.* Cyclotrimeratrylene **1**: The ionic liquid tributylhexylammonium bis(trifluoromethylsulfonyl)amide (2 ml), recovered from a previous experiment (and therefore saturated with **1**), was stirred with 1 drop of H<sub>3</sub>PO<sub>4</sub> and liquid **3a** (1.035 g, 6.15 mmol) added to form a viscous solution of the monomer in  $N_{6444}$  Imide. The temperature was raised (oil bath) to 75–80 °C with stirring, resulting in a single liquid phase. Reaction was allowed to proceed for 4 h by which time all monomer, as measured by TLC analysis (dichloromethane:ethyl acetate, 4:1), had been consumed. After cooling methanol (15 ml) was added and product **1** separated by filtration followed by washing with 5 ml of methanol. 822 mg (89%) of white crystalline product was

collected and shown to be pure **1** by comparison with authentic samples of **1** with respect to melting point, and  $^1\text{H}$  NMR analysis. Ionic liquid recycling was achieved by removal of methanol under vacuum and reuse without further purification. The ionic liquid reaction medium was recycled five times.

**Tris-(O-allyl)cyclotrimeratrylene 2:** The ionic liquid tributylhexylammonium bis(trifluoromethylsulfonyl)amide (2 ml), recovered from a previous experiment (and therefore saturated with **2**) was stirred with 1 drop of  $\text{H}_3\text{PO}_4$  and solid **3b** (510 g, 2.63 mmol) added to form a slurry of the monomer in  $\text{N}_{6444}$  Imide. The temperature was raised (oil bath) to 70–75 °C with stirring, resulting in a single liquid phase. Reaction was allowed to proceed for 4.5 h by which time all monomer, as measured by TLC analysis (dichloromethane:ethyl acetate, 4:1), had been consumed. After cooling methanol (15 ml) was added and product **2** separated by filtration followed by washing with 5 ml of methanol. 384 mg (83%) of white crystalline product was collected and shown to be pure **2** by comparison with authentic samples of **2** with respect to melting point, and  $^1\text{H}$  NMR analysis. The molecular structure of **2** was confirmed by single crystal diffractometry of clear, colourless needle-like crystals grown from methanol/dichloromethane. Ionic liquid recycling was achieved by removal of methanol under vacuum and reuse without further purification. The ionic liquid reaction medium was recycled three times.

**Recycling of  $\text{N}_{6444}$  Imide:** The products **1** and **2** are not completely insoluble in the  $\text{N}_{6444}$  Imide/methanol mixture and product recovery is only maximised on recycling of the ionic liquid. This is readily achieved by removal of methanol under vacuum (the ionic liquid having no measurable vapour pressure) yielding  $\text{N}_{6444}$  Imide saturated in product. Reuse of this reaction medium as described above leads to good yields of product.

**No-solvent reactions—solid monomer.** Tris-(O-allyl)cyclotrimeratrylene **2:** Solid **3b** (300 mg, 1.54 mmol) and *p*-toluenesulfonic acid monohydrate (16 mg, 0.08 mmol) were ground in a mortar and pestle until a homogeneous mixture was obtained. The resultant powder slowly become a sticky syrup as the reaction proceeded. After 10 d at ambient temperature the reaction mixture solidified and TLC analysis (dichloromethane:ethyl acetate, 4:1) indicated very little unreacted **3b**. The major spot on TLC analysis had  $R_f$  identical to that of an authentic sample of tris-(O-allyl)-CTV. The product was isolated by dissolution in dichloromethane, followed by filtration of any undissolved material (*p*-toluenesulfonic acid and any polymeric products formed) and crystallisation by slow evaporation of the solvent. 95 mg (35%) of the white crystalline product obtained proved to be pure **2** when compared with authentic samples of tris-(O-allyl)CTV by melting point, TLC and  $^1\text{H}$  NMR analysis.

**No-solvent reactions—liquid/molten monomer:** Cyclotrimeratrylene **1:** Liquid **3a** (2.049 g, 12.18 mmol) was placed in a round bottomed flask, heated in an oil bath to 75–80 °C and a drop of  $\text{H}_3\text{PO}_4$  added with stirring. After 5 h (when the reaction was shown to be substantially complete by TLC analysis as described above) the reaction mixture was cooled and 20 ml of methanol added. The solid material obtained was filtered off, taken up in dichloromethane and recrystallised to yield 750 mg (41%) of pure **1** identified as described above.

**Tris-(O-allyl)cyclotrimeratrylene 2:** Solid **3b** (666 mg, 3.42 mmol) were placed in a round bottomed flask, heated in an oil bath to 75–80 °C and a drop of  $\text{H}_3\text{PO}_4$  added with stirring. After 4 h the reaction mixture was cooled, whereupon it solidified. Methanol (12 ml) was added to the solid material (shown by TLC analysis to contain a significant amount of **2**) which yielded a slurry from which the product was readily separated by filtration. 255 g (59%) of finely divided crystalline product were obtained and identified as **2** as described above.

## Acknowledgements

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## Notes and references

† This anion is also commonly described in the materials and electrochemistry literature as the bis(trifluoromethylsulfonyl)imide ion hence the abbreviation  $\text{N}_{\text{xyyy}}$  Imide.

‡ *Crystal data:*  $\text{C}_{33}\text{H}_{36}\text{O}_6$ , **2**, *M* 528.62, monoclinic, space group  $P2_1/n$ ,  $a = 14.4429(5)$ ,  $b = 8.0609(3)$ ,  $c = 24.3908(7)$  Å,  $\beta = 99.519(2)^\circ$ ,  $V = 2800.6(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $\mu(\text{Mo-K}\alpha) = 0.085$  cm<sup>-1</sup>, 21634 reflections measured, 6441 unique, 3817 with  $I > 2\sigma(I)$ . Final *R* indices [ $I > 2\sigma(I)$ ]  $R1 = 0.0689$ ,  $wR2 = 0.1581$ , GoF on  $F^2 = 1.031$ . Electron density  $\Delta$  maps reveal minor disorder in one of the allyl groups resulting in a peak of 1.69 e Å<sup>-3</sup>. This disorder was not modelled. Both enantiomers are present and no solvent molecules are occluded in the structure. CCDC 1048/2. See <http://www.rsc.org/suppdata/gc/b0/b000825g/> for crystallographic files in .cif format.

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# Reductive dechlorination of polychlorinated biphenyl compounds in supercritical carbon dioxide

Qixiang Wu,<sup>a</sup> Abdul Majid<sup>b</sup> and William D. Marshall<sup>\*a</sup>

<sup>a</sup> Dept. of Food Science and Agricultural Chemistry, Macdonald Campus of McGill, 21,111 Lakeshore Road, Ste-Anne-de-Bellevue, Qué., Canada H9X 3V9.

E-Mail: marshall@agradm.lan.mcgill.ca

<sup>b</sup> Institute for Chemical Process and Environmental Technology, National Research Council of Canada, Montréal Road, Ottawa, ON, Canada

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Polychlorinated biphenyl mixtures (Aroclor 1242 and 1248) are dechlorinated efficiently (but not quantitatively) with heated columns of zero-valent metal or bimetallic mixture in a continuous process. Supercritical carbon dioxide transfers the substrates through the reactor and cumulative ten minute fractions of eluate are trapped in hexane during 1 h of continued operation. The extent of dechlorination is influenced appreciably by the identity of the zero-valent (ZV) metal ( $\text{Fe}^0 > \text{Ni}^0 > \text{Zn}^0 > \text{Cu}^0$ ), by the temperature ( $400 \geq 300 > 200$  °C) and pressure ( $\leq 4500$  psi) within the reactor column(s) and especially by the composition of the feedstock. Although water is both unnecessary and detrimental to the dechlorination yields, the inclusion of methyl ketone(s) in the feedstock solution appreciably improves the extent of the dechlorination. Two columns ( $25 \times 1$  cm) of  $\text{Ag}^0/\text{Fe}^0$  or  $\text{Ag}^0/\text{Ni}^0$  bimetallic mixture result in a virtually quantitative dechlorination of substrate Aroclor 1242 ( $\sim 28$  mg  $\text{min}^{-1}$ ). Moreover, during 1 h of continued operation, the dechlorinations are very repeatable. In preliminary treatments of 30% (v/v) acetone–hexane extracts (*ca.* 600 ppm PCBs) of a spiked sandy loam soil, no chlorinated organics could be detected in the PCB eluting region by GC-MS.

## Introduction

A popular strategy to effect abiotic dehalogenations has been to mediate the reduction in aqueous media in the presence of a sacrificial metal in its elemental form. Zero-valent iron<sup>1–8</sup> and iron–palladium<sup>9–11</sup> bimetallic mixtures have become especially popular for this purpose. In anoxic aqueous media, free metal ions, chloride ion and hydrogen gas were produced by reaction at the surface of metal particles and protons were consumed. The process kinetics were dependent on solution pH, surface area of the metal particle, substrate concentration, buffer selection and solvent composition.<sup>6</sup> Dechlorination approximately followed first-order kinetics and rate coefficients tended to increase with time, an observation that was postulated to have resulted from an increase in reactive metal surface area due to cathodic depolarization and pitting of the iron surface.<sup>3</sup> Dechlorination occurred under oxic conditions as well, although the rates were appreciably slower. A rapid pH increase was synchronous with dissolved oxygen consumption and the pH remained constant after the oxygen had been depleted. This was attributed to the proton and oxygen consuming aerobic corrosion of the  $\text{Fe}^0$  surface.<sup>3</sup>

Normalisation of the apparent rate constants for the dechlorination of different halogenated substrates to the iron surface area yielded a specific rate constant ( $k_{\text{SA}}$ ) that varied by only one order of magnitude for individual halocarbons. Surface area normalised rate constants for nanoscale  $\text{Fe}^0$  particles (1–100 nm diameter) were 10–100 times higher than for commercial particles.<sup>7</sup> Correlation analysis also revealed that dechlorination is generally more rapid at saturated carbon centres than at unsaturated carbons and that high degrees of halogenation favoured rapid reduction.<sup>6</sup>

Based on the low concentration of chlorinated degradation products in the solution phase it was suggested that most of the substrate remained sorbed to the iron surface until complete dechlorination had been achieved.<sup>5</sup> Prolonged exposure of the

Fe or Pd/Fe surface to a saturated solution of aqueous organochlorine compounds resulted in the growth of a hydroxylated iron oxide film that deactivates the Pd/Fe surface. The thick hydroxylated iron oxide film could be removed and the original activity of the Fe (Pd/Fe) surface restored by washing the surface with a dilute acid.<sup>2,9,11,12</sup>

A mechanistic model for the zero-valent metal ( $\text{Fe}^0$ ) mediated dechlorination has suggested a surface mediated process<sup>13</sup> and indicated that rates of decomposition were limited by the sparing solubilities of substrates in the aqueous phase.<sup>8</sup> When iron was used to mediate anoxic dechlorination, the slow adsorption of the target compounds to the iron surface and the desorption of hydrocarbon products became the rate-limiting steps that retarded the rate of the overall process appreciably.<sup>14</sup> It is often considered that water is a necessary component of metal-mediated corrosion reactions with chlorinated alicyclics.

## Green Context

Dechlorination has become one of the most important reactions in clean technology. The conversion of toxic or in other ways environmentally damaging compounds into useful and more benign molecules is a subject of growing importance. This paper presents the latest results from attempts to develop and optimise the operation of a continuous reactor to dechlorinate polychlorobiphenyls (PCBs). It shows how supercritical carbon dioxide can be used to mobilize PCBs from particulate matter and transport them through the reactor. The advantages of using SCFs in this context include good substrate solubility and enhanced diffusion rates coupled with the general advantages of  $\text{scCO}_2$  such as zero toxicity, reactivity and flammability. *JHC*

However, there are several literature reports<sup>15–18</sup> emphasising that zero-valent iron or aluminium can react directly with these substrates to yield chlorocarbon radicals, metal chlorides and/or chloride ion.

Somewhat less is known about reactions of halogenated aromatics with zero-valent metals. Copper metal has been reported to dechlorinate polychlorodibenzo dioxin (PCDD) and furan (PCDF) derivatives<sup>19</sup> and Fe<sup>0</sup> can mediate the dechlorination of chlorinated benzenes,<sup>20</sup> DDT and derivatives<sup>21</sup> and chlorinated phenols.<sup>22</sup> Although polychlorinated biphenyl compounds (PCBs) are generally considered to be unreactive to Fe<sup>0</sup> at ambient temperature, they have been dechlorinated efficiently with bimetallic iron mixtures. For a methanol–water solution of a commercial mixture of PCBs when contacted for a short time with palladized iron at ambient temperature, the only reaction products were biphenyl and chloride ions.<sup>10</sup> Success has also been achieved using Fe<sup>0</sup> at elevated temperatures. At 400 °C in the absence of solvent, PCB mixtures underwent hydrodehalogenation in the presence of Fe<sup>0</sup> powder that resulted in the complete loss of chlorinated congeners<sup>23</sup> and the efficient recovery of biphenyl. Nanoscale Fe<sup>0</sup> particles have also been demonstrated to mediate PCB dechlorinations efficiently.<sup>7,24</sup> More recently sub-critical water at 250 °C and 10 MPa pressure has been used to mediate PCB dechlorinations by Fe<sup>0</sup>.<sup>25</sup>

As a remediation strategy, extractions are limited in that the target toxicant(s) can only be transferred / concentrated from one medium to another but are not detoxified *per se*. A more efficient strategy would be to couple the extraction with an on-line modification of the toxiforic groups. The objectives of current studies were to develop and optimise the operation of a continuous reactor to dechlorinate PCBs. It was anticipated that supercritical carbon dioxide (sc-CO<sub>2</sub>) could be used advantageously to mobilize PCBs from particulate media and transport them through the reactor. Supercritical fluids including sc-CO<sub>2</sub> possesses several advantages that can be exploited in dechlorinations including appreciable substrate solubility<sup>26</sup> and enhanced rates of solute partitioning and diffusion relative to the liquid phase. On the other hand, CO<sub>2</sub> has been reported to cause the gradual deactivation of Pd supported catalyst.<sup>27</sup> PCBs have been purged efficiently from soils with sc-CO<sub>2</sub><sup>28,29</sup> which remains among the least expensive of solvents. It is non-polar yet is readily separated from non-polar solutes, non-explosive, virtually non-toxic, non-flammable, relatively non-reactive, and waste emissions do not directly increase the burden to greenhouse gases.

## Experimental

### Chemicals

Copper (electrolytic grade, 40–100 mesh, nominally 99.5% purity), iron (40 mesh, nominally 99.5% purity), nickel (50–100 mesh, nominally 99.5% purity), zinc particles (100 mesh, nominally 99.9% purity) and sodium dispersion [40% (w/v) in oil were purchased from Alfa Aesar, Ward Hill, MA] and used as received. Acetic anhydride (Ac<sub>2</sub>O), ethylene glycol dimethyl ether (1,2-DME), hexane, acid washed sea sand and silver nitrate were purchased from Fisher Scientific, Ottawa, ON and were used as received. Aroclor 1242 and Aroclor 1248 mixtures were kindly donated by Monsanto Company, Sauget, IL.

### Ag<sup>0</sup>/metal<sup>0</sup> bimetallic mixtures

The general preparations described by Zhang *et al.*<sup>30</sup> were followed. Ag/Fe<sup>0</sup> and Pd/Fe<sup>0</sup> were prepared from *ca.* 40-mesh iron that had been washed copiously with 6 M HCl and rinsed with distilled water. Sufficient aqueous AgNO<sub>3</sub> or K<sub>2</sub>PdCl<sub>6</sub> to

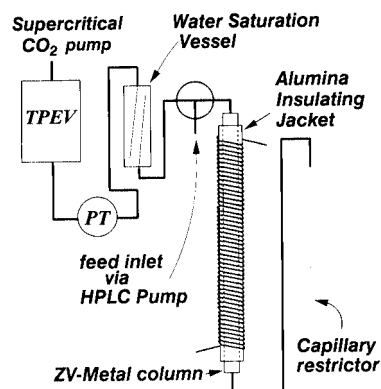
result in a 2% (w/w) surface coverage of the iron, was added to the aqueous iron suspension that was gently mixed on a rotary evaporator for 12 h. Ag/Ni<sup>0</sup> was prepared in similar fashion by reaction of aqueous AgNO<sub>3</sub> [sufficient to provide a 2% (w/w) surface coverage] with an aqueous suspension of pre-washed 50–100 mesh nickel granules during 12 h.

### Mixed particle size Pd<sup>0</sup>/Fe<sup>0</sup>

Prepared by mixing freshly precipitated micron-scale iron particles with 40-mesh iron granules.<sup>30</sup> Aqueous 1.6 M NaBH<sub>4</sub> was added dropwise to 1.0 M FeCl<sub>3</sub>·6H<sub>2</sub>O with constant stirring. The precipitated product was mixed with an equal quantity of freshly washed 40-mesh Fe<sup>0</sup> particles and the mixture was treated with sufficient aqueous K<sub>2</sub>PdCl<sub>6</sub> to result in a 2% surface deposit of Pd<sup>0</sup>.

### Reactor

The dechlorination assembly (Fig. 1) consisted of standard HPLC fittings and column assemblies that were rated to 6000 psi. A diaphragm compressor (Newport Scientific, Jessup, MD) delivered liquid carbon dioxide from the eductor tube of the K-type cylinder of CO<sub>2</sub> [bone dry grade ex MEGS, Montréal Que] to a large heated (1.4 L) reservoir (temperature and pressure equilibration vessel, TPEV) that served as both a pressure dampener and as a source of supercritical carbon dioxide (sc-CO<sub>2</sub>) for the system. The supercritical solvent [*ca.* 0.8 or 1.5 l min<sup>-1</sup> of decompressed gas as measured at the exit of the capillary restrictor with a digital flow meter (ADM1000, J and W Scientific, Folsom, CA)] was transferred to a 5 ml saturation vessel (SV, V = 5 ml, Keystone Scientific, Bellefonte, PA) mounted vertically, a pressure transducer (PT, Model PX300, 15–5000 psig capacity, Omega Engineering, Laval, QC) connected to a digital readout meter (Model DP280, Omega Engineering), a mixing tee and a reactor unit. Polychlorinated biphenyl (PCB) substrate, dissolved in a suitable solvent, was delivered at 0.1 ml min<sup>-1</sup> to the mixing tee (1/16 inch i.d.), merged with the sc-CO<sub>2</sub> stream (*ca.* 4 ml min<sup>-1</sup>) and fed to one or two stainless steel (ss) HPLC column assemblies [10 mm inner diameter (i.d., 12 mm o.d.) × 25 cm] that were filled with test zero-valent metal (or metal mixture, *ca.* 21 g) encased in an insulating alumina jacket (fashioned from thin walled alumina 12 mm o.d. 10 mm i.d. tube, Alfa Aesar, that had been cut lengthways to provide two semi-cylinders) and mounted in series. The ss column-alumina jacketed assemblies were heated separately with 80-turn coils of high resistance heating wire that were energised from variable transformers. Pressure within the



**Fig. 1** Dechlorination reactor assembly consisting of a temperature and pressure equilibration vessel (TPEV), a pressure transducer (PT), a saturation vessel (SV), a mixing tee to merge the supercritical carbon dioxide with feedstock solution, one or more columns containing zero valent metal and a capillary restrictor all connected in series.



assembly was maintained at the desired level with a flexible polyamide coated silica capillary restrictor (*ca.* 25 cm × 0.050 mm i.d.), Chromatographic Specialties, Brockville, ON). The components of the extractor (standard HPLC components, tubing and fittings) were pressure rated to 6000 psi.

### Reactor operation

After a short delay to purge residues of air from the system (during which time only *sc*-CO<sub>2</sub> was fed to the reactor), feedstock 0.1 ml min<sup>-1</sup> of 2–20% (*v/v*), was added continuously *via* the HPLC pump to the *sc*-CO<sub>2</sub> stream and transported to the reactor. Measurements at the exit of the capillary restrictor indicated a flow rate corresponding to 800–850 ml min<sup>-1</sup> of decompressed gas. The exit tip of the capillary restrictor was immersed in hexane (25 ml, contained in a 30 × 2 cm test tube) to trap products from the reactor eluate. Each experiment was continued until six successive traps had been collected, each corresponding to 10 min of cumulative trapping of reactor eluate. The course of the dechlorination was monitored by gas chromatography (GC) or occasionally by GC-MS to monitor the spectrum and identities of products and by titration to measure levels of residual organically bound chlorine in the eluate.

### Organically bound chlorine

The general procedure of Ware *et al.*<sup>31</sup> was followed. Residual organically bound chlorine in the hexane trapping solution was determined by titration with standardised AgNO<sub>3</sub> (*ca.* 0.01 M). Sodium dispersion, 2 ml, was added to a vigorously stirred 10 ml aliquot of hexane trapping solution that had been further diluted 5-fold with fresh hexane. Methanol, 1 ml, was added dropwise; the reaction was continued for 5 min then quenched by the addition of propan-2-ol (15 ml) followed by 90 ml water. The aqueous phase, after separation from the organic phase, was diluted to 100 ml in a volumetric flask. A 20 ml aliquot of the reaction mixture was acidified to pH 6–7 with nitric acid (7 M), supplemented with 5 drops of potassium chromate indicator solution then titrated with AgNO<sub>3</sub>. Blank determinations for chloride in reactor eluate consisted of an identical procedure in the absence of added sodium dispersion. The reduction efficiency was calculated as:

$$\text{Percent reduction efficiency} = \frac{W_i - W_f}{W_i} \times 100$$

where  $W_i$  and  $W_f$  are the initial and final weights of organically-bound chlorine in the sample.

### Biphenyl formation from PCB mixtures

Aroclor mixtures were converted quantitatively to biphenyl by reaction with a solid mixture of Mg and K<sub>4</sub>PdCl<sub>6</sub> following the procedure of Doyle *et al.*<sup>32</sup>

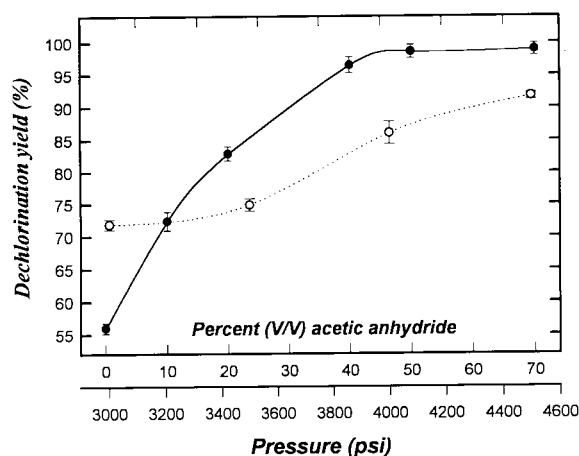
### Gas chromatography

This was performed on a Varian Model 3700 GC fitted with a 0.53 mm i.d. × 25 m megabore DB5 column and a flame ionisation detector. Helium, delivered at 30 ml min<sup>-1</sup>, served as the carrier gas. A splitless injection of sample (2 μl) was transferred to the column inlet and after an initial temperature hold at 50 °C during 5 min, the temperature was ramped to 250 °C during 30 min then held at the upper temperature for a further 5 min. GC-MS were performed on a Saturn-3400 system. The DB-5 capillary column (30 m × 0.2 mm), eluted

with helium at 1 ml min<sup>-1</sup>, was temperature programmed from 40–300 °C during 45 min then held at the final temperature for a further 5 min. Eluting components were identified tentatively by comparison of experimental mass spectra with spectra catalogued in the data base [National Institute of Standards and Technology (NIST) or Saturn, Varian Associates] and corroborated by co-chromatography and spectral matching with authentic standards. Quantitation was achieved with external standards.

## Results and discussion

The dechlorination efficiency (yield) was defined as one minus the ratio of the quantity of organically-bound chlorine in the reactor eluate divided by the chlorine content in an equivalent quantity of feedstock. The extent of dechlorination was influenced appreciably by the identity of the zero-valent (ZV) metal, by the temperature and pressure within the reactor column(s) and especially by the composition of the feedstock. As summarised in Table 1, the replacement of water–ethylene glycol dimethyl ether (1,2-dimethoxyethane, DME) mixture with acetic anhydride (Ac<sub>2</sub>O) was beneficial to both the dechlorination yield and the repeatability among the six samples collected sequentially during 1 h of operation. For these and all subsequent trials the saturation vessel was removed from the reactor assembly. The dechlorination efficiency seemed to depend on the content of acetic anhydride in the transporting solvent. Whereas 5% and 10% (*v/v*) of acetic anhydride (Ac<sub>2</sub>O) in the DME feedstock provided mean dechlorination efficiencies of 63 ± 10 and 74 ± 9% respectively, an increase in the Ac<sub>2</sub>O content to greater than 40% (*v/v*) resulted in the virtually complete (*ca.* 99%) dechlorination of feedstock containing 10% PCBs (Fig. 2). The error bars of this Figure reflect one relative standard deviation (RSD) associated with three replicate determinations, by titration, of residual organically bound chlorine in the eluate trap (mean RSD for the ten separate samples was ± 1.3%). Fig. 2 also summarises the influence of operating pressure on the mean dechlorination efficiency. An increase of 1500 psi in operating pressure increased the dechlorination yield by approximately twenty percent. Increased operating pressures result in increased densities of the *sc*-CO<sub>2</sub> and a greater solvating power of the fluid for the substrate PCBs. Because the components of the reactor were standard HPLC fittings that were rated to 6000 psi at ambient temperature, it was decided arbitrarily to limit the operating



**Fig. 2** Variations in the dechlorination efficiency for 10% (*v/v*) solutions of Aroclor 1242 in 1,2-dimethoxyethane with (a) increasing percent of acetic anhydride in the solvent mixture (—●—) delivered to two Ag<sup>0</sup>/Fe<sup>0</sup> columns at 400 °C and 4500 psi or (b) with increasing pressure (---○---) for the same feedstock delivered to two Fe<sup>0</sup> columns at 400 °C.

**Table 1** Variations in the mean<sup>a</sup> percent dechlorination ( $\pm 1$  RSD) for 2 successive columns (i) containing various zero-valent metals and (ii) with different solvent compositions to transfer 20% (v/v) Aroclor 1242 to the reactor

ZV-Metal	Feedstock composition (v/v) in the presence of 20% (v/v) Aroclor 1242	Mean % dechlorination for two columns
Cu	5% H <sub>2</sub> O, 75% DME	36 $\pm$ 11
Cu	70% Ac <sub>2</sub> O, 10% DME	86 $\pm$ 8
Fe	5% H <sub>2</sub> O, 75% DME	36 $\pm$ 30
Fe	70% Ac <sub>2</sub> O, 10% DME	94 $\pm$ 4
Ni	5% H <sub>2</sub> O, 75% DME	68 $\pm$ 8
Ni	70% Ac <sub>2</sub> O, 10% DME	91 $\pm$ 6
Zn <sup>b</sup>	5% H <sub>2</sub> O, 75% DME	67 $\pm$ 11
Zn <sup>b</sup>	70% Ac <sub>2</sub> O, 10% DME	90 $\pm$ 8

<sup>a</sup> Mean percent dechlorination for six successive traps of reactor eluate.  
<sup>b</sup> Determined at 200 °C.

pressure of the reactor to 4500 psi or less for reasons of safety.

The presence of water was not necessary for the dechlorination reaction (Table 1). The requirement for at least some water in the reductive dehalogenation at metal surfaces had been suggested by the reported lack of any measurable reaction at ambient temperature of neat chlorinated liquid substrate in contact with reducing metal surfaces. We had anticipated that in the presence of sc-CO<sub>2</sub>, the pH of the entrained aqueous phase would be decreased sufficiently [2.8–2.95<sup>33</sup>] to minimise the build-up of an oxide(hydroxide)/carbonate layer on the ZV metal surfaces. In consequence, we had added the saturator vessel (SV, Fig. 1) to the sc-CO<sub>2</sub> inlet line. However, when water was removed from the transporting solvent and the SV was removed from the inlet train no differences in the dechlorination efficiencies were detected. In all subsequent trials no water was added to the mobile phase. When a 20% (v/v) Aroclor solution in Ac<sub>2</sub>O alone or diluted with ethylene glycol dimethyl ether was mixed with sc-CO<sub>2</sub> and fed to a single reactor column containing ZV iron (Fe<sup>0</sup>) (400 °C, 4500 psi) no organically bound chlorine was detected in any of the six traps of column eluates. Fourier transform infrared (FTIR) spectroscopy indicated that in addition to residual dissolved carbon dioxide, the product mixture was composed predominantly of methyl ketone(s). A possible source for these compounds would involve the capture of alkyl radicals by a methylated carbon monoxide radical species. sc-CO<sub>2</sub> is known to form short chain (C<sub>1</sub>–C<sub>5</sub>) alkyl radicals by catalytic reduction at iron surfaces.<sup>34</sup>

The dechlorination process was also temperature dependent. As summarised in Table 2, an increase in the operating temperature as measured by the outer skin temperature of the reactor columns improved both the extent of dechlorination and the repeatability between the six cumulative 10-minute traps

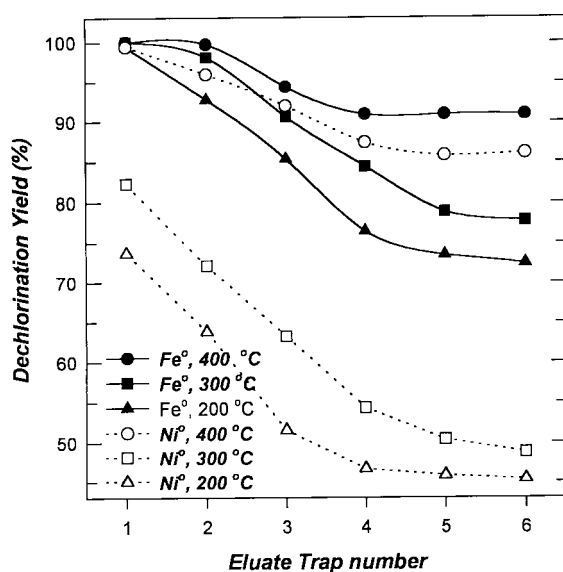
**Table 2** The influence of temperature of two reactor columns connected in series on the mean percent dechlorination ( $\pm 1$  RSD) of feedstock containing 20% (v/v) Aroclor 1242 (or Aroclor 1248), 70% (v/v) acetic anhydride and 10% (v/v) dimethoxyethane

ZV-metal	Temperature					
	200 °C		300 °C		400 °C	
	1242	1248	1242	1248	1242	1248
Cu	69 $\pm$ 9		71 $\pm$ 23		86 $\pm$ 8	
Fe	86 $\pm$ 7	69 $\pm$ 15	88 $\pm$ 10	72 $\pm$ 14	94 $\pm$ 4	92 $\pm$ 6
Ni	55 $\pm$ 12	42 $\pm$ 8	61 $\pm$ 14	67 $\pm$ 2	91 $\pm$ 6	89 $\pm$ 2
Zn	69 $\pm$ 15					
Ag/Fe	63 $\pm$ 17		73 $\pm$ 9		97 $\pm$ 3	
Pd/Fe	60 $\pm$ 22	56 $\pm$ 25	74 $\pm$ 15	64 $\pm$ 19	96 $\pm$ 3	93 $\pm$ 5

that had been collected sequentially during 1 h. The dechlorination efficiency was seen to decrease gradually with increasing trap number. The decrease is reflected in the elevated RSDs at 200 and 300 °C. For ZV-zinc, the metal granules were observed to soften appreciably at reactor skin temperatures above 200 °C, so that dechlorination trials were limited to this temperature. Trials were also conducted with Aroclor 1248 (Table 2). Yields between the 1248 and 1242 are not directly comparable because of differences in density (20 °C) (1.44 vs. 1.38<sup>31</sup> respectively) and differences in the spectrum of congener for these mixtures.<sup>32</sup> The 1248 mixture was more highly chlorinated (48 vs. 42%). Additionally, for incomplete dechlorinations, identical rates of reaction would have resulted in lower dechlorination yields for 1248 because of the greater chlorine concentrations in this substrate.

