EDITORIAL

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Green Chemistry: a new phase

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Green Chemistry has been a major success story ever since the first volume was published in February 1999. Therefore, it was a great honour for me when I was approached and asked whether I would be willing to follow James Clark as the Scientific Editor for this journal. At the same time, I realised that it would be a very challenging task to foster the successful growth of such a well-renowned journal. However, I was more than happy to devote myself to this endeavour as I am absolutely convinced that both the journal and the field of *Green Chemistry* have many reasons to be optimistic for their future development.

It would have been impossible for *Green Chemistry* to actually materialize as a journal on our PCs or desks and in many libraries without the dedication and the excellent work of the first Scientific Editor James Clark and his team at York. The most recent evidence for the prospering development seeded through this effort is the decision of the Royal Society of Chemistry to increase the publication rate of *Green Chemistry* to 12 issues per year from 2004. In a situation where many long-existing journals are facing increasing difficulties through budget cuts in libraries, this step constitutes at the same time a reward for a truly successful history and a challenge for the future. *Green Chemistry* is all set to accept that challenge! The Editorial Board headed by Colin Raston and the International Advisory Board continue to shape the journal to become one of the leading sources of reference in chemistry and its neighbouring disciplines. The RSC team led by Harp Minhas as the Managing Editor handles all publishing affairs efficiently and – with the aid of the referees – ensures rapid turnaround of manuscripts. Authors from all over the world submit fascinating research articles in a variety of disciplines and the latest impact factor of 2.54 in 2002 indicates that this work is followed by a very broad and active audience.

Scientific publications addressing the field of “green chemistry” are emerging rapidly in many places. In the period 1999–2002, the number of publications with this key word has more than doubled every year and as of December 2003 over 1700 entries can be identified in SciFinder. Interestingly, this includes a significant number of patents and patent applications. Naturally, a large portion of these contributions deal with synthetic chemistry, but important areas such as life cycle assessment, toxicology, and green engineering are also at the heart of the development. Thus, the pool of potential contributions for the journal *Green Chemistry* can be expected to expand substantially in the next few years. At the same time, *Green Chemistry* will continue to establish rigorous scientific standards to attract top quality contributions. In 2003 the acceptance rate was just over 30% and maintaining and fostering these rigorous criteria will help to strengthen the journal’s “scientific spine.”

Green Chemistry can also capitalize on its role as a reliable catalyst for encouraging communication between researchers, institutions, governmental bodies, funding agencies, and the public. The News and Views section forms an ideal platform for exchange of the latest news on events and trends. Conference announcements and reports are, for example, an integral part of this information. The section also features Highlights from other journals and – a relatively new format – Research Profiles of eminent scientists in the field. It would be nice to see this section used increasingly also as a forum to express opinions and for scientific debate. Markus Hölscher has accepted responsibility as the new “News Editor” and any information that seems suitable for this part of the journal can be submitted either to him or to the Cambridge Office directly.

Thus, there is no doubt that *Green Chemistry* has grown up, both as a journal and as a field of scientific endeavour. As a visualisation of this maturation, research articles are no longer accompanied by the “Green Boxes” that helped to define the context of the contributions in the early phase. All the enthusiasm and the hard work of those involved in the making of *Green Chemistry* would have been in vain, however, without the excellent scientific work of all the authors and without the critical interest of their audience. Therefore, I would like to encourage you to continue to send your best work to *Green Chemistry* and to make your colleagues aware of the benefits of publishing in the leading journal in the field.

I wish all colleagues, authors, and readers a peaceful year in 2004, happiness in their private life, fruitful research in an exciting science, and success with *Green Chemistry*!

Professor Walter Leitner
Scientific Editor, *Green Chemistry*
leitner@itmc.rwth-aachen.de

FOCUS

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A brief structured view of green chemistry issues

Ramon Mestres

Departament de Química Orgànica, Universitat de Valencia, Dr. Moliner 50, 46100, Burjassot, València, Spain.
ramon.mestres@uv.es; + 34 93 588 84 03; + 34 93 588 84 03

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Green chemistry is commonly presented as a set of twelve principles, fruit of great intuition and chemical common sense, together with the related concepts, research fields and significant results which have emerged from the principles.[1–9] It might be worthwhile now to provide some kind of order or structure to the aims, concepts, research areas, implications and connections of green chemistry, which may facilitate its presentation for the education of future and young chemists. Although the present article is just an incipient attempt, it has the virtue of being open to many additions.

Green chemistry is part of a wide multidisciplinary area, comprehensively termed Chemistry *and* the Environment, where chemistry focuses its attention on the links existing between anthropogenic activity and environmental contamination by chemicals. Within this, the observation and understanding of the harmful effects, origin, mobility and persistence of chemical pollutants is the subject of Chemistry *of* the Environment, whereas the term Chemistry *for* the Environment denotes striving for provision of chemical solutions to chemical contamination. The desired decrease in the concentration of pollutants could in principle be attained by removing them from the environment, when already present, by preventing their dissemination, when still confined, and especially, by avoiding their generation. The last of these is none other than the aim of green chemistry.

It may be a matter for discussion whether green chemistry can be expected to afford adequate answers to chemical contamination derived from sources other than anthropogenic chemical activity, but there cannot be any doubt that the main objective of green chemistry is the chemical process itself and the final products of the chemical industry, employed by other industries or activities.

The introduction of mineral or organic fossil material from under the earth's surface into the production stream may be regarded equivalent to the preparative generation of chemicals and justifies that contribution to reduction of use of these materials may be assumed to be within green chemistry's aims.

Up to this point green chemistry has been presented in the context of chemistry and the environment, where it in fact was born. Indeed, there would be no green chemistry without the prior concern for contamination by chemicals. However, it must be also be acknowledged that green chemistry is not only meant to improve the environment but also to provide the chemical industry with a new view for overcoming the serious issues met as a consequence of its being the source of a great deal of the chemical pollution and, consequently, the culprit of environmental damage. Realisation of a number of present and future problems existing for chemistry and the conviction that convenient chemical solutions can be attained by application of green chemistry philosophy become the starting point for the structure of green chemistry.

These problems may be enumerated as follows:

Pollution through chemicals
Risks caused by dangerous chemicals
Exhaustion of sources of primary materials

When pollution by chemical contamination is taken into account, it is possible to realise that many of the polluting chemicals are synthetic and that they are released to the environment, in a more or less continuous flow, by chemical industries. Fluids leak; waste materials are either disposed of or released as aqueous effluents. A significant proportion of the final products of chemical industry are disseminated into the environment; not by the chemical industry that produced them, but by other industries or activities which employ these products in agriculture, textile, building, automotive, cleaning, pharmacy, *etc*.

It may be convenient to recognise here the existence of a significant quantitative distinction between *dangerous* and *polluting* chemicals. Highly toxic, flammable, explosive or aggressive chemicals, which have been or can be the cause of highly dramatic personal or public events are here categorised simply as *dangerous* chemicals. They are nothing new to chemists and have been a permanent cause of concern since their early industrial application in the XIXth century.

Polluting chemicals are certainly harmful and dangerous, but rather through long term effects: ecotoxicity, greenhouse effect, depletion of stratospheric ozone, *etc*. The noxious effects of many pollutants have frequently been unforeseen by chemists. It may then be convenient to maintain a distinction between prevention of release of pollutants and precaution against immediate serious personal harm.

Industries have usually dealt with these chemical pollution and safety issues by introduction of a kind of palliative engineering technology, which requires great unprofitable expenditure, frequently without attempting modification of the chemical process itself. Industries have also met awkward situations when final products already launched into market have subsequently been found to be harmful to humans or to the environment. The green chemistry approach to all these pollution, immediate risk and noxious final product situations is that it is better and cheaper to find new, cleaner and safer chemical technologies for the synthesis of a particular chemical and to know to what extent a final product may be harmful before it is first synthesised in the laboratory.

The third problem for chemistry identified here derives from the depletion of fossil feedstocks for chemical industry. Although how far into the future complete exhaustion may occur is open to discussion, the shortage of easily recovered oil will certainly cause a rise in feedstock prices in the near future. This leads to the need for the use of renewable feedstocks and for the modification or development of novel chemical technologies for this purpose. It cannot be overlooked that other materials and water are or may become scarce either locally or at global level. This accessibility to resources must also be considered if development of young nations and the future sustainability of chemistry is to be guaranteed.

From what has been said so far four general objectives can be derived from green chemical philosophy.

1 Reduction of use and generation of polluting chemicals in the chemical process

2 Reduction of use of dangerous chemicals in the chemical process
3 Reduction of the harmful effects of final products
4 Reduction of the use of exhaustible feedstock materials and of scarce resources

When the reduction of use and generation of polluting chemicals is considered, attention must be paid first of all to the chemical process and to all that it implies, namely starting materials, reagents, solvents, isolation and purification of the product and treatment and disposal of by-products. The ultimate aim is an ideal process that starts from non-polluting starting materials, leads to no secondary or concomitant products and requires no solvents in order to carry out the chemical conversion or to isolate and purify the product. Such an intrinsically clean process seems unattainable, but it is to be expected from the ingenuity and resourcefulness of chemists that, as the result of a single modification or more probably from successive approaches, a much more satisfactory process than that currently in operation will be achieved.

General objectives for the chemical process, along with related concepts, namely selectivity, and atom economy, some intermediate objectives and procedures to attain them are shown in Table 1, together with some significant areas of research where progress can be expected to help to achieve substantially cleaner processes.

A similar approach can be assumed for the reduction of danger, as shown in Table 2. Dramatic events are usually linked to solvents, reagents, or reaction conditions. Little need to be added here about solvents, except to say that solvents are not usually both persistently polluting and dangerous.

Broadly speaking, it may be assumed that the dangerous character of reagents is associated with their high reactivity, frequently due to their highly positive enthalpy of formation, or to a high enthalpy for their reaction with oxygen or water. Use of less reactive reagents will require higher reaction temperatures, a feature which will increase reaction risk and decrease selectivity. Milder reagents can become convenient and effective when an adequate catalyst causes a reduction of the activation enthalpy. Catalytic methods are thus expected to provide suitable conditions for use of safer milder reagents. Mild conditions using poorly reactive reagents can also be attained by adequate selective energy sources, which activate one of the reacting molecules above or near the energy of the transition state. This is the case for photochemical or electrochemical processes or for sonochemical or microwave activation.

Table 1 Reduction of use and generation of polluting chemicals in the chemical process

General objectives and *related concepts*	Intermediate objectives	Areas of research
Use of non-polluting starting materials	Renewable resources	
	Chemicals near to the sources	
Reduction of secondary products in chemical processes	Selective novel reactions	Catalytic and biocatalytic procedures
	Selectivity of current reactions	Reaction mechanisms Real time control of ongoing processes Continuous processes Process intensification
Selectivity		
	Reduction of number of synthetic steps	
Reduction of environmentally significant concomitants	New procedures with no environmentally significant concomitants	Catalytic and biocatalytic procedures Reactions with O_2, N_2, H_2O as concomitants
Atomic economy	Reduction of number of synthetic steps	Catalytic and biocatalytic procedures
Reduction of use of polluting solvents as reaction media	Reactions without solvent Reactions in special solvents	Solventless reactions Reactions in water Solvents under supercritical conditions Ionic liquids
	Reactions in low toxicity organic solvents	
Reduction of use of polluting solvents for separation or purification	No secondary products	
	Separation and purification procedures Reaction conditions with separation of products	Solvents under supercritical conditions Biphasic conditions Polymeric reagents Heterogeneous catalysis
Reduction of energy consumption	Chemicals close to the sources Reactions at room temperature	

A great variety of industries and productive sectors employ chemicals with harmful and noxious after-effects, which frequently end up disseminated in the environment unchanged or chemically modified. Reduction of these harmful effects requires a knowledge frequently lacking in chemical education, namely toxicity and ecotoxicity. Thus, the launching of new products into the market will require learning first how to establish the toxicity and ecotoxicity of a chemical structure before it has been prepared. As shown in Table 3, use of natural products, whenever possible, may be a good guarantee of dealing with ecotoxicologically harmless substances, even when they are toxic. Especially interesting for pest control is the use of natural chemicals, whether naturally or synthetically produced, which can alter the specific physiology or behaviour of insects or other pests.

Chemical materials which are used in large amounts should ideally be easily recovered by any convenient form of recycling, or degraded under easily controlled conditions. The same comment about the foreknowledge of toxicity would apply here in order to succeed in the design of useful materials which could be cheaply and easily recycled or degraded.

Last, but not least, as far as possible fossil derived feedstocks must be substituted and renewable feedstocks, mostly plant derived, must be developed (Table 4). The largest amount of such plant derived materials is biomass. There is a renewed interest in the use of biomass for production of fuels and of basic chemicals and solvents. When combined with biotechnological methods biomass may become the carbon source for the production of advanced intermediates or final products. Materials obtained from renewable specific production, namely vegetable oils or starch and traditional natural products, as carotenoids or quinine are now receiving special attention. It may be added here that recycling of large bulk materials may also become a form of recovering part of the fossil derived feedstocks.

Reduction of the depletion rate of fossil materials may come also from increasing the efficiency in use of fuels. This is expected, for instance from the development of fuel cells.

In conclusion, this article presents here a first attempt at providing a structure or scheme for some of the concepts and issues related to green chemistry, which may become valuable for the education of young and future chemists. The present structure is amenable to change and addition. Where some particular issues have been placed in this scheme may be a cause of argument. Photochemistry, for instance, is not constrained to the provision of safer reactions to the synthetic chemical armoury, but it is true that typical photochemical reactions do not require use of strong reagents. Similar comments could be made about the place for other issues. Thus, many published results show that other activation techniques go hand in hand with solvent free reactions. Catalytic methods, including biocatalysis, are exceptional in being found in the scheme in connection with selectivity, atomic economy and safety. This should not be surprising when it is considered that the great source of inspiration for green chemistry is no other than nature, especially in its living chemical reactors, where selectivity, atomic economy, and mildness of reactions are at their utmost.

Table 2 Reduction of use of dangerous chemicals in the chemical process

General objectives and *related concepts*	Intermediate objectives	Areas of research
Processes without dangerous reaction solvents		
Processes without dangerous solvents for separation and purification		
Processes without dangerous reagents	Safer reagents	Catalytic and biocatalytic procedures
Safer reaction conditions	Selective activation techniques	Photochemistry Electrochemistry Microwaves Sonochemistry
Mild reaction conditions	Room temperature and ordinary pressure	
	Reduced scale	Continuous processes Process intensification``

Table 3 Reduction of the harmful effects of final products

General objectives and *related concepts*	Intermediate objectives	Areas of research
Harmless final products	Natural products	Bioactive products based on specific physiology and behaviour
	New harmless products	Design of intrinsically non toxic chemicals
Degradable products after their function		Design of degradable materials
Recyclable products after their function		Design of recyclable materials

Table 4 Reduction of the use of exhaustible feedstock materials and of scarce resources

General objectives and *related concepts*	Intermediate objectives	Areas of research
Development of renewable sources of feedstocks	Biomass	Production of fuels Production of basic chemicals Production of synthetic intermediates and final products
	Renewable materials for specific production	Production of basic chemicals
	Natural products	Production of synthetic intermediates and final products
	Recycled materials	Feedstock recycling of plastics
Improvement of efficiency in use of non-renewable sources	Reduction of energy consumption Improvement in generation of energy	
Improvement of efficiency in use of scarce sources	Economy of water	

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Giacomo Ciamician (1857–1922)

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The birth of green chemistry is often thought to have been a response to the recent realisation of the damage caused to the environment by man-made materials and the processes used to produce them.

A hundred years ago, a great scientist Giacomo Ciamician, confronted the problem of finding "green" synthetic methods that could be carried out under conditions as mild as those found in nature. He had no doubt about the answer to this problem; it was solar light.

Angelo Albini and Maurizio Fagnoni describe the approach and discoveries of Ciamician and place them within the context of present day green chemistry in a Tutorial Review (http://dx.doi.org/10.1039/b309592d) in this issue.

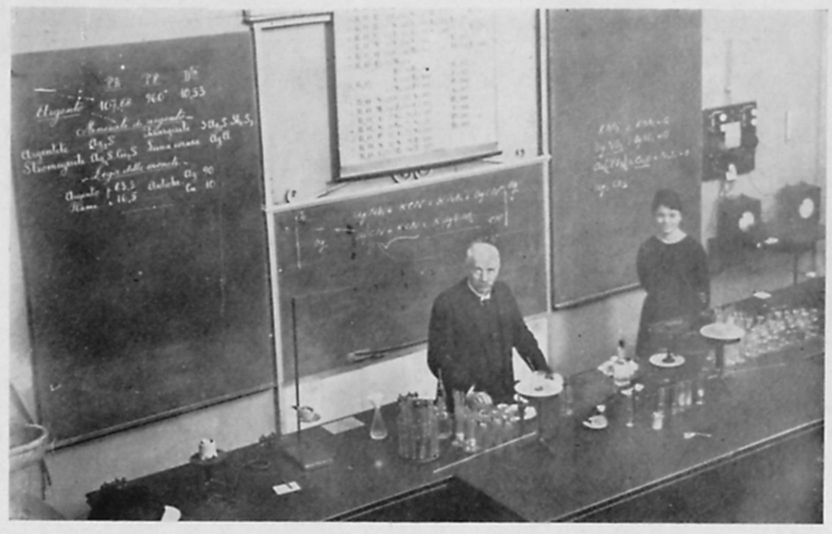

Fig. 1 Giacomo Ciamician teaching in Bologna.

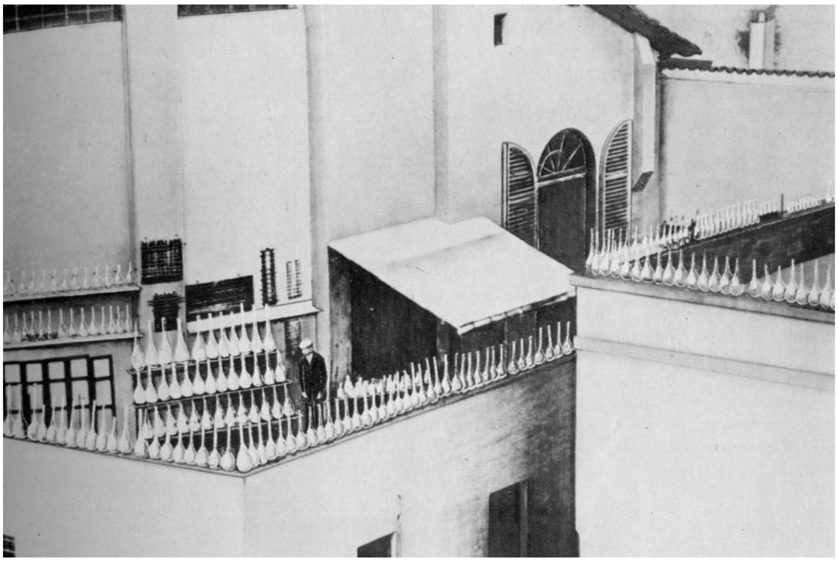

Fig. 2 Giacomo Ciamician on the roof of the Chemical Institute in Bologna among the flasks he is exposing to solar light

New Board Member

Steve Howdle was born in Rotherham, South Yorkshire in 1964 and his main interests are family and football. He obtained a first degree in Chemistry from Manchester in 1986 and his PhD on "Spectroscopy in Liquefied Noble Gases" from Nottingham in 1989.

Steve's academic interests focus on the utilisation of supercritical carbon dioxide for polymer synthesis, polymer processing and preparation of novel polymeric materials for tissue engineering and drug delivery. Steve currently holds a chair of Chemistry at the School of Chemistry, University of Nottingham and prior to this held a Royal Society University Research Fellowship (1991–1999). In 2001 he was recipient of the Jerwood–Salters Environment Award and the Corday–Morgan Medal and Award of the Royal Society of Chemistry. In 2003 he received a Royal Society–Wolfson Research Merit Award. A more detailed description of his research and some movies of supercritical fluids can be viewed at http://www.nottingham.ac.uk/~pczctg/Index.htm

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Highlights

Markus Hölscher reviews some of the recent literature in green chemistry

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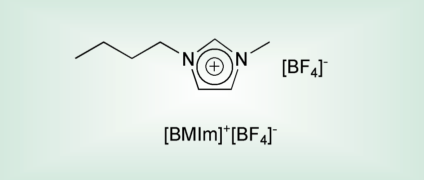
Structure of ionic liquids

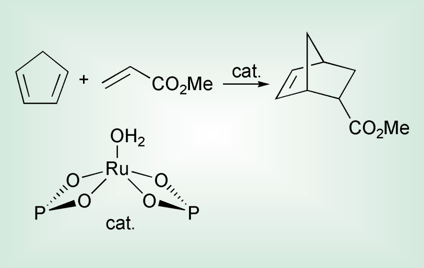
Room temperature ionic liquids (RTILs) have been established during recent years as "green" solvents in catalytic applications due to their recyclability and their advantageous physical and chemical properties. Owing to their hygroscopic nature RTILs can absorb substantial amounts of water, which not only changes their properties but makes them depend crucially on the water content. In a detailed NMR investigation Mele *et al.* have collected information on the microscopic structures of the well known RTIL 1-*n*-butyl-3-methylimidazolium tetrafluoroborate $[BMIm]^+[BF_4]^-$ by evaluating the role of cation–cation, cation–water, and cation–anion interactions (*Angew. Chem., Int. Ed.*, 2003, **42**, 4364–4366).



The authors found the imidazolium ring protons to interact with the anion, when no water is present in the RTIL. With increasing amounts of water the $C(sp^2)–H\cdots F$ interactions are progressively replaced by water contacts, with the water acting as an acceptor toward the cation and a donor towards the anion. Also the imidazolium–imidazolium interaction present in the water free RTIL becomes looser with increasing water content, shifting the rings away from each other. In the pure liquid the cations and anions are associated as tight ion pairs, and this structure is preserved at low water contents and even in DMSO solution. The short range structure of this RTIL is governed by $C(sp^2)–H\cdots F$ interactions between cation and anion.

Heterogeneous catalysts for Diels–Alder and aldol reactions

Heterogeneous Lewis acid catalysts often suffer from inferior activities and leaching of active components. Homogeneous catalysts are highly selective but difficult to recover. A novel catalyst design may help to solve these problems, by combining the advantages of homogeneous and heterogeneous catalysis while avoiding their drawbacks. Kaneda *et al.* from the Graduate School of Engineering Science, Osaka University have exploited the unique features of hydroxyapatite (HAP) as a macroligand for Ru^{3+} ions (*J. Am. Chem. Soc.*, 2003, **125**, 11460–11461).

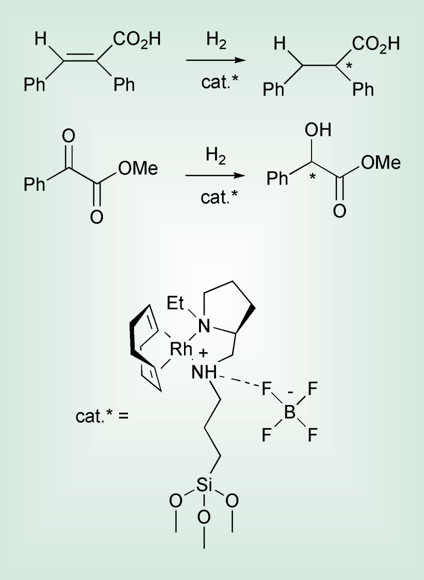


Simple cation exchange of Ca^{2+} by Ru^{3+} yields cationic RuHAP catalysts which surprise with high selectivities in Diels–Alder reactions and no observable trend for product inhibition as known from other Al-, Ti- or B-based Lewis acid catalysts. Also the less reactive methyl acrylate dienophile undergoes the reaction smoothly with cyclopentadiene as the diene (yield 82%, *endo* : *exo* = 91 : 9).

The RuHAP catalysts also tolerate the presence of water in aldol reactions of nitriles and carbonyl compounds, yielding α,β-unsaturated nitriles in high yields. No leaching was detected over a reaction period of 24 h by ICP analysis and the recovered catalyst could be reused without loss of activity.

Asymmetric heterogeneous catalysis

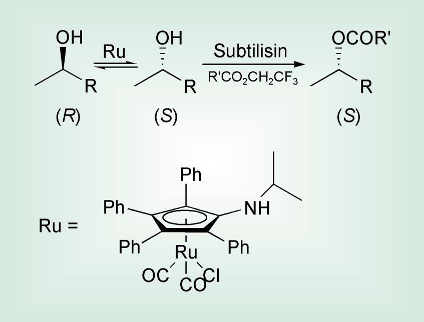
Another example of successful heterogenization of homogeneous catalysts for asymmetric hydrogenation has recently been accomplished using new Rh- and Pd catalysts by the groups of Raja, Thomas, Lewis and Harris (*Angew. Chem., Int. Ed.*, 2003, **42**, 4326–4331). Chiral pyrrolidine and amine ligands, which are anchored to porous silica supports with concave and convex surfaces comprise cationic Rh- and Pd catalysts, which efficiently and selectively catalyse the hydrogenation of *E*-α-phenylcinnamic acid and methyl benzoylformate.



Most striking is the fact that these heterogenized catalysts outperform their homogeneous counterparts, and the authors also stress the fact that it is the concavity of the pores which is superior to supports with convex surfaces. Product selectivities (up to 98%) and enantioselectivities (up to 99% ee) reach high values with conversions between 74 and 100%. Leaching tests showed the catalytic process to be truly heterogeneous and up to the second recycle the Rh catalysts showed no marked loss of conversion, selectivity and ee value.

Kinetic resolution of secondary alcohols

Dynamic kinetic resolution (DKR) is a useful tool for the conversion of racemic substrates to single enantiomeric products. DKR relies on a metal complex, which acts as a racemizing catalyst and an enzyme as a resolving catalyst. So far enzyme/metal-catalyzed DKR systems employed lipases as resolving catalysts, which in the case of simple secondary alcohols have thus yielded only products with (*R*)-configuration. This has now been changed by Park, Kim and coworkers of the Laboratory of Chirotechnology at the

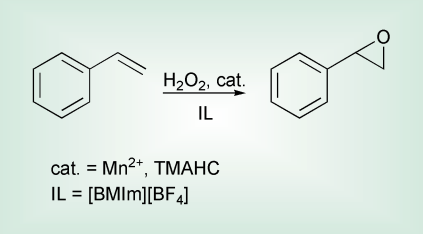


University of Science and Technology, Korea (*J. Am. Chem. Soc.*, 2003, **125**, 11494–11495). They chose subtilisin as the resolving catalyst and aminocyclopentadienylruthenium complexes as racemizing catalyst.

The problem of low subtilisin activity in organic solvents was overcome by using a nonionic polyoxyethylene(10) cetyl ether surfactant increasing the activity by a factor of 3 orders of magnitude. On the basis of test experiments with 1-phenylethanol THF was chosen as a suitable solvent and TFEB as acyl donor for the resolution of various secondary alcohols. As an example *p*-chlorophenyl methyl carbinol transformed with 92% yield and 99% ee.

Epoxidation of alkenes in ionic liquids

The search for environmentally friendly methods for the synthesis of epoxides *via* alkene epoxidation has recently been stimulated by the findings of Burgess *et al*. who reported on the catalytic activity of manganese sulfate and sodium bicarbonate for this reaction in aqueous media with hydrogen peroxide as the oxidant (*Chem. Rev*., 2003, **103**, 2457). This approach has been modified by Chan *et al*. (*Org. Lett*., 2003, **5**, 3423–3425), who succeeded in employing an ionic liquid instead of an organic cosolvent for the water-insoluble lipophilic substrates.



The combination of 1-butyl-3-methylimidazolium tetrafluoroborate $[BMIm]^+[BF_4^-]$ as the solvent for the alkene and an aqueous phase with catalytic amounts of manganese sulfate and tetramethylammonium hydrogen carbonate (TMAHC) yields an active catalytic system, which converts various internal alkenes readily into the corresponding epoxides upon addition of hydrogen peroxide. Conversions and yields were 99% or more in many cases and the ionic liquid can directly be reused at least 10 times after extraction of the product. Even though manganese sulfate must be added after a few cycles to retain activity it is a cheap, recyclable, catalytic and environmentally benign reaction.

Photochemical water splitting—summary of a recent debate

As early as 1972 Fujishima and Honda had reported about n-TiO_2 electrodes splitting water photoelectrochemically into hydrogen and oxygen (*Nature*, 1972, **238**, 37). This important finding has stimulated research over the past thirty years. Most recently Khan *et al*. reported about a new n-type TiO_2 splitting water with a maximum photoconversion efficiency of 8.35%—a result that would have to be considered a major progress in the development of these materials (*Science*, 2002, **297**, 2243). However, several researchers have strongly challenged this report and a considerable debate has emerged only a few days after the publication of these results. In a first answer by Lackner it was argued that Khan *et al*. had not supplied sufficient data to reliably judge the given efficiency (*Science*, 2003, **301**, 1673c). Even more pertinently Lackner hinted at the possibility of the external power supply used by Khan *et al*. being the only source of electrolysis. The debate went on when Fujishima, who claimed to have invented the same type of material already in 1975 (only three years after his original publication) argued also that there were not data presented which evidenced hydrogen generation induced by visible light (*Science*, 2003, **301**, 1673a). In a further comment by Hägglund, Grätzel and Kasemo, who approached Khan’s work from different angles, it was shown on theoretical grounds that the calculation method used by Khan *et al*. was misleading (*Science*, 2003, **301**, 1673b). The authors came to the conclusion that the reported efficiency is by far too large.

Khan *et al*. responded quickly. They defended their work on technical and ethical grounds and dealt with every single comment in detail (their answer to the comments is longer than the original article), and found their work to be justified. They admitted, however, that they should have cited the 1975 publication by Fujishima (*Science*, 2003, **301**, 1673d). It looks as if not all arguments were settled by this “battle” and more work on these interesting materials might help to clarify the situation in the future.

CONFERENCE REPORT

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Green approaches: a new horizon for future scientists

Student voices from the Pan-American Advanced Studies Institute on Green Chemistry

Darren Anderson,[a] Jennifer L. Anthony,[b] Arani Chanda,[c] Ginger Denison,*[d] Melissa Drolet,[e] Diego Fort,[f] María Joselevich[g] and Justin R. Whitfield[h]

[a]*Department of Chemistry, University of Toronto, Toronto, Canada. danderson@chem.utoronto.ca; +1 416 978 4526; +1 416 978 4526*

[b]*Department of Chemical and Biomolecular Engineering, University of Notre Dame, Notre Dame, IN 46556, USA. janthony@nd.edu; +1 574 631 8366; +1 574 631 7708*

[c]*Department of Chemistry, Carnegie Mellon University, Pittsburgh, PA, USA. achanda@andrew.cmu.edu; +1 412 268 1061; +1 412 268 6177*

[d]*Department of Chemistry, University of North Carolina, Chapel Hill, NC 27599-3290, USA. denison@email.unc.edu; +1 919 962 5467; +1 919 962 3396*

[e]*Department of Physical Sciences, University of New Brunswick, New Brunswick, Canada. g848h@unb.ca; +1 506 648 5948; +1 506 648 5563*

[f]*Departamento de Química Orgánica, Universidad de la República, Montevideo, Uruguay. dfort@fq.edu.uy; +592 2 9241906; +592 2 9244856*

[g]*Departamento de Química Orgánica – Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, Argentina. maria@qo.fcen.uba.ar; +54 11 4576-3346; +54 11 4576-3346*

[h]*Green Chemistry Ph.D. Program, University of Massachusetts Boston, Boston, MA, USA. Justin.Whitfield@verizon.net; +1 617 287 6127; +1 617 287 6128*

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Introduction

It's time to accept our share of responsibility for the modern state of the world. With real concerns mounting on the state of global sustainability and newer considerations such as endocrine disruption, we must aggressively pursue the ideals of green chemistry.

We are a new generation of scientists. We have chosen *not* to ignore the potential consequences of our chosen professions. We realize that we have responsibilities in the education, acceptance, and implementation of green chemistry principles.

As a new generation of scientists and engineers, we need to recognize that our actions and decisions will affect the future well being of our planet. While we have the tools to create products and processes that improve our quality of life, we must consciously make choices to ensure that our actions do not endanger life or the environment around us. We strongly believe that by applying the principles of green chemistry to all aspects of science and engineering, we can continue to improve the society in which we live without simultaneously harming it.

In a field where one cannot always go to the literature to discover the answers that one seeks, the Pan-American Advanced Studies Institute on Green Chemistry (PASI-GC) gave us the opportunity to network with people leading their field. Through this program we gained valuable professional experiences as individuals; however, we also realized that these ideals must spread beyond our inner circle in order to be truly effective.

The dissemination of green chemistry will be no easy task. Interdisciplinary cooperation between all scientific fields will be necessary to create new methods of measuring the toxicity, environmental impact, and energy requirements of new and existing chemical compounds and commercial materials. This technology and theory must then be implemented into as many industrial, academic, and government applications as possible. This unique conference has given us the tools to aggressively pursue these goals, rather than to merely talk about them.

Two weeks of intensive presentations, discussions, and actual laboratory time pertaining to green chemistry, its theory, policy, and application, made this a conference like none before it. There were no hierarchical communication barriers between the students involved and the presenters and organizers of this event. The ability to converse casually yet meaningfully about current and future technologies with the people who were responsible for their existence was an experience previously unmatched. This event will have a special place in the memories of all involved for some time to come, as both a model of interaction and an impetus for change.

In this report, we wish to convey the ideology we have acquired through the PASI on Green Chemistry and emphasize how much is still left to be accomplished in the field. We begin with a description of the PASI-GC, followed by a discussion of why green chemistry is important, the multinational and multidisciplinary aspects of the field, and its role in education. We conclude with some specific actions we believe are important for the advancement of green chemistry. We hope to encourage all to reflect upon our actions and beliefs as scientists, ensuring that we promote the principles of green chemistry[1] to the greatest extent.

The PASI on Green Chemistry, 2003

The first PASI on Green Chemistry opened on July 7, 2003 at the Universidad de la República in Montevideo, Uruguay. The PASI was the first course of its style in the Americas, where 59 young scientists from nine different countries underwent an intensive, 10-day study of green chemistry. The directors of the course were Dr Patrick Moyna of the Universidad de la República and Dr Mary Kirchhoff of the American Chemical Society's Green Chemistry Institute. The National Science Foundation, US Department of Energy, and International Union of Pure and Applied

Chemistry (Chemrawn) provided funding for all the participants and instructors.

The course was mostly lecture style,† with active participation from students and instructors; recent scientific papers were analyzed and discussed, educational materials were presented, and views on chemistry and sustainability were debated. The topics included the general principles of green chemistry and their applications, specific issues such as alternative solvents, polymers, catalysts and biochemistry, as well as global sustainability problems such as nonrenewable feedstocks and persistent pollutants. The chemists and engineers were exposed to each other's disciplines as processes pertaining to both fields were deliberated.

This course was unique in that it offered as many opportunities for students to contribute as the instructors. Lively poster sessions were held on three afternoons, demonstrating the extraordinary range of green research being conducted by the various participants. Collaborative activities included analyzing recent papers on ionic liquids for their potential environmental benefits and weaknesses as well as discussing green process improvements being incorporated by industry, such as Pfizer's synthesis of Zoloft®. Hands-on laboratory work was performed in the areas of solvent-free aldol condensations, enantioselective reduction using carrots, and the destruction of halogenated pollutants using the TAML® catalyst.

The PASI-GC course was quite intensive, lasting each day from sunrise until sundown. However, our group interactions continued in the evenings, with the Uruguayans introducing the foreigners to their typical activities and customs. Throughout the course of the two weeks, the North Americans were introduced to and participated in the extremely popular local tradition of *mate*, sipping a concentrated 'green tea' drink from a gourd. Several evenings, we played *Fútbol 5*, a popular sport played primarily by men in South America; however, both men and women from our group participated equally in these 'friendly' competitions. Another day, we traveled to *Punta del Este*, a popular tourist beach resort in Uruguay. We had lunch on a farm and partook of local delicacies of roasted meats, including beef kidney and intestine. The course was concluded with a visit to a winery, where we tasted the wines and reminisced on the previous weeks, with keen intentions of continuing communication between participants. Over the two weeks, our entire group became very close, unified under the same objective: to learn, strengthen and disseminate the concepts of green chemistry.

Why green chemistry?

The principles of green chemistry and engineering form a solid foundation as a scientific and ethical tool to assist chemists and chemical engineers in making intelligent decisions about risk and sustainability. However, in order to encourage young chemists and chemical engineers to adopt these principles, it is important to examine the underlying motivations behind green chemistry. Putting it another way, why *should* young chemists and chemical engineers decide to do green chemistry? We believe there are four fundamental reasons: necessity, responsibility, interest, and efficiency.

Necessity

Green chemistry is necessary chemistry. As things currently stand, human consumption is not a sustainable process. This problem will be exacerbated as developing countries industrialize and our fossil fuel resources become depleted. Furthermore, recent discoveries about eco-toxic effects such as endocrine disruption have made it clear that synthetic chemicals released into the environment are disrupting world ecosystems in new and terrifying ways. An approach including the green chemistry principles of sustainability and the use and synthesis of benign substances whenever possible will help mitigate the effects of man-made interference in the natural environment.

Responsibility

Green chemistry is responsible chemistry. Many workers in the chemical field, in either academic or industrial settings, have had accidents with the potential to cause long-term damage to their health and well-being. As chemical workers, however, we have knowingly chosen to accept the risks of working in a chemical laboratory and typically have the opportunity to protect ourselves by gathering as much information about the potential risks as possible. The general public, however, has not chosen to accept the same risks, and our contribution to pollution and sustainability problems amounts to an experiment carried out on an entire generation of human beings. The general public's perception of this helps to explain the staggering fact that 'trust' of scientists is at a much lower level than most scientists would like to believe.[2]

Interest

Green chemistry is interesting chemistry. Few analogues to traditional chemical practices exist using green alternatives, and the development of these analogues will provide new research areas for young chemists and chemical engineers. Furthermore, green chemistry requires a large amount of cross-disciplinary interaction, which will lead to new developments as researchers in differing disciplines interact with one another.

Efficiency

Green chemistry is efficient chemistry. The development of benign, non-wasteful alternatives to traditional chemistry has the potential to save industrial and academic interests large amounts of money due to decreased regulation compliance costs and disposal costs. Furthermore, the basic decrease in process hazards drastically increases both worker and consumer safety.