The effect of increased operating temperature can be seen more clearly in Fig. 3 which compares Fe<sup>0</sup> mediated dechlorination efficiencies for sequential traps at different operating temperatures. There was a gradual decrease in dechlorination yield with increasing trap number. The gradual decrease in efficiency was characteristic of all four ZV-metals and the three bimetallic mixtures that were studied. The negative slopes of the spline curves were greater at lower than at higher operating temperatures for different zero-valent (ZV) metal substrates. Other ZV metals (Cu<sup>0</sup>, Ni<sup>0</sup> and Zn<sup>0</sup>) behaved similarly but the dechlorination was not as extensive.

In addition, three bimetallic mixtures of ZV-metals (Ag<sup>0</sup>/Fe<sup>0</sup>, Ag<sup>0</sup>/Ni<sup>0</sup> and Pd<sup>0</sup>/Fe<sup>0</sup>) were assessed for dechlorinating efficiency in this system. All three mixtures further improved both the dechlorination yield and the repeatability of the reaction over 1 h (Table 3). For these trials, the reactor temperature was maintained at 400 °C and the substrate composition was varied using two ZV-metal columns. Although efficient, the reactions were not quantitative. For a single reactor column (Table 4), there was no apparent differences between the use of acetic anhydride or methyl isobutyl ketone (MIBK) in the transporting solvent although the use of heptan-2-one depressed dechlorination by approximately 10 percent. Surprisingly, the inclusion of 1,2-DME (10% v/v) in the solvent increased the yield by 9 and 14 percent over neat acetic anhydride for the Ag<sup>0</sup>/Fe<sup>0</sup> and the Ag<sup>0</sup>/Ni<sup>0</sup> mixtures respectively. The dechlorinating activities of silver-coated iron and nickel were also more durable as seen in



**Fig. 3** Efficiencies for Fe<sup>0</sup> mediated (filled symbols) or Ni<sup>0</sup> mediated (open symbols) dechlorinations of 20% (v/v) Aroclor 1242 solution delivered at 0.1 ml min<sup>-1</sup> to two reactor columns maintained at 4500 psi and 400 °C [mean dechlorination in six traps that had been trapped successively = 95  $\pm$  4% and 91  $\pm$  6% respectively], or at 300 °C [mean = 88  $\pm$  10% and 67  $\pm$  6% respectively] or at 200 °C [mean = 84  $\pm$  12% and 54  $\pm$  11% for Fe<sup>0</sup> and Ni<sup>0</sup> mediated reactions respectively].

**Table 3** Variations in the mean<sup>a</sup> percent dechlorination ( $\pm 1$  RSD) for 2 columns maintained at 400 °C and 4500 psi (i) containing different bimetallic mixtures and (ii) with varying acetic anhydride–dimethoxyethane mixtures to transfer Aroclor 1242 to the reactor

ZV-Bimetallic mixture	% (v/v) PCB content	Feedstock composition (v/v) in the presence of 20% (v/v) Aroclor 1242	Mean % dechlorination <sup>a</sup>
Ag/Fe	2	20% Ac <sub>2</sub> O, 78% DME	99.8 $\pm$ 0.1
	10	50% Ac <sub>2</sub> O, 40% DME	98.3 $\pm$ 1.2
	15	50% Ac <sub>2</sub> O, 35% DME	98.0 $\pm$ 1.3
	20	50% Ac <sub>2</sub> O, 35% DME	88.5 $\pm$ 5.2
	20	70% Ac <sub>2</sub> O, 10% DME	97.0 $\pm$ 2.6
	20	80% Ac <sub>2</sub> O	88.9 $\pm$ 4.5
Ag/Ni	2	20% Ac <sub>2</sub> O, 78% DME	99.9 $\pm$ 0.2
	10	50% Ac <sub>2</sub> O, 40% DME	97.8 $\pm$ 1.1
	15	50% Ac <sub>2</sub> O, 35% DME	90.9 $\pm$ 5.0
	20	50% Ac <sub>2</sub> O, 35% DME	83.9 $\pm$ 8.9
	20	70% Ac <sub>2</sub> O, 10% DME	95.8 $\pm$ 2.1
	20	80% Ac <sub>2</sub> O	81.1 $\pm$ 3.9
Pd/Fe	2	20% Ac <sub>2</sub> O, 78% DME	99.9 $\pm$ 0.2
	5	20% Ac <sub>2</sub> O, 75% DME	99.0 $\pm$ 0.8
	10	50% Ac <sub>2</sub> O, 40% DME	97.8 $\pm$ 2.1
	15	70% Ac <sub>2</sub> O, 15% DME	97.0 $\pm$ 2.4
	20	70% Ac <sub>2</sub> O, 10% DME	96.1 $\pm$ 3.1
	20	80% Ac <sub>2</sub> O	84.3 $\pm$ 4.6

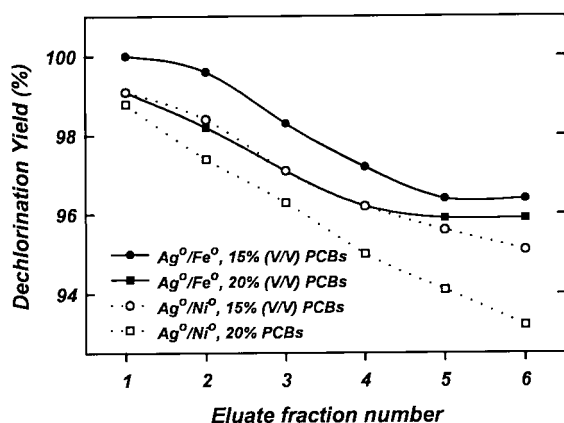
<sup>a</sup> Mean  $\pm$  1 relative standard deviation (RSD) of six successive traps of reactor eluate.

**Table 4** Variations in mean dechlorination efficiencies ( $\pm 1$  RSD) for one column of silver (2% w/w) iron bimetallic mixture maintained at 400 °C and 4500 psi for 15 or 20% (v/v) Aroclor 1242 and different transporting solvent mixtures

% (v/v) Aroclor 1242	Feedstock composition <sup>a</sup> (v/v)	Mean % dechlorination <sup>b</sup>
15	40% Ac <sub>2</sub> O, 45% DME	97 $\pm$ 7
20	70% Ac <sub>2</sub> O, 10% DME	92 $\pm$ 5
15	70% MIBK, 15% DME	92 $\pm$ 5
20	80% MIBK	89 $\pm$ 3
15	60% heptan-2-one, 25% DME	93 $\pm$ 4
20	70% heptan-2-one, 10% DME	80 $\pm$ 6
20	80% heptan-2-one	80 $\pm$ 6

<sup>a</sup> DME = 1,2 dimethoxyethane, MIBK = methyl isobutyl ketone. <sup>b</sup> Mean in six 10 minute cumulative traps that were collected sequentially during 1 h.

Fig. 4. Although the efficiency of dechlorination appeared to decrease continuously for the Ag<sup>0</sup>/Ni<sup>0</sup> bimetallic mixture, it appeared to level off for the Ag<sup>0</sup>/Fe<sup>0</sup> support in these short-term trials. The mixed particle size palladium iron mixture proved to



**Fig. 4** Dechlorination efficiencies for 15% (●, ○) or 20% (■, □, v/v) 1242 feedstock delivered to two columns mounted in series of Ag<sup>0</sup>/Fe<sup>0</sup> (filled symbol, mean dechlorination for six successive traps = 98  $\pm$  2% and 97  $\pm$  3%) or to Ag<sup>0</sup>/Ni<sup>0</sup> (open symbol, mean = 97  $\pm$  2% and 96  $\pm$  2% for 15 and 20% PCB feedstock respectively) at 400 °C and 4500 psi.

be less efficient under these conditions and was not investigated further.

The GC chromatograms of reaction products from PCB dechlorinations were gradually shifted to more rapidly eluting components as the dechlorination efficiency was increased. Two Fe<sup>0</sup> reactor columns in sequence, that resulted in a 95% reduction in organically-bound chlorine, provided a chromatogram that was reduced approximately 94% in total peak areas in the PCB eluting region indicating that the majority of products were eluted more rapidly. When only biphenyl dissolved in DME comprised the feedstock for the Ag<sup>0</sup>/Fe<sup>0</sup> column (operated under optimised dechlorination conditions), a maximum of only 84% could be recovered in the hexane traps indicating further reaction. There were no products that were more retained than biphenyl on the GC column. With Ag<sup>0</sup>/Fe<sup>0</sup> bimetallic mixture and 99.5% dechlorination of the 1242 substrate only two chlorinated products (*o*-chlorobiphenyl and 2,4-dichlorobiphenyl and/or 2,6-dichlorobiphenyl (which collectively accounted for appreciably less than 1% of the starting material) were detected by GC-MS. Similarly, for substrate that had been 99.8% dechlorinated, only *o*-chlorobiphenyl was detected among the chlorinated products. Other non-chlorinated products that were identified tentatively included methylbiphenyl(s), dimethylbiphenyl(s), toluene and short chain esters of benzene-1,2-dicarboxylic acids. The latter products (that were observed for 2% loadings of Aroclor 1242 in the mobile phase) are thought to arise *via* carboxylation and reductive catenation of the CO<sub>2</sub>.

Having optimized the reaction conditions for virtually complete PCB dechlorination (based on the loss of organically-bound chlorine) a series of further trials were undertaken to corroborate the efficiency of the process. Initially, the temperature of the single Pd<sup>0</sup>/Fe<sup>0</sup> column was lowered to 300 °C and 20% (v/v) PCB feedstock in hexane was delivered to the reactor column at 0.1 mL min<sup>-1</sup>. The mean recovery of organically-bound chlorine in successive traps of hexane was virtually quantitative at this temperature (Aroclor 1242, 99.0  $\pm$  4.7%; Aroclor 1248, 103.9  $\pm$  6.6%). Further experiments monitored the eluate content of products that could be converted to biphenyl. Aliquots of eluate were reacted with Mg<sup>0</sup> and K<sub>2</sub>PdCl<sub>6</sub> to produce biphenyl. With 20% (v/v) 1242 in acetic anhydride (70% v/v) dimethoxyethane (10% v/v) as feedstock, the recovery of biphenyl was virtually quantitative, 99.1  $\pm$  8.7% at 300 °C but was reduced to 84.0  $\pm$  12.9% at 400 °C. For these trials, the reactor column was packed freshly prior to each trial. Despite equilibration with mobile phase in the absence of substrate, the contents of the first trap were converted to biphenyl less efficiently. Mean recoveries were based on traps two to six. These results indicated that at the higher operating temperature a portion of the biphenyl derivatives were further degraded on column. To demonstrate an active role for the zero-valent metal(s) in the dechlorinations, companion experiments were also conducted using silica (sea sand) to fill the reactor column. With the optimized reaction conditions (400 °C/4500 psi, 800 ml min<sup>-1</sup> of decompressed flow), the mean recovery of substrate(s) in the six trapping solutions that could be converted to biphenyl was virtually quantitative (104  $\pm$  11%). Finally the chloride ion accumulated on the Pd<sup>0</sup>/Fe<sup>0</sup> column during 1 h of continued operation (optimal operating conditions) as determined by titration of the wash water accounted for 99.6% of the total chlorine in the feedstock.

In further trials, acetone/hexane extract from a spiked sandy loam soil that had been extracted using a patented SESR (Solvent Extraction Soil Remediation technology)<sup>37</sup> were dechlorinated with a single Ag<sup>0</sup>/Fe<sup>0</sup> column maintained at 4500 psi and 400 °C. No chlorine containing materials were detected by GC-MS in the reactor eluate when acetone/hexane extract supplemented with 30% (v/v) Ac<sub>2</sub>O, that had contained approximately 600 ppm PCBs, was fed continuously at 0.1 ml min<sup>-1</sup> to the reactor. Of equal importance, soil co-extractives in

the PCB solution did not seem to affect either the course of the efficiency of the reaction perceptibly.

Thus, it has been demonstrated that zero-valent metal mediated reactions of Aroclor mixtures at elevated temperature in sc-CO<sub>2</sub> provides an efficient technique for PCB detoxification by dechlorination. The quantities of 1242 or 1248 substrate that were dechlorinated efficiently (but not quantitatively) are considered to far exceed the burdens in concentrated extracts that could be isolated from polluted environmental matrices.

## Acknowledgements

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# Molten salts as a reusable medium for the preparation of heterocyclic compounds

Tomoya Kitazume,\* Fazila Zulfiqar and Genji Tanaka

Department of Bioengineering, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku Yokohama 226-8501, Japan. E-Mail: tkitazum@bio.titech.ac.jp

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The utility of molten salts ([bmim][BF<sub>4</sub>], [bmim][PF<sub>6</sub>], [emim][OTf], [EtDBU][OTf], [MeDBU][OTf]) as a safe recyclable reaction medium for the one-pot synthesis of heterocyclic compounds is described.

## Introduction

Studies of low waste routes and/or reusable media for improved selectivity and energy minimisation have brought us closer to achieving the social, economic and environmental goals that are required both now and in the future.<sup>1</sup> Especially, studies of reusable media such as molten salts (ionic liquids), which in some cases can serve as a solvent, are having an important impact on organic reactions.<sup>2,3</sup> One pot synthetic methods are one of the most important synthetic reactions especially in the synthesis of heterocycles which often exhibit unique physicochemical properties.<sup>3,4</sup> Usually, the synthesis of these heterocycles are carried out in polar organic solvents (such as THF, DMF, DMSO *etc.*) and, after quenching with water, the products are extracted with organic solvents. These processes generate waste containing solvent media and catalyst. As part of our research aimed at greener chemistry,<sup>6</sup> we describe here the preparation of new ionic liquids and the use of molten salts (ionic liquids) as replacements for the more expensive organic solvents in the one pot synthesis of heterocycles.

## Results and discussion

Molten salts (such as 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **1** and 8-methyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **2**) are prepared directly from the reaction of 1,8-diazabicyclo[5,4,0]-7-undecene with ethyl or methyl trifluoromethanesulfonate in the same manner as for 1-ethyl-3-methylimidazolium trifluoromethanesulfonate **3**.<sup>7</sup> The structures were conformed by spectral data.

Before the use and reuse of ionic liquids (**1**, **2** and **3**), molten salts (ionic liquids) were purified under dynamic vacuum at 70 °C for 1 h and then checked for purity and structure by <sup>1</sup>H and <sup>19</sup>F NMR. As shown in Table 1, the reaction of benzaldehyde with 2-aminobenzyl alcohol in a molten salt **1** smoothly proceeded for 30 min at room temperature. The

produced 4*H*,2*H*-2-phenyl-3,1-benzoxazine was separated by extraction with diethyl ether and the molten salt **1** was recovered in more than 98% yield. Furthermore, the recycling of the molten salt **1** is under investigation from both environmental and economical points of view. Successive reuse of the recovered molten salt **1** in the same reaction yielded amounts of product as high as in the first cycle shown in Fig. 1. In the third cycle, reuse of molten salt **1** recovered from the second cycle is possible to produce the same heterocycle in the same reaction. After quenching the third cycle, molten salt **1** was recovered in more than 90% yield relative to the starting molten salt. Furthermore, the molten salt (ionic liquid **3**) can be reused in the same heterocyclic reaction without any problems.

When tetrahydrofuran was used as a solvent in the above reaction (91% yield) it was not easy to separate the solvent and product by direct distillation. If water was used to quench the reaction, tetrahydrofuran can not be reused for the same reaction.

## Experimental

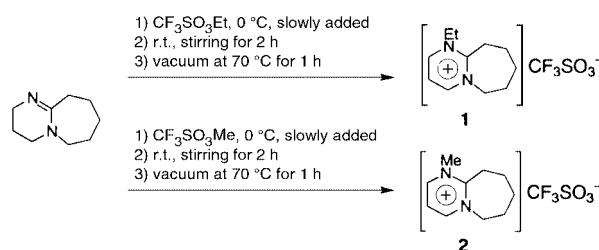
### General

All commercially available reagents were used without further purification. Chemical shifts of <sup>1</sup>H (300 MHz) and <sup>13</sup>C NMR (75 MHz) spectra were recorded in ppm (δ) downfield from Me<sub>4</sub>Si (δ 0.00) in CDCl<sub>3</sub>. The <sup>19</sup>F (282 MHz) NMR spectra were recorded in ppm downfield from C<sub>6</sub>F<sub>6</sub> in CDCl<sub>3</sub> using a VXR 300 instrument.

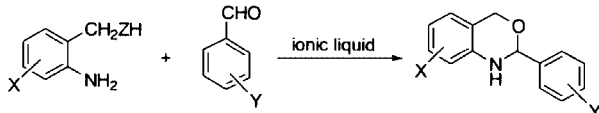
## Green Context

The replacement of toxic organic solvents is one of the most important issues in Green Chemistry. Their use in organic synthesis inevitably leads to solvent emissions and/or waste. The synthesis of heterocyclic compounds can be particularly troublesome in this respect as traditional methods commonly employ dipolar aprotic solvents which are toxic and reactive, and in many cases they are removed from the final reaction mixture by a water quench which leads to an aqueous waste stream. Here, effective methods for the synthesis of various heterocyclic compounds based on the use of involatile molten salts are described. The molten salts described are safe to use and are fully recyclable with no process emissions.

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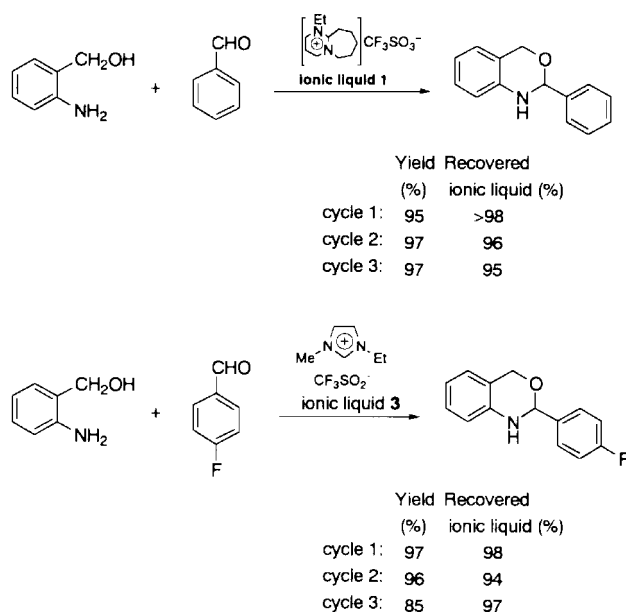


Scheme 1 Preparation of ionic liquids.

**Table 1** Synthesis of heterocycles in ionic liquid **1**


Entry	Arene	Aldehyde	Ionic liquid	Yield(%)	Recovered ionic liquid(%) <sup>a</sup>
1		PhCHO	<b>1</b>	95	>99
2		PhCHO	<b>2</b>	89	>98
3		PhCHO	<b>3</b>	98	95
4		PhCHO	<b>4</b>	98	98
5		PhCHO	<b>5</b>	98	>98
6		4-FC <sub>6</sub> H <sub>4</sub> CHO	<b>3</b>	97	98
7		4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	<b>3</b>	95	98
8		PhCHO	<b>1</b>	96	97
9		PhCHO	<b>2</b>	84	99
10		PhCHO	<b>3</b>	>99	>99
11		PhCHO	<b>4</b>	98	>99
12		PhCHO	<b>5</b>	97	97
13		4-FC <sub>6</sub> H <sub>4</sub> CHO	<b>3</b>	99	>99
14		PhCHO	<b>1</b>	92	>99
15		PhCHO	<b>2</b>	94	95
16		PhCHO	<b>3</b>	>99	>99
17		PhCHO	<b>4</b>	96	>99
18		PhCHO	<b>5</b>	94	99
19		4-FC <sub>6</sub> H <sub>4</sub> CHO	<b>3</b>	97	94

<sup>a</sup> 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-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **3**; 1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate **4**; 1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate **5**.

**Fig. 1** Recycling ionic liquids.**8-Ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate 1**

Into a cooled (ice bath) flask containing 1,8-diazabicyclo[5.4.0]-7-undecene (60.8 g, 0.4 mol), ethyl trifluoromethanesulfonate (71.2 g, 9.4 mol) was added slowly. After the mixture was stirred for 2 h at room temperature, the products were heated at 70 °C for 1 h to remove volatile materials to give 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate **1** in 98% yield.  $\delta_{\text{H}}(\text{CDCl}_3)$  1.28 (3 H, t,  $J = 7.32$  Hz), 1.75–1.84 (8 H, m), 2.15 (2 H, m), 2.87 (2 H, m), 3.55–3.59 (2 H, m), 3.60 (2 H, q,  $J = 7.32$  Hz), 3.68 (2 H,

m).  $\delta_{\text{C}}(\text{CDCl}_3)$ : 13.554, 19.950, 22.841, 25.937, 28.069, 28.475, 46.210, 48.855, 48.968, 55.080, 120.584 (q,  $J = 320.4$  Hz), 165.966.  $\delta_{\text{F}}(\text{CDCl}_3)$ : 83.37 from internal C<sub>6</sub>F<sub>6</sub>.  $\nu/\text{cm}^{-1}$  2928, 2932, 2296, 1626. Anal. calc. for C<sub>12</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>SO<sub>3</sub>: C, 43.63; H, 6.41; N, 8.48. Found: C, 43.43; H, 6.41; N, 8.50%.

**8-Methyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate 2**

Into a cooled (ice bath) flask containing 1,8-diazabicyclo[5.4.0]-7-undecene (30.4 g, 0.2 mol), methyl trifluoromethanesulfonate (32.8 g, 0.2 mol) was added slowly. After the mixture was stirred for 2 h at room temperature, the products were heated at 70 °C for 1 h to remove volatile materials to give 8-methyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate **2** in 95% yield.  $\delta_{\text{H}}(\text{CDCl}_3)$ : 1.29 (3 H, t,  $J = 7.14$  Hz), 2.13–2.81 (4 H, m), 3.07 (2 H, t,  $J = 7.96$  Hz), 3.48 (6 H, m), 3.79 (2 H, t,  $J = 7.69$  Hz).  $\delta_{\text{C}}(\text{CDCl}_3)$ : 19.856, 22.132, 26.165, 28.649, 28.718, 41.203, 48.707, 48.847, 55.243, 120.459 (q,  $J = 320.4$  Hz), 166.516.  $\delta_{\text{F}}(\text{CDCl}_3)$ : 83.37 from internal C<sub>6</sub>F<sub>6</sub>.  $\nu/\text{cm}^{-1}$  2939, 2294, 1632.

**4*H*,2*H*-2-Phenyl-3,1-benzoxazine**

(a) To a mixture of benzaldehyde (318 mg, 3 mmol) and 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate **1** (1.007 g), 2-aminobenzyl alcohol (309 mg, 3 mmol) was added at room temperature. After stirring for 30 min at room temperature, diethyl ether (10 × 10 ml) was added and the upper organic layer separated. The organic layer was dried over anhydrous MgSO<sub>4</sub>, and the diethyl ether removed. 4*H*,2*H*-2-Phenyl-3,1-benzoxazine was obtained in 95% yield, and the ionic liquid **1** was recovered in >98% yield.  $\delta_{\text{H}}(\text{CDCl}_3)$ : 4.95 (1 H, d,  $J = 14.56$  Hz), 5.35 (1 H, d,  $J = 14.56$  Hz), 5.95 (1 H, s), 6.70–7.60 (Ar-H).  $\delta_{\text{C}}(\text{CDCl}_3)$ : 67.641,

85.126, 116.879, 119.596, 121.951, 124.831, 126.371, 127.247, 128.469, 128.890, 128.913, 138.913, 141.428, 159.500. Anal. calc. for  $C_{14}H_{13}NO$ : C, 79.60; H, 6.20; N, 6.63. Found: C, 79.35; H, 6.45; N, 6.70%. (b) In the above reaction, 8-methyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **2** (1.00 g) was used, and then worked-up similarly. 4*H*,2*H*-2-Phenyl-3,1-benzoxazine was obtained in 89% yield and ionic liquid **2** recovered in 98% yield. (c) In the same reaction, 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **3** (1.01 g) was used and worked-up similarly, 4*H*,2*H*-2-Phenyl-3,1-benzoxazine was obtained in 98% yield and ionic liquid **2** recovered in 95% yield. (d) In the same reaction, 1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate **4** (1.07 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-3,1-benzoxazine was obtained in 98% yield and ionic liquid **4** recovered in 98% yield. (e) In the same reaction, 1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate **5** (1.03 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-3,1-benzoxazine was obtained in 98% yield and ionic liquid **5** recovered in >98% yield.

#### 4*H*,2*H*-2-(4-Fluorophenyl)-3,1-benzoxazine

In the above reaction, 2-aminobenzyl alcohol (309 mg, 3 mmol), 4-fluorobenzaldehyde (372 mg, 3 mmol) and 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **3** (1.00 g) were used and worked-up similarly. 4*H*,2*H*-2-(4-Fluorophenyl)-3,1-benzoxazine was obtained in 97% yield and ionic liquid **3** recovered in 98% yield.  $\delta_H(\text{CDCl}_3)$ : 4.95 (1 H, d,  $J = 14.55$  Hz), 5.10 (1 H, d,  $J = 14.55$  Hz), 5.57 (1 H, s), 6.70–7.60 (Ar-H).  $\delta_C(\text{CDCl}_3)$ : 67.592, 84.466, 115.391 (d,  $J = 21.5$  Hz), 116.944, 119.797, 121.917, 124.846, 127.323, 128.304 (d,  $J = 8.3$  Hz), 134.915 (d,  $J = 1.7$  Hz), 141.284, 162.819 (d,  $J = 247$  Hz).  $\delta_F(\text{CDCl}_3)$ : 49.1 (1 F, m). Anal. calc. for  $C_{14}H_{12}FNO$ : C, 73.35; H, 5.28; N, 6.11. Found: C, 72.99; H, 5.01; N, 6.15%.

#### 4*H*,2*H*-2-(4-Trifluoromethylphenyl)-3,1-benzoxazine

In the above reaction, 2-aminobenzyl alcohol (309 mg, 3 mmol), 4-trifluoromethylbenzaldehyde (522 mg, 3 mmol) and 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **3** (1.00 g) were used, and worked-up similarly. 4*H*,2*H*-2-(4-Trifluoromethylphenyl)-3,1-benzoxazine was obtained in 95% yield and ionic liquid **3** recovered in 98% yield.  $\delta_H(\text{CDCl}_3)$ : 4.10 (NH, bs), 4.94 (1 H, d,  $J = 14.55$  Hz), 5.10 (1 H, d,  $J = 14.55$  Hz), 5.63 (1 H, s), 6.70–7.70 (Ar-H).  $\delta_C(\text{CDCl}_3)$ : 67.402, 84.314, 117.467, 120.244, 124.558 (q,  $J = 352.7$  Hz), 124.948, 125.474 (q,  $J = 3.7$  Hz), 126.895, 127.445, 128.800, 131.000 (q,  $J = 60$  Hz), 140.928, 142.699.  $\delta_F(\text{CDCl}_3)$ : 63.3 (3 F, s). Anal. calc. for  $C_{15}H_{12}F_3NO$ : C, 64.52; H, 4.33; N, 5.06. Found: C, 64.31; H, 4.76; N, 5.07%.

#### 4*H*,2*H*-2-Phenyl-5-chloro-3,1-benzoxazine

(a) In the above reaction, 2-amino-5-chlorobenzyl alcohol (246 mg, 2 mmol), benzaldehyde (212 mg, 2 mmol) and 8-ethyl-1,8-diazabicyclo-[5,4,0]-7-undecenium trifluoromethanesulfonate **1** (1.00 g) were used, and worked-up similarly. 4*H*,2*H*-2-Phenyl-5-chloro-3,1-benzoxazine was obtained in 96% yield and ionic liquid **1** recovered in 97% yield.  $\delta_H(\text{CDCl}_3)$ : 4.10 (1 H), 4.88 (1 H, d,  $J = 14.84$  Hz), 5.05 (1 H, d,  $J = 14.84$  Hz), 5.54 (1 H, s), 6.62–7.56 (Ar-H).  $\delta_C(\text{CDCl}_3)$ : 67.216, 85.137, 118.177, 123.454, 124.516, 124.789, 126.352, 127.350, 128.609, 129.122, 138.587, 140.006. Anal. calc. for  $C_{14}H_{12}ClNO$ : C, 68.44; H, 4.92; N, 5.70. Found: C, 68.17; H, 4.65; N, 5.61%. (b) In the same reaction, 8-methyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **2** (1.00 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-

5-chloro-3,1-benzoxazine was obtained in 84% yield and ionic liquid **2** recovered in 99% yield. (c) In the same reaction, 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **3** (1.01 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-5-chloro-3,1-benzoxazine was obtained in >99% yield and ionic liquid **1** recovered in >99% yield. (d) In the same reaction, 1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate **4** (1.00 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-5-chloro-3,1-benzoxazine was obtained in 98% yield and ionic liquid **4** recovered in >99% yield. (e) In the same reaction, 1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate **5** (1.03 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-5-chloro-3,1-benzoxazine was obtained in 97% yield and ionic liquid **5** recovered in 97% yield.

#### 4*H*,2*H*-2-(4-Fluorophenyl)-5-chloro-3,1-benzoxazine

In the above reaction, 2-amino-5-chlorobenzyl alcohol (246 mg, 2 mmol), 4-fluorobenzaldehyde (248 mg, 2 mmol) and 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **3** (1.00 g) were used and worked-up similarly. 4*H*,2*H*-2-(4-Fluorophenyl)-5-chloro-3,1-benzoxazine was obtained in 99% yield and ionic liquid **1** was recovered in >99% yield.  $\delta_H(\text{CDCl}_3)$ : 4.88 (1 H, d,  $J = 14.83$  Hz), 5.19 (1 H, d,  $J = 14.83$  Hz), 5.54 (1 H, s), 6.64–7.57 (Ar-H).  $\delta_C(\text{CDCl}_3)$ : 67.129, 84.462, 115.491 (d,  $J = 21.8$  Hz), 115.635, 118.184, 123.385, 124.747, 127.373, 128.289 (d,  $J = 8.3$  Hz), 134.590 (d,  $J = 3.2$  Hz), 139.877, 162.956 (d,  $J = 247.1$  Hz).  $\delta_F(\text{CDCl}_3)$ : 49.41 (1 F, m) from  $C_6F_6$ . Anal. calc. for  $C_{14}H_{11}ClFNO$ : C, 63.77; H, 4.20; N, 5.31. Found: C, 63.00; H, 3.96; N, 5.33%.