Green chemistry is necessary, responsible, interesting, efficient, and above all, good chemistry. Furthermore, a rational approach to chemistry in which attempts are made to develop and use green alternatives has no significant drawbacks, assuming reasonable societal investment in the process. For these reasons, the principles of green chemistry should form the fundamental philosophical underpinnings for the next generation of young chemists and chemical engineers. This foundation will preserve our function in society while minimizing the harm we cause to ourselves and to the world around us.

Multinational aspects of green chemistry

In the modern world, our way of living and the processes for generating consumer products can cause pollution correlating to undesirable global change. Toxic chemicals released into the environment, mostly in developed countries, eventually circle the globe and can affect everyone. Universal concerns that were presented at the PASI-GC, such as greenhouse gases, CFCs, and VOCs, have roots in past methods of practising chemistry; green chemistry proposes solutions for preventing these problems in the future.

Developed countries

In the developed nations, our relatively high standard of living often means a high resource usage along with the generation of large quantities of waste materials. The amount of waste produced per person is much higher in developed countries,

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†Various presentations from the PASI-GC are posted on the Green Chemistry Institute's webpage at www.chemistry.org/greenchemistryinstitute

resulting in numerous problems such as abandoned hazardous waste sites. Green chemistry offers strategies to help reduce or eliminate the waste in chemical processes. Industrialized countries also bear the cost of past wars; World War II and the Cold War came with a high cost for many nations, leaving behind a nuclear legacy. The sites that once were involved in weapons grade uranium and plutonium production in the US, such as Hanford and Savannah River, are now contaminated and are facing colossal costs for the evaluation and management of waste. Additionally, pollution has negatively affected or destroyed many natural habitats in the industrialized countries. Knowing the problems created by our actions in the past, it would seem only logical to turn to green chemistry to ensure that we do not go down the same path again.

Developing countries

From the perspective of the developing world, green chemistry could and should be regarded as an important tool for development. It can be used to improve the people's quality of life while avoiding poor choices for progression and depletion of natural resources. In developing countries there is a different and equally difficult situation as their immediate social and economic problems are the priority, which are often believed to be distinct from the rational use of natural resources.

In a recent editorial by Paul Anastas,[3] he presented a graph (Fig. 5) that shows that resource use upon development has historically followed an unsustainable trajectory. He also showed an alternative situation (Fig. 6) where developing countries are able to 'leap-frog' to a state of higher development without the traditionally high resource usage. This jump could be made possible by employing the fundamental principles of green chemistry in the process of development.

In this regard, the development of these countries should be a highly desirable point of interest for global citizens. However, there is an apparent contradiction, as an increase in quality of life has historically been related to increased resource utilization and degradation of the environment. Current technologies offer us an alternative: the use of scientific knowledge for a new way of development that would be more sustainable, more efficient, and more economical. Green chemistry is a practice that minimizes the impact on human health and the environment and ensures a sustainable future for the next generations. All of humanity is responsible for conservation, sustainability, and the development of the human species, in the developed and developing worlds alike.

Multidisciplinary nature of green chemistry

The field of chemistry is becoming more interdisciplinary within both academia and industry. Therefore, it is only natural for the implications of 'green chemistry' to reach beyond the traditional field of chemistry as well. The PASI-GC Conference included faculty and student representatives from various areas of chemistry and chemical engineering; roughly 1/3 of the participants involved were from departments other than chemistry, including chemical engineering, ecology, and toxicology. This diversity emphasized how readily the fundamentals of green chemistry can be integrated in areas outside the specific field.

Green chemistry is frequently considered a separate branch under the general field of chemistry, yet it is truly an entity to be included within all the traditional branches. Most branches of engineering also have begun embracing the concept of 'green engineering'. While concepts such as energy and waste minimization have long been principles in engineering design due to their economic advantages, concepts like incorporating environmental impact within process development are relatively new to the engineering fields. These same environmentally conscious concepts can be incorporated in all scientific fields, including physics, biology, ecology, and medicine.

Other 'non-scientific' fields also have green applications. Law and political science already have 'green' platforms that are becoming increasingly more important to the public. Business and economic ventures should be encouraged to add environmental impact as a factor when conducting cost assessments. During a discussion at the PASI-GC, it was mentioned that the fields of journalism, communications, and marketing would be particularly helpful in the public relations efforts necessary for educating communities on the importance of 'thinking green'.

Virtually any material project, regardless of field, has 'green' implications and applications when the ramifications of the project are considered from the raw starting materials though its end-of-use lifespan. Therefore it is imperative that we begin to look for and understand the links between disciplines because as scientists we cannot solve these problems alone. Educating ourselves, our colleagues, and our communities on the importance of incorporating 'greenness' in multiple disciplines is absolutely necessary in order to accomplish our lofty goal of a truly sustainable planet.

Green chemistry and engineering education

Education plays a pivotal role in materializing the concepts and principles of green chemistry and engineering. Integration of these ideas into mainstream education is necessary for such an endeavor.

The incorporation of green chemistry and engineering principles into chemical education and process design needs to start at least from the undergraduate level and preferably earlier in students' primary and secondary education. It is necessary to equip the present and future generations of scientists and engineers with the ideas of waste minimization, innovation of safe and energy efficient synthetic processes, real time analysis for pollution prevention, and use of inherently safer chemicals for accident prevention to sustain our current high-tech civilization further into the future.

Along with the progress in education at academic institutions, development towards an entirely sustainable civilization requires the involvement of people from every aspect of society. The responsibility lies with the scientific community to increase awareness among the general population about the need for their participation and involvement in the development and use of greener alternatives and also about the risk of existing technologies that may not sustain in the future. Also, an intimate and well-knit academia–industry relationship needs to be nurtured to obtain economically viable sustainable technologies.

Sustainable development means protecting and improving the environment and developing economic security through education–which can be fulfilled only by a strong commitment from everyone. Specific steps must be taken to ensure that the principles of green chemistry are effectively communicated both within the scientific community and to the general public so that all can benefit.

Future directions

Through participating in the PASI on Green Chemistry, we as young scientists have been empowered both to practise and teach the principles of green chemistry. We can proactively pursue these principles through the base of knowledge we have acquired and the compelling contacts we have made. We now have colleagues, ranging from new students to well-established faculty and professionals, to act as our supporters and collaborators. Thus, we can set forth goals for ourselves and others to become active members of the green chemistry community.

Before we can direct others in the

principles, we must educate ourselves, putting green chemistry into practice within our own laboratories. Examining the footprint of the labs we currently work in is an excellent place to start; solvent selection, lab energy, and water use are good places to target. When possible, we must learn about the toxicities of the chemicals available for use as well as researching and considering the potential alternative, greener reactants. In order to solve the problems, we must first understand them. To become practising 'green chemists', we must learn to think in new and different ways and be able to recognize and correct our past mistakes.

Next, we must educate those within the chemical community, expanding green chemistry beyond the inner circle. A paradigm shift is necessary to enable all scientists to make conscious efforts to recognize hazard as a design flaw and acquire a 'cradle to grave' mindset. We recognize that past mistakes have been made that scientists are held accountable for, but we also emphasize that future mistakes can be prevented with proper training and effective technical leadership. To encourage these transitions, we believe that green chemistry should be implemented at both undergraduate and graduate levels and incorporated into peer-reviewed journals; for example, the experimental section should include atom economy in place of percent yield as well as an estimate of waste production for each process. We suggest that classes, such as introductory organic chemistry, should cover the toxicity component of any chemical along with its different reactivity and spectroscopic properties with similar stress and importance. Additionally, inherently safer alternatives and hazard components of a process design might be taught with equal magnitude in a chemical engineering class. While we believe it is possible to convert all scientists to green practices, we encourage focusing on hose that are more willing to change first, such as entrepreneurs and privately held firms.

The most difficult obstacle for us as green chemists is education outside the chemical community. However, green chemistry is an easy and effective way for us to improve the public image of chemists and chemical engineers. One of the most useful and influential resources we can use is school teachers; volunteering at those levels is an excellent way to encourage students to pursue science while teaching them the value of green practices, which will continue throughout their adult careers. Additionally, we encourage collaborations outside of our respective fields. Whether this is achieved within the scientific community, such as between the chemists and engineers, or with other

List of faculty participants

Paul Anastas	White House Office of Science And Tech. Policy, USA
Eric Beckman	University of Pittsburgh, USA
Joan Brennecke	University of Notre Dame, USA
Ian Brindle	Brock University, Canada
Eduardo Cassel	Universidade Católica do Rio Grande do Sul, Brazil
Terry Collins	Carnegie Mellon University, USA
José De Oliveira	Universidade Regional Integrada, Brazil
Roberto Fernández-Prini	Facultad de Ciencias Exactas y Naturales, Argentina
David González	Facultad de Química, Uruguay
Dennis Hjeresen	Green Chemistry Institute, USA
Mary Kirchhoff	Green Chemistry Institute, USA
Patrick Moyna	Facultad de Química, Uruguay
Gustavo Seoane	Facultad de Química, Uruguay
Robin Rogers	University of Alabama at Tuscaloosa, USA
Carmen Rossini	Facultad de Química, Uruguay
Tracy Williamson	US EPA Office of Pollution Prevention & Toxics, USA

List of student participants

Jorge Adum	Universidad de la República, Uruguay
Darren Anderson	University of Toronto, Canada
Jennifer Anthony	University of Notre Dame, USA
Lourdes Arellano	Universidad de la República, Uruguay
Ana Bellomo	Universidad de la República, Uruguay
James Brown	Georgia Institute of Technology, USA
Amy Cannon	University of Massachusetts at Boston, USA
Arani Chanda	Carnegie Mellon University, USA
Timothy Davis	University of Connecticut at Storrs, USA
Boris de Mattos	Universidad de la República, Uruguay
Ginger Denison	University of North Carolina at Chapel Hill, USA
David Drab	University of Iowa, USA
Melissa Drolet	University of New Brunswick, Canada
Natalia Ferraz	Universidad de la República, Uruguay
Anne Fischer	Michigan State University, USA
Diego Fort	Universidad de la República, Uruguay
David Frankowski	North Carolina State University, USA
Micheal Fultz	University of Tennessee at Martin, USA
Mylene Gagnon	University du Quebec a Trois-Rivieres, Canada
Ely Greenberg	University of South Carolina, USA
Jason Hein	University of Manitoba, Canada
Caudia Ibañez Ojeda	Universidad de la República, Uruguay
Ana Inés Torres	Universidad de la República, Uruguay
Iván Jachmanian	Universidad de la República, Uruguay
William Jacoby	University of Missouri at Columbia, USA
María Joselevich	Universidad de Buenos Aires, Argentina
Amy Keirstead	Dalhousie University, Canada
Cecilia Kiarie	University of Massachusetts at Boston, USA
Angelina Kulbick	University of Delaware, USA
Michele La Merrill	University of North Carolina at Chapel Hill, USA
Paola Liberati	Universidad de la República, Uruguay
Virginia López	Universidad de la República, Uruguay
Dinorah Lorenzo	Universidad de la República, Uruguay
Angela Lueking	University of Michigan, USA
Karrie Manes	University of Detroit Mercy, USA
Lucía Margenat	Universidad de la República, Uruguay
Deborah Martino	University of Massachusetts at Boston, USA
Ian McAninch	University of Delaware, USA
Lallie McKenzie	University of Oregon, USA
Lucila Mendez De Leo	Universidad de Buenos Aires, Argentina
Sujit Mondal	Carnegie Mellon University, USA
Jonathan O'Dwyer	Texas A&M University, USA
Oksana Olkhovyk	Kent State University, USA
Paola Panizza	Universidad de la República, Uruguay
Joan Patterson	North Carolina State University, USA
Frederic Perreault	Queens University, Canada
Carolina Pesce	Universidad de la República, Uruguay
Carina Plada	Universidad de la República, Uruguay
Claudia Pidstra	Universidad de la República, Uruguay
W. Matthew Reichert	University of Alabama, USA
Carolyn Reid	Tulane University, USA
Leonardo Rorig	Sao Carlos Federal University, Brazil
Germán Sciaini	Universidad de Buenos Aires, Argentina
Prerna Sonthalia	Michigan State University, USA
Richard Swatloski	University of Alabama, USA
Colin Thomas	Georgia Institute of Technology, USA
Julio Miguel Vago	Universidad de Buenos Aires, Argentina
Paula Viapina	Universidad de la República, Uruguay
Justin Whitfield	University of Massachusetts at Boston, USA

economic and public interest fields, demonstrating that green chemistry is good chemistry can be a mechanism for change in others. In any situation, we will strive to speak out and be ambassadors for green chemistry

Conclusions

We want a sustainable situation. Green chemistry is critical to that. In an ideal future, ‘green chemistry’ will cease to exist as an independent field, and instead be incorporated as a fundamental aspect within the field of chemistry. However, it will require education, leadership, and a conscious effort by all scientists for this change to occur. In general, chemists are a group of people that are not necessarily aware of the extent of their power or they take that power for granted. With action and conviction, it is in our hands to fix the problem and deliver the message.

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TUTORIAL REVIEW

www.rsc.org/greenchem

Green chemistry and photochemistry were born at the same time

Angelo Albini and Maurizio Fagnoni
Department of Organic Chemistry, The University of Pavia, I 27100 Pavia, Italy.
E-mail: angelo.albini@unipv.it

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Where to look for really ‘green’ synthetic methods, under conditions as mild as those nature uses? A hundred years ago, a great scientist, Giacomo Ciamician, confronted the problem. He had no doubt of the answer: it was solar light. The approach and the discoveries by Ciamician are illustrated in connection with present-day green chemistry.

1 Introduction

‘Green’ chemistry is the effort of ‘reducing or eliminating the use or generation of hazardous substances in the design, manufacture and application of chemical products’.[1] Its birth is generally connected with the rather recent realization of the damage to the environment caused by the diffusion of polluting man-made materials and to the pollution generated in the process of producing them. Thus, the research for more environment friendly materials and for mild, direct, non-polluting synthetic methods is driven primarily by the moral imperative of avoiding an irreversible damage to the environment and by the economic motivation of avoiding the high cost of recovering polluted air and water.

However, behind a research in green chemistry there might be also an intellectual motivation, the desire to show that a chemical process can be carried out in a cleaner, nicer way. Probably many synthetic chemists have felt this nowadays as well as in early times. An unparalleled example of clear-sightedness on this question is offered by the work of Giacomo Ciamician at the beginning of the 20th century.[†]Work during the last decades of the 19th century had laid the foundations for a large part of present day-used key paths in organic synthesis. In parallel the structure of many classes of primary and secondary metabolites had been recognized. He had himself participated in this effort, being among the founders of the chemistry of pyrrole.[6,7] Thus, the basis of organic chemistry had been laid and the synthesis of artificial compounds, *e.g.* of dyes, was rapidly acquiring industrial significance.

However, he felt some dissatisfaction with this otherwise towering example of ingenuity. Addressing the French Chemical Society on June 8, 1908,[8] he made the following remarks.

‘It has often been a reproach to the great successes of modern organic chemistry that victory has been obtained with too great a show of strength. Indeed, one has to admit that such an objection is not deprived of some ground. Using aggressive reagents and high temperatures is almost always unavoidable when carrying out an organic synthesis in the laboratory. Deploying energy would, on the other hand, not be so frustrating for modern organic chemistry, were it not that the living world, in particular plants, gives us the marvelous example of great results obtained, at least from what appears, by using minimal means.

Chemistry in the laboratory differs from chemistry of organisms not in the materials, but in the reagents used. It is thus apparent that the further advancement of biology requires that all of the compounds present in nature can be produced by using only reagents present in nature, rather than agents that do not belong to the living world.’

Angelo Albini is currently Professor of Organic Chemistry at the University at Pavia. He is active in the field of organic photochemistry, organic synthesis via *radicals and photoinitiated reactions, applied photochemistry (*e.g. *photodegradation of dyes and plastics, photodegradation of pollutants, phototoxicity of drugs). He is coauthor of two books and* ca. *200 research papers.*

Maurizio Fagnoni is currently Research Associate at the University of Pavia. His research concentrates on new synthetic methods, particularly through the mild photochemical generation of active intermediates such as radicals and ions. He is coauthor of ca. *40 research papers.*

Green Context

One of the more neglected techniques available to green chemistry is photochemistry. The use of light as an energy source, and as an agent of chemical change, can allow very mild reaction conditions, and is certainly a sustainable raw material, at least for the next few tens of millions of years. This paper is an interesting and thought-provoking overview of the work of one of the pioneers in the area, and illustrates nicely the potential which has been around for a century in the field of photochemical synthesis. ***DJM***

[†] Giacomo Ciamician was born in Trieste in 1857 from a family of Armenian origin. He studied chemistry at the University of Vienna and after graduation (1880 at Gießen) joined the very active group led by Cannizzaro in Rome. Here he pursued the study of the animal gelatin distillate begun in Vienna. This led to important contributions to the chemistry of pyrrole and other five-membered nitrogen heterocycles, and to the fundamental intuition of the similarity in the chemical behavior with phenols. In the same group worked the German chemist Paul Silber, who was to follow him when he accepted calls first to Padua (1887) and then to Bologna (1889) and was a life-long collaborator. In Bologna he extended his work on pyrrole, on several alkaloid families and on flavones, and then gave full impetus to the work on photochemistry, begun in 1886 in Rome. In this work, carried out by exposing for days or months sealed flasks of solutions to solar light on the roof of the Institute, Ciamician and Silber showed an extraordinary experimental skill in the identification of the sometimes labile photoproducts. In the final part of his work he studied chemical reactions in plants and the biological role of alkaloids. An internationally well known personality, he was proposed for the Nobel Prize (with the support of Emil Fischer) and strived throughout his life for cooperation among different disciplines, in particular of chemistry with physics on one hand and with biology on the other. Whoever, Italian[3] or foreigner,[2] had the opportunity of attending his lectures, was deeply impressed by his clear and logical presentations and by the enthusiasm he poured into them. Key accounts of his life and work may be found in refs. 2–5.

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He had therefore wondered on which grounds may lie the superior ability of nature.

‘From this point of view, one should first consider enzymes. These are the main catalysts of the living world and recent results give us a sense of what we can expect in the future.

However, there is another agent of the highest importance, at least for plants, and which deserves to be studied in detail, and this is light. For plants, light is the source of energy. Through the intervention of chlorophyll, green plants accumulate solar energy and transform it into chemical energy.’

Therefore, he considered whether photochemical reactions could be carried out artificially, and considered also the energy-saving side of the matter.

‘It may also happen that the problem of using solar energy becomes interesting under another respect. When oil will have been all burned in our prodigal industries, it may become necessary, even on social grounds, to come to exploit solar energy.’