#### 4*H*,2*H*-2-Phenyl-3,1-benzdiazine

(a) In the above reaction, 2-aminobenzyl amine (244 mg, 2 mmol), benzaldehyde (212 mg, 2 mmol) and 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **1** (1.00 g) were used, and worked-up similarly. 4*H*,2*H*-2-Phenyl-3,1-benzdiazine was obtained in 92% yield and ionic liquid **1** recovered in >99% yield.  $\delta_H(\text{CDCl}_3)$ : 4.00 (1 H, d,  $J = 16.75$  Hz), 4.28 (1 H, d,  $J = 16.75$  Hz), 5.25 (1 H, s), 6.58–7.54 (Ar-H).  $\delta_C(\text{CDCl}_3)$ : 46.510, 69.583, 114.918, 118.055, 121.090, 126.094, 126.455, 127.160, 128.435, 128.628, 141.352, 143.541. Anal. calc. for  $C_{14}H_{14}N_2$ : C, 79.97; H, 6.71; N, 13.32. Found: C, 79.14; H, 6.86; N, 13.24%. (b) In the same reaction, 8-methyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **2** (1.00 g) were used, and worked-up similarly. 4*H*,2*H*-2-Phenyl-3,1-benzdiazine was obtained in 94% yield and ionic liquid **2** recovered in 95% yield. (c) In the same reaction, 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **3** (1.00 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-3,1-benzdiazine was obtained in >99% yield and ionic liquid **1** recovered in >99% yield. (d) In the same reaction, 1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate **4** (1.06 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-3,1-benzdiazine was obtained in 96% yield and ionic liquid **4** recovered in >99% yield. (e) In the same reaction, 1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate **5** (1.05 g) was used and worked-up similarly. 4*H*,2*H*-2-Phenyl-3,1-benzdiazine was obtained in 94% yield and ionic liquid **5** recovered in 99% yield.

#### 4*H*,2*H*-2-(4-Fluorophenyl)-3,1-benzdiazine

(a) In the above reaction, 2-aminobenzyl amine (244 mg, 2 mmol), 4-fluorobenzaldehyde (248 mg, 2 mmol) and 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **3** (1.00 g) were used and worked-up similarly. 4*H*,2*H*-2-(4-Fluorophenyl)-

nyl)-3,1-benzodiazine was obtained in 97% yield and ionic liquid **3** recovered in 94% yield.  $\delta_{\text{H}}(\text{CDCl}_3)$ : 3.98 (1 H, d,  $J = 16.75$  Hz), 4.26 (1 H, d,  $J = 16.75$  Hz), 5.24 (1 H, s), 6.59–7.53 (Ar-H).  $\delta_{\text{C}}(\text{CDCl}_3)$ : 46.025, 68.593, 114.781, 115.114 (d,  $J = 21.3$  Hz), 117.987, 120.825, 125.905, 126.982, 128.054 (d,  $J = 8.3$  Hz), 137.081 (d,  $J = 2.9$  Hz), 143.147, 162.264 (d,  $J = 244.7$  Hz).  $\delta_{\text{F}}(\text{CDCl}_3)$ : 48.18 (1 F, m) from  $\text{C}_6\text{F}_6$ .

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# One-pot aza-Diels–Alder reactions in ionic liquids

Fazila Zulfiqar and Tomoya Kitazume\*

Department of Bioengineering, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku  
Yokohama 226-8501, Japan. E-mail: tkitazum@bio.titech.ac.jp

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The utility of ionic liquids as a safe recyclable reaction media and microencapsulated scandium trifluoromethanesulfonate as a catalyst for the one-pot aza-Diels–Alder reaction to produce 5,6-dihydro-4-pyridone derivatives are described.

## Introduction

The aza-Diels–Alder reaction is well known especially in the synthesis of azasugars and their derivatives, which often exhibit unique physicochemical properties.<sup>1</sup> Usually, the aza-Diels–Alder reaction is carried out in the presence of a Lewis acid (such as ZnCl<sub>2</sub>, BF<sub>3</sub>, TiCl<sub>4</sub>, etc.) in organic solvents.<sup>2</sup> In contrast, recent studies of ionic liquids as new alternative reaction media are having an important impact on organic reactions<sup>3</sup> such as Friedel–Crafts reactions,<sup>4</sup> alkylation reactions,<sup>5</sup> Diels–Alder reactions,<sup>6</sup> palladium catalyzed allylation<sup>7</sup> and asymmetric hydrogenation.<sup>8</sup> As part of our research aimed at greener chemistry,<sup>9</sup> here we describe one-pot aza-Diels–Alder reactions for the preparation of 6-aryl-5,6-dihydro-4-pyridones in ionic liquids.

## Results and discussion

Recently we have reported that new ionic liquids (such as 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate and 8-methyl-1,8-diazabicyclo[5,4,0]-undecenium trifluoromethanesulfonate) are prepared directly from the reaction of 1,8-diazabicyclo[5,4,0]-7-undecene with ethyl or methyl trifluoromethanesulfonate.<sup>10</sup> In our continuing studies of ionic liquids in organic synthesis,<sup>1</sup> initially we examined the aza-Diels–Alder reaction of *N*-phenyl phenyl imine with 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene in an ionic liquid (8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **1**). The uncatalysed reaction did not proceed. The addition of Lewis acid (microencapsulated scandium trifluoromethanesulfonate, Wako Pure Chemical Industries, Ltd.) dramatically increases the yield to 75% (ionic liquid **1**) and 67% (ionic liquid **2**), respectively. The present reaction smoothly proceeded at room temperature in an ionic liquid (Table 1)

In view of ‘green chemistry’, one-pot synthesis and the reuse of catalyst and solvent are preferable. Therefore, we have developed a second version of this tandem Mannich–Michael-type reaction which can be carried out in one pot. In this reaction system, the corresponding imines were initially prepared *in situ* from the reaction of aldehyde and amine in an ionic liquid, and then Lewis acid (microencapsulated scandium trifluoromethanesulfonate, Wako Pure Chemical Industries, Ltd.) and 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene were added. After stirring at room temperature for 20 h, *N*-aryl-6-aryl-5,6-dihydro-4-pyridone was obtained following extraction with diethyl ether, and ionic liquid **1** and microencapsulated Lewis acid were recovered in more than 92% yield (Table 2).<sup>12</sup>

Before the reuse of ionic liquids, they were purified under dynamic vacuum at 70–80 °C for 1 h, with the purity and structure determined by the <sup>1</sup>H and <sup>19</sup>F NMR spectroscopy. Successive reuse of the recovered ionic liquid **1** in the same reaction yielded amounts of product as high as in the first cycle shown in Fig. 1.

In this reaction system, microencapsulated scandium trifluoromethanesulfonate is recovered smoothly in an ionic liquid layer after extracting *N*-phenyl-6-phenyl-5,6-dihydro-4-pyridone with diethyl ether, making a convenient Lewis acid reusable catalyst.

The structure of *N*-phenyl-6-phenyl-5,6-dihydro-4-pyridone was confirmed by <sup>1</sup>H NMR spectra. The observed <sup>1</sup>H NMR chemical shifts and coupling constants of the compound at δ 2.80 (1H, ddd, *J* = 16.48, 3.02, 1.10 Hz) and 3.32 (1H, dd, *J* = 16.48, 7.14 Hz) suggest two protons attached to the CH<sub>2</sub>CO.

Table 1 Synthesis of 5,6-dihydro-4-pyridones

Entry	R	RA	Ionic liquid <sup>a</sup>	Yield(%)
1	Ph	Ph	<b>1</b>	75
2	Ph	Ph	<b>2</b>	67
3	Ph	3,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>1</b>	74

<sup>a</sup> 8-Ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate **1**; 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **2**.

## Green Context

Diels–Alder reactions are one of the most important classes of organic reactions. They are however, commonly associated with two major sources of waste: organic solvents and soluble Lewis acids (such as TiCl<sub>4</sub> and BF<sub>3</sub>). In this paper, we see how both of these problems can be dealt with in a new, low-waste and recyclable reaction system based on an ionic liquid as a low volatility reaction medium and an encapsulated metal triflate as a recoverable catalyst. The successful application of this combination of environmentally friendly solvent and solid catalyst is exciting and is likely to open the door to the development of similar reaction systems for other important organic reactions. *JHC*

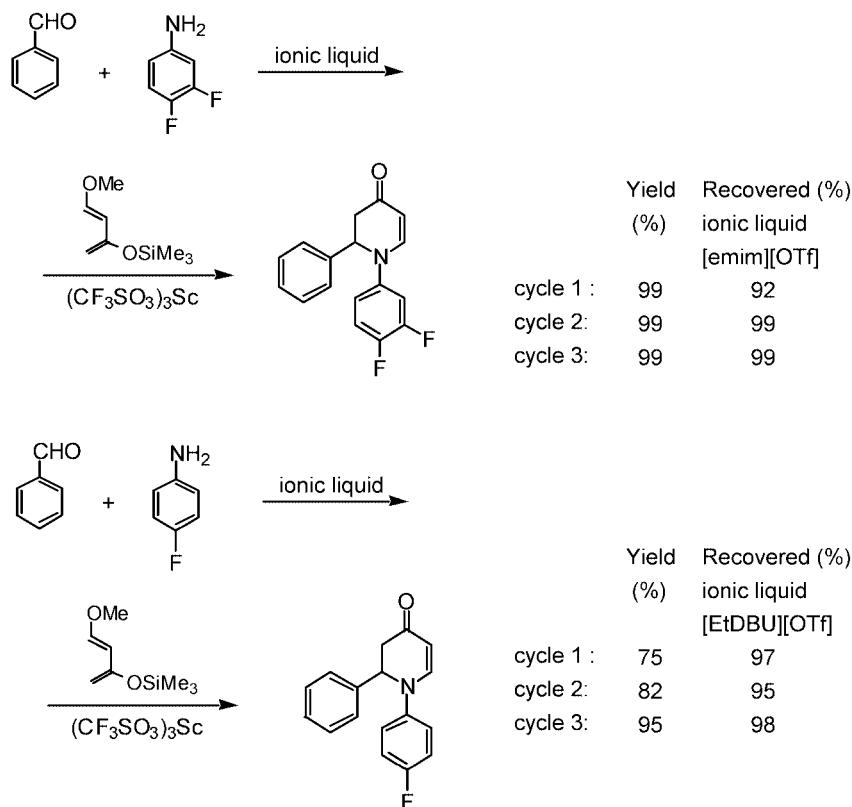


Fig. 1 Recycling ionic liquids.

Table 2 One-pot synthesis of 5,6-dihydro-4-pyridones

Entry	R	RA	Ionic liquid <sup>a</sup>	Yield <sup>b</sup> (%)	Recovered ionic liquid (%)
1	Ph	Ph	1	82 <sup>c</sup>	98
2	Ph	Ph	2	80 <sup>c</sup>	99
3	Ph	3,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1	95	92
4	Ph	3,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2	99	92
5	Ph	4-FC <sub>6</sub> H <sub>4</sub>	1	75	97
6	Ph	4-FC <sub>6</sub> H <sub>4</sub>	2	79	97
7	4-FC <sub>6</sub> H <sub>4</sub>	Ph	1	85	98
8	4-FC <sub>6</sub> H <sub>4</sub>	Ph	2	95	98
9	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Ph	1	85	98
10	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Ph	2	88	98

<sup>a</sup> 8-Ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate **1**; 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate **2**. <sup>b</sup> Yields determined by <sup>19</sup>F NMR integral intensities. <sup>c</sup> Isolated yield.

The signals at  $\delta$  5.30 (COCH=CH, 1H, dd,  $J = 7.69, 1.10$  Hz) and 7.68 (CH=CHN, 1H, dd,  $J = 7.69, 1.10$  Hz) suggest olefinic protons.

Successive reuse of the recovered ionic liquids (**1** and **2**) and microencapsulated Lewis acid in the same reaction yielded amounts of product as high as in the first cycle shown in Fig. 1. In the third cycle, the reuse of ionic liquids and microencapsulated Lewis acid recovered from the second cycle is possible and produce the same 5,6-dehydroxy-4-pyridone in the

same reaction. After quenching the third cycle, ionic liquids were recovered in more than 90–98% yield compared to the starting ionic liquid.

In conclusion, we have shown that ionic liquids are a good alternative reaction media for one-pot aza-Diels–Alder reactions.

## Notes and references

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- 8-Ethyl-1,8-diazabicyclo(5,4,0)-7-undecenium trifluoromethanesulfonate: Into a cooled (ice-bath) flask containing 1,8-diazabicyclo(5,4,0)-7-undecene (60.8 g, 0.4 mol), ethyl trifluoromethanesulfonate

nate (71.2 g, 0.4 mol) was added slowly. After stirring for 2 h at room temperature, the mixture was heated at 70 °C for 1 h to remove the volatile materials, giving 8-ethyl-1,8-diazabicyclo(5,4,0)-7-undecenium trifluoromethanesulfonate **1** in 98% yield.  $\delta_{\text{H}}(\text{CDCl}_3)$ : 1.28 (3H, t,  $J = 7.32$  Hz), 1.75–1.84 (8H, m), 2.15 (2H, m), 2.87 (2H, m), 3.55–3.59 (2H, m), 3.60 (2H, q,  $J = 7.32$  Hz), 3.68 (2H, m).  $\delta_{\text{C}}(\text{CDCl}_3)$ : 13.554, 19.950, 22.841, 25.937, 28.069, 28.475, 46.210, 48.855, 48.968, 55.080, 120.584 (q,  $J = 320.4$  Hz), 165.966.  $\delta_{\text{F}}(\text{CDCl}_3)$ : 83.37 ppm from internal  $\text{C}_6\text{F}_6$ . IR: 2928, 2932, 2296, 1626  $\text{cm}^{-1}$ .

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- 12 *N*-Phenyl-6-phenyl-5,6-dihydro-4-pyridone: Typical procedure is as follows. A mixture of benzaldehyde (318 mg, 3 mmol) and aniline (279 mg, 3 mmol) in 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium

trifluoromethanesulfonate **1** (1 g) was stirred for 30 min at room temperature, and then 1-methoxy-3-(trimethylsilyl)oxybuta-1,3-diene (1207 mg, 7 mmol) and Lewis acid (50 mg, microencapsulated scandium trifluoromethanesulfonate (10–15%), Wako Pure Chemical Industries, Ltd.) was added to the mixture. After 20 h of stirring at room temperature, the product was extracted with diethyl ether (10 × 20 ml), and then ionic liquid **1** (98% recovery) and microencapsulated Lewis acid were recovered by biphasic extraction. After removal of the solvent, *N*-phenyl-6-phenyl-5,6-dihydro-4-pyridone was obtained in 82% yield by silica gel chromatography gel using hexane–ethyl acetate (10:1).  $\delta_{\text{H}}(\text{CDCl}_3)$ : 2.81 (1 H, ddd,  $J = 16.48, 3.02, 1.10$  Hz), 3.33 (1 H, dd,  $J = 16.48, 7.14$  Hz), 5.28 (1 H, m), 5.30 (1 H, dd,  $J = 7.69, 1.10$  Hz), 7.68 (1 H, dd,  $J = 7.69, 1.10$  Hz), 7.05–7.38 (Ar-H).  $\delta_{\text{C}}(\text{CDCl}_3)$ : 67.641, 85.126, 116.879, 119.596, 121.951, 124.831, 126.371, 127.247, 128.456, 128.913, 138.913, 141.428. Anal. calc. for  $\text{C}_{17}\text{H}_{15}\text{NO}$ : C, 81.90; H, 6.06; N, 5.62, found, C, 81.24; H, 5.76; N, 5.23%.



# Selected syntheses of ureas through phosgene substitutes

Franca Bigi, Raimondo Maggi and Giovanni Sartori\*

Dipartimento di Chimica Organica e Industriale dell'Università Parco Area delle Scienze 17A, I-43100 Parma, Italy. E-Mail: sartori@unipr.it

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Ureas have been traditionally synthesised by methodologies mainly based on the use of dangerous reagents such as phosgene and isocyanates. In the last few years, however, these reagents have been increasingly substituted by cleaner alternative and inherently safer compounds since the goal of the modern environmentally friendly synthetic chemistry is the development and optimisation of reaction conditions to reduce or eliminate the use and production of hazardous materials while maximising energy usage. Thus different and sometimes sophisticated phosgene substitutes such as bis(4-nitrophenyl)carbonate, triphosgene, di-*tert*-butyl dicarbonate, 1,1-carbonylbisimidazole, 1,1-carbonylbisbenzotriazole, *S,S*-dimethyldithiocarbonate and trihaloacetylchlorides have been utilised as safer reagents which can be stored and handled without special precautions. Moreover, the large scale production of urea derivatives has been more conveniently performed by using simpler and cheaper raw materials such as CO and CO<sub>2</sub> in catalytic processes, avoiding production of large amounts of saline by-products which represent the main constituent of chemical waste.

## 1. Introduction

In all the developed countries the chemical industry is under continuous and strong pressure by increasingly stringent regulations and by the adverse public opinion; as a consequence, it will not survive without environmental awareness and action.

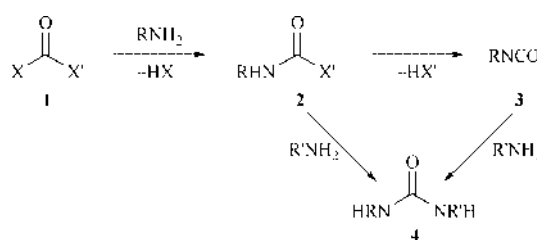
The focus of environmental protection will shift from cleaning up after a possible damage is done to preventing pollution through research and education.<sup>1</sup> Thus chemistry has today an important challenge both in the labs and in the plants: driving toward pollution prevention and waste minimisation. Nevertheless, many industrial processes still utilise hazardous and toxic reagents and solvents or use catalysts in stoichiometric amounts. As clearly recognised by Sheldon, this is the consequence of the fact that most of these processes are based on reactions discovered and studied more than 50 years ago with the main objective of making products without any interest in the environmental pollution.<sup>2</sup> These methodologies are not longer accepted and the development of environmentally safer processes represents one of the most important target for today's synthetic chemists.

Ureas have found use in a wide variety of areas ranging from applications as dyes for cellulose fibre to the use as antioxidants in gasoline, corrosion inhibitors and intermediates for the production of carbamates which represent raw materials for agrochemicals. Their biological activities as plant growth regulators, agroprotectives as well as tranquillising and anti-convulsant agents are also important.<sup>3</sup> Ureas substituted with amino acid groups have been shown to be potent HIV-1 protease inhibitors.<sup>4</sup>

The simplest and direct synthesis of substituted ureas is described by the general and merely strategic Scheme 1. The process essentially involves two steps: (1) reaction of the selected amine with the reagent **1** containing the carbonyl group to form the intermediate **2**, still possessing a leaving group linked to the carbonyl; (2) further reaction of the intermediate **2** with the same amine or with a different amine to form the symmetrical or the unsymmetrical substituted urea **4** directly or through the more reactive isocyanate **3**.

Apart from the preparation of the parent urea, commercially produced by dehydration of ammonium carbamate obtained by

direct reaction of ammonia with carbon dioxide,<sup>5</sup> the most early and classical method for the preparation of *N,N'*-symmetrical substituted ureas involves the reaction of amines with phosgene (reagent **1**, X, X' = Cl). The addition of amines to isocyanates **3** can be regarded as the main route for the synthesis of the more



Scheme 1

## Green Context

Ureas have a range of uses including dyes for cellulose fibres, as antioxidants in gasoline and as intermediates *en route* to carbamates which are used in agrochemistry. They also have useful biological activity and derivatives have proven to be potent HIV-1 protease inhibitors. Traditionally, however, ureas have been prepared by methods based on hazardous reagents such as phosgene and isocyanates. The production and use of phosgene is under close scrutiny — in terms of the use and storage of large amounts of chlorine, the production of large volumes of waste containing chlorinated by-products and the high risk of storing and transporting a volatile and very toxic compound. Despite these concerns, *ca.*  $2 \times 10^6$  tonne  $y^{-1}$  of phosgene are produced and used worldwide. One of the goals of Green Chemistry is to reduce or eliminate the use and production of hazardous materials and several interesting phosgene substitutes have been reported in recent years. These are generally noted for being safe to handle and easy and safe to store. In this review, greener synthetic pathways to useful ureas based on phosgene substitutes are described. JHC

challenging *N,N'*-unsymmetrical substituted ureas **4**. However, it is important to underline that isocyanates themselves are toxic and are usually prepared from phosgene.<sup>6</sup>

Unfortunately, production and use of phosgene opens many worrying toxicological and environmental problems connected with use and storage of large amounts of chlorine, production of a lot of waste constituted of aqueous solutions contaminated by chlorine by-products and high environmental risk in storage, transportation and use of a reagent characterised by high toxicity and volatility. Nevertheless, about 2 million tons per year of phosgene are produced and utilised worldwide.<sup>7</sup>

Under the new environmental legislation of the developed countries, industrial and academic research groups have performed methodologies for preparation of ureas based on the use of reagents which are less toxic and less hazardous than phosgene.

In this review we deal with the use of these phosgene substitutes for the synthesis of ureas and we particularly emphasise the advantages of completely phosgene-free synthetic methods based on the use of CO, CO<sub>2</sub>, alkyl carbonates and other miscellaneous carbonylating reagents. We have not included methods based on supported reagents, which represent a specific field of application.

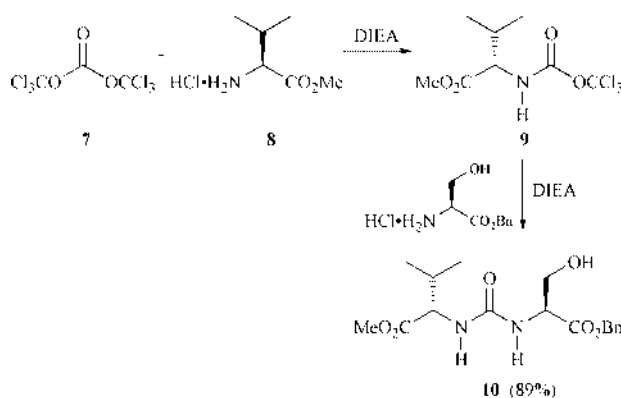
## 2. Use of substitutes for phosgene (symmetrical reagents 1)

We first describe the use of phosgene substitutes **1** containing two identical leaving groups (Scheme 1: X = X') which can be utilised to prepare both symmetrical and unsymmetrical ureas. The success of this approach in the synthesis of unsymmetrical *N,N'*-disubstituted ureas is critically dependent on the second step being much slower than the first, so that the formation of the symmetrical urea is minimised.

Bis(4-nitrophenyl)carbonate **5**, a very stable reagent, can be converted into carbamates **6** (44–78% yield) by reaction with equimolecular amounts of primary aliphatic or aromatic amines within 2 h in dichloromethane. Intermediates **6** react further with different primary amines giving the unsymmetrical ureas **4** in good yields (50–96%) (Scheme 2). The second step is considerably slower than the first and requires a longer reaction time of *ca.* 4 h.<sup>8</sup> By reacting **5** with an excess of amine (1:2 ratio), symmetrical ureas are formed directly in high yield (50–95%).

Triphosgene [bis(trichloromethyl)carbonate] **7**, a crystalline solid which represents a safe and stable replacement for phosgene and can be handled without special precaution,<sup>9</sup> is successfully utilised to the sequential synthesis of unsymmetrical ureas also bearing chiral amino acid derivatives, without having to purify the intermediates.<sup>10</sup> Thus, in a model reaction valine methyl ester hydrochloride **8** is reacted with triphosgene **7** in the presence of diisopropylethylamine (DIEA) in dichloro-

methane at room temperature for 30 min giving the intermediate **9**. Serine benzyl ester hydrochloride and DIEA in dichloromethane are then added over 10 min. Product **10** is obtained in 89% yield *via* a typical sequential, three-component reaction (Scheme 3). The reaction is successfully applicable to different amines containing multiple functionalities such as unprotected primary and secondary alcohols (85–88% yield).



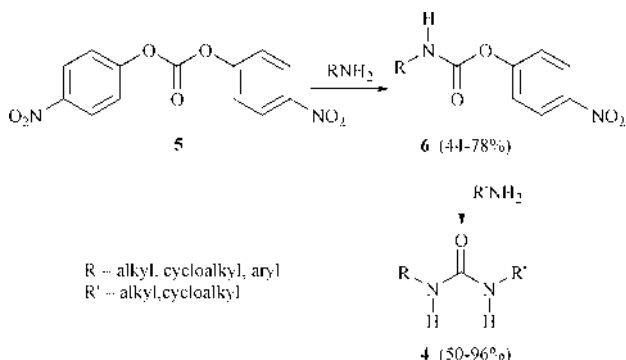
Scheme 3

An important application of this strategy is represented by the use of *O*-trimethylsilyl protected amino acid hydrogen chlorides to produce half-acid/half-ester urea dipeptides in 45–49% yield,<sup>11</sup> starting materials for a variety of pharmacologically active compounds. Addition of the selected *O*-trimethylsilyl protected amino acid hydrogen chloride to a solution of triphosgene in chloroform and in the presence of DIEA results in the formation of the isocyanate intermediate which is converted *in situ* into the urea dipeptide upon reaction of a second amino acid methyl ester in methanol.

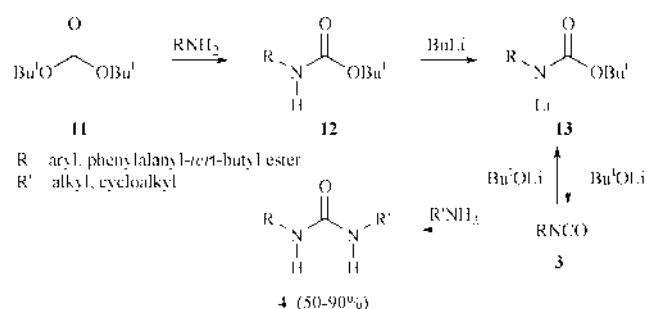
Similar application is reported for di-*tert*-butyldicarbonate **11** [(BOC)<sub>2</sub>O], a well known reagent utilised for protecting the amino group giving *N*-BOC-primary amines **12** with high yield and selectivity. Reagents **12** can be converted into unsymmetrical substituted ureas **4** by reaction with a second amine. The reaction requires the use of strong bases such as alkyllithiums which convert **12** into the isocyanate **3** capable of undergoing fast addition of a second amine affording the final unsymmetrical urea **4**<sup>12</sup> (Scheme 4). Softer and more *safely handled* organic bases such as 4-dimethylaminopyridine (DMAP) can be utilised and eventually recovered at the end of the reaction, giving symmetrical as well as unsymmetrical ureas in 80–99% yield by stirring the reaction mixture for 14 h at 40 °C.<sup>13</sup>

The crucial role of isocyanates as intermediates in this approach is confirmed by a detailed mechanistic study which demonstrates that carbamates are by-products which are not convertible into ureas.<sup>14</sup>

The commercially available and easily handled crystalline solid *N,N'*-carbonyldiimidazole **14** (CDI) is utilised as starting reagent for the general synthesis of unsymmetrical tetra-

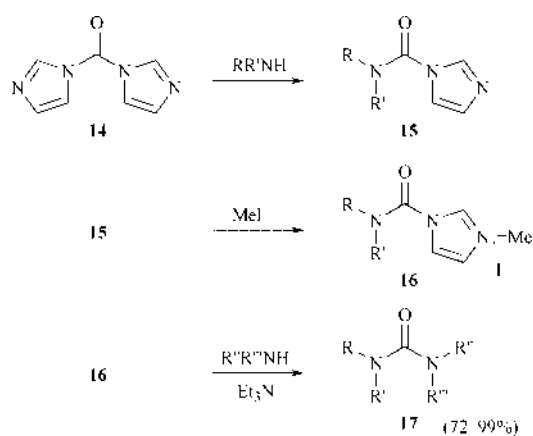


Scheme 2



Scheme 4

substituted ureas. The intermediate carbamoyl imidazole **15** is first obtained by reaction of CDI with a secondary amine. Compound **15** is successively converted into the more reactive and resonance-stabilised imidazolium salt **16** by *N*-alkylation of the imidazole moiety. Addition of a different secondary amine to **16** furnishes *N,N,N',N'*-unsymmetrical tetrasubstituted ureas **17** in high yield (72–99%) (Scheme 5).



R, R', R'', R''' = alkyl, cycloalkyl, aryl, allyl, Cl<sub>12</sub>CN

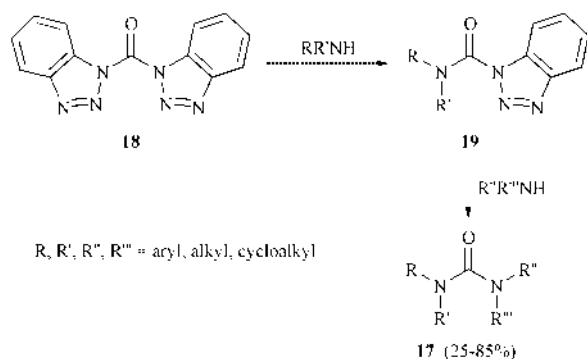
Scheme 5

Imidazolium salts **16** are produced quantitatively and do not require additional purification for the final conversion to the ureas **17**. Although the salts **16** are hygroscopic, they can be stored for several weeks without detectable decomposition.<sup>15</sup>

The carbonyldiimidazole-based approach is successfully applied also to the synthesis of some more sophisticated urea dipeptides which represent building blocks for the preparation of inhibitors of HIV-protease. These compounds are simply obtained by mixing in sequence CDI with the selected amino acid ester hydrochloride salt in the presence of triethylamine, and avoiding use of strong bases such as BuLi or lithium diisopropylamide (LDA) utilised in the methodology described in Scheme 4 which can racemize the stereogenic centers.<sup>16</sup>

Similarly, *N,N'*-carbonyldibenzotriazole **18** can be utilised to synthesise *N,N,N',N'*-unsymmetrical tetrasubstituted ureas **17** by one-pot reaction with the first amine to produce the carbamoylbenzotriazole intermediate **19** that can react under more forceful conditions with a second amine giving the final urea **17** in satisfactory to good yields (24–85%)<sup>17</sup> (Scheme 6).

The reaction conditions and the yields of intermediate **19** are significantly affected by the steric hindrance of the substituents of the amines utilised. The procedure succeeds at room temperature in THF for 2 days in 40–71% yield for cyclic, aliphatic and aromatic amines, whereas harsher conditions are required and lower yields obtained from congested secondary



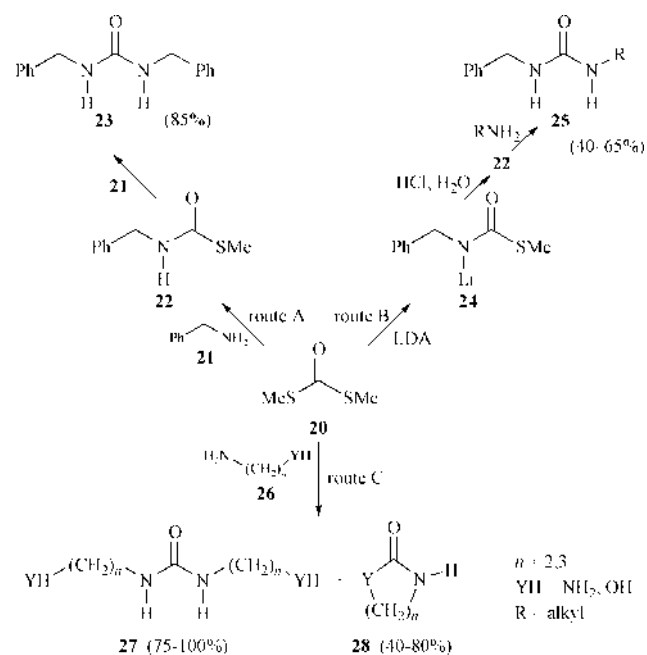
R, R', R'', R''' = aryl, alkyl, cycloalkyl

Scheme 6

amines. Unfortunately reagent **18** is not commercially available and must be synthesised directly by benzotriazole and phosgene. This drawback makes the above approach unattractive and utilisable only in lab-scale preparation.

*S,S*-Dimethyldithiocarbonate (DMDTC) **20** represents a mild and safely handled reagent structurally similar to phosgene which is useful in the synthesis of ureas. DMDTC can be prepared from methanol, carbon disulfide and dimethyl sulfate by a two-step sequence.<sup>18</sup> Even if dimethyl sulfate is a suspected human carcinogen the substance is relatively non-volatile and can be handled safely with care in the laboratory. In a representative example, DMDTC **20** is allowed to react with 2 equivalents of benzylamine **21** at 60 °C for 24 h in methanol or ethanol giving symmetrical dibenzylurea **23** in 85% yield (Scheme 7, route A).<sup>19</sup> Results of mechanistic studies confirm that the second reaction stage is faster than formation of *N*-benzyl-*S*-methylthiocarbamate **22**. By carrying out the reaction under basic conditions (LDA), the intermediate **22** is deprotonated immediately after being formed giving the corresponding lithium salt **24** in quantitative yield, which is relatively stable toward nucleophilic substitution at ambient temperature and will not react further to give dibenzylurea (Scheme 7, route B). Treatment with aqueous HCl affords thiocarbamate **22** that can react further with different aliphatic amines furnishing the unsymmetrical ureas **25** (40–65% yield).

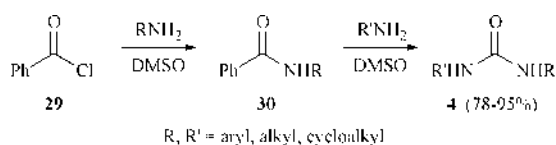
Aliphatic amines **26** bearing an hydroxy or an amino substituent at the β or γ position react with **20** in dilute solution providing predominantly cyclic ureas or carbamates **28** (40–80% yield) (Scheme 7, route C). By increasing the concentration of the starting reagent **26** with respect to DMDTC, the symmetrical ureas **27** are obtained in high yield (75–100%) without need for protection and deprotection procedures.



Scheme 7

### 3. Use of substitutes for phosgene (unsymmetrical reagent 1)

In an alternative strategy, reagents **1** with two different leaving groups attached to the carbonyl group are utilised. Here, it is possible to control the rate of displacement of the leaving group by conveniently selecting X and X'. Thus variously *N,N'*-

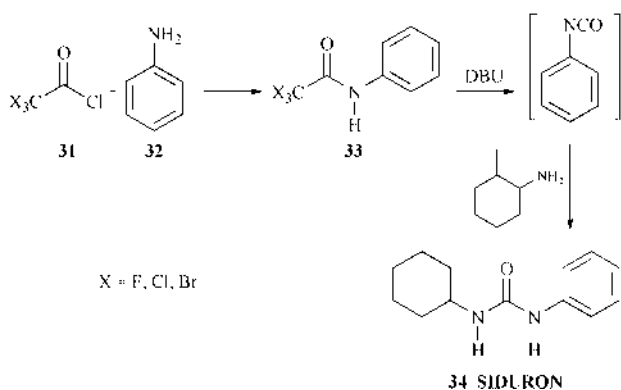


Scheme 8

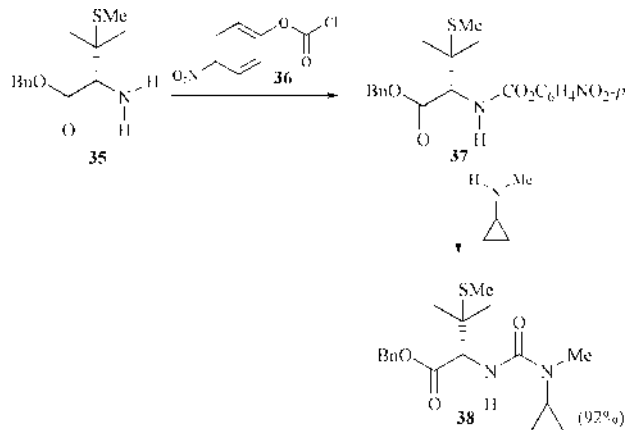
disubstituted ureas **4** including some chiral compounds are efficiently synthesised by reaction of amines with carbamates **30** which in their turn are prepared from phenyl chloroformate **29**<sup>20</sup> (Scheme 8). The reaction occurs at room temperature in 78–95% yield simply by mixing the reagents in DMSO, the only by-product being phenol which is easily removable by an aqueous NaOH wash. The method is also successfully applied to secondary amines to generate *N,N'*-trisubstituted ureas in 78–89% yield independent from the steric hindrance of the reagents. The reaction conditions are compatible with a number of functional groups such as chiral amines, aminoacids and aminoalcohols. A possible drawback of this approach is associated with the use of DMSO as solvent, which is toxic, a possible carcinogen and explosive when mixed with some organic and inorganic reagents.<sup>21</sup> The use of DMSO as solvent is critical to the mildness of the conditions. Compared to DMSO, the reaction is much slower in MeOH, dioxane, DME or CH<sub>2</sub>Cl<sub>2</sub> in which the carbamate **30** is insoluble at the beginning of the reaction.

Trihaloacetylchlorides **31** represent a second class of unsymmetrical reagents **1** which are commercially available at reasonable prices. They can be quantitatively converted into the corresponding trihaloacetamides **33** (80–90%) as easily handled crystalline solids with long shelf life by reaction with convenient aromatic or aliphatic amines. These compounds react with different aliphatic amines in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) giving unsymmetrical ureas such as Neburon and Siduron with biological activity<sup>22</sup> (Scheme 9). As expected from the reaction mechanism, the rates of the reaction of intermediates **33** with bases exhibit a strong dependence on the nature of the trihalomethyl group according to the scale RCOCF<sub>3</sub> < RCOCCl<sub>3</sub> < RCOBr<sub>3</sub>. As for some other reported methodologies, this 'one-pot' synthesis of ureas from readily available trihaloacetanilides has the clear advantage that it avoids the need to isolate the highly toxic isocyanates. The crucial role of the isocyanates in the present reaction is confirmed by the unreactivity of trichloroacetamides derived from *N,N*-disubstituted amines which can not afford isocyanates.

Finally, ureas containing structurally complex frameworks, including aminoacid derivatives, are efficiently prepared from *p*-nitrophenylchloroformate **36**. To give an example, *S*-methyl-*O*-benzyl-L-penicillamine **35** reacts with **36** in acetonitrile at 0 °C for 30 min giving carbamate **37**. Further addition of cyclopropylmethylamine in the same solvent and in the presence of NaHCO<sub>3</sub> gives the aminoacidic urea **38** in 92% yield (Scheme 10). The reaction occurs under very mild conditions owing to the good leaving ability of the *p*-nitrophenyl group and hence is not applicable to tetrasubstituted ureas.<sup>23</sup>



Scheme 9



Scheme 10

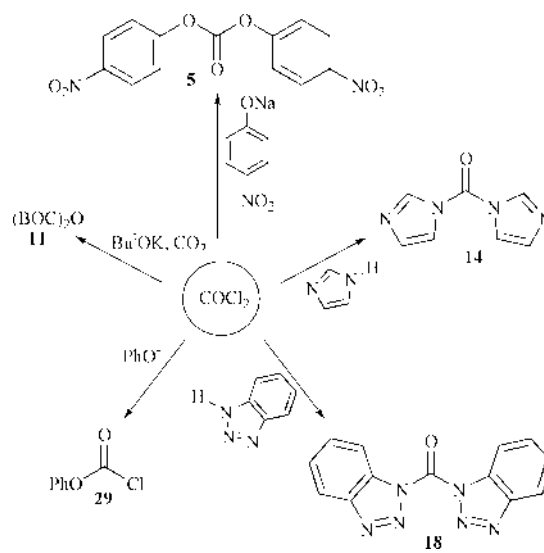
yield (Scheme 10). The reaction occurs under very mild conditions owing to the good leaving ability of the *p*-nitrophenyl group and hence is not applicable to tetrasubstituted ureas.<sup>23</sup>

All the above described methodologies represent results of efforts directed toward the development of mild and safe reagents that can be utilised instead of phosgene in urea synthesis. In fact all the reagents employed are less toxic than phosgene; some of them are crystalline and stable solids and can be stored and handled with the usual safety precautions; however, only few of them are commercially available. Moreover, bis(4-nitrophenyl)carbonate **5**,<sup>8</sup> 1,1-carbonylbisimidazole (CDI) **14**,<sup>15</sup> 1,1-carbonylbisbenzotriazole **18**,<sup>17</sup> phenyl chloroformate **29**<sup>20</sup> and di-*tert*-butyl dicarbonate [(BOC)<sub>2</sub>O] **11**<sup>12</sup> are themselves prepared from phosgene (Scheme 11).

The sole exception is represented by trihalomethyl chlorides **31** and triphosgene **7**. In fact the term triphosgene applied to bis(trichloromethyl)carbonate is a misnomer, since this compound is not derived from phosgene but by exhaustive chlorination of methyl carbonate.<sup>24</sup>

It is thus immediately clear that the utilisation of these reagents is only a way to circumvent and not to face and solve the problem of avoiding the use of phosgene. However, the above described procedures can be applied to the small or medium scale preparation of those ureas which are difficult to efficiently synthesise by other and safer methods, mainly compounds incorporating different functionalities and chiral carbons in the side chains.

Finally, concerning the possible use of particularly toxic reagents such as phosgene, dimethyl sulfate, sodium azide, *etc.*



Scheme 11

and their conversion into more stable and less toxic reactive derivatives, their industrial use would be confined in the future to a small group of experts who are properly equipped to manipulate and contain these materials from which more stable and less toxic derivatives can be prepared.<sup>25</sup> This program is in full accord with the positive and far-seeing concept that eco-compatible chemistry demands elimination and substitution of noxious reagents by safer ones when possible. Concerning the use of dangerous compounds, the good chemist has to act as a lion-tamer, the lion has to be treated with the maximum respect but not feared!

#### 4. Use of CO

Although carbon monoxide is a toxic gas, it is utilised in a wide variety of industrial carbonylation processes owing to its low cost, accessibility and easily controlled reactivity.<sup>26</sup>

Direct carbonylation of primary amines to *N,N'*-symmetrical ureas with a nitrido tungsten(IV) carbonyl complex is performed in good yield (56–67%). The reaction is carried out at room temperature under nitrogen followed by oxidation with air at ambient pressure. Unfortunately the process requires a stoichiometric amount of the carbonyl complex and ureas are only obtained with primary amines since secondary ones afford formamides.<sup>27</sup>

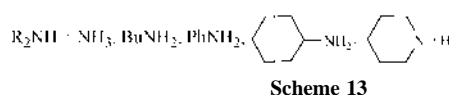
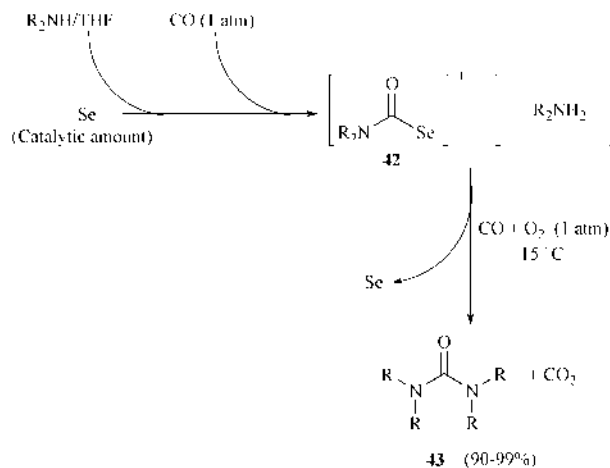
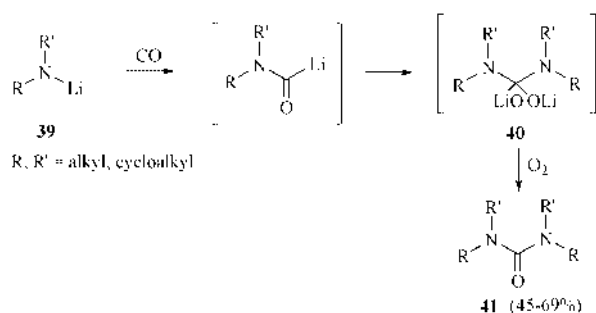
The synthesis of *N,N,N',N'*-tetrasubstituted ureas in variable yield (45–69%) by carbonylation of lithium amides with carbon monoxide at atmospheric pressure under mild conditions has been reported (Scheme 12).

Ureas **41** are shown to be formed in THF solution after the *in situ* oxidation of the intermediate **40** with oxygen. The advantages of this method are the short reaction time and use of molecular oxygen as oxidant.<sup>28</sup>

Selenium reacts with carbon monoxide and amines under mild conditions (15 °C, 1 atm) to give ammonium carbamoseleates **42** which are then converted to the corresponding ureas **43** by aminolysis upon oxidation with molecular oxygen which converts the unwanted hydrogen selenide into selenium so regenerating the catalyst (Scheme 13). Under controlled conditions the reaction proceeds with a catalytic amount of selenium and its turnover number reaches *ca.*  $1 \times 10^4$ . The reaction is strongly accelerated at elevated temperatures and pressured conditions [120 °C, O<sub>2</sub> (4 atm)].<sup>29</sup>

The above approach is applicable to the synthesis of unsymmetrical phenylureas through the selenium-catalysed reductive carbonylation of nitrobenzene in the presence of aliphatic secondary amines as co-reagents. The reaction is characterised by good yields and selectivities (40–80%). By contrast, when primary amines are used as co-reagents, a mixture of all the three possible ureas is obtained.<sup>30</sup>

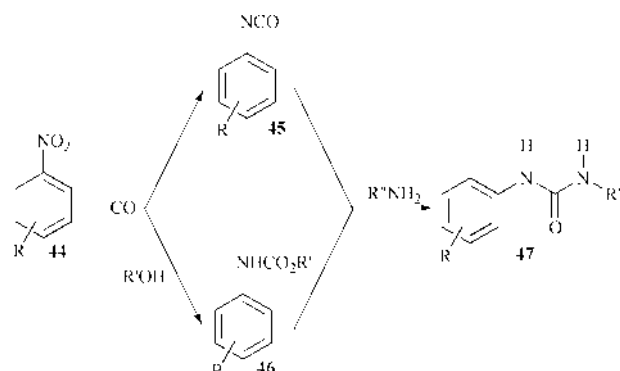
From the above it appears that the synthesis of ureas, with particular regard to the production of fine chemicals and pharmaceuticals,<sup>31</sup> is mainly achieved through carbonylation of amines with generation of large amounts of inorganic salts



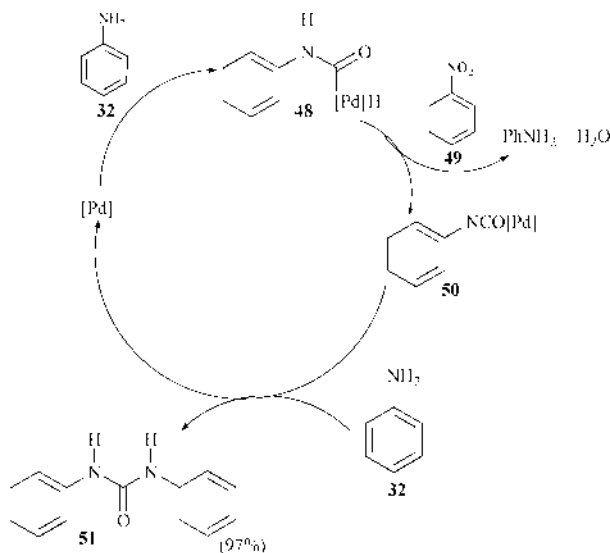
which represent the main components of industrial waste. Consequently, the development of salt-free technologies by industrial and academic research groups is required that not only involve simpler raw materials, but also permit to replace stoichiometric reactions with catalytic processes. Since 1962 the catalytic carbonylation of nitro compounds with particular interest towards nitroaromatic compounds has been extensively studied with the main focus upon the production of isocyanates which have achieved great commercial importance in the preparation of important industrial targets including ureas.<sup>32</sup>

Different catalysts have been used to promote the process including group 8–10 metal compounds (mainly Pd, Ru and Rh) combined with a Lewis acid co-catalyst (mainly FeCl<sub>3</sub>, MoCl<sub>5</sub>, V<sub>2</sub>O<sub>5</sub> and Fe<sub>2</sub>O<sub>3</sub>) or Brønsted acid (*e.g.* trimethylbenzoic acid). The methodology was particularly studied and developed with the aim of producing methylenediphenyl isocyanates and phenyldiisocyanate which are of commercial importance in the manufacture of polyurethanes. Concerning the synthesis of monoisocyanates, because of their instability under the reaction conditions, the process was better utilised in the production of *N*-phenylcarbamates **46** by trapping isocyanates with alcohols (Scheme 14). Furthermore isocyanates can be converted *in situ* into symmetrical diphenyl ureas by reaction with amines either added to the reaction mixture or produced *in situ* by reduction of the nitro compound.<sup>26</sup>

Diphenylurea (DPU) **51** is synthesised in almost quantitative yield from nitrobenzene **49**, aniline **32** and CO in the presence of a Pd(II) complex with triphenylphosphine (0.2 mol% with respect to aniline) dissolved in a non-polar solvent such as toluene or xylene at 120 °C (Scheme 15). The carbamoyl complex [PhNCO(Pd)] **50** or nitrene complex-[PhN(Pd)] can be formed depending on whether nitrobenzene or aniline interact







Scheme 15

with the catalyst. Studies with deuterated nitrobenzene suggest that the reaction involves the carbamoyl intermediate **50** even if it is not clear how important this pathway is.<sup>33</sup>

Unsymmetrical substituted ureas are likewise synthesised by reductive carbonylation of 4-substituted nitrobenzenes in the presence of an excess of an aliphatic secondary amine using palladium acetate, bipyridyl and copper tosylate as co-catalyst; the best selectivity is obtained by continuously adding the aliphatic amine during the period of reaction (*ca.* 10 h).<sup>34</sup>

Synthesis of *para*-substituted symmetrical diaryl ureas in satisfactory yield (27–88%) is performed by reaction of accessible aromatic nitrocompounds with CO in the presence of  $\text{Ru}_3(\text{CO})_{12}$  in *cis*-cyclooctene as the solvent (substrate/catalyst ratio 25).<sup>35</sup>

*N,N'*-Substituted ureas are obtained in fairly low yields (45–55%) by dioxygen-induced carbonylation of amines in the presence of nickel carbonyl complexes (substrate/catalyst ratio 100)<sup>36</sup> or ( $\eta$ -methylcyclopentadienyl)manganese tricarbonyl irradiated with UV light,<sup>37</sup> which are less expensive than palladium-based catalysts.

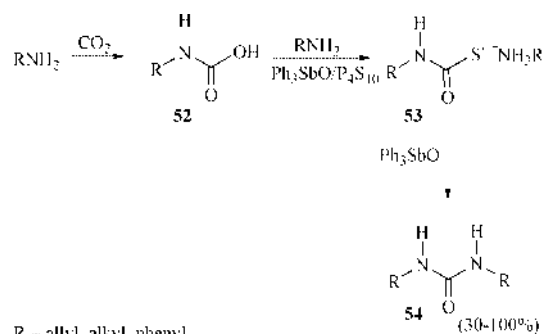
## 5. Use of CO<sub>2</sub> and carbonates

The use of carbon dioxide in industrial applications represents an important goal since minimisation of carbon dioxide emission can be achieved by direct fixation into the target compound.<sup>38</sup> Despite the fact that activation and use of carbon dioxide in chemical reactions is not an easy process, several important applications have been developed such as the production of carbamates which are utilised *per se* and as intermediates to fine chemicals including unsymmetrical ureas.

The formation of ureas from carbamic acids, however, requires high reaction temperatures near 200 °C and pressure of CO<sub>2</sub> higher than 10 MPa, since degradation of carbamic acids to isocyanates, the more active intermediates, occurs only under such conditions. Moreover the synthesis of ureas from amines and CO<sub>2</sub> involves elimination of water. Although the use of some dehydrating agents such as carbodiimides<sup>39</sup> and diorganophosphites<sup>40</sup> converts this method into a direct condensation, the methodology is of little practical interest since it involves the use of expensive and problematic reagents in stoichiometric amounts.

Triphenylstibine oxide ( $\text{Ph}_3\text{SbO}$ ) catalyses the carbonylation of diamines  $\text{H}_2\text{N}(\text{CH}_2)_n\text{NHR}$  ( $n = 2, 3$ ;  $\text{R} = \text{Me}, \text{CH}_2\text{CH}_2\text{OH}, \text{CH}_2\text{CHMeOH}$ ) with CO<sub>2</sub> in the presence of 3 Å molecular

sieves, giving the corresponding cyclic ureas in 83–98% yield.<sup>41</sup> The modified catalyst  $\text{Ph}_3\text{SbO}/\text{P}_4\text{S}_{10}$  utilised in the molar ratio amine/ $\text{Ph}_3\text{SbO}/\text{P}_4\text{S}_{10}$  40/1.0/2.0 is highly effective for the carbonylation of both amines and diamines giving linear and cyclic ureas at 80–150 °C for 12 h with CO<sub>2</sub> (4.9 MPa).<sup>42</sup> Monitoring the reaction by <sup>13</sup>C NMR spectroscopy revealed that the reaction course constitutes thiolation of the carbamic acid **52** to an intermediate antimony carbamate species followed by aminolysis of the carbamothioic acid thus formed (Scheme 16).



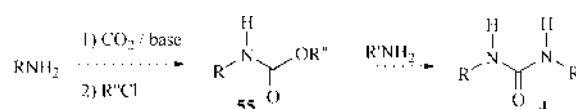
Scheme 16

In a more sophisticated manner propargyl alcohols are utilised in stoichiometric amounts as water scavengers. The reaction of aliphatic and aromatic primary amines with CO<sub>2</sub> is performed at 120–140 °C in the presence of a mixture of  $\text{RuCl}_3 \cdot \text{H}_2\text{O}$  and  $\text{Bu}_3\text{P}$  (amine/Ru molar ratio: 100) and an excess of the propargyl alcohol derivative (generally 2-methylbut-3-yn-2-ol) affording *N,N'*-disubstituted symmetrical ureas in 41–68% yield.<sup>43</sup> However, both the triphenylstibine oxide and propargyl alcohol based processes seem to be exploitable only at the laboratory scale owing to the use of toxic and/or expensive reagents.

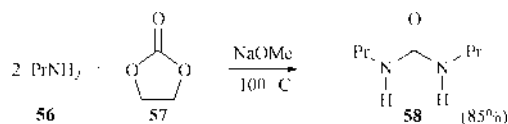
More conveniently carbamate esters **55** can be synthesised by reaction of amines with carbon dioxide and alkyl halides in the presence of bases (Scheme 17).<sup>44</sup>

Use of sterically hindered guanidine bases gives best results (80–99% yield with virtually 100% selectivity). Aminoacids and diamines are efficiently converted into the corresponding carbamates which can be utilised as intermediates to ureas. However, the use of stoichiometric amounts of bases represents a serious limit for the large scale application of the process. A further drawback of this methodology is represented by the alkylation of the amine which affords unwanted by-products. The above side reaction can be avoided by performing alkylation of alkylammonium *N*-alkylcarbamates which are easily obtained from primary amines and CO<sub>2</sub> in the presence of 18-crown-6 which can be recovered quantitatively at the end of the reaction.<sup>45</sup> An advantage which increases the industrial interest of the methodology is represented by the possibility of reducing the production of chloride wastes. In fact, different alkylating agents instead of alkyl chlorides can also be employed. The entire process occurs with yields close to 100%.<sup>38</sup>

Carbonic acid diesters are very attractive reagents and of great economic interest because they represent safe, non-corrosive and environmentally acceptable alternative to phosgene for carbonylation and carboxylation reactions. For example, methoxycarbonylation with dimethylcarbonate offers a



Scheme 17



Scheme 18

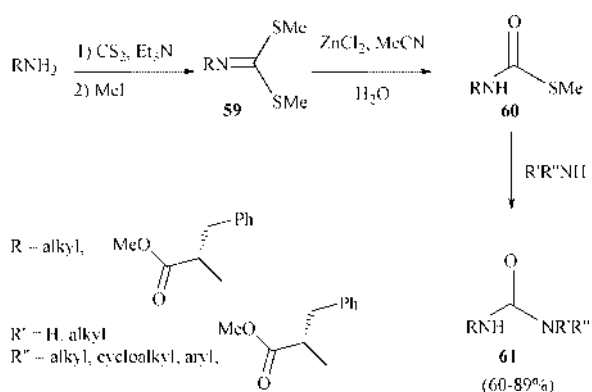
phosgene-free route for the production of carbamates and isocyanates<sup>46</sup> comparable, by the environmental point of view, with the transition metal catalysed carbonylation of nitro compounds and amines with CO. Ethylene carbonate **57**, which is prepared in large amounts by reacting ethylene oxide with CO<sub>2</sub>,<sup>47</sup> represents an effective carbonylating reagent for conversion of propylamine **56** into *N,N'*-dipropylurea **58** (Scheme 18). Reaction of **57** with an excess of **56** in 28% methanolic NaOMe in autoclave at 100 °C for several hours affords the product **58** in 85% yield.<sup>48</sup> The procedure can be efficiently applied to the large scale synthesis of both symmetrical and unsymmetrical *N,N'*-disubstituted ureas in high yield.

## 6. Miscellaneous methods

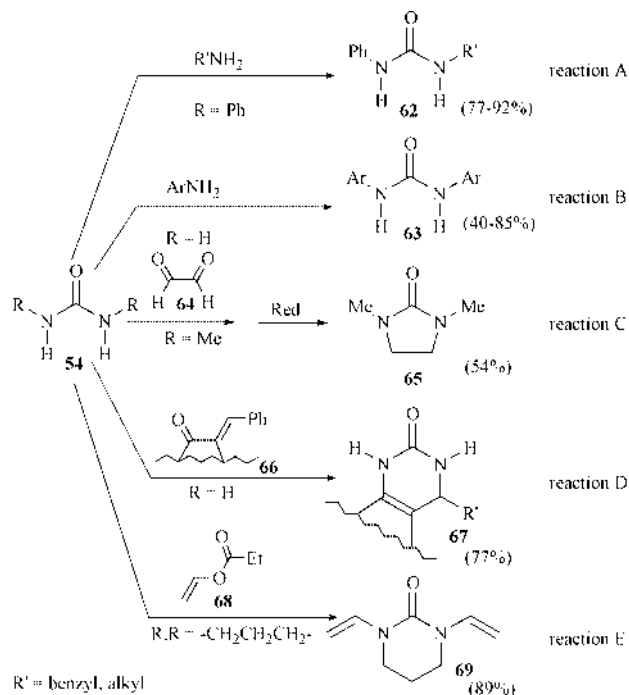
Some further phosgene-free methodologies have been developed for the synthesis of ureas which are not classifiable into the previously described groups of reactions. These include special carbonylation and carbamoylation processes as well as *N*-alkylation of simple ureas. Carbonimidodithioates **59**, which can be regarded as thiochetal of isocyanates, are easily prepared by reaction of primary amines or amino acid esters with CS<sub>2</sub> followed by methylation with MeI. These compounds are converted into *S*-methylthiocarbamates **60** upon treatment with ZnCl<sub>2</sub> in MeCN–H<sub>2</sub>O (3:1) at 60 °C for 6–10 h in good yields (Scheme 19). Further treatment of **60** with 2 equivalents of another primary or secondary amine in MeCN at 30–80 °C leads to unsymmetrical ureas **61** in 60–89% yield. The second amine molecule can also be an amino acid ester, leading in such cases to the urea dipeptides.<sup>49</sup>

Urea itself and *N,N'*-substituted ureas can be conveniently utilised as versatile and environmentally safe building blocks for the synthesis of more complex targets containing the ureido moiety through different reactions including displacement of one or both amino groups, *N*-alkylation and imine/enamine formation. Some recent applications are summarised in Scheme 20.