2 Discovering photochemical reactions

Ciamician reported in Paris on the work in photochemistry he had been carrying out in the previous ten years. The hypothesis was that the absorption of light was what allowed plants to synthesize chemicals in the cells under much milder conditions than chemists could in a flask. As we now know, it is not exactly like this. Plants use solar energy to accumulate NADPH and ATP and these are used in the actual (thermal) synthesis of chemicals. Ciamician had a feeling of the complexity of the topic and in the last years of his work he devoted pioneering studies to a better understanding of the actual chemistry occurring in cells, in particular to the role of glycosidation and how this affects the metabolism of chemicals in plants.[9]

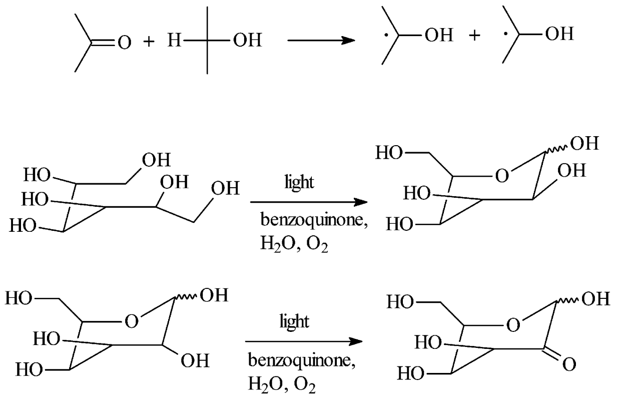
At any rate, in collaboration with Paul Silber, he set out to examine which chemical reactions are facilitated by, or require, solar light and, as he declared, ‘these studies aimed first of all to rationalize organic chemistry in plants’.‡ He could not achieve this goal, nor was there any indication of which classes of chemicals may be significantly photoreactive. However, an intensive and patient work based on the systematic exposition of all the chemicals he could get hold of to solar light, resulted in the discovery of a range of interesting photochemical processes. These occurred, as he had hoped, under unparalleled mild conditions in what can be considered the first deliberate, and highly successful, effort to establish ‘green’ procedures for chemical synthesis.

A large part of the key photochemical reactions now known was indeed present in his 1908 talk. In the following paragraphs, his classification will be followed (including also his later papers), and it will be attempted to relate his discoveries with the present-day significance of such processes for green synthesis.

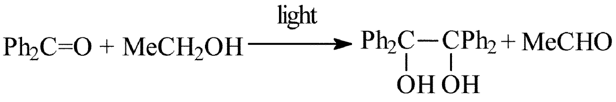
2.1 Oxidations and reductions

A large group of reactions comes under this heading and, as he notices, involves straightforward hydrogen transfer, having no parallel in thermal chemistry. A convenient application is as a mild oxidation method, *e.g.*, benzoquinone is quite effective in the selective oxidation of alcohols to aldehydes.[10–12] Most usefully, polyalcohols are transformed into sugars identical to the natural products. As he remarks, photoinduced oxidation is a substitute for the use of strong oxidants, such as bromine or nitric acid. A step further, glucose is mildly oxidized to glucosone (Scheme 1).

The reducing side of the reaction is likewise useful. Ciamician and Silber found that, while aliphatic aldehydes and ketones also abstract hydrogen, but give complex mixtures, aromatic ketones (and, with a lower yield, aldehydes) undergo clean bimolecular reduction to pinacols (Scheme 2). In this case not only alcohols, but also alkylaromatics function as reducing agents.[13] Further products containing a C=O bond undergo reductive dimerization, *e.g.* alloxane to alloxantin.[14]



Scheme 1

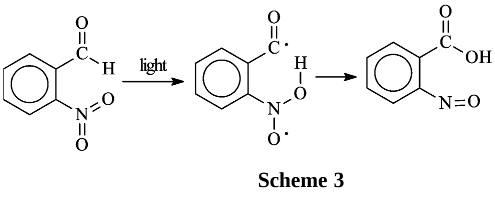


$$\mathrm{Ph_2C{=}O + MeCH_2OH \xrightarrow{light} \underset{OH}{Ph_2C}-\underset{OH}{CPh_2} + MeCHO}$$

Scheme 2

As we now know, all of these reactions exploit the fast hydrogen abstraction by excited carbonyls generating radicals. The principle has been extended in recent literature to poor hydrogen donors, even to alkanes, where photochemistry offers an extremely mild entry for the functionalization of non-activated C–H bonds.[15] Further abstracting species, such as inorganic anions (*e.g.* polyoxometalates) or solid materials (*e.g.* titanium dioxide powder) have been added to ketones,[16–18] with the advantage of being more easily regenerated under the conditions of the experiments and thus having a high turnover number. The radicals generated react with oxygen to give oxidized derivatives or add to electrophilic alkenes to form new C–C bonds (see below).

Nitroaromatics also work as photooxidants. Ciamician and Silber demonstrated the formation of aniline and all of the intermediate products of reduction from the irradiation of nitrobenzene in alcohols,[19,20] and further demonstrated the structure of the several photoproducts formed from nitrobenzene and benzaldehyde or its phenylhydrazone.[21]



Scheme 3

Importantly they found an example of intramolecular redox reaction in the smooth photoconversion of *o*-nitrobenzaldehyde into *o*-nitrosobenzoic acid, both in the solid state and in inert solvents (Scheme 3).[22] They noted the higher efficiency of this reaction with comparison to the previous ones (actually due not to a higher quantum yield, but to the lower inhibiting effect by oxygen in this intramolecular reaction). They concluded that this is the only reaction ‘comparable in rate with the photographic processes’. Ciamician was pleased to find that another intramolecular reaction of a nitroaromatic was later used by Pfeiffer for preparing a nitrophenylisatogen[23] and noted that this bore analogy with the then all important synthesis of indigo and possibly opened the way to the photochemical production of dyestuffs. The field in which intramolecular hydrogen abstraction by nitro group has nowadays found the largest application is actually the use of the *o*-nitrobenzyl

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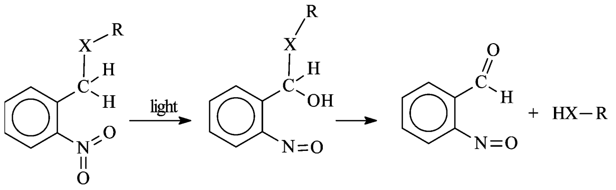
‡ The first paper of the photochemical series was published in 1900,[10] but he mentions that he had begun work in the field 14 years earlier.

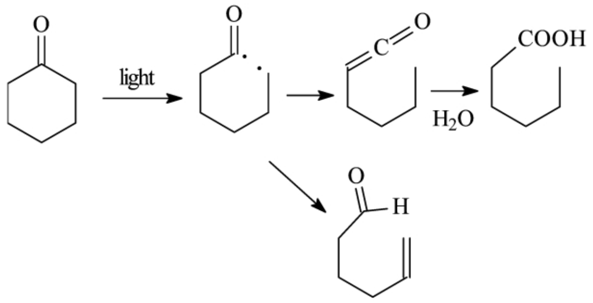
moiety§ as a protecting group removable under exceptionally mild conditions (Scheme 4).[25]



Scheme 4

2.2 Fragmentations

The irradiation of ketones causes α-cleavage, leading to *e.g.* methane and acetic acid from an acetone–water mixture.[26] This is what is now known as the 'Norrish I Type' reaction of ketones. Particular attention was given to the efficient cleavage of cyclic ketones in aqueous media, which is quite effective and gives two types of products. These are open-chain saturated acids and unsaturated aldehydes, *e.g.* cyclohexanone gives hexanoic acid and 5-hexenal (Scheme 5).



Scheme 5

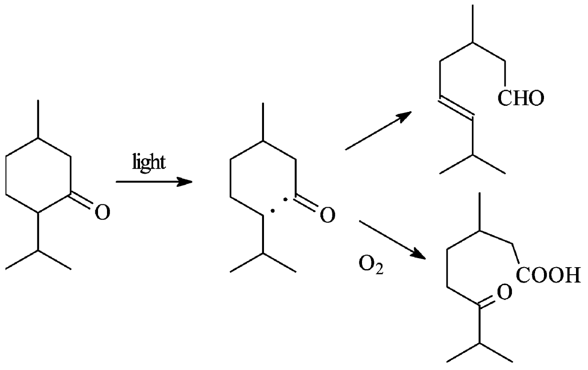
This was also proved by Ciamician and Silber through experiments quite demanding at the time, due to the difficulty of characterizing aliphatic aldehydes.[26,27] The reaction has been later rationalized as involving α-cleavage, and the two alternative disproportionations of the biradical, leading either to the unsaturated aldehyde ('Norrish Type II reaction') or to the ketene (that undergoes water addition).[28] The cleavage to acids has been later used for example for the mild synthesis of secosteroids.[29] Furthermore, Ciamician and Silber noted that oxygen had an important effect on the reaction, due, as it is now understood, to trapping of the intermediate radicals. Oxidative cleavage may result under these conditions; *e.g.* menthone was converted to a ketoacid (whereas it gave 3,7-dimethyl-5-octenal in the absence of oxygen, Scheme 6, see also below).[30,31]

2.3 Autooxidations

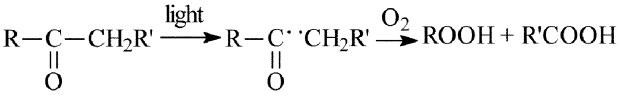
Under this category the Authors considered various processes. One is the above α-cleavage of aldehydes and ketones. Under oxygen the radicals are trapped and *e.g.* acetone gives acetic and formic acids, which may be viewed as a mild version of the permanganate cleavage of ketones (Scheme 7).[8]

Furthermore, they noticed the conversion of stilbene to benzaldehyde (Scheme 8, also in the solid state), and drew an analogy between this oxidative cleavage and the results with a more aggressive reagent, ozone.[8]

A large number of useful (also industrially) photoinduced oxygenation reactions have been since developed and recognized as involving the reaction of photogenerated radicals with oxygen (as it happens with ketones), or reactions with activated forms of oxygen, such as singlet oxygen or superoxide anion (as it happens with stilbene).[32]

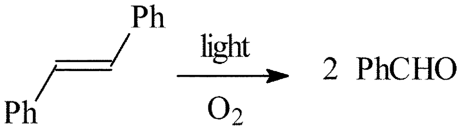


Scheme 6



$$R-\underset{\displaystyle O}{\underset{\|}{C}}-CH_2R' \xrightarrow{\text{light}} R-\underset{\displaystyle O}{\underset{\|}{C^{\cdot}}}\ {}^{\cdot}CH_2R' \xrightarrow{O_2} ROOH + R'COOH$$

Scheme 7

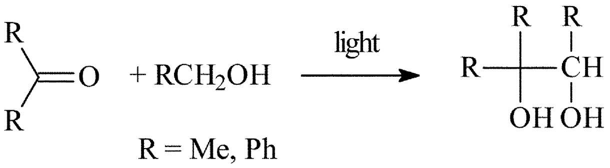


Scheme 8

Ciamincian and Silber also found that many substrates not themselves liable to auto-oxidation become active in the presence of xylene. As an example alcohols are oxidized to aldehydes (and polyalcohols to sugars) in the presence of *p*-xylene, reasonably because of the role of adventitious oxidation products from the aromatic in absorbing the light.[33]

2.4 Polymerizations and condensations

At the time, this title applied to carbon–carbon bond forming reactions in general. In the above mentioned H-abstraction reactions by ketones, cross-coupling products were formed. Thus, isobutyleneglycol was obtained from acetone and methanol (Scheme 9)[34] and a similar coupling was obtained with ethers.[35]



Scheme 9

The reaction was particularly efficient when using aromatic ketones or alcohols, due to the stability of the radicals. Furthermore, cross coupling may be obtained from ketones. 2-Butanone gave 2-butanol and 3,4-dimethyl-1,5-hexandione (Scheme 10).[36] As one may have expected from his experience with pyrroles, Ciamician promptly converted this to tetramethylpyrrole and wondered whether this may have a connection with the formation of chlorophyll in plants. Many years later, the final step in the celebrated first synthesis of chlorophyll a was indeed to be a photochemical step, though of a different type (an oxidative cleavage, as in the previous section).[37]

Besides some polymerization reactions of aldehydes, possibly again involving radicals, the Authors classed here a different, and quite important, reaction, *viz.* 2 + 2 cycloaddition. Examples included the dimerization of cynnamic acid, confirming previous

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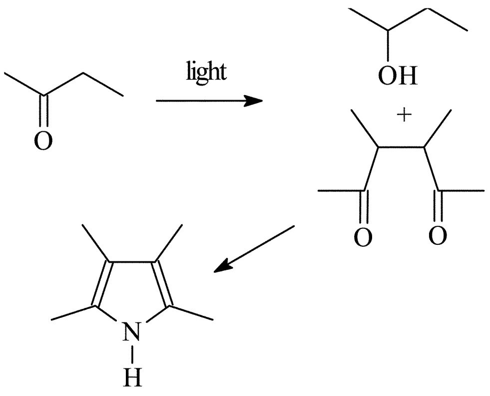
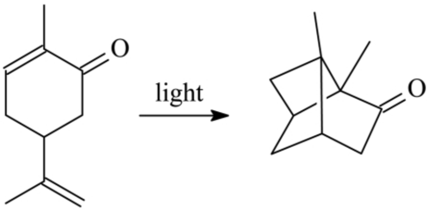
§ The intramolecular reactivity of *o*-nitrobenzyl alcohols has been reported in 1904 by Sachs.[24]



Scheme 10

reports that it occurred only in the solid state, as well as the dimerization of stilbene and coumarine, which, they found, occurs also in solution.[38,39] The Authors were quite excited by finding an intramolecular example of 2 + 2 cycloaddition in the case of carvone, in what may be considered a prototype for the use of photochemistry for the smooth and direct building of a highly congested molecule[30] (Scheme 11, the product structure was correctly proposed, but finally proved later).[40]



Scheme 11

Together with the 2 + 2 carbonyl–olefin cycloaddition discovered (likewise with correct product structure proposal, though finally established later) by the other Italian scientist Paternò,[41] this reaction has been then largely applied[42] and represents an ideal example of directness in organic synthesis, another pillar of modern green chemistry.

2.5 Rearrangements

The Authors mention several cases of C=C and N=N double bond isomerization, as well as of syn–anti oxime isomerization.[43] These reactions are of obvious importance in applications, *e.g.* with regard to dye photostability.

3 The nature of photochemical processes

Most of the reactions that Ciamician and Silber discovered are based on the polymorph reactivity of the triplet state of carbonyls and other $n\pi^*$ states and on their ability to generate C-centered radicals. This is exactly the same point from which photochemistry started again after World War 2, when 40 years neglect had elapsed (his Alma Mater, Bologna, being one of the places where it flourished). The ability of photochemical reactions of generating highly reactive species with high selectivity and under exceptionally mild (and thus versatile) conditions is what gives significance to this discipline in the field of green chemistry.[44] This actually was the target of the quest for synthetic methods as mild as those used by nature that had passionate Ciamician. This concept was still mentioned in the literature for some time after his death,[45] but then faded away until present days.

As for rationalization, a clear representation of electronically excited states (and still less of their reactivity) was not possible at the time, though Ciamician concurred[6] with Plotnikow[46] in thinking that light 'produces a different ionization from that due to electrolytic dissociation; the separation of an ion requires a quantity of light that is determined by the theory of Planck and Einstein'¶

Quenching of the triplet states by oxygen dissolved in the solvents caused the typical induction periods that worried him and led to long irradiation times. Sealing the reaction vessels made the reaction faster after the initial period in which oxygen was consumed. At the moment, attention mainly was at recognizing the reaction occurring, rather than optimizing the yields (and this generally, not only in the case of photochemical reactions). However, Ciamician was highly pleased with the intramolecular reaction of *o*-nitrobenzaldehyde that, as mentioned above, did not suffer of these limitations. The cleanness of that reaction actually allowed it to be used, some years later, for the first measurement of quantum yield, giving an experimental support to Einstein's predictions (now known as the 2nd law of photochemistry).[47]

From another perspective, it is the chemistry of carbon-centered radicals that he has been discovering, and there is no need to stress how important in modern chemistry are syntheses based on such versatile intermediates.[48] Indeed, photochemical initiation is now giving a contribution for the mild generation of radicals and their addition to electrophilic alkenes.[49] In this case, a relation to some of his reactions can be recognized, since the high energy of excited states is exploited for generating radicals by cleaving strong C–H or C–C bond radicals, and such intermediates then are used for the desired bond forming reaction.

4 Exploiting solar energy and creating a photochemical industry

Ciamician had a clear idea of the importance of photosynthesis in the energetic balance of the Earth and the role of chlorophyll in it. In the 1908 lecture he recognized that 'photochemical phenomena can themselves undergo the influence of catalysts, and it is probably to this class that the imposing phenomenon of assimilation‖ has to be ascribed. Chlorophyll can be considered as a photocatalyst, which absorbs red light and causes the decomposition of carbon dioxide and its transformation into sugars'.[8] At this time, no artificial photocatalytic reaction was known, but the great example of chlorophyll in nature showed that something of this type must be possible.

In a general lecture before the International Congress of Applied Chemistry, held in New York in 1912,[50] Ciamician was concerned with the contribution of photochemistry as a source of energy. Following recent contributions by Ramsay and Engler, he evaluated the available amount of coal and that mined yearly. He remarked that this was nothing else than a form of fossil *solar* energy.[50,51] He compared available coal with the much larger amount of solar energy daily received by the Earth, and found that this was the only form of energy that could offer a lasting supply to industrialization (except, he noted, for the then barely suspected enormous energy involved in 'atomic disintegration'). Yet, only a minimal fraction of that energy was stored by plants (still, an amount much larger than that daily production of coal). Advancement should then be in two directions.

The first one was a more advanced agriculture, specialized towards different aims, *viz.* both for food and for industrial supply, at this time the typical example being rapidly growing trees affording pulp for the paper industry. He thought however that plants could be adapted for the production of a harvest that, dried by the sun, could be converted 'entirely to gaseous fuel, taking care

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¶ Ciamician was among the first scientists to use systematically spectroscopy and a physical chemistry approach in both research and teaching organic chemistry. He, though seriously ill, was present at a lecture by Einstein in Bologna in 1922.[3]

‖ This indicated the 'assimilation' of carbon dioxide and water yielding carbohydrates.

during this operation to fix ammonia',[50] to be reused for inorganic fertilizers that thus would have been used in a closed cycle, minimizing waste (clearly the idea of 'green gasoline' had not to wait for the present decades). Furthermore, many industries elaborated agricultural products (cotton, starch, sugar, *etc.*) and of course would take advantage of an advanced agriculture.

However, he envisaged as even more important the second topic, the development of solar photochemistry on an industrial scale. He considered that plants produced an enormous amount of secondary metabolites, ultimately exploiting solar energy for the conversion. Chemists were learning how to produce a variety of compounds through artificial reactions and he was hoping the progress of science would have made these available also through *photochemical* reactions in the laboratory. A small example was offered by the photoreactions that he had been finding in those years.

Furthermore, the then growing fine chemicals industry (particularly for dyes) had experienced trouble in finding starting materials that were available in sufficient amounts and at convenient prices from the only source available for bulk chemicals, *i.e.* coal tar (as an example, naphthalene had to be chosen for making indigo, since toluene was not available in sufficient amounts). But what would happen if prices sored or supplies decreased? On the contrary, if a convenient panel of photochemical reactions could be developed, this would never suffer any shortcoming of the starting material, since non-exhaustible light would convert easily available raw materials into the desired compounds. He thought that there must be a way to transform water and carbon dioxide into methane and oxygen by the action of light in the presence of an appropriate catalyst, and similarly for other simple molecules such as ozone, sulfur trioxide or ammonia. As for fine chemicals, his own work had indeed shown that oxidation–reduction processes as well as carbon–carbon forming reactions, which he envisaged as an alternative to base catalyzed reactions such as aldolic condensation, were indeed possible. He did not confront the question of the efficiency of photochemical reactions (which at any rate could not be measured at the time), possibly because he felt that the flux of solar energy was so large as to make the point unimportant.