*N,N'*-Diphenylurea **54** (R = Ph) is converted into *N*-phenyl-*N*-alkylurea **62** in 77–92% yield by treatment with a large excess of primary amine and a small amount of Et<sub>3</sub>N in DMF at reflux for 4 h<sup>50</sup> (Scheme 20, reaction A). The method does not proceed with hindered secondary amines, gaseous amines or aromatic amines bearing electron withdrawing substituents



Scheme 19



Scheme 20

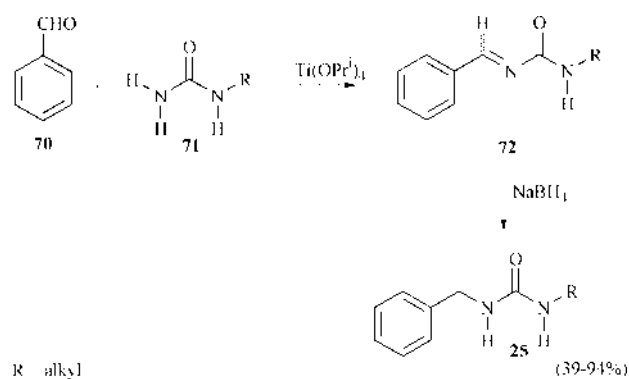
which, however, are converted into symmetrical *N,N'*-diaryllureas **63** in 40–85% yield by microwave irradiation for 4 min of a 2:1 molar mixture of the selected amine and urea **54** (R = H) (Scheme 20, reaction B).<sup>51</sup>

Cyclic ureas **65** and **67** can be prepared in satisfactory yield (54 and 77%, respectively) by condensation of urea or *N,N'*-dialkylureas with glyoxal **64** or  $\alpha$ -functionalised carbonyl compounds **66** followed by hydrogenolysis or removal of water (Scheme 20, reactions C and D).<sup>52</sup>

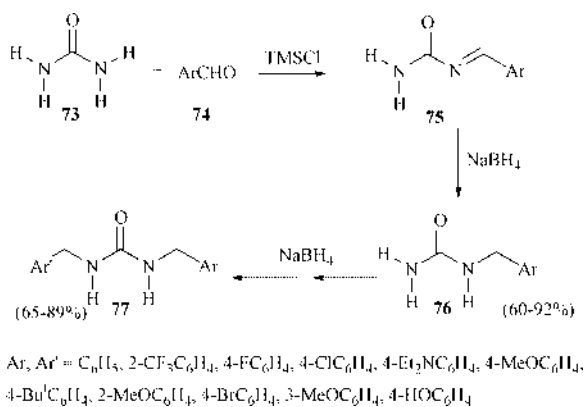
*N*-Alkylation of ureas represents a further useful method for the selective synthesis of *N,N,N',N'*-tetrasubstituted ureas, including cyclic ones. Thus *N,N'*-divinylpropylurea **69** is prepared in 89% yield by addition of vinylpropionate **68** over 15 min to a mixture of propylurea and DMAP at 95 °C and refluxing for 5.5 h (Scheme 20, reaction E).<sup>53</sup>

The reductive amination of aldehydes with monoalkylureas in the presence of titanium(IV) isopropoxide and sodium borohydride in THF represents a viable, lab-scale route to unsymmetrical *N,N'*-disubstituted ureas (39–94% yield) (Scheme 21). Titanium (IV) isopropoxide behaves as the Lewis acid as well as an efficient acid scavenger compatible with a variety of functional groups such as lactams, acetamides, acetals and *tert*-butyldimethylsilyl ethers. Unfortunately aldehydes with an  $\alpha$ -hydrogen do not undergo selective reactions.<sup>54</sup>

A quite similar method based on reductive alkylation of urea involves use of trimethylsilyl chloride (TMSCl) as the catalyst



Scheme 21



Scheme 22

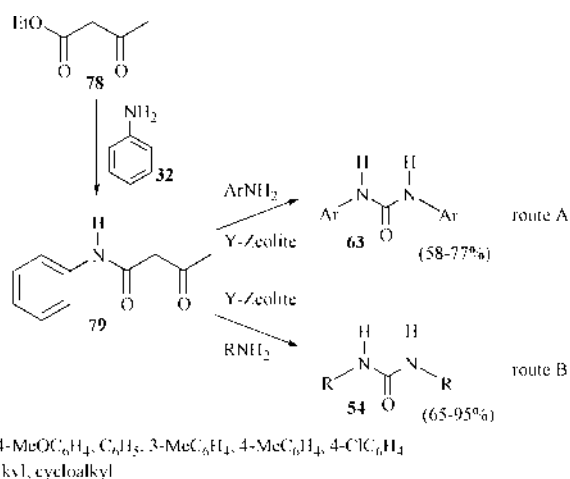
in the condensation step and still utilise sodium borohydride as the reducing agent.<sup>55</sup>

Under these conditions the parent urea can be converted into monosubstituted as well as disubstituted ureas in 70–89% yields (Scheme 22).

Both methods provide some advantages over the previous ones and are able to produce a variety of unsymmetrical substituted ureas without use of gas phase or highly toxic reagents. However all these processes have a major drawback connected with the production of large amounts of salts. More conveniently and more environmentally friendly unsymmetrical *N,N'*-disubstituted ureas, including sterically hindered ones, are synthesised (76–93% yield) from *N*-aryl substituted formamides and amines in the presence of catalytic amounts of Ru(PPh<sub>3</sub>)<sub>3</sub> (substrate/catalyst ratio 20).<sup>56</sup> A catalytic cycle involving the formation of an isocyanate coordinated dihydride ruthenium intermediate is postulated.

A commercially available acid zeolite is also reported as the efficient catalyst in the completely salt-free production of ureas. Reaction of aromatic amines with ethyl acetoacetate **78** in the presence of HY zeolite HSZ-360 (1 g of zeolite/20 mmol of amine) under solventless conditions, gives symmetrical diarylureas **63** in good yield (58–77%) and excellent selectivity (93–96%) through an easy and simple procedure (Scheme 23, route A). Acetone, ethanol and traces of acetoacetanilides are the sole by-products.<sup>57</sup>

This type of synthesis can not be applied to the aliphatic amines because these compounds undergo nucleophilic attack to the keto-group producing β-alkylaminocrotonic acid ethyl esters as the main products. However, symmetrical aliphatic ureas **54** can be successfully made (65–95% yield) by reacting primary aliphatic amines with acetoacetanilide over the same zeolitic catalyst (Scheme 23, route B).<sup>58</sup>



Scheme 23

The zeolite catalyst can be recovered and reused in both cases at least for five runs without lowering the activity.

## 7. Concluding remarks

The data reviewed here demonstrate that great effort has been dedicated in recent years and continues to be devoted to the development of environmentally friendly methodologies for the production of ureas. All procedures exhibit some interesting advantages over the traditional synthetic routes based on the use of phosgene and isocyanates and lead to the minimisation of waste production with concomitant benefit of using safer reagents. In most of these new approaches isocyanates are produced and converted *in situ* into ureas by reaction with amines, avoiding purification and handling of noxious compounds. In this regard a first crucial improvement to the more environmentally friendly approaches to ureas is represented by the use of phosgene replacements such as bis(4-nitrophenyl)carbonate, *S,S*-dimethyldithiocarbonate, 1,1-carbonylbis-imidazole, di-*tert*-butyl dicarbonate and phenyl chloroformate. Most of these reagents are themselves prepared from phosgene but are less toxic and more stable than phosgene and can consequently be stored and handled without special precautions. The most appealing and promising strategy however is represented by the carbonylation of amines and/or nitro-compounds with CO over transition metal complexes which permit use of safer raw materials and catalytic reactions and avoids production of large amounts of saline by-products. A further important improvement which allows the manufacture of ureas with concomitant reduction of waste at source is represented by the application of carbon dioxide that combines the use of a non toxic reagent with the benefit of reducing the emission of CO<sub>2</sub> in a direct way by fixation of the molecule into chemicals.

## 8. Acknowledgements

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# Enantioselective allylic substitution catalyzed by Pd<sup>0</sup>-ferrocenylphosphine complexes in [bmim][PF<sub>6</sub>] ionic liquid

Štefan Toma,<sup>\*a</sup> Battsengel Gotov,<sup>a</sup> Iveta Kmentová<sup>a</sup> and Eva Solčániová<sup>b</sup>

<sup>a</sup> Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, 842 15 Bratislava, Slovakia. E-Mail: toma@fns.uniba.sk

<sup>b</sup> Institute of Chemistry, Faculty of Natural Sciences, Comenius University, 842 15 Bratislava, Slovakia

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Enantioselective allylic substitution reactions of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate (DMM) are studied in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF<sub>6</sub>]) as an ionic solvent; the reactions are catalyzed by Pd<sup>0</sup> complexes of two homochiral ferrocenylphosphine ligands, (*S,R*)-BPPFA and (*R,S*)-BPPFDEA with the recycling of the catalytic system being tested. A similar reaction with 1-phenyl-3-acetoxyprop-1-ene is also studied with only a linear achiral product being isolated.

## Introduction

Transition-metal complexes of homochiral ferrocenylphosphine ligands are often used for homogeneous enantioselective reactions.<sup>1,2</sup> Asymmetric allylic substitution reactions of C-nucleophiles catalyzed by Pd<sup>0</sup> complexes of ferrocene ligands have been described by Hayashi and co-workers.<sup>3,4</sup> Nevertheless the application of homogeneous catalytic systems is limited due to complications with the catalyst recovery. Several methods such as immobilization of homochiral ferrocene ligands to carriers-insoluble polymers,<sup>5</sup> silicagel,<sup>6,7</sup> mesoporous silica<sup>8</sup> or dendrimers<sup>9–11</sup>—open the possibility for the efficient recovery of the catalytic system. In the last few years, room temperature ionic liquids have also been studied as an alternative for the most harmful solvents.<sup>12,13</sup> Ionic liquids are miscible with polar organic solvents as are lower alcohols and ethyl acetate, but non-miscible with water on one hand and less-polar organic solvents like aliphatic or aromatic hydrocarbons, diethyl ether *etc.* on the other hand. From this point of view ionic liquids also offer potential for easy catalyst separation. Achiral transition-metal catalyzed Heck reactions in ionic solvents have been described.<sup>14,15</sup> Xiao and co-workers described recently<sup>16</sup> palladium catalyzed allylation reactions in [bmim][BF<sub>4</sub>] ionic solvent with a Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> catalytic system. It was found that a P: Pd molar ratio 4:1 was optimal and products were obtained in good yields (54–91%).

According to the best of our knowledge there are only a few examples known of enantioselective transition-metal catalysed reactions in ionic liquids. Dupont and co-workers described the enantioselective hydrogenation of alkenes<sup>17,18</sup> as well as enantioselective hydroformylation of styrene<sup>19</sup> in [bmim][BF<sub>4</sub>] as the solvent.

We report herein our preliminary results of enantioselective allylation reactions catalyzed by Pd<sup>0</sup>-ferrocenylphosphine ligand complexes in ionic liquids. The main goals of this work were: 1. To examine the homochiral ferrocenylphosphine ligands for the enantioselective Pd<sup>0</sup> catalyzed allylation of DMM and to compare the results to classical procedures (THF as solvent). 2. To examine the possibility of recycling the Pd<sup>0</sup>/ferrocenylphosphine ligand complexes in ionic solvent.

## Results and discussion

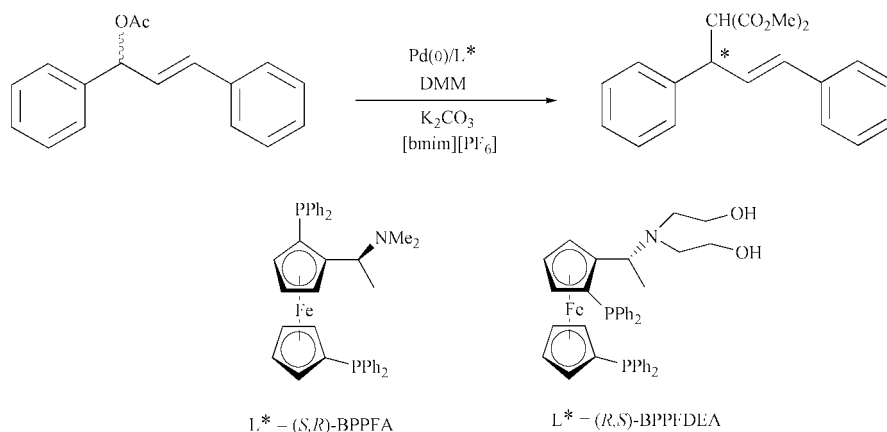
Ferrocenylphosphine ligands (*S,R*)-BPPFA and (*R,S*)-BPPFDEA were examined as ligands for enantioselective Pd<sup>0</sup>-catalyzed allylic substitution reactions of dimethyl malonate and (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene in the ionic solvent 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF<sub>6</sub>]) (Scheme 1).

The procedure developed by Xiao and co-workers<sup>16</sup> was used (2 mol% Pd; P: Pd ratio 4: 1). The product was extracted into toluene, the ionic solvent containing the catalytic system was washed with water and dissolved in ethyl acetate. This solution was dried over anhydrous sodium sulfate, the solvent was evaporated and the catalytic system in the ionic liquid was used in the subsequent reaction. The enantiomeric purity of the product was determined by <sup>1</sup>H NMR using the chiral shift reagent Eu(hfc)<sub>3</sub>. The results obtained and the isolated yields of product and its enantioselectivity are given in Table 1. Similar reaction with (*S,R*)-BPPFA in THF<sup>20</sup> gave the product in 62% yield but only 40% ee (*R*) after 24 h.

A significant increase of enantioselectivity was observed with the (*S,R*)-BPPFA/Pd<sup>0</sup> catalytic system (68% ee *vs.* 40% ee in THF), the configuration of product being the same (*R*). After

## Green Context

One of the major difficulties associated with the use of transition metal complexes in organic chemistry is their efficient recovery. The high costs of most complexes and their toxicity make this essential. There are several methods for trying to overcome this including immobilisation. One of the less exploited but potentially very appropriate methods in this context is the use of ionic liquids. Here some very encouraging results are reported from the study of enantioselective allylic substitution reactions using palladium complexes of two homochiral ferrocenylphosphine ligands. Effective reuse has been demonstrated. *JHC*



Scheme 1

the recycling procedure the catalytic system was used for the second time. The product was isolated in lower yield (24% vs 53%), but the enantioselectivity was retained [62% ee (*R*)].

It was known<sup>3,4</sup> that ferrocenylphosphines containing the  $\alpha$ -(2-hydroxyethylamino) side chain have been superior to the BPPFA ligand for allylic substitutions *via*  $\pi$ -allyl Pd<sup>0</sup>-complexes. High enantioselectivity was explained by hydrogen bonding interactions of the hydroxy groups with the C-nucleophile. We therefore examined the homochiral (*R,S*)-BPPFDEA ligand in the catalytic system and found out that this ligand was better than system with (*S,R*)-BPPFA ligand. The yield of the product was lower, but enantioselectivity of the reaction was higher [first reaction 74% ee (*S*), repeated reaction 70% ee (*S*)]. An opposite configuration of ligands resulted in an opposite products configuration. After recycling a decrease of product yield was observed again (12% compared to 36%). Prolongation of the reaction time to 15 h resulted in a substantial rise of the product yields (fresh catalyst 81%, reused catalyst 56%).

We decided to also examine the biphasic allylation procedure using toluene or cyclohexane as the second phase. The (*R,S*)-BPPFDEA ligand was used in the catalytic system. The reaction time was 15 h and a similar high yield of product was achieved (fresh catalyst 80%, reused catalyst 55%) with toluene as the second phase and 70%, resp. 64% with cyclohexane as the second phase. On the other hand a large decrease in enantioselectivity was observed in the experiments using the recycled catalytic system [49% ee (*S*) for toluene and 47% ee (*S*) for cyclohexane]. Decrease of selectivity with the recycled ionic solvent/catalyst system can be explained by leaching of the ligand during extraction of product after reaction from the ionic liquid.<sup>16</sup> This operation should change the optimal Pd:ligand ratio which can result in decreasing stereoselectivity.

The reaction of DMM with 1-phenyl-3-acetoxyprop-1-ene using the (*R,S*)-BPPFDEA ligand was also examined. This reaction catalyzed by homogeneous homochiral ferrocenylphosphine ligand Pd<sup>0</sup>-complexes gave only linear achiral products, the branched chiral product was not isolated.<sup>8</sup> We achieved similar results in ionic solvent [bmim][PF<sub>6</sub>] because the linear product was isolated in 78% yield and 2% yield of its double allylated product was also isolated. Only traces of branched product were detected in the <sup>1</sup>H NMR spectrum of double allylation product. No further study of this reaction was undertaken, because just achiral product was formed.

## Experimental

<sup>1</sup>H NMR ( $\delta$ , ppm) spectra of samples were obtained for CDCl<sub>3</sub> solutions on a Varian Gemini 2000 spectrometer operating at 300 MHz frequency with tetramethylsilane as internal standard.

**Table 1** Allylic of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene catalyzed by homochiral ferrocenylphosphine ligand/Pd(0) complexes in [bmim][PF<sub>6</sub>]

Catalytic system	<i>t</i> /h	Yield (%)	Solvent	Ee (%) (config.)
( <i>S,R</i> )-BPPFA/Pd <sup>0</sup> 20	24	62	THF	40 ( <i>R</i> )
( <i>S,R</i> )-BPPFA/Pd <sup>0</sup>	5	53	[bmim][PF <sub>6</sub> ]	68 ( <i>R</i> )
( <i>S,R</i> )-BPPFA/Pd <sup>0</sup> reused	5	24	[bmim][PF <sub>6</sub> ]	62 ( <i>R</i> )
( <i>R,S</i> )-BPPFA/Pd <sup>0</sup>	5	36	[bmim][PF <sub>6</sub> ]	74 ( <i>S</i> )
( <i>R,S</i> )-BPPFDEA/Pd <sup>0</sup> reused	5	12	[bmim][PF <sub>6</sub> ]	70 ( <i>S</i> )
( <i>R,S</i> )-BPPFDEA/Pd <sup>0</sup>	15	81	[bmim][PF <sub>6</sub> ]	74 ( <i>S</i> )
( <i>R,S</i> )-BPPFDEA/Pd <sup>0</sup> reused	15	56	[bmim][PF <sub>6</sub> ]	71 ( <i>S</i> )
( <i>R,S</i> )-BPPFDEA/Pd <sup>0</sup>	15	80	[bmim][PF <sub>6</sub> ]-toluene	68 ( <i>S</i> )
( <i>R,S</i> )-BPPFDEA/Pd <sup>0</sup> reused	15	55	[bmim][PF <sub>6</sub> ]-toluene	49 ( <i>S</i> )
( <i>R,S</i> )-BPPFDEA/Pd <sup>0</sup>	15	70	[bmim][PF <sub>6</sub> ]-cyclohexane	72 ( <i>S</i> )
( <i>R,S</i> )-BPPFDEA/Pd <sup>0</sup> reused	15	64	[bmim][PF <sub>6</sub> ]-cyclohexane	47 ( <i>S</i> )

Solvents were purified and dried according to known procedures. Ionic solvent [bmim][PF<sub>6</sub>] was prepared as described.<sup>21</sup> Homochiral ferrocenylphosphine ligands (*S,R*)-BPPFA and (*R,S*)-BPPFDEA were prepared according to Hayashi and co-workers.<sup>22,23</sup> 1-Phenyl-3-acetoxyprop-1-ene and (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene were prepared by acylation of appropriate alcohols with Ac<sub>2</sub>O in diethyl ether under DMAP catalysis. The complex Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> was prepared according to published methods.<sup>24</sup>

### General procedure for the allylic substitution of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene and DMM in ionic solvent [bmim][PF<sub>6</sub>]

Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (10.4 mg, 0.01 mmol, 2 mol% Pd) and ferrocenylphosphine ligand (0.04 mmol, 8 mol% P) were added to pre-dried [bmim][PF<sub>6</sub>] (1 mL) and the resulting mixture was stirred at 80 °C under an Ar atmosphere for 20 min. Substrate (252 mg, 1 mmol), DMM (0.17 mL, 1.5 mmol) and K<sub>2</sub>CO<sub>3</sub> (276 mg, 2 mmol) were added to the cooled reaction mixture which was stirred at room temperature under Ar for 5 h. Toluene (2 mL) was then added and the mixture was vigorously stirred for 5 min. The separated toluene layer was collected and the procedure was repeated until no product was detected in the toluene layer (*ca.* 10 times). The combined toluene extracts were washed with water (20 mL), dried and the solvent was evaporated. The residue was purified by chromatography on a SiO<sub>2</sub> column (30 g, 12.5% EtOAc/hexane as eluent). The product was obtained after evaporation of the solvent as a clear

colorless oil which crystallized in the freezer. The ionic solvent was washed with water ( $2 \times 2$  mL) and dissolved in EtOAc (10 mL), dried, solvent evaporated, dried at  $40^\circ\text{C}/1$  mmHg for 3 h and stored under Ar in the freezer before reusing in the next reaction.

$\delta_{\text{H}}(\text{CDCl}_3)$  (*rac*)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene: 2.12 (s, 3 H,  $\text{CH}_3$ ), 6.34 (dd,  $^3J_{12} = 15.4$ ,  $^3J_{23} = 6.9$  Hz, 1 H,  $\text{H}_2$ ), 6.45 (d, 1 H,  $\text{H}_3$ ); 6.63 (d, 1 H,  $\text{H}_1$ ); 7.25–7.40 (m, 10 H, Ph, Ph).  $\delta_{\text{H}}(\text{CDCl}_3)$  of product: 3.52 (s, 3 H,  $\text{COOCH}_3$ ), 3.71 (s, 3 H,  $\text{COOCH}_3$ ); 3.96 (d, 1 H,  $^3J_{34} = 11.0$  Hz,  $\text{H}_4$ ), 4.26 (dd,  $^3J_{23} = 8.5$  Hz, 1 H,  $\text{H}_3$ ), 6.33 (dd,  $^3J_{12} = 15.7$  Hz, 1 H,  $\text{H}_2$ ), 6.49 (d, 1 H,  $\text{H}_1$ ), 7.20–7.40 (m, 10 H, Ph, Ph).

### General procedure for the allylic substitution of 1-phenyl-3-acetoxyprop-1-ene and DMM in ionic solvent [bmim][PF<sub>6</sub>]

The allylic substitution was carried out as described above, with 1-phenyl-3-acetoxyprop-1-ene (176 mg, 1 mmol) only used as the substrate. The allylation product was isolated in 78% yield with 2% of the double allylation product isolated.  $\delta_{\text{H}}(\text{CDCl}_3)$  of 1-phenyl-3-acetoxyprop-1-ene: 2.10 (s, 3 H,  $\text{CH}_3$ ), 4.73 (d,  $^3J_{23} = 6.3$  Hz, 2 H,  $\text{CH}_2$ ), 6.29 (dt,  $^3J_{12} = 15.9$  Hz, 1 H,  $\text{H}_2$ ), 6.66 (d, 1 H,  $\text{H}_1$ ); 7.28–7.41 (m, 5 H, Ph).

$\delta_{\text{H}}(\text{CDCl}_3)$  of allylation product: 2.81 (dd,  $^3J_{23} = 6.9$ ,  $^3J_{34} = 7.2$  Hz, 2 H,  $\text{CH}_2$ ), 3.54 (t, 1 H,  $\text{H}_4$ ); 3.75 (s, 6 H,  $\text{COOCH}_3$ ), 6.14 (dt,  $^3J_{12} = 15.9$  Hz, 1 H,  $\text{H}_2$ ); 6.48 (d, 1 H,  $\text{H}_1$ ), 7.19–7.35 (m, 5 H, Ph).  $\delta_{\text{H}}(\text{CDCl}_3)$  of double allylation product: 2.84 (d,  $^3J_{23} = 7.5$  Hz, 4 H,  $\text{CH}_2$ ), 3.74 (s, 6 H,  $\text{COOCH}_3$ ), 6.06 (dt,  $^3J_{12} = 15.8$  Hz, 2 H,  $\text{H}_2$ ); 6.46 (d, 2 H,  $\text{H}_1$ ), 7.19–7.35 (m, 10 H, Ph).

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# Envirocat EPZG<sup>®</sup> catalysis: an efficient and rapid procedure for the deprotection of 1,1-diacetates without solvent

B. P. Bandgar,\* S. P. Kasture, Kamal Tidke and S. S. Makone

Organic Chemistry Research Lab., School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded-431606, Maharashtra, India.  
E-Mail: upekam@hotmail.com

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A variety of 1,1-diacetates are easily deprotected in good to excellent yield using envirocat EPZG<sup>®</sup> as a catalyst under microwave irradiation and solvent-free conditions.

## Introduction

Selective protection and deprotection of functional groups is of great importance in synthetic organic chemistry. In the course of the last decade, 1,1-diacetates have received increasing attention, since these compounds are easily prepared,<sup>1–6</sup> and stable<sup>1</sup> and can serve as an alternative to acetals for the protection of aldehydes<sup>7</sup> and as starting materials for Diels–Alder cycloaddition reactions.<sup>8,9</sup>

Recently, a number of methods have been developed for conversion of 1,1-diacetates to the corresponding aldehydes. To our knowledge the following methods have been applied: (a) use of alcoholic sulfuric<sup>10</sup> or hydrochloric acid,<sup>11</sup> (b) use of either sodium hydroxide or potassium carbonate in aqueous THF overnight,<sup>1</sup> (c) use of a boron triiodide–*N,N*-diethylaniline complex,<sup>12</sup> (d) use of ceric ammonium nitrate (CAN) coated on silica gel in dichloromethane,<sup>13</sup> (e) use of neutral alumina,<sup>14</sup> (f) potassium phenoxides,<sup>15</sup> or (g) montmorillonite K10<sup>16</sup> or KSF.<sup>17</sup> Each of the above methods has its own merits and drawbacks. Method (a) requires the use of a strong acid which other functional groups in the molecule may not tolerate; method (b) requires a long reaction time and no detailed results are given; method (c) provides a low yield (<66%) while method (g) requires drastic conditions.

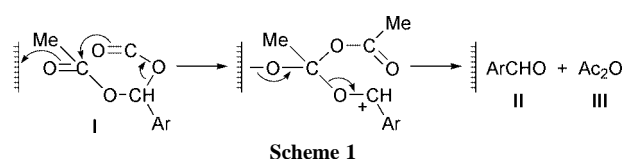
Envirocats<sup>®</sup>, a new family of solid-supported reagents are a significant break-through in environmentally friendly chemistry.<sup>18</sup> Envirocats<sup>®</sup> have been extensively used as efficient catalysts for a variety of organic reactions.<sup>19</sup> Recently, we have developed an efficient and convenient procedure for preparation of 1,1-diacetates from aldehydes using Envirocat EPZG<sup>®</sup> catalyst.<sup>20</sup> However, the deprotection of 1,1-diacetates directly using Envirocat EPZG<sup>®</sup> as a catalyst remains unreported. In connection with our work on envirocat catalysis, we now report an efficient deprotection of 1,1-diacetates under catalysis with envirocat EPZG<sup>®</sup> using microwaves.

## Results and discussion

When a mixture of 1,1-diacetates **I** and envirocat EPZG<sup>®</sup> is exposed to microwaves (Scheme 1), the corresponding aldehyde **II** is obtained in excellent yield (Table 1). No additional water is required for the reaction. However, the reaction proceeds equally well in the presence of water as a solvent and with formation of acetic acid as a by-product. (*o*-Nitrophenyl)methanediol diacetate (entry 6) and (*p*-nitrophenyl)methanediol diacetate (entry 7) only give poor conversion (30–40%) in refluxing benzene for 6 h whereas 90–91% cleavage yields

are obtained under microwave irradiation within a period of 1–1.5 min, the low conversion in the first method possibly due to the strongly electron-withdrawing nitro substituent which requires high refluxing temperature and longer reaction times. It is interesting that the phenolic acetate function (entries 11 and 12) remains unaffected under these reaction conditions. We also attempted catalysis reactions of phenyl acetate, 4-methoxyphenyl acetate, benzyl acetate and cyclohexyl acetate in the presence of envirocat EPZG<sup>®</sup> for 10 min under microwave irradiation. However, none of these substrates gave the hydrolysis products and the materials were recovered quantitatively. Therefore, the present procedure is selective for deprotection of aldehyde diacetates to aldehydes in the presence of phenolic acetate (entries 11 and 12). Furthermore, it is also pertinent to note that the methylene dioxy group (entry 10) and methoxy groups (entries 8 and 9) tolerate these reaction conditions.

It is noteworthy that the reaction times required are longer in the absence of microwave radiation. For example, complete conversion of (4-methoxyphenyl)methanediol diacetate (entry 8), (3,4,5-trimethoxyphenyl)methanediol diacetate (entry 9) and (3,4-methylenedioxyphenyl)methanediol diacetate (entry



## Green Context

The protection and subsequent deprotection of functional groups in a synthetic pathway are generally best avoided as they are likely to add to the waste generated and chemicals consumed on route to the desired product. However, where such a methodology is required, it is important that both of these steps are achieved with high efficiency and minimal consumption of reagents and solvent (the major causes of waste). There are numerous methods for deprotecting diacetates but those previously reported tend to rely on corrosive or toxic reagents with associated waste generation on separation. Here a commercially available clay-based catalyst is found to be very effective for such a reaction in the absence of solvent. Thus the waste resulting from this step is minimised.

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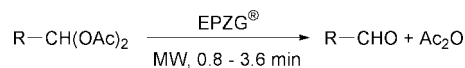
**Table 1** Deprotection of 1,1-diacetates catalyzed by envirocat EPZG® under microwave irradiation

Entry	Substrate	Product	Reaction time/min	Yield (%)
1			3.6	89
2			3.0	88
3			2.5	90
4			2.5	93
5			0.8	94
6			1.5	91
7			1.0	90
8			2.0	92
9			2.5	83
10			2.5	93
11			1.5	87
12			2.0	91
13			1.8	88
14			2.0	87

10) to the corresponding aldehydes require 4–4.5 h in benzene at 80 °C using envirocat EPZG®.

This deprotection methodology appears to be general. Not only 1,1-diacetates of aromatic aldehydes but also 1,1-diacetates of a dialdehyde (entry 13) and aliphatic (entries 1 and 2), heterocyclic (entry 14) and  $\alpha,\beta$ -unsaturated aldehydes (entry 5) undergo smooth deprotection under these reaction conditions. Although the mechanism of the hydrolysis of aryl aldehyde diacetates in aqueous hydrochloric acid has been studied,<sup>21</sup> the mechanism of the present reaction is different. The hydroxamate test identifies the presence of acetic anhydride in the reaction products. Furthermore, neither the presence of additional water nor anhydrous conditions affect the reaction rate. These results show that the reaction corresponds to a unimolecular decomposition of 1,1-diacetates to give an aldehyde and acetic anhydride (Scheme 2) in which Envirocat EPZG® acts as a Lewis acid.

In conclusion, we have developed a rapid, selective, simple and efficient procedure for deprotection of 1,1-diacetates, which does not require aqueous work-up.

**Scheme 2**

## General procedure for deprotection of 1,1-diacetates

A mixture of 1,1-diacetate (5 mmol prepared according to our previous method<sup>20</sup>) and Envirocat EPZG (100 mg) in a beaker covered with a watch glass was irradiated with microwaves for the time indicated in Table 1 and the reaction was monitored by TLC. After cooling, dichloromethane (10 ml) was added in the reaction mixture. The catalyst was then removed by filtration and washed with dichloromethane (2 × 10 ml). Removal of solvent *in vacuo* resulted in pure product. The identity of the products were confirmed by their physical constants, IR, <sup>1</sup>H NMR spectra and comparison with authentic samples.

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# Natural kaolinitic clay: a remarkable reusable solid catalyst for the selective cleavage of thioacetals without solvent

B. P. Bandgar\* and S. P. Kasture

Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431 606, Maharashtra, India.  
E-Mail: upekam@hotmail.com

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A variety of thioacetals are deprotected to give their carbonyl compounds using natural kaolinitic clay under microwave irradiation, avoiding the use of toxic reagents and excess solvent.

## Introduction

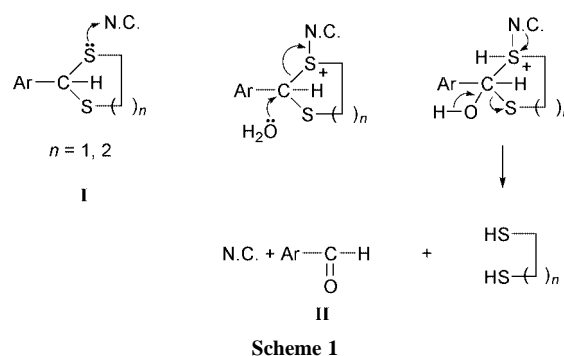
Protection of carbonyl compounds as thioacetals and thioketals is important in organic synthesis<sup>1</sup> and, in particular, in multistep natural product synthesis.<sup>2</sup> This is because of the stability of thioacetals and thioketals in both acidic and basic conditions and so their deprotection into their parent carbonyl compounds is an important task.<sup>3</sup> Dethioacetalization is generally performed using heavy metal salts such as mercury(II) chloride,<sup>4a</sup> mercury(II) oxide–boron trifluoride etherate,<sup>4b</sup> ceric ammonium nitrate<sup>4c</sup> and selenium dioxide<sup>4c–d</sup> which are very toxic. However, non-metallic reagents<sup>5</sup> like trimethyloxonium tetrafluoroborate, methyl fluorosulfonate and, more recently, nitrogen tetroxides have also been used for the deprotection. These methods are, however, less attractive due to their expense and non-availability of reagents. Though the other methods using photolytic<sup>6</sup> and electrochemical techniques are safe and preserve the environment, these methods have less practical utility. Recently, other methods using metal nitrate<sup>8a–c</sup> and zirconium sulfophenyl phosphate,<sup>8d</sup> also deprotect under different reaction conditions.

In view of the conservation of the environment, literature<sup>9</sup> demands the development of a metal ion-free, environmentally safe and convenient deprotection using an easily accessible and relatively cheap reagent. Clays have many advantages such as ease of handling, non-corrosiveness, low cost and regeneration. Owing to their Bronsted and Lewis acidities, clays, both in their natural and ion-exchanged forms, function as efficient catalysts for various organic transformations.<sup>10</sup> Recently, natural kaolinitic clay has been used for the selective protection of carbonyl compounds as their acetals and thioacetals.<sup>11</sup> However, the deprotection of thioacetals using directly natural kaolinitic clay as a catalyst remain unreported.

Here we report an efficient deprotection of thioacetals under the catalysis of natural kaolinitic clay (N.C.) in the presence of water using microwaves, Scheme 1.

## Results and discussion

The natural kaolinitic clay was obtained from the Padappakara mine of Quilon, District Kerala, India and it was subsequently purified<sup>12</sup> and characterized<sup>11</sup> by FTIR, XRD, UV, ESR, SEM, EDX and chemical analysis by AAS. The composition of the clay was determined by wet chemical analysis (%): SiO<sub>2</sub> = 67.45, Al<sub>2</sub>O<sub>3</sub> = 22.2, Fe<sub>2</sub>O<sub>3</sub> = 6.1, TiO<sub>2</sub> = 3.45 and K = 0.8. The natural kaolinitic clay was supplied by Dr Lalithambika, RRL, Trivandrum and it was used as supplied without further pre-treatment or activation.



When a mixture of thioacetal, a catalytic amount of natural kaolinitic clay and 2 drops of water was irradiated with microwaves for the time indicated in Table 1, the carbonyl compound was regenerated in good yield. This environmentally conscious and manipulatively simple protocol avoids the use of an excess of solvents and toxic oxidants. The present dethioacetalization procedure is equally effective or better than any other reagent reported so far and is also effective for the cleavage of cyclic trimethylene dithioacetal derivatives (entries 17 and 18) which are more stable to the action of a variety of reagents.<sup>13</sup> It is important to note that the present methodology is useful for chemoselective dethioacetalization in the presence of thioketals (entries 15 and 16). The dithioacetals of *p*-chlorobenzaldehyde (entry 7) and *p*-nitrobenzaldehyde (entry 14) in refluxing toluene for 8.5 h gave the corresponding aldehydes in poor yield (40–50%) whereas 91–92% cleavage yields are obtained under microwave irradiation within 2–3.0 min. The low conversion in the first method was possibly due to the strong electron-withdrawing nitro- and chloro-substituents which require a high refluxing temperature (110 °C) and longer

## Green Context

The protection and deprotection of carbonyl compounds is an integral part of the remarkable synthetic flexibility of this class of compounds. Thioacetals are excellent protecting groups and are used widely for a range of reactions. However, the satisfactory removal of these protecting groups is not a trivial task, and new cleaner methods are required. Here, the use of a naturally occurring clay, coupled with microwave activation, provides an effective, clean and energy efficient method for deprotection. *DJM*

**Table 1** Natural kaolinitic clay catalyzed chemoselective cleavage of thioacetals without solvent

No.	Substrate	Product <sup>15</sup>		Reaction time/min	Yield <sup>ab</sup> (%)
1			IIa	2.5	87
2		PhCO	IIb	2.0	91
3		PhCHO	IIb	2.0	89
4			IIc	3.0	89
5		Ph-CH=CHO	IIId	2.3	92
6			IIe	2.0	94
7			IIIf	2.0	92
8			IIIg	3.0	85
9			IIHh	2.5	96
10			IIii	3.0	97
11			IIjj	2.5	78
12			IIkk	2.0	97
13			IIll	3.5	78
14			IIIm	2.5	91
15			IIIn	3.0	85
16			IIIo	2.5	88
17		Ph-CH=CHO	IIIp	2.5	87
18		PhCHO	IIb	2.0	91

<sup>a</sup> Yields are of isolated pure products; <sup>b</sup> Products<sup>15</sup> characterised by their physical constants, IR, <sup>1</sup>H NMR and comparison with authentic samples.

reaction times. It is interesting to note that dithioacetal was selectively deprotected in the presence of phenolic acetate (entries 12 and 16) under these reaction conditions. However, when dithioacetal containing a phenolic acetate group (entries 12 and 16) was treated with natural clay in methanol at 25 °C, the phenolic acetate was cleaved to phenol without deprotection of dithioacetal. Therefore, the present procedure for the deprotection of dithioacetal under microwave irradiation and solvent-free conditions is selective and superior than that involving solvent (methanol). Furthermore, it is also pertinent to note that the phenolic group (entries 9, 10 and 15), the methylenedioxy group (entry 11) and the methoxy group (entries 8, 10, 12 and 13) tolerate these reaction conditions. This deprotection methodology appears to be general. Not only dithioacetals of aromatic aldehydes but also dithioacetals of aliphatic (entries 1 and 4), heterocyclic (entry 6) and  $\alpha,\beta$ -unsaturated aldehydes (entries 5 and 17) underwent smooth cleavage under microwave irradiation to the corresponding carbonyl compounds. When dethioacetalization was carried out using microwave irradiation for a limited time period (2.0 min each), the corresponding yields of the carbonyl compounds were lower than those reported in Table 1 (entries 1, 4, 5, 8–11 and 13–17). Reported deprotection methods<sup>14</sup> of dithioacetals require 2–3 times excess reagents and the catalyst can be recovered by simple filtration and reused at least for 4 times without loss of activity. It makes this methodology more attractive and superior than reported methods. Furthermore, this dethioacetalization methodology worked very well on gram scale reactions.

In conclusion, the present results demonstrate the novelty of natural kaolinitic clay under microwave irradiation which shows unique selectivity and constitutes a useful alternative to the commonly accepted procedure for dethioacetalization. Moreover, this simple and eco-friendly procedure affords regeneration of carbonyl compounds in excellent yields. Ease of availability of the natural and inexpensive catalyst and the solvent-free conditions make the method more attractive.

## Experimental

### Typical procedure

4-Acetoxy-3-methoxybenzaldehyde ethylene dithioacetal (5 mmol) and natural kaolinitic clay (100 mg) was mixed and then moistened with 2 drops of water before irradiation with microwaves for 2 min. After completion of the reaction (TLC), the product was extracted with ethyl acetate. After drying with sodium sulfate, the solvent was removed under vacuum to give 4-acetoxy-3-methoxybenzaldehyde.

**IIIk:** Yield 97%, UV 275 nm;  $\nu/\text{cm}^{-1}$  1210, 1510, 1600, 1690, 1735, 2715;  $\delta_{\text{H}}$  (90 MHz,  $\text{CDCl}_3$ ): 3.4 (s, 3 H,  $\text{OCH}_3$ ), 3.82 (s, 3 H,  $\text{OCOCH}_3$ ), 7.3 (m, 3 H, Ar-H), 9.7 (s, 1 H, CHO); MS (70 eV).  $m/z$  (%) 194 (47,  $\text{M}^+$ ), Anal. calc. for  $\text{C}_{10}\text{H}_{10}\text{O}_4$  (194): C, 61.86; H, 5.15; Found: C, 61.81; H, 5.18%.

**IIo:** Mp 130 °C;  $\nu/\text{cm}^{-1}$  1190, 1500, 1595, 1680, 2710, 3540.  $\delta_{\text{H}}$  (90 MHz,  $\text{D}_2\text{O}$ ): 2.5 (s, 3 H,  $\text{CH}_3$ ), 3.3 (s, 4 H,  $2 \times \text{S-CH}_2$ ), 7.2 (m, 3 H, Ar-H), 9.5 (s, 1 H, CHO); MS (70 eV)  $m/z$  (%) 240

(27,  $\text{M}^+$ ). Anal. Calc. For  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}_2$  (240): C, 55.00; H, 5.00; S, 26.67; Found: C, 54.91; H, 5.08; S, 26.71%.

**IIe:** Mp 147 °C;  $\nu/\text{cm}^{-1}$  1200, 1505, 1600, 1690, 1730, 2720;  $\delta_{\text{H}}$  (90 MHz,  $\text{CDCl}_3$ ): 2.6 (s, 3 H,  $\text{CH}_3$ ), 3.35 (s, 4 H,  $2 \times \text{S-CH}_2$ ), 3.81 (s, 3 H,  $\text{OCH}_3$ ), 7.2 (m, 3 H, Ar-H), 9.5 (s, 1 H, CHO); MS (70 eV)  $m/z$  (%) 282 (41,  $\text{M}^+$ ). Anal. Calc. for  $\text{C}_{13}\text{H}_{14}\text{O}_3\text{S}_2$  (282): C, 55.32; H, 4.97; S, 22.70; Found: C, 55.27; H, 5.06; S, 22.78%.

## Acknowledgements

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# Simple and clean synthesis of 9,9-bis[4-(2-hydroxyethoxy)phenyl]fluorene from the aromatic alkylation of phenoxyethanol with fluoren-9-one catalysed by titanium cation-exchanged montmorillonite

Kohki Ebitani, Tomonori Kawabata, Kohji Nagashima, Tomoo Mizugaki and Kiyotomi Kaneda\*

Department of Chemical Science and Engineering, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan.  
E-Mail: kaneda@cheng.es.osaka-u.ac.jp

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9,9-Bis[4-(2-hydroxyethoxy)phenyl]fluorene is simply obtained by the condensation of phenoxyethanol with fluoren-9-one using a  $\text{Ti}^{4+}$  cation-exchanged montmorillonite as a strong solid acid catalyst.

## Introduction

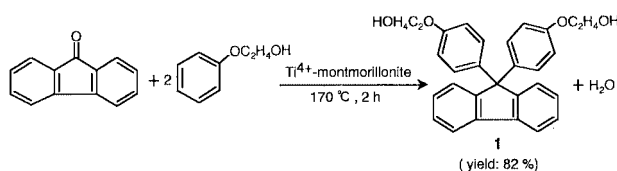
9,9-Bis[4-(2-hydroxyethoxy)phenyl]fluorene (BHEPF, **1**) is a highly stable, valuable raw material for the highly functionalised polymers used in optical products.<sup>1</sup> BHEPF is usually obtained by a multi-step procedure of a condensation of fluoren-9-one with phenol using hydrogen chloride to afford 9,9-bis(4-hydroxyphenyl)fluorene, followed by treatment with ethylene oxide.<sup>2</sup> Recently, Yamada *et al.* have reported a one-step synthesis of BHEPF from the condensation of fluoren-9-one with phenoxyethanol in the presence of concentrated sulfuric acid and 3-mercaptopropionic acid.<sup>3</sup> However, the above two synthetic methods suffer from some serious disadvantages: 1) large amounts of acids result in the production of hazardous wastes which entails environmental pollution, and 2) use of corrosive acids corrodes reactor walls.<sup>4,5</sup>

Montmorillonites of smectite clays are composed of negatively charged layers and an interlayer with cationic species. The cationic species can be easily replaced by other metal polycations and these ion-exchanged montmorillonites have great potential as solid acid catalysts for many environmental-friendly reactions because the selection of different polycations enables tuning of their acidity.<sup>6</sup>

We report here a simple and clean synthesis of BHEPF from the aromatic alkylation of phenoxyethanol with fluoren-9-one using metal cation-exchanged montmorillonite catalysts. This heterogeneous alkylation reaction has the advantages of no waste production and of a simple work-up procedure. Furthermore, the montmorillonite catalyst was reusable without an appreciable loss of its high catalytic activity and selectivity.

## Results and discussion

The reaction of phenoxyethanol with fluoren-9-one in the presence of the  $\text{Ti}^{4+}$ -exchange montmorillonite ( $\text{Ti}^{4+}$ -mont)



Scheme 1

catalyst gave 82% yield of BHEPF at 170 °C after 2 h; increasing the reaction temperature over 200 °C resulted in a sharp decrease of the BHEPF yield together with the formation of by-products such as bis(phenoxyethyl) ether and polymers of BHEPF. Studies of various solvents having high boiling points, revealed that BHEPF was not formed in benzonitrile, dimethyl sulfoxide, *N,N*-dimethylformamide, propane-1,2-diol and ethylene glycol. Up to now, the solventless reaction gave the best result for the formation of BHEPF.

Reactions using various  $\text{M}^{n+}$ -monts were carried out which are summarized in Table 1. The  $\text{M}^{n+}$ -montmorillonites containing high valent metal cations such as  $\text{Ti}^{4+}$ ,  $\text{Al}^{3+}$  and  $\text{Zr}^{4+}$  were effective (entries 1–3); especially,  $\text{Ti}^{4+}$  cation-exchanged montmorillonite ( $\text{Ti}^{4+}$ -mont) gave BHEPF in the highest yield. The parent  $\text{Na}^{+}$ -mont had no catalytic activity for the above alkylation reaction (entry 8). The yields of the BHEPF increased in line with the amount of strongly adsorbed  $\text{NH}_3$  observed for the  $\text{M}^{n+}$ -mont catalysts. The amount of strongly adsorbed  $\text{NH}_3$  on the  $\text{Ti}^{4+}$ -mont was over twice as much as those of the  $\text{Al}^{3+}$ - and  $\text{Fe}^{3+}$ -mont catalysts. The  $\text{M}^{n+}$ -montmorillonites showed higher catalytic activities as well as surface acidities than sulfate ion-treated zirconium oxide<sup>7</sup> ( $\text{SO}_4^{2-}$ - $\text{ZrO}_2$ ) and  $\text{H}^{+}$ -exchanged zeolites such as  $\text{H}^{+}$ -mordenite,  $\text{H}^{+}$ -ZSM-5, and USY (entries 1–4 vs. entries 9–12). These results imply that the above alkylation reaction might be catalysed by strong acid sites of the  $\text{M}^{n+}$ -mont catalysts. Bulk  $\text{TiO}_2$  itself was inactive for this alkylation reaction and therefore we think that the prominent

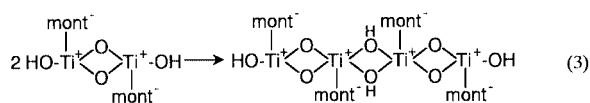
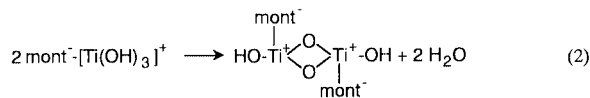
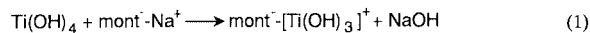
## Green Context

Acid-catalysed alkylation reactions are potentially valuable routes to several products. These reactions often suffer from drawbacks including difficult isolations and destruction of the acid catalyst. Many attempts (some successful) to move away from the traditional liquid phase acids towards solid replacements have been made. Here a  $\text{Ti}^{\text{IV}}$  exchanged montmorillonite has been developed which can catalyse the preparation of a dialkyl fluorene derivative of use in speciality polymers. The acidic sites are associated with  $\text{TiO}_2$  domains within the clay structure. DJM

catalysis of the  $\text{Ti}^{4+}$ -mont could be ascribed to the novel structure of titanium oxide within the layer of the montmorillonite.

The Ti K-edge XANES of the  $\text{Ti}^{4+}$ -mont resembles the spectrum of the anatase  $\text{TiO}_2$  and is different from that of an isolated  $\text{Ti}^{4+}$  species with a tetrahedral symmetry located in the framework of molecular sieves.<sup>8,9</sup> The coordination number ( $CN$ ) and distance ( $R$ ) for the Ti–O shell of the  $\text{Ti}^{4+}$  species in the montmorillonite are 4 and 1.94 Å, respectively, while both values for the Ti–Ti shell are 1.5 and 3.04 Å, respectively. These values are different from those of a bulk anatase  $\text{TiO}_2$  ( $CN_{\text{Ti-O}} = 6$ ,  $R_{\text{Ti-O}} = 1.96$  Å,  $CN_{\text{Ti-Ti}} = 4$ , and  $R_{\text{Ti-Ti}} = 3.06$  Å).<sup>10</sup> Such small coordination numbers of Ti–O and Ti–Ti shells as well as the interlayer space of the  $\text{Ti}^{4+}$ -mont of 2.7 Å support that a two-dimensional titanium oxide structure might be formed along a layer of the montmorillonite.† Sodium cations in the interlayer space are replaced by  $\text{Ti}(\text{OH})_4$  species formed by the reaction of  $\text{TiCl}_4$  with  $\text{H}_2\text{O}$  [eqn. (1), Scheme 2]. The successive dehydration of two neighboring  $\text{Ti}(\text{OH})_4$  species would occur to generate the two-dimensional titanium oxide species along the negatively charged layers [eqns. (2) and (3), Scheme 2].

The activity of the spent  $\text{Ti}^{4+}$ -mont was regenerated by treatment with  $\text{H}_2\text{O}$ . The protonic acid sites are probably located on the oxygen anions of the Ti–O–Ti bonds and the efficient interactions through the oxygen anions between  $\text{Ti}^{4+}$  and  $\text{Si}^{4+}$  of  $\text{SiO}_4$  tetrahedra in the layer can strengthen the acidity of the protons.<sup>4a</sup> The protonic acids<sup>11</sup> associated with the  $\text{Ti}^{4+}$  cations might act as active sites for the alkylation of phenoxyethanol with fluoren-9-one.



Scheme 2

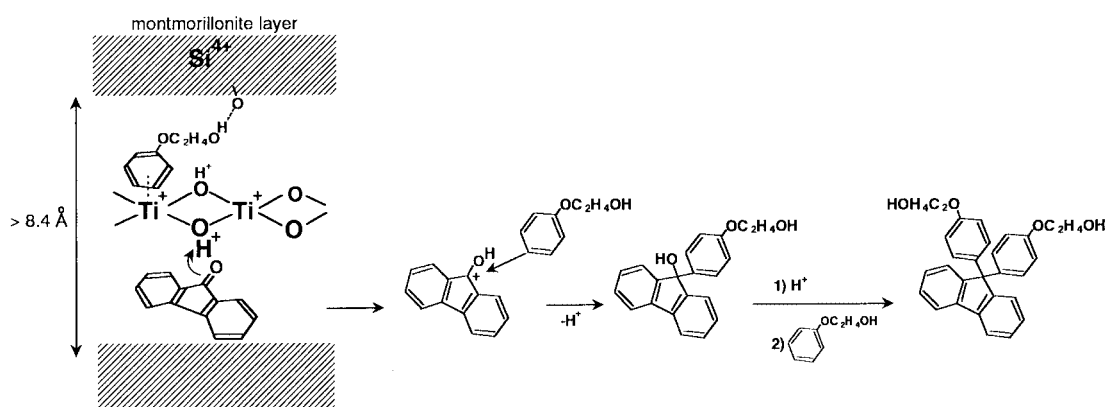
One of the prominent characteristics of the montmorillonite materials is an enlargement of the interlayer distance in polar solvents to form a card-house structure.<sup>12</sup> Indeed, the interlayer space of the  $\text{Ti}^{4+}$ -mont was expanded from 2.7 to 8.4 Å when soaked in phenoxyethanol (Table 1).‡ After the soaking, phenoxyethanol molecules form  $\pi$ -arene complexes with Ti cations in the interlayer space.<sup>13</sup> The interlayer distance of 8.4 Å is comparable to the molecular sizes of the fluoren-9-one of  $ca. 9 \times 6$  Å. Fluoren-9-one can react with the protonic acid sites within the interlayer space.§

Scheme 3 shows a possible reaction path for BHEPF. An oxygen atom of fluoren-9-one is protonated at an acid site on the  $\text{Ti}^{4+}$  ions within the interlayer space. An electrophilic attack of phenoxyethanol at a benzyl position of fluoen-9-one gives a monoalkylated intermediate, followed by successive reactions

**Table 1** Aromatic alkylation of phenoxyethanol with fluoren-9-one catalysed by the  $M^{n+}$ -montmorillonites and typical solid acids<sup>a</sup>

Entry	Catalyst	Conv. (%)	Yield of BHEPF (%) <sup>b</sup>	Amount of adsorbed $\text{NH}_3$ ( $\text{mmol g}^{-1}$ ) <sup>c</sup>	Interlayer distance (Å)	
					Without soaking <sup>d</sup>	With soaking in phenoxyethanol <sup>e</sup>
1	$\text{Ti}^{4+}$ -mont	100	82	1.89	2.7	8.4
2	$\text{Al}^{3+}$ -mont	80	62	0.75	3.4	8.6
3	$\text{Zr}^{4+}$ -mont	58	50	0.81	4.5	8.3
4	$\text{Fe}^{3+}$ -mont	58	27	0.95	2.2	n.m. <sup>f</sup>
5	$\text{Ni}^{2+}$ -mont	32	16	n.m.	2.4	n.m.
6	$\text{Cu}^{2+}$ -mont	16	12	0.74	2.6	8.0
7	$\text{Zn}^{2+}$ -mont	0	0	n.m.	4.2	n.m.
8	$\text{Na}^+$ -mont	0	0	0.17	2.9	8.6
9	$\text{SO}_4^{2-}/\text{ZrO}_2$	27	14	0.44	—	—
10	$\text{H}^+$ -mordenite	12	trace	0.24	—	—
11	$\text{H}^+$ -ZSM-5	trace	trace	n.m.	—	—
12	USY	24	trace	0.36	—	—
13	$\text{TiO}_2$ <sup>g</sup>	20	trace	n.m.	—	—

<sup>a</sup> Reaction conditions: catalyst 0.15 g; fluoren-9-one 1.0 mmol; phenoxyethanol 5 ml; 170 °C; 2 h. <sup>b</sup> Based on fluoren-9-one used. <sup>c</sup> Measured volumetrically. See text for details. <sup>d</sup> Determined by XRD after drying the sample at 110 °C. <sup>e</sup> Obtained after soaking the sample in 5 ml of phenoxyethanol at 25 °C. <sup>f</sup> Not measured. <sup>g</sup> JRC-TIO-1 was used.



Scheme 3

with a proton and phenoxyethanol to lead to the formation of BHEPF together with the regeneration of the protonic acid sites. A prominent catalysis of the metal cation-exchanged montmorillonites could be ascribed to the expansion of the interlayer space in phenoxyethanol as well as their strong acidity associated with the metal cations in the interlayer.

In conclusion, we have found a clean and simple alternative synthesis of BHEPF by the condensation of phenoxyethanol with fluoren-9-one using a recyclable  $\text{Ti}^{4+}$  cation-exchanged montmorillonite as a strong solid acid catalyst. The  $\text{Ti}^{4+}$ -mont replaces liquid acids for this alkylation reaction. The acid sites may be originated from the two-dimensional  $\text{TiO}_2$  sheets in the interlayer, where the alkylation can take place within the expanded interlayer space under the reaction conditions. At present, we are continuing to investigate selective C–C bond formations using functionalised montmorillonite catalysts with the aim of developing environmentally benign chemical processes.

## Experimental

### Catalyst preparation

Various metal cation-exchanged montmorillonites ( $\text{M}^{n+}$ -mont) were prepared by conventional cation-exchange. A representative example is for the preparation of the  $\text{Ti}^{4+}$ -exchanged montmorillonite ( $\text{Ti}^{4+}$ -mont). A mixture of parent  $\text{Na}^{+}$ -montmorillonite of 3.0 g ( $\text{Na}_{0.66}(\text{OH})_4\text{Si}_8(\text{Al}_{3.34}\text{Mg}_{0.66}\text{Fe}_{0.19})\text{O}_{20}$ , Kunipia F, Kunimine Industry Co. Ltd.) and 100 ml of aqueous  $\text{TiCl}_4$  (1.8 mol  $\text{L}^{-1}$ ) was stirred at 50 °C for 24 h. The obtained slurry was filtered and washed with 1000 ml of distilled water to ensure the removal of chlorine, followed by drying at 110 °C to afford 2.5 g of whitish gray powder. Elemental analysis: Na, 0.06; Al, 11.2; Ti, 3.25; Fe, 1.34%. X-Ray photon spectroscopy (XPS): Ti 2p<sub>2/3</sub> = 458.7 eV; Al 2p = 74.1 eV, Ti:Al = 0.21. The XPS peak positions are referred to C 1s at 284.5 eV. The exchange degree of sodium cations in the  $\text{Ti}^{4+}$ -mont was 97.7%. The layered structure of the powder was confirmed by its X-ray diffraction pattern and the interlayer space was estimated to be 2.7 Å, which is slightly smaller than that of the parent  $\text{Na}^{+}$ -mont (2.9 Å). The proton-exchanged zeolites of USY(Si:Al = 10), H-mordenite (Si:Al = 10) and H-ZSM-5 (Si:Al = 25) were purchased from N. E. Chemcat Co. Ltd.

### The alkylation of phenoxyethanol with fluoren-9-one

A typical example for the alkylation of phenoxyethanol with fluoren-9-one is as follows. Into a reaction vessel with a reflux condenser was placed the  $\text{Ti}^{4+}$ -mont (0.15 g), and heated under an  $\text{N}_2$  at 195 °C for 2 h. After cooling, phenoxyethanol (5 ml) was poured onto the catalyst, followed by the addition of fluoren-9-one (1 mmol). The mixture was stirred at 170 °C under  $\text{N}_2$  for 2 h. The  $\text{Ti}^{4+}$ -mont was separated by centrifugation and LC analysis of the filtrate showed 82% yield of BHEPF. The structure of BHEPF was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR.

An isolated  $\text{Ti}^{4+}$ -mont was washed with water and then can be reused for the above alkylation reaction; the first and second runs of the experiments using the spent  $\text{Ti}^{4+}$ -mont gave BHEPF in over 75% yields, under the same reaction conditions as the fresh samples. The loss of Ti in the spent  $\text{Ti}^{4+}$ -mont catalyst after several reuse experiments was negligible: the Ti content in the catalyst even after the third reuse was 3.23 wt%. Treatment of the spent  $\text{Ti}^{4+}$ -mont with water was necessary to retain its catalytic activity.¶

### Characterizations of prepared catalysts

The amount of adsorbed  $\text{NH}_3$  on the solid catalysts was volumetrically measured at 0 °C using a MKS Baratron type

627 absolute pressure instrument. The amount of irreversibly or strongly adsorbed  $\text{NH}_3$  was estimated from the difference of the first and second isotherms at about 50 Torr of equilibrium pressures. The second isotherm was obtained after degassing the  $\text{NH}_3$ -covered sample at 80 °C. In contrast to the  $\text{NH}_3$  adsorption isotherms obtained for the zeolites as typical microporous solid acids, the first adsorption for the  $\text{M}^{n+}$ -mont catalysts at low equilibrium pressures showed S-shaped isotherms. Similar types of the S-shaped adsorption isotherm have been also observed on other clay materials.<sup>14</sup>

The Ti K-edge X-ray absorption spectra were measured in a transmission mode at the EXAFS facilities installed at BL01B1 line of SPring-8 at JASRI, Harima, Japan, using a Si(311) monochromator. A detailed procedure for data reductions is described in elsewhere.<sup>15</sup> The curve-fitting analysis of the reverse FT was carried out by using empirical values of back scattering amplitude and phase shift, assuming the first and second peaks were originated from the scatterings by neighboring oxygen and titanium atoms, respectively.

## Acknowledgements

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## Notes and references

† Similar types of two-dimensional  $\text{TiO}_2$  structure have also been reported for a  $\text{TiO}_2/\text{SiO}_2$  sample prepared by the impregnation of tetraisopropoxytitanium(IV) solution with  $\text{SiO}_2$ .<sup>16</sup>

‡ The interlayer space of the  $\text{Ti}^{4+}$ -mont was also expanded by soaking it in ethylene glycol (7.2 Å), propane-1,2-diol (8.4 Å), and DMSO (4.4 Å), where the values in parentheses are interlayer distances after the soaking.

§ The expanded interlayer distance of 8.4 Å was greater than those of the ZSM-5 (0.51 × 0.54, 0.54 × 0.56), mordenite (0.67 × 0.70), and USY (0.74), where the values in parentheses are each pore size in nm.

¶ The deactivation of the  $\text{Ti}^{4+}$ -mont catalyst might be ascribed to a loss of the strong protonic acid sites during the alkylation reaction.

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# Wacker reaction in supercritical carbon dioxide

Huanfeng Jiang,\* Lanqi Jia and Jinheng Li

LCLC, Guangzhou Institute of Chemistry, Chinese Academy of Sciences, Guangzhou 510650  
China. E-Mail: jhf@mail.gic.ac.cn

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It is reported for the first time that the Wacker reaction can be carried out smoothly in supercritical carbon dioxide or ROH/supercritical carbon dioxide. Results show that both scCO<sub>2</sub> and co-solvent can remarkably affect the selectivity towards methyl ketone and the presence of ROH accelerates the reaction. The mechanism of the Wacker reaction in scCO<sub>2</sub> is also discussed.