He thought that industry should not wait for a possible shortage of fossil fuel, but begin immediately and take advantage of photochemistry. With no prejudice against the development of advanced agriculture on suitable land, on arid lands a photochemical industry 'without smoke and smokestacks' would flourish. A 'forest of glass tubes' would rise and produce chemicals more abundantly than nature, 'for nature is not in a hurry and mankind is', through clean processes that would not harm the environment. This, he hoped, would lead the way for mankind to a 'quieter civilization based on the utilization of solar energy', where progress and happiness should not find the drawback that had characterized the 'black and nervous civilization based on coal'.[50]

5 Conclusions

Ciamician pursued his research plan at a time where chemical industry was on the verge of the dramatic development that would make man-made materials predominant over natural ones in the course of the 20th century. Still in these early days, the supply of fossil fuel seemed next to inexhaustible and what seemed important was the extraordinary advancement in chemical synthesis, not on any drawbacks in the methods used. It is appalling how this great chemist foresaw the need that scientists should find alternative methods that were economic and non-polluting for giving mankind the chemicals it needed for a more prosperous life without exhausting natural resources or degrading the environment. These are the principles of present day green chemistry. Very little has been done in exploiting solar light (an in general really alternative paths for green chemistry) at the industrial level.[52] However, academic research has opened many paths and, as Ciamician pointed out, 'it has been established that modern industry is affiliated intimately with pure science; the progress of one determines necessarily that of the other'.[50] His proposal, photochemistry, remains one of the basic alternatives to be considered for a really green synthesis and the progress of science now suggests how to use it.

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CRITICAL REVIEW

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Kinetic studies for processes of liquid-phase alkylation of aromatics over solid acid catalysts

Paolo Beltrame* and Giovanni Zuretti

Dipartimento di Chimica Fisica ed Elettrochimica, Università degli Studi di Milano, Via Golgi 19, I-20133 Milano, Italy. E-mail: paolo.beltrame@unimi.it; Fax: +39-02-50314300

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The liquid-phase alkylation of aromatics has been effected traditionally with catalysis by inorganic acids or $AlCl_3$ and similar compounds. However the increasing importance of solid acid catalysts is changing the procedures in this field. One of the prerequisites for the development of relevant processes, and the design of reactors, is knowledge of the kinetic data in reactions catalyzed by solid acids. This review examines the information available on the kinetics of alkylations catalyzed by solid acids, mainly zeolites, supported metal chlorides and oxides, mesoporous (MCM) materials, and heteropolyacids, but also other less studied materials.

Introduction

The alkylation of aromatic compounds with olefins, halides or alcohols, traditionally catalyzed by the highly corrosive inorganic Brønsted and Lewis acids, can be carried out over solid acid catalysts, the advantages being easier handling, less equipment corrosion, few problems with regard to environmental disposal and toxicity, simple product separation, and catalyst recycling.

The mechanism proposed for these reactions is the general one for electrophilic aromatic substitution. In particular, it is proposed that the alkylating agent gives rise to an adsorbed organic cation. This may happen by protonation over protonating acids, producing, for instance, $(C_6H_5CH_2^+)_{ads}$ from benzyl chloride[1] or $(C_6H_{11}^+)_{ads}$ from cyclohexene[2] over a heteropolyacid, or by homolytic redox mechanism producing the cation from benzyl chloride over supported metallic oxides or chlorides such as Fe^{3+} chloride.[3,4] The next step is the reaction of the adsorbed cation with the aromatic reagent, present either in the fluid phase or itself adsorbed on the catalytic surface.

Our aim is to review liquid-phase alkylations over solid acid catalysts from the viewpoint of reaction kinetics. The articles on the subject found in the literature have been classified into four categories:

a) work including a discussion on mass transfer resistances and their weight in the process (the conclusions drawn are that such resistances are negligible), followed by a search for kinetic equations and an evaluation of the relevant parameters. The results in these cases can be reasonably considered as pertaining to *intrinsic kinetics*;

b) kinetic studies similar to those in (a), apart from the discussion on mass transfer resistances;

c) studies including the measurement of reaction rates, without a search for kinetic equations;

d) other articles containing kinetic data, although of less straightforward interpretation.

From the point of view of chemical engineering, that requires intrinsic kinetic equations, the first two categories are the most useful, although the results of type (b) may not be as reliable as those of type (a).

The reactions are usually carried out with an excess of aromatic reagent with respect to the alkylating agent, and in many cases it is the aromatic itself that is the reaction solvent; however in some cases there can be a different (usually non-aromatic) solvent.

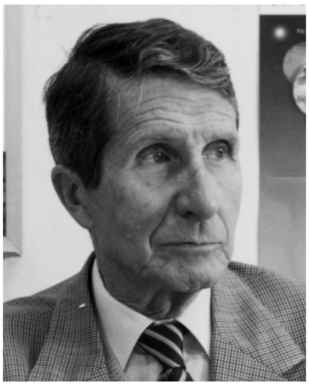
This literature review has revealed great variety in the approaches to kinetic measurement, so that, given the differences in meaning of the parameters, it is not easy to make comparisons. Thus it has been considered important to unify, as far as possible, parameter definitions along the following lines.

Some authors give pseudo-first order rate coefficients with a dimension time^{-1}, while others give them with dimensions volume·mass^{-1}·time^{-1}. We have chosen to take eqn. (1) as a typical first-order rate equation:

$$r = k_1 \cdot C_{alk} \cdot C_{cat} \qquad (1)$$

with r as mol l^{-1}·min^{-1}, C_{alk} (molar concentration of alkylating agent) as mol l^{-1}, C_{cat} (mass concentration of the catalyst in the suspension) as g l^{-1}, so that k_1 is given as l g^{-1}·min^{-1}. As a consequence, when it is necessary to convert pseudo-first order rate

Paolo Beltrame was born in Milano, Italy, in 1930. He received his "Laurea" in Industrial Chemistry from the University of Milano, in 1954. In 1955 he joined the same University as assistant professor. He carried out research work at University College London, UK, in 1959, and at University of California at Los Angeles, USA, in 1962. In 1970 he joined the University of Cagliari, Italy, as full professor. Currently he is full professor at the University of Milano, for Industrial Chemistry curricula. His current research interests are chemical kinetics and catalysis of reactions of industrial importance.



Green Context

The alkylation of aromatics is a particularly important area of industrial chemistry. In searching for more environmentally benign replacements for traditional hazardous acid catalysts such as aluminium chloride, numerous solid acid catalysts have been suggested. Determining the most appropriate of these is very difficult and here the information available on the kinetics of these reactions is renewed in an attempt to help progress the development of new greener processes. ***JHC***

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coefficients with dimension time^{-1} into k_1 coefficients as l g^{-1}·min^{-1}, C_{cat} is evaluated from the experimental details given by the authors. Obviously, such coefficients must be taken as monoalkylation coefficients.

Other authors have chosen to give second-order rate coefficients. In these cases, we have chosen a kinetic equation for monoalkylation such as eqn. (2):

$$r = k_2 \cdot C_{\text{arom}} \cdot C_{\text{alk}} \cdot C_{\text{cat}} \tag{2}$$

expressing r, whenever possible, as mol l^{-1}·min^{-1}, C_{arom} and C_{alk} (molar concentration of the aromatic and the alkylating agent, respectively) as mol l^{-1}, C_{cat} (mass concentration of the catalyst in the suspension) as g l^{-1}, so that k_2 is given as l^2 mol^{-1}·g^{-1}·min^{-1}.

In some cases, kinetic equations of the Langmuir–Hinshelwood type have been proposed. For monoalkylation such equations have the form of eqn. (3), *i.e.*, they contain a numerator similar to eqn. (2) but also a denominator which includes one or more adsorption constants K_{ads} for one or more components of the reaction system.

$$r = \frac{k_{\text{m}} \cdot C_{\text{arom}} \cdot C_{\text{alk}} \cdot C_{\text{cat}}}{(1 + \Sigma K_{\text{ads,j}} \cdot C_{\text{j}})^n} \tag{3}$$

where $n = 1$ or 2.

Analogous equations are employed for dialkylations and other reactions. It should be noted that in these equations the coefficient k_{m} is not a “true” rate coefficient because it also includes adsorption coefficients.

Finally, some authors were concerned about the deactivation rate of their catalysts, leading them to also study the kinetics of this phenomenon and to provide deactivation rate coefficients, with dimension time^{-1}. We have given such coefficients as k_{d} (min^{-1}). It is worth noting that they appear as first-order coefficients, but the relevant equations usually employ dimensionless variables so that the dimension of k_{d} does not give an idea of the actual form that the kinetic equation takes. Such forms will be specified when mentioning these deactivation coefficients.

In the cases of type (c), the measured rates given by the authors have been converted to units mmol g^{-1}·min^{-1}, for easier comparison.

As to the equipment for kinetic measurement, most articles mention stirred batch reactors, obviously slurry reactors, given the presence of solid catalyst. In some cases, when the nature of the alkylating agent and the reaction temperature required pressures higher than ambient pressure, stirred autoclaves were used. With gaseous alkylating agents, a semi-batch reactor was sometimes employed, maintaining a known C_{alk} value in the system.

2 Kinetic equations and kinetic parameters

Studies of type (a) were carried out at high stirring speed, checking, in most cases, that a further enhancement of the speed had no effect on the kinetics. In this way significant external mass transfer resistance was excluded. With regard to intraparticle resistance, care was taken (in most cases) to use very fine catalyst particles; in such cases very low Thiele modulus values and therefore catalyst effectiveness values close to unity can be calculated.

Table 1 shows typical results of studies of this type. The catalysts presented by the papers mentioned in Table 1 are zeolites (microporous crystalline aluminosilicates),[17] amorphous silica-aluminas, supported metal oxides, HAlMCM-41 (mesoporous aluminosilicates presenting uniform channels from 15 to 100 Å in size),[18,19] sulfated zirconia supported on HMS (a mesoporous material similar to MCM-41),[20] and Nafion (a perfluorinated polymeric sulfonic acid)[21] in the form of a Nafion–Silica composite.[22]

The alkylating agents in Table 1 are, in many cases, benzyl chloride or benzyl alcohol, and, less commonly, olefins. Most of the studies were carried out at relatively low temperatures, in the 60–100 °C range, with catalyst doses of a few grams per liter.

Table 2 shows typical results of studies of type (b). The catalysts concerned include, besides the kind of solid acids already present in Table 1, K10 (an acid-treated montmorillonite clay of large surface area), Clayzic (zinc chloride supported on K10 montmorillonite),[33] a heteropolyacid $H_{0.5}Cs_{2.5}PW_{12}O_{40}$, and supported metal chlorides.

The most common alkylating agent present in Table 2 is again benzyl chloride, benzyl alcohol and olefins being less commonly employed. The reaction temperatures were low, even lower than those of Table 1.

The values shown in Tables 1 and 2 concern several different reactions, a fact that makes comparison difficult. The kinetic measurements (pseudo-first order coefficients) on benzene alkylation using benzyl chloride, carried out at 80 °C or at temperatures close to 80 °C, provide the largest data set, allowing comparison of the different catalysts. The order of decreasing catalytic activity appears to be the following:

In_2O_3/Hβ[7] > $FeCl_3$/K10, $InCl_3$/K10[32] > $GaCl_3$/K10[32] > TlO_x/ZrO_2[30] > $H_{0.5}Cs_{2.5}PW_{12}O_{40}$[1] > Ga_2O_3/HZSM–5[31] > Clayzic[24]

with k_1-values differing by one order of magnitude from the first to the last member of the series. Note that, apart from one case, the mentioned catalysts are supported metal chlorides or oxides.

A few reactions have been carried out using a solvent different from the aromatic reagent. Eight different solvents were used in the reaction of phenol with cyclohexene over HY zeolite (Table 1), revealing that the alkylation rate had a peak for solvents of medium polarity.[5] Since the measured parameter was a pseudo-first order coefficient with respect to C_{alk}, it could be expected that these reactions, having a lower C_{arom} value, would show lower k_1-values than reactions carried out with an aromatic excess, the excess acting as both reagent and solvent. Further examples are given by the reactions of biphenyl with benzyl chloride in cyclohexane[6] (Table 1), and benzene with 1-dodecene in decane[28] (Table 2); both reactions employ a HY zeolite catalyst.

Among the cases listed in Table 2, some values are noteworthy: it is surprising how slow the reaction of toluene with benzyl alcohol over MCM-41[29] is, and how fast is that of benzene with 1–dodecene over HY;[26,27] in the latter case, the reason could be that the authors used a particularly efficient reactor.

Table 2 offers, for the same catalyst (Clayzic), the opportunity to compare an unactivated sample with a thermally activated one, under the same conditions:[23,24] activation increased the rate by more than one order of magnitude. The kinetic effect of alkyl substituents on benzene is less clear: with Clayzic as the catalyst, toluene and ethylbenzene reacted faster than benzene,[24,25] while with $InCl_3$/K10 as catalyst, toluene and mesitylene were found to be slightly less reactive than benzene.[32]

One group of studies (Table 1) employed the kinetic model corresponding to eqn. (3). In these, no straightforward comparison of the different reactions can be made as the rates depend not only on the coefficients k_{m} in the numerator but also on the constants $K_{\text{ads,j}}$ and the value of n in the denominator of the kinetic equations. However, it is possible to see that for the benzylation of biphenyl, the high-alumina silico-aluminate catalyst (Si/Al = 2.7) is more active than the low-alumina catalyst (Si/Al = 6.2),[13] and catalyst HAlMCM-41 is more active than either of the previous ones.[13,14] For the naphthalene reactions, data for the same temperature and the same solvent are available, but different benzylating agents and different catalysts were used, so the figures in Table 2 cannot be compared directly. However, it has been reported that BzOH is much more reactive than BzCl on the Nafion-silica composite, while the chloride is more reactive than the alcohol on the MCM-41 catalyst.[16]

Table 1 Evaluation of parameters within a kinetic equation, after tests about mass transfer resistance: typical results

Reference	Aromatic (solvent)[a]	Alkylating agent (pressure)[b]	Reactor [rpm][c]	T/°C	Catalyst	C_{cat}/ g l^{-1}	Parameter values (at temp. T,°C)
Pseudo-first-order kinetic equation (k_1/l g^{-1} min^{-1}) (k_d/min^{-1})							
5	phenol	c-hexene	batch	100	HY, Si/Al = 25		
	(dichlorobenzene)		[1000]			1.4	$k_1 = 0.0125$
	(cyclohexane)					1.5	$k_1 = 0.0056$
	(nitropropane)					1.7	$k_1 = 0.0011$
6	biphenyl (cyclohexane)	BzCl[d]	batch [825]	80	HY, Si/Al = 7	5–13	$k_1 = 0.0010$ $k_d = 0.25$[e]
7	benzene	BzCl	batch	60–80	In_2O_3/Hβ, Si/Al = 27	7.1	$k_1 = 0.090$ (80)
	anisole		[high speed + N_2 flux]	80			$k_1 = 0.014$
Second-order kinetic equation (k_2/l^2 mol^{-1} g^{-1} min^{-1})							
8	*p*-cresol	MTBE[f] (> 1 atm)	autoclave [700]	80–115	sulfated ZrO_2/HMS	30.8	$k_2 = 0.000020$ (100)
9,10	benzene	1-dodecene (24 atm)	fixed bed	85–125	$H_3PW_{12}O_{40}/SiO_2$	[g]	$k_2 = 0.000012$ (100)
Second-order kinetic equation (k_2/mol g^{-1} min^{-1} (mol fraction)$^{-2}$)							
11	benzene	propene (40 atm)	fixed bed	200–240	CaHY	[g]	$k_2 = 0.0024$ (230)
Langmuir–Hinshelwood kinetic model (k_m/l^2 mol^{-1} g^{-1} min^{-1}) (K_{ads}/l mol^{-1})							
12,13	biphenyl (cyclohexane)	BzCl	batch [825]	80	amorphous silica-alumina, Si/Al = 6.2	8–16	$k_m = 0.00058$ $K_{BzCl} = 10.6$ ($n = 1$)
13	biphenyl (cyclohexane)	BzCl	batch [825]	80	amorphous silica-alumina, Si/Al = 2.7	5–16	$k_m = 0.0021$ $K_{BzCl} = 12.2$ ($n = 1$)
	biphenyl (cyclohexane)	BzCl	batch [825]	80	HAlMCM-41, Si/Al = 19	3	$k_m = 0.0118$ $K_{BzCl} = 6.53$ ($n = 1$)
14	biphenyl (cyclohexane)	BzCl	batch [825]	80	HAlMCM-41, Si/Al = 19	2–4	$k_m = 0.0714$ $K_{BzCl} = 24.3$ $K_{BIP} = 5.4$ ($n = 2$) $k_d < 0.001$[e]
15	naphthalene (cyclohexane)	BzCl	batch [1000 + N_2 flux]	80	HAlMCM-41, Si/Al = 19.5	5	$k_{m1} = 0.46$[h] $k_{m2} = 0.19$[h] $K_{BzCl} = 10.3$ $K_{NA} = 12.6$ ($n = 2$)
16	naphthalene (cyclohexane)	BzOH[i]	batch [1000 + N_2 flux]	80	Nafion-Silica composite (15%)	2–3	$k_m = 0.50$ $K_{BzOH} = 110$ ($n = 2$)

[a] If different from the aromatic itself. [b] If different from ambient pressure (1 atm = 101.325 KPa). [c] Stirrer speed, when specified. [d] Benzyl chloride. [e] For an equation $-da/dt = k_d a^2$, where a is the catalyst activity coefficient. [f] Methyl-*tert*-butyl ether, as a source of isobutene. [g] Reaction carried out in a continuous tubular reactor. [h] k_{m1} and k_{m2} correspond to the monobenzylation to 1-benzyl- and 2-benzyl-naphthalene, respectively. [i] Benzyl alcohol.

3 Other kinetic measurements

Table 3 gives results typical of the type (c) studies, where the catalysts of interest include, besides the kind of solid acids seen in the previous paragraph, also an ion-exchange resin (Amberlyst 15) and SAPO–11 (a component of a class of microporous silicoaluminophosphates).[45] The alkylating agents are benzyl chloride and benzyl alcohol, olefins, and adamantyl bromide. Note that the temperatures are often higher than those in Tables 1 and 2.

The reactions considered in Table 3 were carried out at different temperatures and almost all differ one from the other, making it hard to compare the reaction rates. However for a common temperature an evaluation reveals the reaction rates of benzyl chloride with benzene and substituted benzenes to be similar (within an order of magnitude), apart from the case of the benzene reactions over supported $FeCl_3$ catalysts, where the rates were exceptionally high.[4] Again, the lowest rates were measured for reactions in solutions having low values of C_{arom}, as for biphenyl + propene in decalin[38] and for naphthalene + BzCl in dichloroethane.[40]

Needless to say, catalyst preparation matters. Table 3 shows two reactions of benzene with olefins,[43] where two types of Nafion–silica composite can be compared and it can be seen that they are of quite different activity, Type 2 being an order of magnitude more active than Type 1 for the same reaction at the same temperature.

In addition to the papers in Tables 1–3, other articles [type (d)] deal with the use of a heteropolyacid supported on silica,[46] Amberlyst 15 and analogous resins,[47–51] Clayzic,[52] sulfated zirconia,[53–54] MCM–22,[55] zeolite Hβ,[56] and heteropolyacid supported on K10 clay.[57–59]

The rates mentioned are those of forward alkylation reactions, as most authors gave no consideration to backward reactions, and those who did take them into account, for the alkylation of *p*-cresol with isobutene[51] and that of benzene with propene,[56] found them to be negligible.

The values of the kinetic parameters (coefficients, adsorption constants, rates) given in Tables 1–3 are ascribed to a specified temperature. However, some kinetic measurements were carried out at different temperatures, and apparent activation energy values (E_A) have been reported.

Table 4 shows the E_A values available for the reactions mentioned in the previous Tables. They are presented separately for the reactions of Table 1 and 2 (in both cases mostly values from 10 to 20 kcal mol^{-1}), and Table 3. In the case of the reaction of *o*-xylene with BzCl over Hβ, the very low value (4.0 kcal mol^{-1}) is evidence of a diffusional control.

Table 5 shows the E_A values available for additional reactions. In many cases they fall in the 10 to 20 kcal mol^{-1} range, but also values > 20 kcal mol^{-1} have been reported. In two cases values as low as 7–8 kcal mol^{-1} were measured, although the tests performed showed mass transfer resistances to be negligible.

Until now only the kinetic results for the mono-alkylation of aromatics have been considered; however, also kinetic data on consecutive dialkylation reactions are available. As shown in Table 6, the coefficient ratio for dialkylation and monoalkylation is in some cases < 1, in other cases ≅ 1, often > 1. The largest value

Table 2 Evaluation of parameters within a kinetic equation, without tests about mass transfer resistance: typical results

Reference	Aromatic (solvent)[a]	Alkylating agent (pressure)[b]	Reactor [rpm][c]	T/°C	Catalyst	C_{cat}/ g l^{-1}	Parameter values (at temp. T, °C)
Pseudo-first-order kinetic equation (k_1/l g^{-1} min^{-1}) (k_d/min^{-1})							
23	anisole	BzCl[d]	batch	20–50	K10	30.3	$k_1 = 0.000043$ (50)
	benzene	BzCl	batch	20–60	clayzic (unactivated)	35.7	$k_1 = 0.000104$ (50)
24	benzene	BzCl	batch	40	clayzic[e]	35.7	$k_1 = 0.00095$
	chlorobenzene	BzCl	batch	40	clayzic[e]	32.3	$k_1 = 0.00068$
25	toluene	BzCl	batch	40	clayzic[e]	30.8	$k_1 = 0.0319$
	ethylbenzene	BzCl	batch	40	clayzic[e]	30.8	$k_1 = 0.0015$
26,27	benzene	1-dodecene	fluidized bed	70–90	HY, Si/Al = 1.6	[f]	$k_1 = 1.12$ (80) $k_d = 0.31$[g]
1	benzene	BzCl	batch	80	$H_{0.5}Cs_{2.5}PW_{12}O_{40}$	174	$k_1 = 0.027$
28	benzene (decane)	1-dodecene (6–9 atm)	batch [500]	100–140	HY, Si/Al = 2.5	5	$k_1 = 0.0049$ (100)
29	toluene	BzOH[h]	batch [+air flux]	90	HAlMCM-41, Si/Al = *ca.* 10	8.7	$k_1 = 0.00017$
30	benzene	BzCl	batch[i]	80	TlO_x20%/ZrO_2 (low surface)	7.1	$k_1 = 0.0411$
	anisole	BzCl	batch[i]	80	TlO_x20%/ZrO_2 (low surface)	7.1	$k_1 = 0.0287$
31	benzene	BzCl	batch[i]	60–80	Ga_2O_3/HZSM-5, Si/Al = 31	7.1	$k_1 = 0.0210$ (80)
32	benzene	BzCl	batch[i]	60–80	$InCl_3$/K10	7.1	$k_1 = 0.0737$ (80)
	benzene	BzCl	batch[i]	60–80	$GaCl_3$/K10	7.1	$k_1 = 0.0451$ (80)
	benzene	BzCl	batch[i]	60–80	$FeCl_3$/K10	7.1	$k_1 = 0.0772$ (80)
	toluene	BzCl	batch[i]	80	$InCl_3$/K10	7.1	$k_1 = 0.0592$
	mesitylene	BzCl	batch[i]	80	$InCl_3$/K10	7.1	$k_1 = 0.0521$

[a] See the corresponding footnote in Table 1. [b] See the corresponding footnote in Table 1. [c] See the corresponding footnote in Table 1. [d] See the corresponding footnote in Table 1. [e] Thermally activated. [f] Unspecified. [g] For an equation $-\mathrm{d}a/\mathrm{d}t = k_d a^3$, where a is the catalyst activity coefficient. [h] Benzyl alcohol. [i] With N_2 flux.

was found during studies on the reaction of naphthalene with benzyl chloride over a MCM-41 catalyst: the second benzylation is reported as being much faster for 2-benzylnaphthalene than for the 1-benzyl isomer.[15]

4 Catalyst stability

In several cases, the authors also investigated the possibility of re-using the catalyst one or more times after a (batch) run. Table 7 shows the average loss in activity per re-use, evaluated from tabulated data or plotted results.

A different way of testing catalyst stability is to use the catalyst for continuous runs over a period of at least several hours. Runs in the CSTR mode revealed amorphous low-alumina silicoaluminate (Si/Al = 6.2)[12] and HAlMCM-41[14] to have constant behaviour in the reaction of biphenyl with benzyl chloride; an analogous reaction using naphthalene again evidenced the stability of HAlMCM-41[15] and, in the reaction of naphthalene with benzyl alcohol, stability was also found for the Nafion–silica composite.[16] In contrast, the same kind of test showed a slight loss in activity for amorphous high-alumina silicoaluminate (Si/Al = 2.7).[13] Runs in a fixed bed continuous reactor, for the reactions of benzene with ethene or propene, revealed MCM-22 to be stable.[55]

In other cases, the catalysts underwent regeneration and were then proved to be re-usable. This was the case of Hβ[44] and Amberlyst-15.[48]

Among the reactions taken into account, some of the kinetic models of the alkylation processes included catalyst deactivation. In these cases, a deactivation rate coefficient k_d was evaluated. The values reported in Tables 1–3 correspond to different kinetic equations, so their numerical values have to be interpreted. By integrating the kinetic equations, it can be seen that:

for HY (Si/Al = 7) in the benzylation of biphenyl,[6] where k_d = 0.25 min^{-1}, this means that over 60 min the activity is lowered from 100% to about 6%;

for HAlMCM-41 in the same reaction,[14] where $k_d < 0.001$ min^{-1}, this means that over 60 min the activity is lowered from 100% to a fraction > 94%;

for HY (Si/Al = 1.6) in the reaction of benzene with 1-dodecene,[26,27] where k_d = 0.31 min^{-1}, this means that over 60 min the activity is lowered from 100% to 16%.

In the case of *o*-xylene reacting with styrene over Amberlyst-15,[37] k_d = 0.056 min^{-1}, the coke formation measured revealing that about 3% coke is deposited on the catalyst over 60 min.

5 Conclusions

The kinetic parameters for many monoalkylation reactions, over different types of solid acids, often at 40 to 100 °C, are reported in the scientific literature. In several cases, also apparent activation energy has been measured. In the present review, research papers including a discussion on resistances to mass transfer have been indicated.

Aromatics like benzene, toluene, the xylenes, biphenyl, the phenols and anisole are the ones given the most consideration. The most common alkylating agents are benzyl chloride, olefins and alcohols. The most commonly employed catalysts are zeolites, supported metal chlorides and oxides, mesoporous (MCM) materials and heteropolyacids, these are followed by sulfated zirconia, ion-exchange resins, Nafion derivatives, and other minor items.

Data available on the kinetics of successive dialkylation reactions are also presented, the kinetic parameters usually being of the same order as those of the first reaction.

The catalysts were often tested for their stability, particularly keeping in mind their recycling for re-use: in several cases this was found possible, though usually with some loss of catalytic activity.

Table 3 Measured alkylation rates *r* (in most cases, initial rates)

Reference	Aromatic (solvent)[a]	Alkylating agent (pressure)[b]	Reactor [rpm][c]	T/°C	Catalyst	r/mmol g^{-1} min^{-1}
34	benzene	BzCl[d]	batch [900]	95	sulfated ZrO_2	$r = 0.194$
2	*m*-xylene	*c*-hexene	batch	100	$H_{0.5}Cs_{2.5}PW_{12}O_{40}$	$r = 0.41$
	mesitylene	*c*-hexene	batch	100	$H_{0.5}Cs_{2.5}PW_{12}O_{40}$	$r = 0.44$
35	toluene	BzCl	batch [700 + N_2 flux]	110	HY, Si/Al = 20	$r = 1.12$
36	benzene (decane)	1-dodecene (6 atm)	batch [500]	100–130	HY, Si/Al = 2.7	$r = 2.80$ (100)
37	*o*-xylene	styrene	batch [1500]	60–100	Amberlyst 15[e]	$r = 0.49$ (80)
38	biphenyl (decalin)	propene (> 1 atm)	stirred autoclave	250–300	SAPO-11	$r = 0.015$ (300)
	biphenyl (decalin)	propene (> 1 atm)	stirred autoclave	250	H-Mordenite	$r = 0.055$
39	benzene	BzOH[f]	batch [+N_2 flux]	80	Nafion–Silica composite (13%)	$r = 1.72$
	p-xylene	BzOH	batch [+N_2 flux]	100	Nafion–Silica composite (13%)	$r = 2.97$
40	naphthalene (dichloroethane)	BzCl	batch	40–70	Hβ, Si/Al = 13	$r = 0.009$ (70)
41	*o*-xylene	BzCl	batch	90–135	Hβ, Si/Al = 13	$r = 0.21$ (90)
42	toluene	Ad-Br[g]	batch	111	Nafion–Silica composite (13%)	$r = 3.38$
43	benzene	1-dodecene	batch	80	Nafion–Silica comp. (13%) [Type 1]	$r = 0.080$
	benzene	1-dodecene	batch	80	Nafion–Silica comp. (13%) [Type 2]	$r = 1.08$
	benzene	propene	semi-batch	70	Nafion–Silica comp. (13%) [Type 1]	$r = 0.115$
	benzene	propene	semi-batch	70	Nafion–Silica comp. (13%) [Type 2]	$r = 0.72$
44	bromobenzene	BzCl	batch	130	HY, Si/Al = 2.8	$r = 0.50$
	bromobenzene	BzCl	batch	130	Hβ, Si/Al = 4.5	$r = 0.40$
	bromobenzene	BzCl	batch	130	Hβ, Si/Al = 13	$r = 0.23$
	bromobenzene	BzCl	batch	130	K10, Si/Al = 3.1	$r = 0.62$
4	benzene	BzCl	batch [+N_2 flux]	80	$FeCl_3$/K10	$r = 24.2$
	benzene	BzCl	batch [+N_2 flux]	80	$FeCl_3$/Si-MCM41	$r = 19.8$

[a] See the corresponding footnote in Table 1. [b] See the corresponding footnote in Table 1. [c] See the corresponding footnote in Table 1. [d] See the corresponding footnote in Table 1. [e] With catalyst deactivation due to olefin oligomers (coke); for a zero-order reaction of formation of % coke, measured $k_d = 0.056$ min^{-1} (80 °C). [f] Benzyl alcohol. [g] Adamantyl bromide.

Table 4 Apparent activation energies for reactions listed in Tables 1–3

Reference	Reaction (parameter)[a]	E_A/kcal mol^{-1}
from Table 1		
7	benzene + BzCl over In_2O_3/Hβ (k_1)	17.6
9,10	benzene + 1-dodecene over $H_3PW_{12}O_{40}/SiO_2$ (k_2)	10.9–11.5[b]
11	benzene + propene over CaHY (k_2)	23.6
from Table 2		
23	anisole + BzCl over K10 (k_1)	15.6 ± 2.9
	benzene + BzCl over Clayzic (unactivated) (k_1)	14.2 ± 2.2
26,27	benzene + 1-dodecene over HY (k_1)	20.6
28	benzene + 1-dodecene over HY (k_1)	12 ± 3
31	benzene + BzCl over Ga_2O_3/HZSM-5 (k_1)	16.1
32	benzene + BzCl over $InCl_3$/K10 (k_1)	14.5
	benzene + BzCl over $GaCl_3$/K10 (k_1)	15.1
	benzene + BzCl over $FeCl_3$/K10 (k_1)	11.6
from Table 3		
36	benzene + 1-dodecene over HY (r)	15
41	*o*-xylene + BzCl over Hβ (r)	4.0

[a] Kinetic coefficient (k_1, k_2) or rate (r) on which the evaluation of E_A was based. [b] Range of values, according to the product isomer.

Table 5 Apparent activation energies for other alkylations

Reference	Reaction	E_A/kcal mol^{-1}
49	phenol + 1-dodecene over Amberlyst-15[a]	7.4
56	benzene + propene over β zeolite[a]	7.8
48	phenol + isobutene over Amberlyst-15[a]	12.3 (to *p*-alkylate) 13.8 (to *o*-alkylate)
46	benzene + 1-dodecene over $H_4SiW_{12}O_{40}$	13.8
52	anisole + BzCl over Clayzic	15.5
55	benzene + propene over MCM-22	18.4
58	phenol + methyl *tert*-butyl ether over $H_3PW_{12}O_{40}$/K10[a]	18.5
59	benzene + 1-dodecene over $H_3PW_{12}O_{40}$/K10[a]	20.1
53	*p*-cresol + isobutene over sulfated zirconia[a]	22.9
51	*p*-cresol + isobutene over Amberlyst-15[a]	23.2
54	benzene + BzCl over sulfated zirconia[a]	28.0

[a] For these reactions tests are reported showing that mass transfer resistances were negligible.

Table 6 Ratio of kinetic coefficients for dialkylation and monoalkylation

Reference	Reaction	T/°C	Ratio (dialkyl/monoalkyl)
51	*p*-cresol + isobutene over Amberlyst-15	65	0.21
56	benzene + propene over β zeolite	100	0.45
53	*p*-cresol + isobutene over sulfated zirconia		0.65
46	benzene + 1-dodecene over $H_4SiW_{12}O_{40}$	65–150	1
6	biphenyl + BzCl over HY	80	1
11	benzene + propene over CaHY	230	1.15
12,13	biphenyl + BzCl over amorphous silica-alumina		
	having Si/Al = 6.2	80	2
	having Si/Al = 2.7	80	2.5
13,14	biphenyl + BzCl over HAlMCM-41	80	2.5
15	naphthalene + BzCl over HAlMCM-41		
	for 1-benzylnaphthalene	80	1.4
	for 2-benzylnaphthalene	80	45
16	naphthalene + BzCl over Nafion–silica composite	80	4.6

Table 7 Re-use of the catalysts and loss of activity

Reference	Reaction	Catalyst	No. of re-uses	Average loss of activity per re-use
16	naphthalene + BzOH	Nafion–silica composite	3	negligible[a]
31	benzene + BzCl	Ga_2O_3/HZSM–5	3	negligible
32	benzene + BzCl	$InCl_3$/K10	5	~1%
7	benzene + BzCl	In_2O_3/Hβ	5	~2%
7	benzene + BzCl	$InCl_3$/Hβ	5	~5%
54	benzene + BzCl	sulfated ZrO_2–Fe_2O_3	3	~4%
58	phenol + MTBE	$H_3PW_{12}O_{40}$/K10	3	~5%
59	benzene + 1-dodecene	$H_3PW_{12}O_{40}$/K10	2	~6%
8	*p*-cresol + MTBE	sulfated ZrO_2/K10	2	~18%
37	*o*-xylene + styrene	Amberlyst–15	5	~18%
41	*o*-xylene + BzCl	Hβ	3	~23%
4	benzene + BzCl	$FeCl_3$/K10 or $FeCl_3$/SiMCM–41	1	40–50%
54	benzene + BzCl	sulfated ZrO_2	1	>87%

[a] when recycling is effected at reaction temperature

Given the practical importance of catalyst re-use, further work is needed in this field.

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CRITICAL REVIEW
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Electron transfer mediator systems for bleaching of paper pulp

D. Rochefort,[a] D. Leech*[b] and R. Bourbonnais[c]
[a] *Départment de chimie, Université de Montréal, C. P. 6128, Succursale Centre-ville, Montréal, Québec H3C 3J7, Canada*
[b] *Department of Chemistry, National University of Ireland, Galway University Road, Galway, Ireland. E-mail: donal.leech@nuigalway.ie*
[c] *Pulp and Paper Research Institute of Canada, 570 Boul. St-Jean, Pointe-Claire, Québec, Canada H9R 3J9*

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The participation of biological agents in pulp bleaching systems has received a lot of attention from research teams around the world, driven by the environmental benefits that biobleaching could bring. Nature showed us the ability of some of its agents, such as wood-decaying fungi, to delignify and bleach wood and wood pulp. What we need to do is to enhance the efficiency of such agents to make them cope with the fast pace of our modern pulp mills. To do so, a profound understanding of the biobleaching system is required. Our efforts to discover new efficient mediators for the laccase-mediator system (LMS) brought us to use several techniques to analyse the reactions involved in mediated enzymatic delignification. Mostly based on electrochemistry, these techniques are reviewed in this paper, along with key results. Cyclic voltammetry was used to characterize electron transfer rates between each element of the LMS. We found, along with other authors, that the mediator redox potential has a great influence on its efficiency. We used bulk electrolysis to simulate the oxidative action of laccase on mediators and model compounds of lignin. Such electrolysis techniques allowed us to study mediated lignin oxidation outside of normal laccase working conditions. Finally, an electrolysis-based method for mediated pulp delignification that we developed, based upon our research on biobleaching, is presented.

1.0 Introduction

Wood is the main source of fibre for pulp and paper production. It is composed of cellulose, lignin, hemicelluloses, and extractives compounds in proportions that vary with the type and essence of the wood. The structure of wood can be represented as an agglomeration of long and slim fibres that are maintained together by the lignin, acting as a natural glue to give wood its physical properties. The wood fibres are mainly composed of cellulose and hemicelluloses, but also contain lignin within the fibre wall. To produce chemical pulp, the lignin is removed in order to free the fibres, which will eventually be used to make paper. During mechanical pulping, however, the fibres are separated from one another by a mechanical action. Lignin remains in mechanical pulps and the use of such pulps (newspaper) does not require complete bleaching. The present text will only be concerned with chemical pulp. Lignin is a very complex polymer, which is composed of phenyl-propane subunits linked together by various types of bond. The aromatic groups, found in great proportion in the lignin, can be classified as either phenolic or non-phenolic and may contain different substituents. The lignin has therefore no defined structure and its composition may also vary with the type of wood. However, a detailed scheme showing the known lignin structural elements has been published by Adler in 1977 (Fig. 1).[1] Chemical pulping processes use strong chemicals, mostly sodium hydroxide, to hydrolyse the covalent links of the lignin and to depolymerise it. The kraft pulping process uses a combination of sodium hydroxide and sodium sulfide, the latter being able to extend the delignification to lower lignin content than NaOH alone. Pulp obtained by this process is also stronger than without Na_2S, hence the name kraft, which is the German word for strength. Along with these advantages, the kraft process can be operated in a closed circuit, where the cooking chemical solutions (known as cooking liquors) are burnt, allowing production of heat and chemical recovery. Kraft pulping is the most widely used method of pulp production, leading the market with almost 70% of all the pulp produced worldwide.[2] The specific chemical reactions involved in kraft pulping will not be reviewed here as we will focus on bleaching reactions. The interested reader will find more information on chemical pulping in the literature.[3]

Although very efficient, the kraft process does not remove all of the lignin contained in wood. The lignin surrounding fibres is removed but there is a residual of lignin within the fibre wall. Unbleached kraft pulp contains about 5% of lignin per unit of weight, lignin that must be removed since unbleached kraft pulp is very dark. This remaining lignin is tightly bound and strong oxidants must be used to remove it, which is a part of the objective of pulp bleaching. These oxidants, such as chlorine, chlorine dioxide, and oxygen, are necessary to oxidise and depolymerise the remaining lignin, to delignify pulp. The specific delignification reactions of these agents will be discussed in the text. Furthermore, side reactions during chemical cooking of wood produce light absorbing compounds such as quinones, which darken the pulp. To improve optical properties of the pulp, it must be bleached.