## Introduction

In recent years supercritical carbon dioxide (scCO<sub>2</sub>) has been increasingly used as an environmentally friendly reaction medium in place of toxic and volatile organic solvents.<sup>1</sup> The very high concentrations of dissolved gases in scCO<sub>2</sub> favor some reactions involving gases. For example, hydrogenation and hydroformylation reactions lead to more satisfactory results in scCO<sub>2</sub> than in organic solvents.<sup>2,3</sup> In addition, slight changes of temperature and pressure, especially near the critical point of CO<sub>2</sub>, can affect the reaction rate and selectivity remarkably.<sup>4</sup> In scCO<sub>2</sub> phase control is also used to separate the reaction products from reaction system and realize the unity of reaction–separation.<sup>5</sup>

Transition-metal catalysis has been readily carried out in some organic solvents but scarcely so in scCO<sub>2</sub> owing to lack of solubility. In order to increase the solubility of catalysts and accelerate the reaction rate, cosolvents can be added to modify the solvent polarity of scCO<sub>2</sub>. In our previous work, we found that the presence of co-solvent can accelerate the reaction rate as well as improving the reaction selectivity.<sup>6</sup> Here we report the results of Wacker reactions in supercritical carbon dioxide or cosolvent-modified supercritical carbon dioxide and discuss the cosolvent effect on solubility.

## Results and discussion

### Wacker reaction and different media

The prototypical Wacker reaction is the palladium-catalyzed oxidation of ethylene to acetaldehyde.<sup>7</sup> The Wacker reaction is also applied to higher terminal alkenes leading to oxidation to methyl ketones and is very useful for terminal alkenes. Lloyd and Luberoff<sup>7b</sup> reported that the palladium-catalyzed oxidation reaction of oct-1-ene **1a** in *n*-propanol gave octan-2-one **2a**, octan-3-one **3a** and octan-4-one (**4a**) in 68, 9 and 3% yields, respectively.

In order to investigate the Wacker reaction in scCO<sub>2</sub> and compare the results in different media, we chose methanol as the organic cosolvent. At first, we studied the reaction of **1a** in pure supercritical carbon dioxide or pure methanol. The experiments showed that for a reaction time of 24 h, the product distribution in pure methanol solvent was **2a** (60.4%), **3a** + **4a** (13%) and octanal 1,1-dimethyl acetal **5a** (1.9%) (run 1 in Table 1). In pure scCO<sub>2</sub>, the selectivity of **2a** (66.7%) was increased, relative to methanol solution, although the conversion (33.8%) in scCO<sub>2</sub> was decreased (run 2 in Table 1). When the reaction time was prolonged to 48 h, the product distribution in scCO<sub>2</sub> was **2a**

(62.4%) and **3a** + **4a** (10.7%), while **5a** was not detected (run 3 in Table 1). These results implied that less isomerization occurred in pure scCO<sub>2</sub>, and since inorganic salts such as PdCl<sub>2</sub> and CuCl<sub>2</sub> are insoluble in scCO<sub>2</sub>,<sup>6c</sup> the reaction system is heterogeneous, which slows the reaction.

### Cosolvent effect on the Wacker reaction

PdCl<sub>2</sub> and CuCl<sub>2</sub> both dissolve in methanol which is miscible with scCO<sub>2</sub>. 1 mL of methanol acting as a co-solvent was added to scCO<sub>2</sub> to promote the partial dissolution of PdCl<sub>2</sub> and CuCl<sub>2</sub>. The experimental results showed that the rate of reaction was remarkably increased, similar to that found in methanol alone, with the selectivity towards **2a** raised from 66.7 to 85.5%. In contrast to methanol solution the main by-product was acetal **5a** (4.5%) while the amount of ketone isomer was reduced to < 1%. The results show that methanol-modified scCO<sub>2</sub> accelerates the Wacker reaction rate and reduced the isomerization of **1a**.

When CO<sub>2</sub> was at high density and near the supercritical state (29 °C, 13MPa), the conversion and selectivity were low (run 1 in Table 2) whilst at 40 °C in which the system reached the supercritical state, the conversion and selectivity were raised notably (run 2 in Table 2). At 60 °C, the selectivity towards **2a** reached 90.1% (run 4 in Table 2). These results indicate that scCO<sub>2</sub> is a good solvent for the Wacker reaction because of its very low viscosity and weaker cage effects which allow the Wacker products to rapidly diffuse and so reduce side reactions.

## Green Context

**The Wacker reaction is one of the very important reactions for the functionalisation of alkene feedstocks. In this reaction, Pd and Cu salts are used in an aqueous acidic environment with oxygen as oxidant. Obviously, this reaction medium is not ideal from the point of view of waste disposal. This article introduces the concept of using supercritical carbon dioxide scCO<sub>2</sub> as an alternative solvent. This solvent is easily handled and recovered, but suffers from the drawback that polar compounds are at best sparingly soluble. The authors have shown that the use of cosolvents such as methanol can get round this problem, and their results are very promising. Not only can very good conversions be obtained, but selectivity can be altered by careful choice of the solvent composition.** DJM

**Table 1** The Wacker reaction of oct-1-ene in different media<sup>a</sup>

Run	MeOH/mL	$P_{CO_2}$ /MPa	$t/h$	Conv. <sup>b</sup> (%)	Product distribution <sup>b</sup> (%)			Selectivity (%)
					2a	3a + 4a	5a	
1	1	0	24	98.9	60.4	13.0	1.9	60.1
2	0	13	24	50.7	33.8	<1	—	66.7
3	0	13	48	92.5	62.4	10.7	—	67.5
4	1	13	24	80.2	68.6	<1	4.5	85.5

<sup>a</sup> Reaction conditions: 5 mmol oct-1-ene; O<sub>2</sub> 15 atm;  $T = 40\text{ }^\circ\text{C}$ ; 3 mol% PdCl<sub>2</sub>; 2 mmol CuCl<sub>2</sub>. <sup>b</sup> Based on GC.

Simultaneously, raising the temperature will accelerate the reaction rate and quicken the diffusion rate of the products.

Raising the pressure of oxygen also speeded up the reaction and increased the yield of **2a** (runs 2 and 3 in Table 2). Using EtOH as co-solvent led to **2a** as the main product but the amount of acetal formed was increased (runs 5 and 6 in Table 2).

### The effect of water and copper salts on the Wacker reaction

When a small amount of water was added to the reaction system, the reaction rate decreased distinctly but a high selectivity was still retained (run 7 in Table 2 and run 1 in Table 3). When crystalline copper(II) chloride (CuCl<sub>2</sub>·2H<sub>2</sub>O) replaced anhydrous copper(II) chloride, the reaction rate decreased to a great extent; and by-products, such as acetal, octan-2-ol and 2-chlorooctane, were increased. When CuCl replaced CuCl<sub>2</sub>, the reaction gave unsatisfactory conversion and selectivity.

### The Wacker reaction with styrene or cyclohexene

In normal organic solvents, the Wacker process for styrene and cyclohexene gave satisfactory results,<sup>7a</sup> but in scCO<sub>2</sub> or alcohol-modified scCO<sub>2</sub> some abnormal phenomena were observed. Although the conversion of styrene was fair to good, the selectivity towards the expected product acetophenone **2b** was low (Table 4). When alcohol (methanol or ethanol) was present, by-product **5b** was obtained in almost equal amounts to the expected product **2b**. When cyclohexene was used as substrate, the product distribution in MeOH/scCO<sub>2</sub> was cyclohexanone (17.7%), acetal (8.6%) and  $\beta$ -chlorocyclohexyl methyl ether (17.5%) (Scheme 1).

Noting the by-products under different conditions, some interesting conclusions can be drawn. When liquid CO<sub>2</sub> and methanol or ethanol were used respectively as reaction media, the main by-products were octan-3-one **3a** and octan-4-one **4a**.

Use of scCO<sub>2</sub> only as the medium, the by-products were still **3a** and **4a**, but their amounts were decreased to a great extent. When ROH/scCO<sub>2</sub> was used as the reaction medium, the main by-product was acetal **5**. It is evident that **3a** and **4a** are produced from inner octenes, such as oct-2-ene, oct-3-ene and oct-4-ene, which were isomerized from **1a**. The acetal **2a** was obtained *via* oxidation of the terminal carbon in **1a** by the oxygen nucleophile. Since styrene can not be isomerized, the main by-product was acetal **5b**. In view of above observations, use of scCO<sub>2</sub> or ROH/scCO<sub>2</sub>, as reaction media, decreases the isomerization reaction of **1a** and the formation of isomerized ketones such as **3a** or/and **4a**. The major distinction between scCO<sub>2</sub> and ROH/scCO<sub>2</sub> lies in the regioselectivity of **1a**.

### Mechanism

The question arises as to whether the Wacker reaction is homogeneous or heterogeneous. While PdCl<sub>2</sub> and CuCl<sub>2</sub> are insoluble in scCO<sub>2</sub> they are partially soluble in MeOH/scCO<sub>2</sub>.<sup>6c</sup> It is also reported that an organopalladium complex could be soluble in scCO<sub>2</sub>.<sup>1a</sup> Therefore, we suggest that the reaction in scCO<sub>2</sub> or MeOH/scCO<sub>2</sub> is homogeneous since palladium and substrates may form organopalladium complexes in the oxidative process.

**Table 3** Effect of other factors on the Wacker reaction in scCO<sub>2</sub><sup>a</sup>

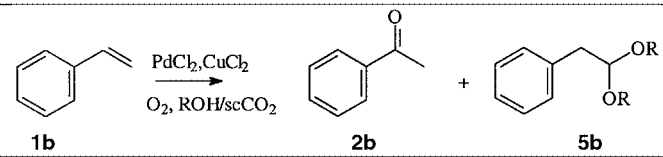
$t/h$	Conv. <sup>b</sup> (%)	Product distribution <sup>b</sup> (%)			Selectivity <sup>b</sup> (%)
		2a	3a + 4a	5a	
0.1 mL water	48	19.2	16.1	—	81.7
CuCl <sub>2</sub> ·2H <sub>2</sub> O	24	50.0	23.3	5.1	46.6
CuCl	12	13.8	6.5	3.0	47.1

<sup>a</sup> Reaction conditions: 5 mmol oct-1-ene, 1 mL MeOH, 3 mol% PdCl<sub>2</sub>, 2 mmol Cu(II or I) salt, O<sub>2</sub> 15 atm, CO<sub>2</sub> 13 MPa,  $T = 40\text{ }^\circ\text{C}$ . <sup>b</sup> Based on GC.

**Table 2** Effect of temperature and pressure on the oxidation reaction<sup>a</sup>

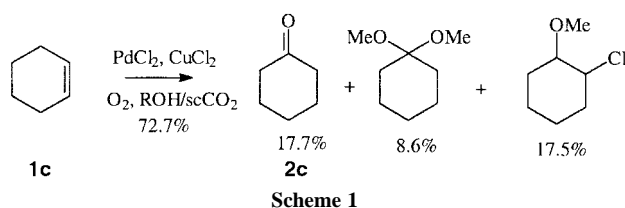
Run	ROH/1 mL	$P_{O_2}$ /MPa	$T/^\circ\text{C}$	$t/h$	Conv. <sup>b</sup> (%)	Product distribution <sup>b</sup> (%)			Selectivity <sup>b</sup> (%)
						2a	3a + 4a	5a	
1	MeOH	1.5	29	24	37.2	17.9	3.2	0.6	48.1
2	MeOH	1.5	40	24	80.2	68.8	<1.0	4.5	85.5
3	MeOH	0.3	40	24	10.6	8.4	<0.1	0.7	79.2
4	MeOH	0.3	60	12	63.5	57.2	<1.0	2.8	90.1
5	EtOH	1.0	40	24	63.4	51.2	3.3	3.7	80.8
6	EtOH	1.5	40	24	91.5	63.4	3.6	10.5	69.3
7	95%EtOH	1.0	40	48	92.2	79.5	—	5.6	86.2

<sup>a</sup> Reaction conditions: 5 mmol oct-1-ene;  $P_{CO_2} = 13\text{ MPa}$ ; 24 h; 3 mol% PdCl<sub>2</sub>; 2 mmol CuCl<sub>2</sub>. <sup>b</sup> Based on GC.

**Table 4** Oxidation of styrene in ROH/scCO<sub>2</sub><sup>a</sup>


Run	ROH	<i>P</i> <sub>O<sub>2</sub></sub> /MPa	<i>P</i> <sub>CO<sub>2</sub></sub> /MPa	<i>T</i> /°C	<i>t</i> /h	Conv. <sup>b</sup> (%)	Product distribution <sup>b</sup> (%)	
							2b	5b
1	—	1.5	13	40	24	84.8	17.4	—
2	MeOH	1.5	10	40	24	56.2	14.0	28.0
3	EtOH	1.5	7.5	50	24	84.4	16.1	14.2
4	MeOH	0.3	12	60	12	42.5	3.8	19.7
5 <sup>c</sup>	MeOH	1.5	12	40	12	28.0	14.4	6.5

<sup>a</sup> Reaction conditions: 5 mmol styrene, 1 mL ROH, 0.15 mmol (3 mol%) PdCl<sub>2</sub>, 2 mmol CuCl<sub>2</sub>. <sup>b</sup> Based on GC. <sup>c</sup> 2 mmol CuCl.

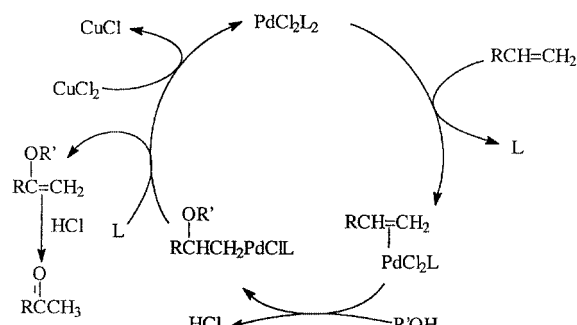


The Wacker reaction of ethylene to acetaldehyde is usually carried out in aqueous solution. Water is a key factor to dissolve the inorganic salt (PdCl<sub>2</sub>/CuCl<sub>2</sub>), to produce H<sub>3</sub>O<sup>+</sup> and provide oxygen to produce acetaldehyde. The solubility of water in scCO<sub>2</sub> is rather poor but the reaction still produces ketones successfully. Therefore the mechanism of the Wacker reaction in scCO<sub>2</sub> or ROH/scCO<sub>2</sub> must be different from that in aqueous solution. It is reported that oxidation in alcoholic solvents occurs readily, even in carefully dried reaction mixtures.<sup>7b</sup> The presumed mechanism in ROH/scCO<sub>2</sub> might be similar to that in alcoholic solvents (Scheme 2). In the presence of ROH, a palladium–alkene complex is converted to a β- or α-alkoxy palladium intermediate which then produces a vinylic ether. The vinylic ether β-intermediate was then converted to a ketone in the presence of hydrogen chloride. As yet, it is not clear that why the Wacker reaction is successful in pure scCO<sub>2</sub>.

## Conclusions

From the above results, the following conclusions are derived.

1. As a reaction medium scCO<sub>2</sub> improves the selectivity of the Wacker reaction to a great extent and reduces the isomerization of oct-1-ene.
2. A suitable amount of methanol/ethanol as co-solvent in scCO<sub>2</sub>, promotes the dissolution of the catalysts, quickens

**Scheme 2** The mechanism of the Wacker reaction in ROH/scCO<sub>2</sub>.

the reaction and raises the selectivity of the product considerably.

3. The presence of a small amount of water reduces the reaction rate although the selectivity was retained.
4. When CuCl replaced CuCl<sub>2</sub>, both reaction rate and selectivity towards the main products were significantly reduced.

## Experimental

### General procedure for the Wacker reaction of oct-1-ene in scCO<sub>2</sub>

A mixture consisting of **1a** (5 mmol), methanol (1 mL), PdCl<sub>2</sub> (0.015 mmol) and CuCl<sub>2</sub> (2 mmol) was placed in a HF-25 autoclave. O<sub>2</sub> was pressurized and then 10 mL of liquid CO<sub>2</sub> was transferred by a cooling pump into the autoclave to the desired pressure. Then the autoclave was put into an oil-bath under magnetic stirring for the desired reaction temperature and reaction time. After the reaction, the autoclave was allowed to cool to −30 °C in a cooler. The CO<sub>2</sub> was vented and the surplus was extracted with diethyl ether. The extract was filtered and condensed under reduced pressure. The product was analyzed using GC (quantitative analysis) and GC–MS (identification of products).

**Octan-2-one 2a:** 128(M<sup>+</sup>, 3), 113(M<sup>+</sup> − CH<sub>3</sub>, 3), 85(M<sup>+</sup> − CH<sub>3</sub>CO, 5), 71(M<sup>+</sup> − CH<sub>3</sub>COCH<sub>2</sub>, 12), 58(M<sup>+</sup> − CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>, 75), 43 (M<sup>+</sup> − C<sub>6</sub>H<sub>13</sub>, 100%).

**Octanal 1,1-dimethoxy acetal 5a:** 143(M<sup>+</sup> − CH<sub>3</sub>O, 8), 111(M<sup>+</sup> − 2CH<sub>3</sub>O − 1, 2), 75(M<sup>+</sup> − C<sub>7</sub>H<sub>15</sub>, 100), 71(C<sub>5</sub>H<sub>11</sub><sup>+</sup>, 10), 69(C<sub>5</sub>H<sub>9</sub><sup>+</sup>, 16), 57(C<sub>4</sub>H<sub>9</sub><sup>+</sup>, 9), 55(C<sub>4</sub>H<sub>7</sub><sup>+</sup>, 14), 43(C<sub>3</sub>H<sub>7</sub><sup>+</sup>, 15), 41(C<sub>3</sub>H<sub>7</sub><sup>+</sup>, 24%).

**Octanal 1,1-diethoxy acetal 5a':** 157(M<sup>+</sup> − C<sub>2</sub>H<sub>5</sub>O, 29), 111(M<sup>+</sup> − 2C<sub>2</sub>H<sub>5</sub>O − 1, 8), 69(C<sub>5</sub>H<sub>9</sub><sup>+</sup>, 35), 57(C<sub>4</sub>H<sub>9</sub><sup>+</sup>, 57%).

**Acetophenone 2b:** 120(M<sup>+</sup>, 27), 105(M<sup>+</sup> − CH<sub>3</sub>, 100), 77(C<sub>6</sub>H<sub>5</sub><sup>+</sup>, 55%).

**2-Phenylethanal 1,1-dimethoxy acetal 5b:** 135(M<sup>+</sup> − CH<sub>3</sub>O, 12), 91(C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub><sup>+</sup>, 28), 75(M<sup>+</sup> − C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, 100%).

**Cyclohexanone 3b:** 98(M<sup>+</sup>, 23), 70(M<sup>+</sup> − CH=CH<sub>2</sub> − 1, 17), 55(M<sup>+</sup> − C<sub>3</sub>H<sub>5</sub>, 100), 42(C<sub>2</sub>H<sub>2</sub>O<sup>+</sup>, 78%).

## Acknowledgements

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# Microwave irradiation in solvent-free conditions: an eco-friendly methodology to prepare indazoles, pyrazolopyridines and bipyrazoles by cycloaddition reactions

Angel Díaz-Ortiz,<sup>\*a</sup> Antonio de la Hoz<sup>\*a</sup> and Fernando Langa<sup>b</sup>

<sup>a</sup> *Facultad de Química, Universidad de Castilla-La Mancha, 13071-Ciudad Real, Spain.*  
E-Mail: adiaz@qino-cr.uclm.es

<sup>b</sup> *Facultad de Ciencias del Medioambiente, Universidad de Castilla-La Mancha, 45001-Toledo, Spain*

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A study on the behaviour of vinylpyrazoles, pyrazolyl imines and pyrazolyl hydrazones as dienes or dipoles is reported. Cycloaddition of the aforementioned compounds with electron-poor reagents under microwave irradiation in solvent-free conditions permits the preparation of indazoles, pyrazolopyridines and bipyrazoles in moderate to good yields. This represents an eco-friendly, green approach to these valuable pyrazole derivatives that avoids the harsh or highly contaminant conditions involving classical heating and offers a reduction or even elimination of solvent use and recovery, simplification of the work up procedures, facility of scale up and savings in energy consumption, in addition with higher yields.

## 1 Introduction

Indazoles, pyrazolopyridines and bipyrazoles are very interesting pyrazole derivatives with wide-ranging biological activities. Most of the pharmacologically active indazole derivatives are useful as antiinflammatory drugs with analgesic and antipyretic properties<sup>1</sup> (e.g. benzydac or benzydamine). Some indazoles show antidepressant activity<sup>2</sup> and have antiarthritic<sup>3</sup> and antimicrobial<sup>4</sup> effects. A number of pyrazolo[3,4-*b*]pyridines display interesting anxiolytic activity<sup>5</sup> (e.g. trazolate), are potentially biologically active compounds as new inhibitors of xantine oxidases<sup>6</sup> and have proved to be active against Gram positive and Gram negative bacteria<sup>7</sup> and also as compounds for the inhibition of cholesterol formation.<sup>8</sup> Some bipyrazolyl derivatives have also proven to be useful as potential anti-inflammatory agents,<sup>9</sup> cytotoxic agents,<sup>10</sup> insecticides,<sup>11</sup> herbicides<sup>12</sup> and fungicides.<sup>13</sup>

In most cases, these pyrazole derivatives have been synthesized by cyclization reactions.<sup>14</sup> Diels–Alder cycloaddition is the most useful and widely employed method for the construction of six-membered rings.<sup>15</sup> However, pyrazole derivatives are very reluctant to participate as dienes in Diels–Alder cycloadditions involving the pyrazole ring, owing to the loss of its aromaticity in the reaction.<sup>16</sup>

We have undertaken the cycloaddition approach to heterocyclic systems using microwave irradiation and solvent-free conditions as an effective and eco-friendly procedure.

The potential of vinylpyrazoles, pyrazolyl imines and hydrazones as dienes or dipoles towards carbon–carbon and carbon–nitrogen double bonds has been exploited.

Microwave irradiation is a non-conventional energy source whose popularity and synthetic utility in organic chemistry has increased considerably in recent years.<sup>17</sup> The rapid heating induced by such radiation avoids harsh classical conditions and decomposition of the reagents, leading to the formation of products under mild reaction conditions, thus increasing the yield.

Solvent-free conditions are especially suitable for microwave irradiation.<sup>18</sup> Environmentally benign synthesis can be easily designed using this methodology:

- The use of large volumes of solvent is avoided, reducing solvent emissions and redistillation.
- Work up is considerably simplified because in many cases the pure product can be obtained directly from the crude reaction mixture by simple extraction, distillation or sublimation.
- Recyclable solid supports can be used, replacing highly polluting mineral acids and oxidants.
- Scale-up is facilitated by the absence of solvent.
- Safety is increased by reducing the risk of overpressure and explosions.<sup>19</sup>

The benefits of one or several of these dot points have been recently employed in a lot of articles on assembly of heterocyclic compounds using microwave procedures.<sup>20</sup>

In the same way, we have employed some advantages of this synthetic methodology as an eco-friendly approach to the synthesis of indazoles, pyrazolopyridines or bipyrazoles by cycloaddition reactions.

## 2 Results and discussion

### 2.1 Diels–Alder cycloaddition of vinylpyrazoles

Some indazole derivatives have been prepared by Diels–Alder cycloadditions starting from 4- or 5-vinylpyrazoles.<sup>21</sup> However, these reactions require the use of harsh conditions: sealed

### Green Context

Cycloadditions (including dipolar cycloadditions) are amongst the most elegant ways to rapidly build complex cyclic compounds. In this paper, methods are described which allow the rapid construction of a range of heterocyclic compounds using microwaves and solventless reaction conditions. The conditions used minimise both solvent usage and energy consumption during the synthesis. *DJM*

vessels and high pressures and temperatures (8–10 atm and 120–140 °C) for long reaction times (several days) to obtain very low or moderate yields (Table 1).<sup>22</sup>

Vinylpyrazoles **1** or **2** react with dimethylacetylenedicarbonylate (DMAD) under microwave irradiation within 6 and 30 min to afford the products shown in Scheme 1 in 72 and 45% overall yield, respectively.<sup>23</sup>

Microwave irradiation of vinylpyrazole **1** and methyl propiolate (MP) for 20 min afforded compounds **8** and **9** along with an inseparable mixture of **10** and **11** (product ratio 3:1) in 39% overall yield. Irradiation of vinylpyrazole **2** and ethyl propiolate (EP) for 25 min give the cycloadduct **12** in 22% yield<sup>23</sup> (Scheme 2, Table 2).

Cycloaddition of **1** with ethyl phenylpropiolate (EPP) under microwave irradiation in a domestic oven gave the aromatic adduct **13** in 12% yield. Cycloaddition of **2** with this dienophile in a focused microwave reactor afforded the non-aromatic product **14** (19%)<sup>23</sup> (Scheme 3).

As these results show, the synergy between microwave irradiation and solvent-free conditions enables vinylpyrazoles to undergo Diels–Alder cycloadditions with acetylenic dienophiles to give indazole derivatives within a few minutes, thus avoiding the harsh reaction conditions that involve classical heating. With this methodology the yields are improved remarkably, the extent of the polymerization process is diminished and the purity of the indazoles is increased. It is possible to employ a dienophile of low reactivity, such as ethyl phenylpropiolate, whose cycloaddition with vinylpyrazoles have not been described under classical conditions.

In all of these reactions the unreacted vinylpyrazole is not recovered owing to its high tendency to polymerize.

## 2.2 Diels–Alder cycloaddition of pyrazolyl imines

There is no general method to obtain pyrazolo[3,4-*b*]pyridines by cycloaddition reactions, perhaps owing to the reluctance of the pyrazole derivatives to act as dienes—particularly if an azadiene is involved.

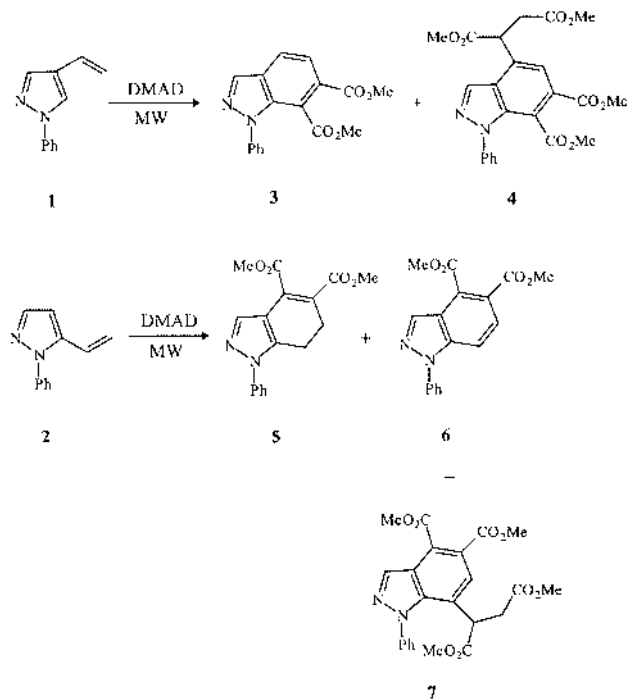
Diels–Alder cycloaddition of alkylidene derivatives of 5-aminopyrazole with nitroalkenes, as electron-poor dienophiles, under microwave irradiation in solvent-free conditions afforded the corresponding pyrazolo[3,4-*b*]pyridines in good or excellent yields<sup>24,25</sup> (Scheme 4).

This is the first example of a [4+2] cycloaddition of a 2-azadiene involving a pyrazole ring, such as **15** or **18**, and it represents a new, interesting, eco-friendly and versatile approach to the preparation of pyrazolo[3,4-*b*]pyridines.

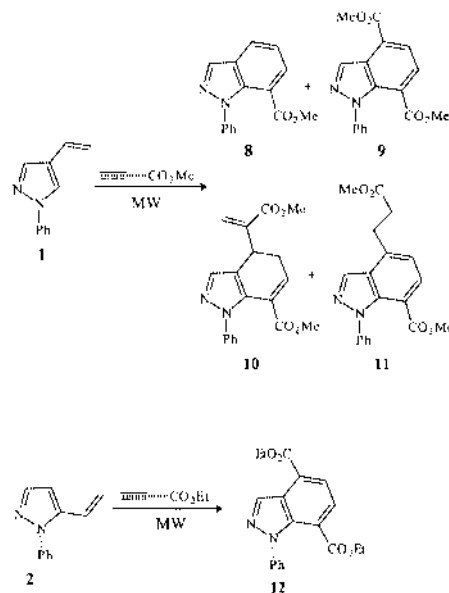
The higher yields obtained and the mild reaction conditions used in the cycloaddition of azadiene **18** with aromatic nitroalkenes can be understood, to a certain extent, in terms of the HOMO (diene)–LUMO (dienophile) energy gaps. These gaps are 0.5 or 1 eV lower than those relating to the cycloadditions with **15** or aliphatic nitroalkenes, respectively. On the other hand, the more stable conformation of 2-azadiene **18** has a torsion angle of 8.7° between the exocyclic double bond and the pyrazole ring, while in azadiene **15** this torsion angle is 18.1°. The greater planarity in compound **18** partly explains its higher reactivity as a diene.

All the reactions were performed at atmospheric pressure in a focused microwave reactor with full control of the incident power and the reaction temperature. The regiochemistry of the adducts was inferred by NOE difference experiments.

In order to extend the scope of this reaction and its utility as a new synthetic approach to pyrazolo[3,4-*b*]pyridines, we also studied the cycloaddition of **15** or **18** with other electron-poor dienophiles<sup>25</sup> (Scheme 5).