Green Context

Traditional bleaching methods in the pulp and paper industry rely heavily on chlorine and its derivatives, and thus place a heavy burden on the environment. Newer methods are available, but often lack the power of the chlorine-based systems. This paper discusses the use of enzymatic systems in bleaching, in particular the use of mediated systems, which promise excellent levels of bleaching with a good environmental performance. ***DJM***

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1.1 Traditional bleaching

Molecular chlorine appeared in the pulping industry in the early 1900s. It is easily produced at low cost, easy to use, and has a high reaction rate. Chlorine-bleached pulp is also of very good quality since Cl_2 is very selective towards lignin, preventing cellulose-degrading reactions. Chlorine reacts with lignin *via* oxidation, substitution, and addition reactions. While the oxidation reactions take place on the substituents of the phenyl groups of lignin, substitution and addition occur mostly on the phenyl. All these reactions result in the depolymerisation of the lignin polymer, giving smaller, soluble fragments that can be removed from pulp with an alkaline extraction. A detailed overview of the reaction of chlorine with lignin can be found in other papers[4,5] and in references cited therein. Overall, chlorine bleaching offers the best efficiency at low cost. However, as stated before, addition reactions of chlorine on lignin phenyl units can occur. The formation of toxic compounds such as dioxins and furans can result from addition, being the major drawback of the use of chlorine to bleach pulp. To avoid accumulation of these stable products in the environment, usage of chlorine decreased significantly since the late 1980s, being replaced by chlorine dioxide.

Chlorine dioxide appeared in the pulping industry in the middle of the 20th century as an additive to chlorine bleaching agent.[6] ClO_2 gradually replaced chlorine as the so-called ECF (elemental chlorine free) bleaching method, and is now the principal kraft pulp bleaching agent. Chlorine dioxide, being an electrophile, will react preferentially with electron-rich structural elements, such as phenyl units. It degrades lignin by oxidation and aromatic substitution reactions. The exact reaction mechanisms leading to bond breaking and subsequent delignification depend upon which position the phenyl group will be oxidised. The radical cation formed on the phenyl unit will then degrade to depolymerise lignin.[4] ClO_2 bleaching is also very efficient and yields a very high quality pulp. However, one of the major environmental drawbacks of its use is the formation of chloride as a reaction product. The presence of chloride in the bleaching wastewater prevents system closure to avoid corrosion of the mill water circuit. The large amounts of water required to wash pulp between and during bleaching sequences must therefore be treated then released in the environment instead of being reused in the mill.

Total chlorine free (TCF) bleaching methods rely on non-chlorinated chemicals to bleach pulp. Oxygen, ozone, and hydrogen peroxide are examples of such TCF bleaching agents, the details of which can be found in other texts.[7–9] Another alternative bleaching method is the use of biological agents that are able to degrade lignin, the biobleaching, which is part of the focus of this paper.

The goal of this paper is to review the electron transfer approaches to pulp bleaching, with a particular emphasis on biobleaching and the laccase-mediator system (LMS). We will present an overview of the mediators used, including recently proposed transition metal compounds, and the various approaches used to characterise their role in the system. Recently electron transfer approaches to pulp bleaching have expanded to include electrochemical methods for pulp bleaching, replacing the biological oxidant with an electrode: electrodelignification. An entire section will thus also be devoted to reviewing electrochemical methods for pulp bleaching and mediated oxidation of kraft pulp lignin.

1.2 Biobleaching

It has been known for over 40 years that some types of fungi, more particularly basidiomycetes (or white-rot fungi) are able to degrade lignin from wood.[10] These fungi grow on dead wood to decay it. Experimental work later showed that basidiomycetes also degrade

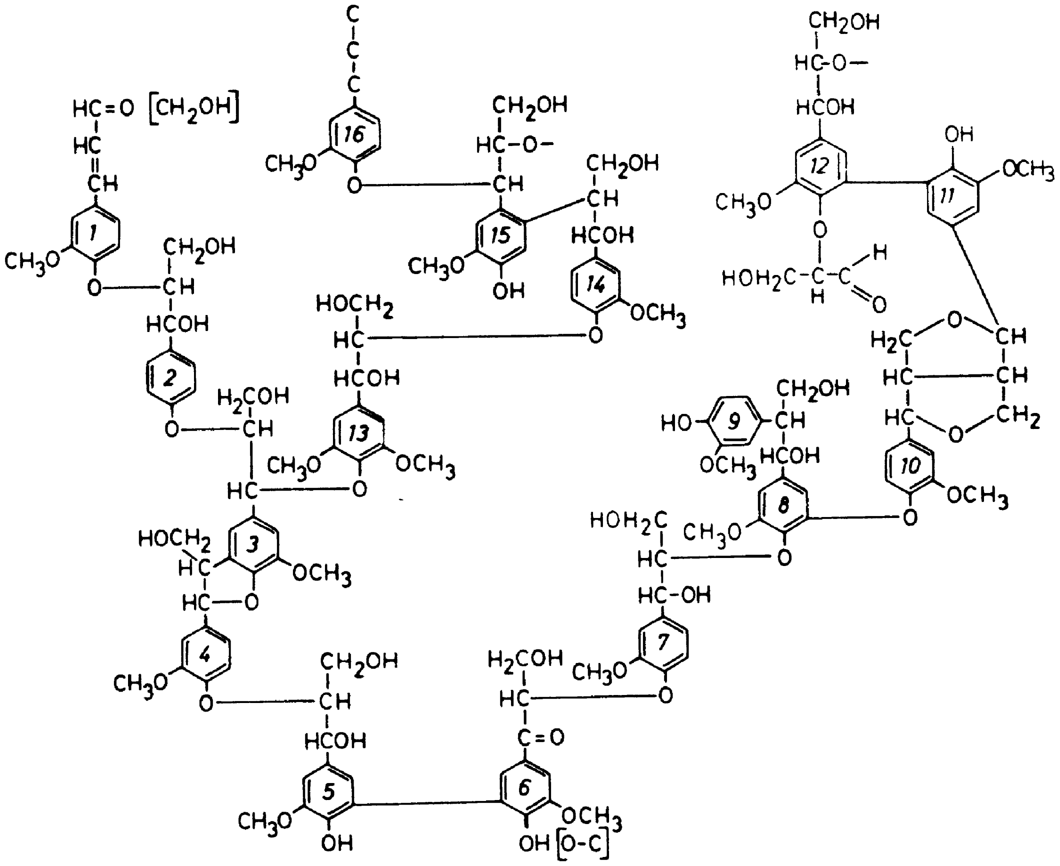


Fig. 1 Softwood lignin structure as proposed by E. Adler, "Lignin Chemistry – Past, Present and Future", *Wood Science and Technology*, 1977, **11**, 169–218 (ref. 1); Figure 30, p. 203. © Springer-Verlag.

lignin remaining in unbleached kraft pulps,[11–13] opening the way for biobleaching. Although capable of extensive delignification (up to 60%), the reaction rates of bleaching with fungi are very low and such delignification can only be obtained in a matter of days. Such reaction time is too long to cope with the high production rate of kraft pulp mills, even if the treatment represents non-negligible chemical savings. Basidiomycetes perform lignin degradation by secreting a variety of oxidative enzymes, including laccases,[14] lignin peroxidases,[15] and manganese peroxidases.[16] Bearing in mind that the secreted enzymes are responsible for the delignifying action, isolating and concentrating these enzymes for direct use on pulp could improve the rate of biobleaching. This would make a more interesting system for a mill application. Among the several enzymes that have been isolated and used to bleach pulp,[17] we focus on the laccases. Laccase is perhaps the most intensively studied enzyme for pulp delignification because of its excellent oxidative properties. However, since there is only one class of enzyme that currently is commonly used in pulp mills, the xylanases, their use is also described.

1.2.1 Xylanases. Biobleaching is not restricted to the use of oxidative enzymes. While their action on pulp is totally different, other enzymes, such as xylanases, can be used to increase the efficiency of pulp bleaching and delignification. In fact, xylanases were the first enzymes to be introduced for pulp biobleaching.[18] In their 1986 paper, Viikari *et al.* showed that adding xylanase in a traditional pulp bleaching sequence greatly reduces the amount of bleaching agent required in the sequence. This enzyme addition allows higher brightness levels to be reached and a reduction in the amount of chlorinated organic compounds in the effluents. Xylanase can be obtained from fungal and bacterial sources, and several industrial suppliers can now be found.[19]

Xylan is one type of hemicellulose found in wood that acts as a linking agent between lignin and cellulose.[20] When wood is cooked using high alkaline charge, xylan is depolymerised and solubilised. As cooking goes on, the alkalinity of the solution decreases, causing some xylan to precipitate on the fibres. One mechanism that could explain the beneficial effect of xylanase on pulp bleaching is that the enzyme catalyses the depolymerisation of precipitated xylan. The bleaching chemical would therefore have easier access to lignin, increasing the efficiency of the bleaching sequence.[19] Xylanase is therefore more a bleaching-aiding enzyme than a true delignification agent like oxidative enzymes such as the laccases.

1.2.2 Laccases. Laccase was discovered in 1883 as being responsible for the coagulation of lacquer produced by lacquer trees.[21] There have been numerous studies on this enzyme since then. The papers from Solomon *et al.*,[22] Reinhammar,[23] Thurston,[24] and Yaropolov *et al.*[25] offer a comprehensive description of the properties and structure of the laccase enzyme. The crystal structure of the *Trametes versicolor* fungal laccase has recently been published.[26] Several applications and an extensive list of fungal sources can be found in the review from Gianfreda *et al.*[27]

Laccase is found in many plants and trees, but also in some bacteria and insects. It is however in fungi that laccase is most commonly found.[27] Laccase, a blue copper enzyme, possesses an active site which consists of four copper atoms sub-classified into three different types, T1, T2, and T3, according to the different EPR spectrum of each copper atom.[22] Laccase can oxidise a substrate *via* the four-electron reduction of dioxygen to water. Substrate oxidation occurs at the T1 monoatomic copper site, while the T2/T3 triatomic copper cluster is responsible for O_2 reduction. This property of the laccase makes it very appealing for delignification since the only chemical necessary for substrate oxidation is oxygen. For several reasons, laccase alone has only a very limited effect on lignin degradation. Firstly, laccase can oxidise the non-phenolic groups (see Fig. 1) of lignin only at a very slow rate due to their high oxidation potential, which can reach values over 1 V *vs.* Ag/AgCl.[28] Fungal laccases such as those from the basidiomycete *Trametes versicolor*),[22] have a redox potential (E^0) of 0.575 V *vs.* Ag/AgCl, which is considered to be high, compared to that of laccases from other sources. The large potential gap between laccase and these non-phenolic groups makes the oxidation reaction thermodynamically uphill, and thus results in slow reaction rates. The enzyme can however oxidise the phenolic groups (laccase's natural substrates) much more rapidly since they have low oxidation potentials. Since kraft pulp lignin contains an appreciable quantity of phenolic groups, this results in unwanted consequences, such as polymerisation. The second reason for the limited action of laccase alone on kraft pulp lies in its size. Due to its size, laccase is unable to rapidly diffuse into the fibre wall to reach the remaining fragments of lignin (see Fig. 2). This severely reduces the quantity of potentially oxidisable groups since only the outermost ones will be readily accessible to laccase. These size and thermodynamic related limitations can be partially overcome with the addition of another element to the system: a mediator.

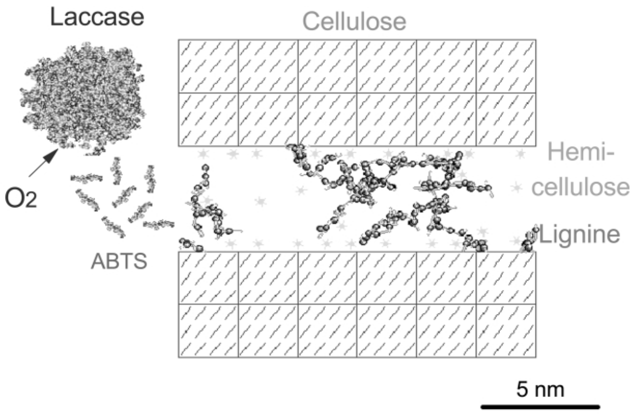
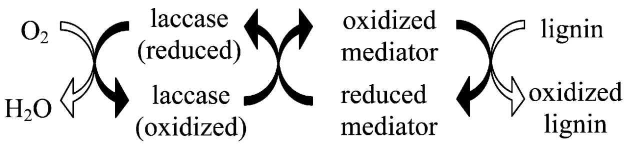


Fig. 2 Representation of a fibre secondary wall from unbleached kraft pulp.[74] The mediator (here ABTS) can diffuse back and forth between laccase and remaining lignin fragments.

1.3 The laccase-mediator system (LMS)

A mediator is a small redox molecule that acts as an electron carrier between lignin and laccase. Once the mediator is oxidised, by giving one or several of its electrons to laccase, it will diffuse into the pulp fibre wall to oxidise lignin. The mediator then gains electrons from the lignin fragment that is oxidised to return to its reduced state, making it available once again for oxidation by laccase. Overall, the laccase-mediator system acts as a catalyst to oxidise lignin by transferring electrons from its oxidisable groups to oxygen. This simplifed mechanism is depicted in Scheme 1. This catalytic cycle will go on as long as there is oxygen present in the system and until oxidation of the lignin becomes too difficult. Contrary to laccase, the mediator is able to diffuse within the fibre wall due to its small size (see Fig. 2) and gain better access therefore to the oxidisable groups of lignin. Also a mediator with a high redox potential will likely react more efficiently with phenolic and non-phenolic groups in lignin than a low redox potential mediator, resulting in enhanced delignification. Finally, because of their



Scheme 1 Representation of the successive oxidation and reduction reactions of the laccase mediator system to delignify pulp.

smaller molecular weight in proportion to the enzyme, accumulation of a higher local concentration of mediator in the pulp fibre may explain the more effective oxidation of laccase-mediator systems. This more effective oxidation makes the laccase-mediator systems interesting for industrial kraft pulp delignification.

The first mediator that was used in the laccase-mediator system for pulp delignification is 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulfonate) (ABTS), which was introduced by Bourbonnais and Paice in 1990.[29] Their research results showed that laccase used in conjunction with a mediator (ABTS) was able to extend the oxidation of lignin to its non-phenolic groups. Further studies demonstrated that the laccase-mediator could be used to efficiently delignify unbleached kraft pulp to high levels (50% delignification).[30,31] It was also shown that the mediated enzymatic oxidation with laccase and ABTS is selective towards lignin. Degradation of cellulose decreases bleached paper quality and so must be avoided during delignification. The laccase–ABTS system does not affect pulp viscosity, which measures the degree of cellulose polymerisation, and is thus indicative of pulp quality.[31]

1.3.1 Mediators

Since that discovery, several other compounds have been introduced for use in the laccase-mediator system for pulp delignification. These mediators and references to their application are presented in Table 1. As it can be noted from Table 1, most mediators are organic-based compounds, often containing an N-hydroxyl functionality. Most of them, when oxidised by laccase, form a radical which is responsible for their high reaction rates for lignin oxidation. Their radical nature, however, causes some problems of stability, limiting their use for catalytic delignification. HBT (1-hydroxybenzotriazole) and violuric acid for instance, are known to degrade rapidly and in some cases, to attack laccase, resulting in a diminution of the enzyme activity.[32,33]

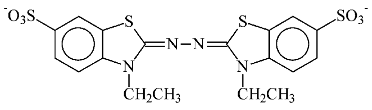
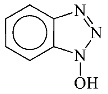
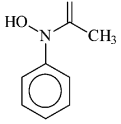
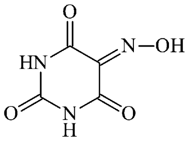
In an effort to improve the laccase-mediator system for pulp delignification, we recently proposed the use of transition metal coordination complexes as mediators.[34,35] These compounds do not form radicals when oxidised by laccase, and the electron exchange is centred on the metallic atom of the complex. This type of electron exchange involving only transition metal redox reactions allows the use of mediators with high stability in both oxidation states. This is a great advantage over the other type of mediators. Comparison of their efficiency with that of radical-forming mediators will be discussed in the following sections.

From the results of the numerous studies on the laccase mediator system, it is possible to define the most essential characteristics required for an efficient mediator.

- The mediator must be a substrate for laccase, which is generally not a problem since this enzyme can oxidise a large variety of compounds. This relatively low selectivity is due to the exposed T1 active site, which is located near the surface of the laccase proteinic skeleton.
- Results of studies on mediator formal potentials ($E^{0\prime}$)[36–39] point out that altering the mediator $E^{0\prime}$ has a very important effect on the overall efficiency of the system. The most significant explanation for its effect lies in the thermodynamic point of view of the electron exchange reaction. As stated earlier in the text, laccases have an oxidation potential that is too low to efficiently oxidise all the groups in lignin, which makes the reaction thermodynamically uphill. To have a thermodynamically favourable reaction, a mediator with a formal potential higher than the oxidation potential of the non-phenolic groups should be used. Unfortunately, this high $E^{0\prime}$ mediator would be only slowly oxidised by laccase, if at all, for the same thermodynamic explanation. These limits heavily restrain the number of compounds that could be used as a mediator.
- The mediator should be stable in both of its oxidation states to prevent losses and unwanted side-reactions during the treatment.
- The electron exchange rate between laccase and mediator, as well as between the mediator and lignin, should be fast.
- Considering an eventual mill application, the mediator should be available in large quantities at a low cost and be non-hazardous for the environment.

With a suitable mediator at hand, the laccase-mediator can be studied either for evaluating the efficiency of a new mediator or to

Table 1 List of most commonly used mediators for pulp delignification studies

Mediator	Pulp delignification references	Lignin model compound oxidation references
 **ABTS** 2,2’-azinobis(3-ethylbenzthiazoline-6-sulfonate)	31,75,76	29,33,44,46,47,77–80
 **HBT** 1-hydroxybenzotriazole	41,58,81–86	32,33,76,80,87–89
 **NHA** N-hydroxyacetanilide	90–93	38
 Violuric acid	94	33,38

elucidate mechanisms. Since the exact mechanisms of pulp delignification are still unclear, the use of different mediators can be useful in explaining the reactions occurring during delignification.

2.0 Characterisation of reactions involved in laccase-mediator system

There are numerous publications on different methods used to study the efficiency of the laccase-mediator system. This section will present the direct pulp delignification technique, the use of lignin model compounds and of electroanalytical methods, to gain knowledge of delignification chemistry as well as to evaluate the efficiency of the laccase-mediator system.