Scheme 1



Scheme 2

**Table 1** Comparison of the reaction of **1** or **2** with DMAD by classical heating or under microwave irradiation

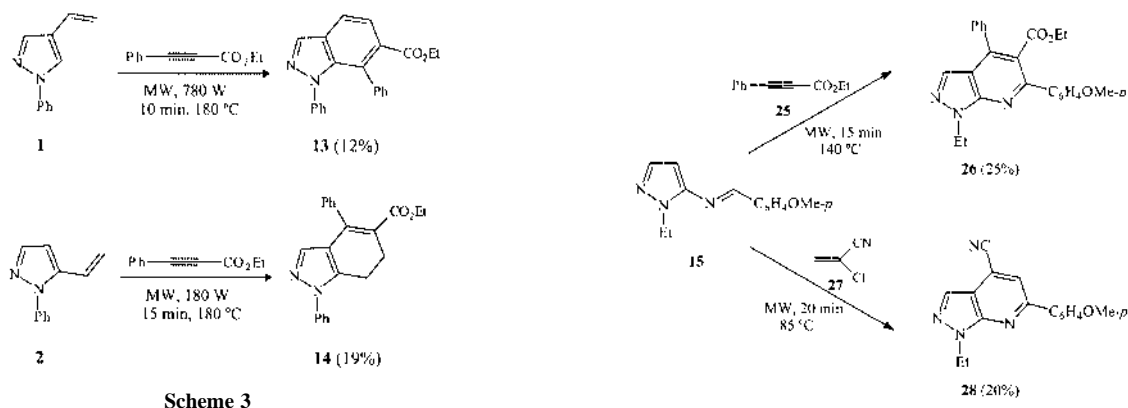
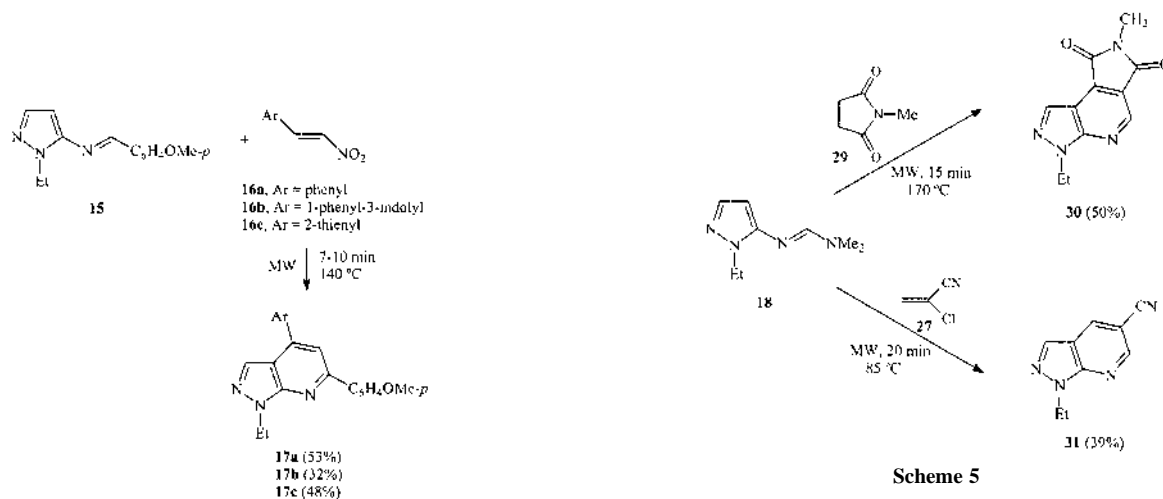
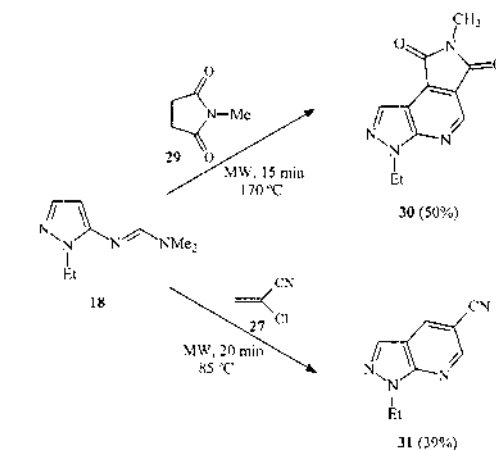
Vinylpyrazole	Reaction conditions	Products (% yield)	Notes/refs.
<b>1</b>	CH <sub>2</sub> Cl <sub>2</sub> , 150 °C, 8–10 atm	<b>3</b> + <b>4</b> (18% overall yield)	21
<b>1</b>	MW, 780 W, 130 °C, 6 min	<b>3</b> ( <b>10</b> ) + <b>4</b> (62)	<i>a</i>
<b>2</b>	CH <sub>2</sub> Cl <sub>2</sub> , 140 °C, 3 days	<b>5</b> (53)	22c
<b>2</b>	MW, 75 W, 160 °C, 30 min	<b>5</b> ( <b>10</b> ) + <b>6</b> (6) + <b>7</b> (29)	<i>b</i>

*a* Reaction performed in a domestic oven. *b* Reaction performed under focused microwaves.

**Table 2** Comparison of the reaction of **1** or **2** with methyl (or ethyl) propiolate by classical heating or under microwaves

Vinylpyrazole	Dienophile	Reaction conditions	Products (% yield)	Notes/refs.
<b>1</b>	Methyl propiolate	CH <sub>2</sub> Cl <sub>2</sub> , 150 °C, 5 days	<b>8</b> (0.65) + <b>10,11</b> (5.2)	22b
<b>1</b>	Methyl propiolate	MW, 780 W, 170 °C, 20 min	<b>8</b> (12) + <b>9</b> (6) + <b>10,11</b> (21)	a
<b>2</b>	Methyl propiolate	CH <sub>2</sub> Cl <sub>2</sub> , 140 °C, 7 days	<b>9</b> (7)	22c
<b>2</b>	Ethyl propiolate	MW, 780 W, 186 °C, 25 min	<b>12</b> (22)	a

<sup>a</sup> Reaction performed in a domestic oven.

**Scheme 3****Scheme 4****Scheme 5**

For 2-chloroacrylonitrile **27**, aromatization of the adduct took place with loss of HCl, a rare process in cycloadditions. The change in the regiochemistry of the cycloadditions on using **15** or **18** as the substrate is remarkable. Considering the LUMO of acrylonitrile, the atomic coefficient values could explain the regiochemistry of adduct **31** but not the regiochemistry of adduct **28**. Calculations at the HF/3-21G level predict an asynchronous transition structure for the latter cycloaddition. From the shape of the FMOs it is clear that in both cases the formation of the 4-cyano adduct can be expected if only orbital control is considered, and this is in good agreement with the activation barriers computed *in vacuo*. In contrast, the electrostatic interactions between the reactants favour the formation of regioisomers **28** and **31**, respectively. Therefore, if the electrostatic contribution of the solution energy is considered, the regiocontrol of the reaction is determined by coulombic interaction.

In order to assess the efficiency of microwave irradiation in inducing these processes, the reactions of **15** or **18** with 2-chloroacrylonitrile with classical heating (in an oil bath) in the absence of solvent under comparable reaction conditions (time and temperature) were also studied. However, in this case the adducts **28** and **31** were not obtained and hydrolysis of the 2-azadiene took place.

### 2.3 1,3-Dipolar cycloaddition of pyrazolyl hydrazones

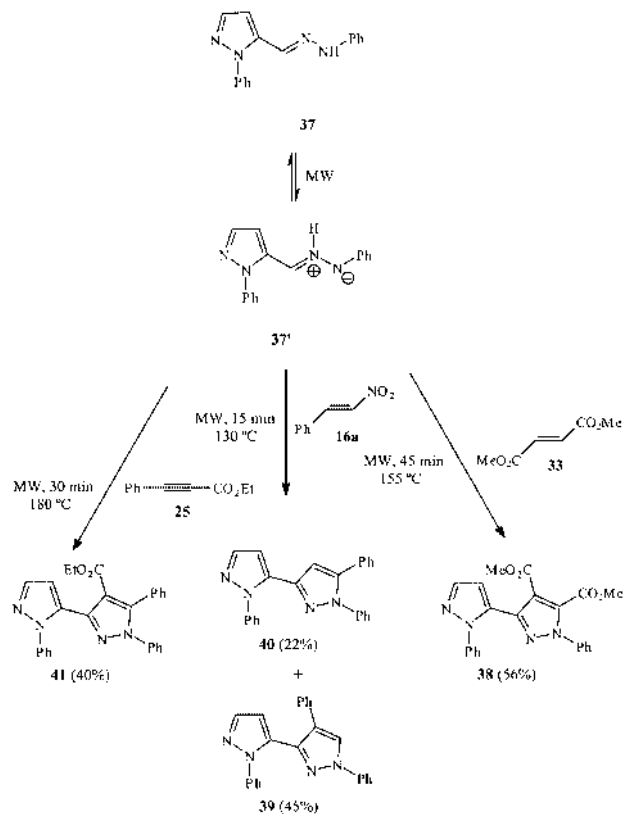
Bipyrazoles have been prepared by 1,3-dipolar cycloadditions using diarylnitrileimines<sup>26</sup> or diazo compounds.<sup>27</sup> Bipyrazoles could be obtained from azomethine imine intermediates, but the cycloaddition, even with very activated dipolarophiles, must be performed under reflux in high boiling solvents and with long reaction times (several hours or days).<sup>28</sup> This fact reduces the synthetic utility of the reaction and this process has not been employed to prepare bipyrazole derivatives.

4-Pyrazolyl hydrazone **32** reacts with electron-poor dipolarophiles under microwave irradiation in solvent-free conditions within 10–45 min to afford the corresponding [4,3']bipyrazoles<sup>29</sup> (Scheme 6).

It has been reported that hydrazones can react through the azomethine imine tautomer with very activated dipolarophiles, such as *N*-phenylmaleimide.<sup>30</sup> Intramolecular reactions with non-activated alkenes have also been achieved.<sup>28,31</sup> In both processes the reaction times are very long and yields are, in most cases, moderate. Acid-catalysed [3+2] cycloadditions of hydrazones are faster and give better yields.<sup>32</sup> Under microwave irradiation, 1,3-dipolar cycloadditions are dramatically accelerated and give good yields of the aromatic bipyrazoles in a few minutes. The effect of microwave irradiation is not exclusively acceleration of the reaction: some of these cycloadditions do not occur by classical heating in an oil-bath under comparable reaction conditions (time and temperature). This simple procedure not only provides an easy access to bipyrazolyl derivatives but avoids the use of acid to catalyse the cycloaddition.

In the same way, microwave irradiation for 15–45 min of the 5-pyrazolyl hydrazone **37** and an electron-poor dienophile affords the corresponding [5,3']bipyrazoles<sup>29</sup> (Scheme 7). In these reactions, the unreacted reagents are not recovered but decompose upon extensive irradiation.

Cycloadditions of hydrazones **32** or **37** with dimethyl fumarate have also been performed by classical heating in an oil-bath in the absence of solvent under comparable reaction conditions (time and temperature). The corresponding bipyrazoles, **34** and **38**, were obtained in 17 and 25% yield, respectively. These results confirm the utility of microwave

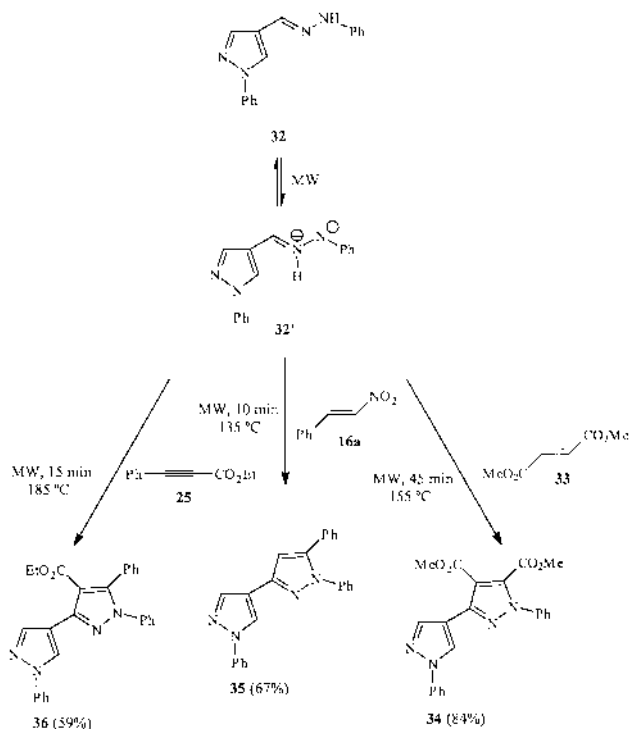


Scheme 7

irradiation in organic synthesis and its advantages in comparison with classical heating, especially in processes that require strong heating and/or vigorous reaction conditions, such as the thermal hydrazone–azomethine imine isomerization.

Owing to their structures, pyrazolyl hydrazones **32** and **37** could also undergo a [4+2] cycloaddition by reacting as 1-azadienes to afford pyrazolopyridines. We have already shown that vinylpyrazoles and pyrazolyl imines can undergo Diels–Alder cycloadditions under microwave irradiation. However, [4+2] cycloadducts have not been obtained from pyrazolyl hydrazones. Curiously, computational studies at the PM3 level predicted that [4+2] transition structures are of lower energy than the [3+2] structures (Table 3). However, in contrast with the PM3 results, our B3LYP/6-31G\* data predict the preferential formation of the [3+2] cycloadducts (Fig. 1). Moreover, inclusion of thermal and entropic factors results in an enhancement in the energy differences between the transition structures associated with the [3+2] and [4+2] cycloadditions (see Table 3). Our calculations suggest an unfavorable entropic balance for the saddle points associated with the [4+2] processes, which is more important at the temperature at which the experiments were conducted.<sup>33</sup> All these effects result in the virtually exclusive formation of the [3+2] cycloadducts, which is in good agreement with the experimental results.

Dimethylhydrazone **42** cannot undergo a thermal 1,2-hydrogen shift to give an azomethine imine intermediate. However, microwave irradiation of a mixture of the dimethylhydrazone **42** and ethyl phenylpropiolate for 10 min afforded the [4,3']bipyrazole **43** in 80% yield.<sup>29</sup> In contrast, compound **43** is not obtained by classical heating in the absence of solvent under comparable reaction conditions. A similar reaction with dimethyl fumarate as the dipolarophile did not afford the corresponding bipyrazole but gave 1-phenyl-4-cyanopyrazole, which was generated from **42** by loss of dimethylamine. In view of this reactivity, these reactions could occur through a Michael-type intermediate. Competition between cyclisation and fragmentation of the intermediate could lead to different products (Scheme 8).



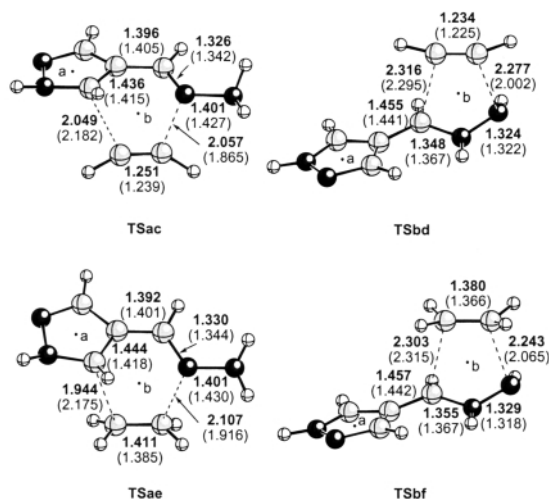
Scheme 6



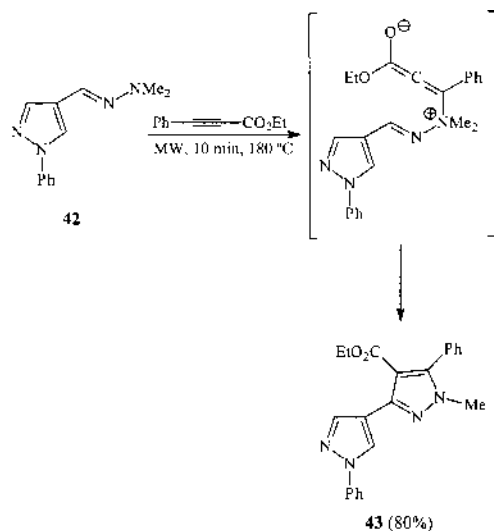
**Table 3** Heats of formation ( $\Delta H_f^\circ$ /kcal mol<sup>-1</sup>), energies ( $E/E_h$ ) and Gibbs energies ( $G_T/E_h$ ) of transition structures depicted in Fig. 1

Parameter	TSbd acetylene/[3+2]	TSac acetylene/[4+2]	TSbf ethylene/[3+2]	TSae ethylene/[4+2]
$\Delta H_f^\circ$ <sup>a</sup>	179.39 (0.00) <sup>d</sup>	175.55 (-3.84) <sup>d</sup>	143.40 (0.00) <sup>e</sup>	140.67 (-2.73) <sup>e</sup>
$E^b$	-452.25061 (0.00) <sup>d</sup>	-452.24954 (+0.67) <sup>d</sup>	-453.51077 (0.00) <sup>e</sup>	-453.50662(+2.60) <sup>e</sup>
$E+ZPVE^{b,c}$	-452.11084 (0.00) <sup>d</sup>	-452.11041 (+0.27) <sup>d</sup>	-453.34561 (0.00) <sup>e</sup>	-453.34207 (+2.22) <sup>e</sup>
$G_{298}^{b,c}$	-452.18637 (0.00) <sup>d</sup>	-452.14368 (+1.26) <sup>d</sup>	-453.38064 (0.00) <sup>e</sup>	-453.37558 (+3.18) <sup>e</sup>
$G_{443}^{b,c}$	-452.18637 (0.00) <sup>d</sup>	-452.18338 (+1.88) <sup>d</sup>	-453.42419 (0.00) <sup>e</sup>	-453.41364 (+6.62) <sup>e</sup>

<sup>a</sup> RHF/PM3 values. <sup>b</sup> B3LYP/6-31G\* values. <sup>c</sup> Zero-point vibrational energies scaled by 0.8929. <sup>d</sup> Relative energies (in kcal mol<sup>-1</sup>) with respect to **TSbd** in parentheses. <sup>e</sup> Relative energies (in kcal mol<sup>-1</sup>) with respect to **TSbf** in parentheses.



**Fig 1** Ball and Stick representations of the fully optimized transition structures **TSac**, **TSae**, **TSbd** and **TSbf** computed at the B3LYP/6-31G\* (bold) and RHF/PM3 (in parentheses) levels. Bond distances are given in Å. Atoms are represented by increasing order of shading as follows: H, C, N.



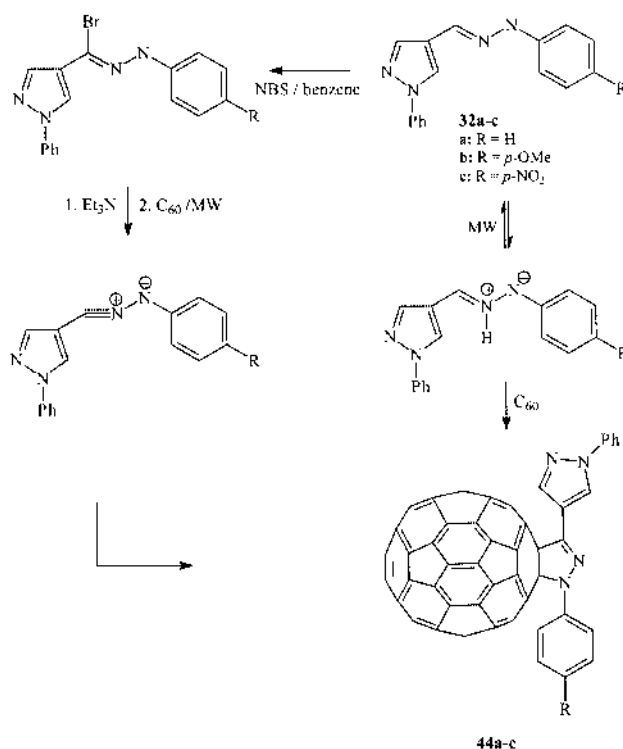
**Scheme 8**

In this context, it was of interest to study the influence of the introduction of a  $\pi$ -donor heterocycle as well as different substituted *N*-aryl groups in the proximity of the C<sub>60</sub> cage in order to get a better insight into this possible CT phenomenon.

According to this approach, hydrazones **32a–c** react with C<sub>60</sub> in *o*-dichlorobenzene or trichlorobenzene as solvent under microwave irradiation to give adduct **44a** in 6% yield and traces of **44b**, while **44c** is not formed (Scheme 9).<sup>37</sup>

As an alternative route, nitrile imines, generated *in situ* from the corresponding hydrazone **32a–c** and NBS in the presence of Et<sub>3</sub>N, react with C<sub>60</sub> under microwave irradiation to give the corresponding adducts **44a–c** (see Table 4).<sup>37</sup>

Unfortunately, the use of the solvent in these reactions cannot be avoided. However, the high interest of the target molecules, that are easily synthesized under microwave irradiation justifies the environmental advantages of this procedure.



**Scheme 9**

The design of novel organic molecules containing electron donor (D) and electron acceptor (A) moieties constitutes a promising field owing to the interesting optical and electronic properties that they can display.<sup>34</sup> It is well known that [60]fullerene is a good electron acceptor and some [60]fullerene derivatives show charge-transfer (CT) interactions.

Although some intermolecular CT complexes of [60]fullerene have been reported,<sup>35</sup> the first direct observation of an intramolecular CT interaction was recently made by attaching a pyrazoline ring to C<sub>60</sub>.<sup>36</sup>

**Table 4** Preparation of **44a–c** under microwave irradiation

	Reaction conditions	% Yield <sup>a</sup>
<b>44a</b>	Benzene, 30 min, 105 W	38 (55) <sup>b</sup>
<b>44b</b>	Benzene, 30 min, 105 W	24 (33) <sup>b</sup>
<b>44c</b>	Benzene, 5 min, 210 W	20 (43) <sup>b</sup>

<sup>a</sup> Of isolated product. <sup>b</sup> Yield considering recovered C<sub>60</sub> is given in parentheses.

## 2.4 Miscellaneous

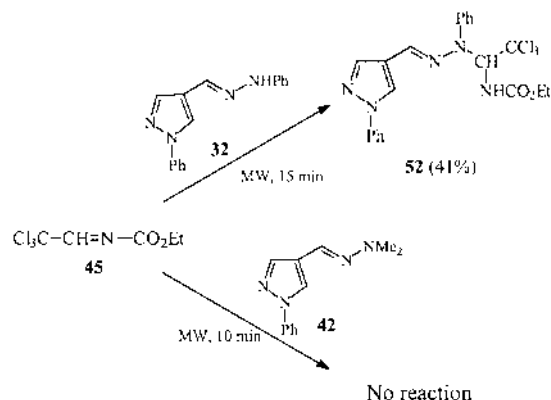
**2.4.1 Reaction of ethyl *N*-trichloroethylidene carbamate with unsaturated pyrazole derivatives.** As a continuation of our investigations into the reactivity of pyrazole derivatives as dienes or 1,3-dipoles in cycloaddition reactions under microwave irradiation, we have studied the reaction of vinylpyrazoles, pyrazolyl hydrazones and imines derived from aminopyrazoles toward ethyl *N*-trichloroethylidene carbamate **45** in order to obtain valuable new pyrazole derivatives condensed with heterocyclic systems (*e.g.*, pyrazolopyrimidines). However, we did not observe any cycloaddition reactions in these cases. In fact, the result of each reaction depends on the nature of the diene system and the substitution of the pyrazole ring.

Reaction of vinylpyrazoles **1**, **2** or **46** with **45** under microwave irradiation occurs through the exocyclic bond to give Michael addition to the conjugated system<sup>38</sup> (Scheme 10).

This reaction must be considered as an electrophilic substitution of the exocyclic bond, which is activated by conjugation with the pyrazole ring. It is remarkable that even in the 5- and 3-substituted pyrazoles, **2** and **46**, reaction occurs at the double bond and not at the activated 4-position of the pyrazole ring. Moreover, when there is no vinyl substituent in the ring, as in 1-phenylpyrazole **51**, no reaction occurs after 30 min of irradiation at 165 °C and only the starting materials are recovered. Under conventional heating in an oil bath in the absence of solvent no reaction takes place under similar conditions of temperature and time, but in this case the starting vinylpyrazoles dimerize and are not recovered.

Reaction of the pyrazolyl hydrazone **32** with **45** leads to Michael addition to the conjugated imine through the NH group. When a second *N*-substituent is introduced and there is no NH group present, as in hydrazone **42**, no reaction takes place<sup>38</sup> (Scheme 11).

Pyrazolyl imine **15** reacts with **45** by an electrophilic substitution at the activated 4-position of the pyrazole ring. Again, under conventional heating in the absence of solvent no reaction occurs in comparable conditions and decomposition of the starting materials takes place. However, imine **54**, in which position 4 is blocked, does not react after 15 min of microwave



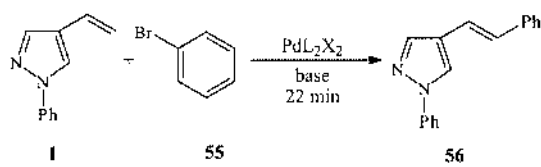
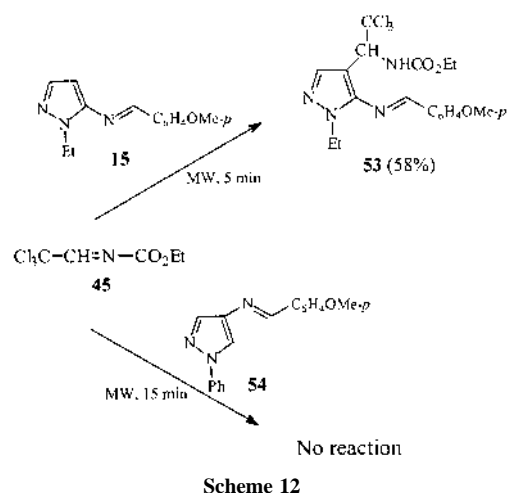
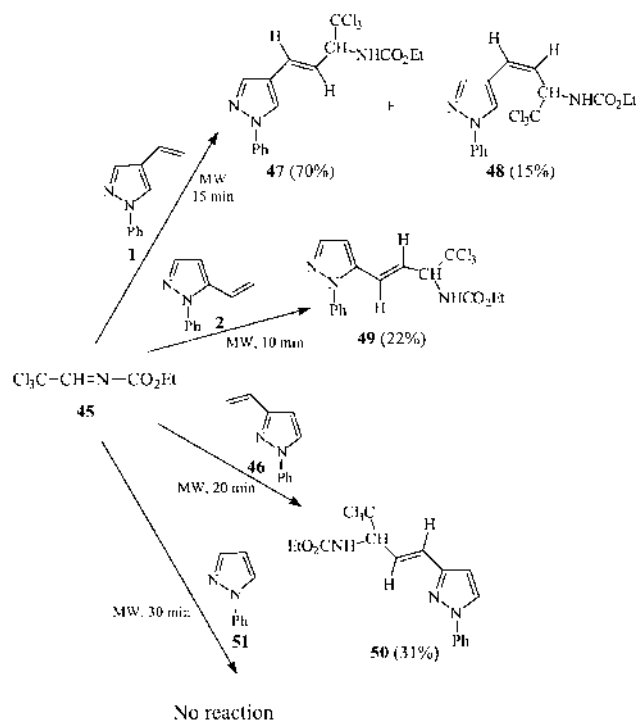
irradiation and the only process observed is the decomposition of the starting materials<sup>38</sup> (Scheme 12).

As mentioned above, these kinds of reactions have not been described previously and cannot be performed by classical heating. Likewise, these reactions could be extended to include other azoles and especially to other activated imines in order to obtain valuable derivatives such as heterocyclic amino acids.

**2.4.2 Heck reaction of 4-vinylpyrazole.** We have studied the Heck reaction of vinylpyrazole **1** under microwave irradiation in solvent-free conditions as an efficient method to introduce substituents at the exocyclic double bond.

Vinylpyrazole **1** reacted with bromobenzene (**55**) under typical Heck conditions<sup>39</sup> (palladium acetate as a catalyst, tri-*o*-tolylphosphine as a ligand and triethylamine as a base) in 22 min to afford the corresponding olefin **56**.<sup>40</sup> If the reaction is performed in a Teflon vessel in a domestic oven the product is obtained in 78% yield;<sup>41</sup> under classical heating the yield is only 39% (Scheme 13).

In this reaction the yields obtained under microwave irradiation, with short reaction times, are far superior to those obtained using classical heating. Once again, the microwave methodology provides an improved procedure to perform vinylation reactions.<sup>42</sup>



### 3 Conclusions

We have shown that valuable compounds such as indazoles, pyrazolopyridines and bipyrazoles can be prepared by a cycloaddition approach using an environmentally benign methodology.

Microwave irradiation in solvent-free conditions produces moderate to good yields of the cycloaddition products, while conventional heating gives only traces of the expected products. The advantages of microwave technology are particularly clear when compounds with low reactivity or high sensitivity are involved. Use of this eco-friendly methodology enables the design of milder reaction conditions that reduce the extent of decomposition of both the starting materials and the reaction products.

### 4 Experimental section

In this Section we have included general procedures to perform the aforementioned reactions, so any researcher can understand how the work was carried out and reproduce it. Flash chromatography has been used to purify the products, hence, the 'eco-friendly' term would be applied only to the synthesis process. However, the liquid products could be purified by distillation and the solid ones by extraction or crystallization.

#### 4.1 Diels-Alder cycloaddition of vinylpyrazoles. General procedures

**Method A.** A Teflon vessel was charged with the vinylpyrazole (1 equiv.) and the acetylenic ester (3 equiv.) and then closed and the reaction mixture irradiated in a Miele Electronic M720 domestic oven at 780 W for the indicated time (see Tables 1 and 2 and Scheme 3). The crude reaction product was purified by flash chromatography on silica gel using hexane–ethyl acetate as the eluent.

**Method B.** A mixture of vinylpyrazole and acetylenic ester (1:3 mole ratio) was irradiated in a focused microwave reactor Prolabo MX350 with measurement and control of power and temperature by IR detection for the time and at the power indicated (see Table 1 and Scheme 3). The crude reaction product was purified by flash chromatography on silica gel using hexane–ethyl acetate as the eluent.

#### 4.2 Diels–Alder cycloaddition of pyrazolyl imines. General procedure

A mixture of the 2-azadiene and the corresponding dienophile (1:2 mole ratio) was irradiated at atmospheric pressure in a focused microwave reactor Prolabo MX350 for the time and at the temperature indicated in Schemes 4 and 5. The crude product was purified by flash chromatography on silica gel using hexane–ethyl acetate as the eluent.

#### 4.3 1,3-Dipolar cycloaddition of pyrazolyl hydrazones. General procedures

**Method A.** A mixture of hydrazone (1 equiv.) and dipolarophile (2 equiv.) was charged to a commercial 25 ml Teflon PTFE vessel, closed and irradiated in a Miele Electronic M720 domestic oven at 780 W for the indicated time (see Schemes 6 and 7). The crude reaction product was purified by flash chromatography on silica gel using hexane–ethyl acetate as the eluent.

**Method B.** A mixture of hydrazone and dipolarophile (1:2 mole ratio) was irradiated in a focused microwave reactor Prolabo MX350 for the time and at the temperature indicated in Schemes 6 and 7. The crude reaction product was purified by flash chromatography on silica gel using hexane–ethyl acetate as the eluent.

#### 4.4 Reaction of ethyl *N*-trichloroethylidene carbamate with unsaturated pyrazole derivatives. General procedure

A mixture of pyrazolyl derivative (1 equiv.) and *N*-trichloroethylidene carbamate (1.5 equiv.) was irradiated at atmospheric pressure in a focused microwave reactor Prolabo MX350 for the time and at the temperature indicated in Schemes 10, 11 and 12. The crude mixture, composed of the product and compounds derived from decomposition or polymerization of the pyrazolyl derivative, was purified by flash chromatography on using hexane–ethyl acetate as the eluent.

#### 4.5 Heck reaction of 4-vinylpyrazole

A mixture of olefin (1.75 mmol), halide (1.40 mmol), palladium acetate (0.014 mmol), tri-*o*-tolylphosphine (0.027 mmol) and dry triethylamine (5 mmol) was charged under argon to a commercial 25 ml Teflon PTFE vessel, closed, placed into an alumina bath and irradiated in a Miele Electronic M720 microwave oven at 450 W for 22 min. Final temperature: 160 °C. The crude reaction was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and washed with an aqueous solution of HCl 5% (2 × 20 ml). The organic layer was dried and the solvent was removed at reduced pressure. The residue was purified by flash column chromatography.

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