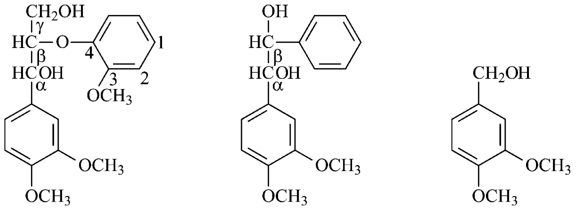
Perhaps the most simple and representative method is the direct pulp treatment, which consists of a lab-scale version of a mill treatment to reproduce mill conditions. The pulp is afterward analysed to evaluate the efficiency of the treatment, most often by measuring three parameters; kappa number, brightness level and viscosity. These three parameters of pulp will be described, since the reader will find several references to these in the text.

The kappa number (K) is used to evaluate the residual lignin content of a pulp. This number corresponds to the volume of a 0.1 N $KMnO_4$ solution that is consumed (reduced) by the lignin contained in one gram of dry pulp. Therefore, a treatment with high delignification efficiency will result in a large decrease of the kappa number. The brightness level of pulp is simply a measure of the light reflected by the sample at a fixed wavelength.[40] Brightness is useful as an indication of the efficiency of a bleaching treatment for highly bleached pulps as kappa number becomes less accurate near very low values. Finally, the viscosity index gives an evaluation of the pulp quality. The viscosity loss due to a treatment should be minimal as a decrease in viscosity indicates a decrease in the average cellulose chain length, which weakens the eventual paper's physical properties.

Although useful to evaluate the overall efficiency of a pulp treatment, measuring these three properties provides neither details on the reactions mechanisms nor on the identity or type of lignin subunits that are being oxidised during the treatment. Furthermore, no information relative to the reaction rates can be extracted from these measurements so we must rely on different, more powerful methods. The most widely used method to obtain detailed insights into the reactions governing pulp delignification by the laccase-mediator system is the study of the effects of the system on lignin model compounds. A literature database search for lignin model compounds over the last ten years returned over 250 entries with nearly 50 concerning studies with the laccase-mediator system. The next section is therefore devoted to this subject.

2.1 Lignin model compounds

Lignin model compounds (LMCs) are soluble low molecular weight molecules that are used to represent some of the functional groups or linkages of lignin. As mentioned in the introduction and as depicted in Fig. 1, lignin is a very complex and irregular polymer that, in addition, varies in structure from wood species to species. Due to these characteristics and to its very low solubility, experimentation on lignin is difficult. To avoid the limitations inherent to the use of lignin, experiments can be conducted on lignin model compounds. Another noteworthy advantage of using LMCs over lignin is that it allows the evaluation of the reactivity of a specific type of linkage, which is represented by the model compound. Most commonly used LMCs are β-O-4 and β-1 dimers, which are used to represent these bonds in lignin. For an example of such types of bond, the reader is referred to the links between phenyls #7 and #8 for β-O-4 model and phenyls #14 and #15 for β-1 model (Fig. 1). Model compounds representing these particular bonds are shown in Fig. 3. The relevance of the use of such model compounds is often questioned on their ability to really represent the reactivity of bonds in the lignin. The LMCs are indeed solvated molecules while the real bonds in lignin are in a complex insoluble matrix. The LMC studies are however undoubtedly useful for mediator screening. It is clear that an oxidative system that is able to oxidise a particular chemical bond will not automatically be able to oxidise the corresponding functional group found in lignin. On the other hand, a mediator that is unable to oxidise the most reactive model compound will have a rather limited efficiency for lignin degradation.



ß-O-4 dimer ß-1 dimer Veratryl alcohol (**VA**)

Fig. 3 Non-phenolic lignin model compounds representing important oxidisable groups in kraft pulp residual lignin.

The procedure used is almost constant throughout the literature on the subject. A solution containing an oxidising agent (such as laccase), a mediator, and the model compound is left to react and then analysed to measure the concentration of unreacted LMC and to identify and quantify oxidation products. This information can then be used to evaluate the efficiency of the treatment and to elucidate oxidation mechanisms from the nature of the oxidation products detected.

2.1.1 Role of the mediator. As stated earlier, the presence of a mediator is a prerequisite for efficient enzymatic delignification. The exact role of the mediator in the laccase-mediator system is however debatable. The few hypotheses on this subject have been enumerated in another paper[32] and are presented here in detail. In the first hypothesis, which has already been presented in this text, the mediator acts as an electron carrier between lignin and laccase (see Scheme 1). This hypothesis, supported in many papers,[34,36,38,41] implies that the mediator reacts by subtracting an electron from the lignin model compound. This is an important difference with the second hypothesis in which the mediator reacts by abstracting a hydrogen atom from the LMC.[42–44] A third possible explanation for the need of a mediator is that it acts as an activator of laccase during enzymatic delignification.[45–47] Once activated, the laccase would be able to oxidise non-phenolic groups in the lignin, a reaction that is not observed without mediator. Finally, the role of the oxidised mediator could be the production of activated forms of dissolved oxygen such as $HO^{\cdot-}$ and $O_2^{\cdot-}$.[7] These radicals could oxidise lignin since they are known oxidants of some model compounds.[48]

2.1.2 Oxidation mechanisms. Together with these hypotheses on the role of mediator there exist also different possible oxidation mechanisms. The fact that different oxidation products from the reaction of model compounds with different mediators are found throughout the literature strongly suggests that the mechanism depends on the nature of the mediator. Mediators can be divided into two classes, depending on whether their oxidised form involves a radical or not. Mediators containing an N–OH functionality such as 1-hydroxybenzotriazole (HBT), the radical form of oxidised ABTS, and *N*-hydroxyphthalimide (HPI) belong to the first class, while dicationic ABTS and transition metal coordination complexes are in the second. Table 1 presents a list of mediators that have been used to oxidise lignin model compounds. As a starting point to our discussion, a recent publication by Fabbrini *et al.*[49] showed that the difference in the type of oxidised state of the mediator has an impact on the type of mechanism that will lead to the oxidation of model compounds. They used HBT and HPI as *N*-oxyl radical mediators and 12-tungstocobaltate(III) to represent true electron transfer mediators. They concluded from the oxidation of their non-phenolic model compound that mediators with a radical oxidised state react by subtracting a hydrogen atom from the Cα position on the LMC (see Fig. 3). Mediators from the other class, or pure electron transfer mediators, will preferentially oxidise the LMC by withdrawing an electron from its structure. The H-atom transfer (HAT) mechanism results in the formation of the corresponding ketone on the LMC. The pure electron transfer mechanism (ET), on the other side, resulted in Cα–Cβ bond cleavage. Unfortunately, such observations cannot be extended to the mediated oxidation of all types of model compounds. Indeed, we showed that direct oxidation of a β-O-4 LMC at a vitreous carbon electrode (an ET mechanism) can form the Cα-ketone as well as cleavage products,[50] and that a HAT mechanism (laccase/HBT) can produce Cα–Cβ cleavage products from a β-1 model compound. Due to the different structures of LMC used by different research groups, it is difficult to conclude that a specified oxidation mechanism will be the same with all LMCs or, even more, with lignin. Useful conclusions can however be drawn from the various results reported. For example, a comparison of such reactions highlights the performance of transition metal based mediators for pulp delignification. Under certain conditions, a $K_4[Mo(CN)_8]$ complex gave similar delignification results to HBT, a much more reactive radical mediator.[34] From the discussion just presented, it could be assumed that the $K_4[Mo(CN)_8]$ complex yields cleavage products at a slow rate, while HBT will form uncleaved ketones, subsequently cleaved with an alkaline treatment (extraction). Direct cleavage obtained with the use of an ET mediator, therefore, can result in efficient delignification although ET reactions with lignin are slower than reactions with radicals. Such a statement on reaction rates is however difficult to prove based only on the amount of model compound oxidised after a given period of time. The next section will present results of our work done to measure the rate constants of laccase-mediator and mediator–lignin reactions. The goal of these measurements is to evaluate which mediator properties and which type of reactions (pure ET or radical reactions) should be favoured in order to enhance the overall delignification system efficiency.

2.2 Electrochemistry of laccase-mediator reactions

An approach that is often neglected is the use of electrochemical techniques to study the reactions of the laccase-mediator system on pulp and on model compounds. Since these reactions involve electron exchange, electrochemical analyses can provide useful information on the system that could otherwise be difficult to obtain. These electrochemical methods are either potentiostatic (electrolysis) or potentiodynamic (polarography and cyclic voltammetry).

2.2.1 Cyclic voltammetry and polarography. Polarography has been used to characterise lignins[51,52] and lignin model compounds.[53,54] Since different types of substituent on the lignin structure will yield different half-wave polarographic reduction potentials,[55] this technique can be useful to identify some structural elements of lignin. However, polarography can not be used for oxidation of species above 0.2 V *vs.* Ag/AgCl, because of oxidation of the mercury electrode so cyclic voltammetry (CV) at solid electrodes is therefore more useful. We have used CV at carbon electrodes to estimate rate constants for the different electron transfer reactions occuring in the laccase-mediator system. The overall reaction, which is the oxidation of a substrate *via* oxygen reduction, is composed of many electron transfers between two species. We evaluated rate constants for three of these reactions individually; the enzymatic oxidation of mediator (laccase-mediator), the oxidation of lignin model compounds by mediator, and the oxidation of lignin by mediator in a real pulp sample.

2.2.1.1. laccase-mediator reaction. The oxidation of a substrate (a mediator in our case) by laccase, with concomitant conversion of oxygen to water is composed of nine steps involving electron transfers between the substrate, the different copper atoms of the enzyme active site, and oxygen. For the purpose of the text, these nine steps will be regarded as one reaction as we will focus on the oxidation rate of mediator by the enzyme. Detailed information on electron transfer reactions of laccase can be found elsewhere.[22] Thus the substrate (mediator) oxidation can be oversimplified by eqn. 1:

$$\text{Lc-Cu}_{\text{T1}}{}^{2+} + M_{\text{red}} \xrightarrow[k_{\text{med}}]{} M_{\text{ox}} + \text{Lc-Cu}_{\text{T1}}{}^{+} \qquad (1)$$

where M_{red} and M_{ox} are the reduced and oxidised states of the mediator and Lc–Cu_{T1} represents the type 1 copper atom of the laccase active site.

Whilst sweep rate-independent pseudo-first-order rate constants (k_f) for this process can be evaluated using CV, according to the method developed by Cass *et al.*[56] based on the Nicholson and Shain[57] approach (*vide infra*), the main difficulty encountered when attempting to evaluate the homogenous second-order rate constant (k_{med}) for a mediator reaction with laccase is the need to determine the active laccase concentration. While precise measurement of enzymatic activity is easily accomplished by spectrophotometric assay with a substrate, such as ABTS,[58] the laccase concentration determination relies on a single absorbance reading at λ = 620 nm (ε = 4900 M^{-1} cm^{-1}[59]). This absorption band, which corresponds to a d–d transition of the T1-type copper atom of the active site, is also responsible for the blue colour of the laccase in solution. The absorbance measurement however only yields the total amount of T1 Cu atoms of laccase molecules, regardless of the activity or inactivity of the enzyme. For instance, the T2/T3 copper atoms cluster site responsible for O_2 reduction could be inhibited without affecting the absorption band at 620 nm. Furthermore, we have noted that storage conditions affect this absorption and the possible contamination of the laccase sample results in an increased absorbance reading with time, whereas laccase activity decreases, as depicted in Fig. 4. For this reason we present, and recommend that others do likewise, only the pseudo-first order rate constants (k_f) for the laccase-mediator reaction with the mediator present at a fixed, excess, concentration. In addition, in order to be able to compare the k_f values for different mediators, all experiments have been conducted using the same laccase activity (based on ABTS as a substrate).

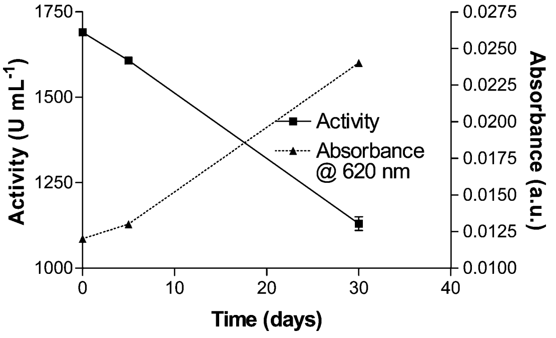


Fig. 4 A comparison between *Trametes versicolor* laccase activity and absorbance measurements, supposedly reflecting laccase concentration changes, over the period of a month.

To evaluate k_f, cyclic voltammograms of 0.2 mM mediator in buffer solution were recorded at several scan rates (1 to 50 mV s^{-1}). The cathodic peak current is measured at peak maximum intensity (labelled diffusion current (i_d)). An example of such a curve obtained for $K_4[Mo(CN)_8]$ is presented in Fig. 5. Following this step sufficient laccase to yield activity of 5 U ml^{-1} is added to the solution. CVs are recorded at the same scan rates. At scan rates slow enough, a decrease of oxidation peak intensity is observed, along with an increase in reduction currents, and a change in shape of CV from tailed diffusion-controlled peaks to sigmoidal, catalytic, curves (see Fig. 5). These changes arise from the enzymatic oxidation of mediator (eqn. 1). In presence of laccase there is continuous regeneration of the oxidised state by the enzyme. Under cathodic polarisation, when the scan rate is low enough, the continuously oxidised mediator will be continuously reduced at the electrode (eqn. 2), generating more current than by the mediator alone in solution.

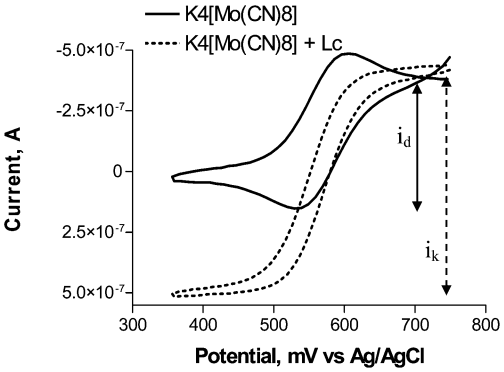


Fig. 5 Diffusion controlled (i_d) and catalytic (i_k) cyclic voltammograms for $K_4[Mo(CN)_8]$ mediator (0.2 mM) in presence and absence of laccase (Lc, 5 U ml^{-1}). CVs were recorded in pH 4.5 citrate buffer at a scan rate of 2 mV s^{-1}.

$$M_{\text{ox}} + ne^- \xrightarrow[\text{electrode}]{} M_{\text{red}} \qquad (2)$$

The faster the enzymatic oxidation rate is, the larger the current increase will be. This cathodic current, labelled catalytic current (i_k) is also measured and the ratio of diffusion current over catalytic current is calculated for each scan rate. The k_f values for the enzymatic oxidation of each mediator are then obtained according to the method developed by Cass *et al.*[56] based on the Nicholson and Shain[57] approach.

In order to investigate optimal conditions for laccase-mediator electron transfer, we have evaluated the effect of pH and mediator $E^{0\prime}$ on k_f. Fig. 6 illustrates the importance of the effect of mediator redox potential ($E^{0\prime}$) on the enzymatic oxidation rate. The general trend for k_f values is to decrease as the $E^{0\prime}$ increases towards the laccase redox potential of 575 mV *vs.* Ag/AgCl, as the reaction becomes less thermodynamically favourable. While mediators with very low $E^{0\prime}$ (with respect to laccase) are rapidly oxidised, they may not, however, be suitable mediators for delignification. To oxidise lignin in pulp, the mediator must have a redox potential as high as possible in order to perform efficient lignin oxidation, as discussed in the next section. The ideal mediator should therefore have at the same time a high k_f and a high $E^{0\prime}$. This is the case with the ABTS mediator for which k_f is clearly higher than the general trend shown in Fig. 6. This high reactivity of ABTS with laccase is a result of several factors. Firstly, the organic aromatic structure of ABTS makes it closer to that of laccase natural substrates, the phenols. The interaction with the laccase active site is probably more favourable with ABTS than with transition metal-based mediators. The fact that ABTS undergoes disproportionation when oxidised must also be taken into account. This disproportionation mechanism, which is the reaction of two radical cation $ABTS^{\cdot+}$ to form one reduced ABTS and one dicationic $ABTS^{++}$ molecule,[60] has already been invoked to explain the high efficiency of ABTS to lignin and its model compound oxidation.[36] The $ABTS^{++}$ produced by such a mechanism has a redox potential higher than that of the radical cation (0.91 compared to 0.47 *vs.* Ag/AgCl, respectively). Finally, pH has an effect on k_f for mediators. All measurements have been performed in pH 4.5 citrate buffer, which is the optimal pH for ABTS oxidation by the *Trametes versicolor* laccase (Fig. 7). Other mediators may have optimal pHs other than 4.5, their k_f will subsequently be lower compared to ABTS at this pH.

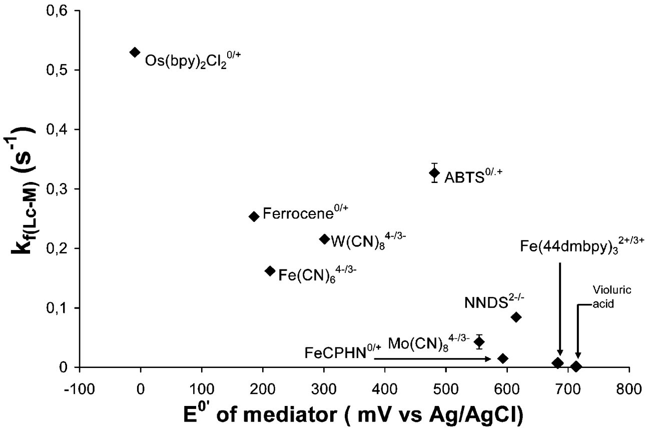


Fig. 6 Effect of mediator $E^{0\prime}$ on pseudo-first-order rate constants, k_f, for the laccase-mediator oxidation (citrate buffer, pH 4.5, laccase = 5 U ml^{-1}, mediator = 0.2 mM). The error bars represent standard deviation calculated from triplicate experiments. The abbreviation used for mediators are: ABTS = 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid), FeCPHN = iron(II) dicyano-*bis*-(1,10-phenantroline), NNDS = 1-nitroso-2-naphtol-3,6-disulfonic acid, $Fe(44dmbpy)_3$ = iron(II) *tris*-(4,4′-dimethyl-2,2′-bipyridine).

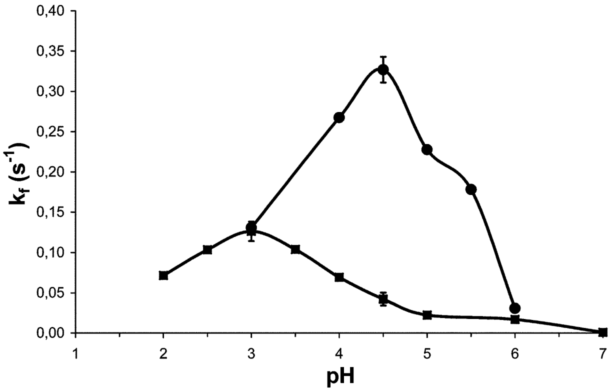


Fig. 7 Effect of pH on pseudo-first-order rate constants for the laccase (5 U ml^{-1})-mediator (0.2 mM) oxidation. Mediators are ABTS (circles) and $K_4[Mo(CN)_8]$ (squares).

The pH can affect several parameters of the laccase-mediator reaction. It is known that the oxidation potential of the enzyme T1 active site is not significantly affected by pH.[61,62] Hydroxyl anions however are known inhibitors of the T2/T3 site, where oxygen reduction takes place.[23] Laccase activity is maximum over a pH range of 3 to 5, depending on the laccase source and on the type of substrate. For mediators that possess $E^{0\prime}$s that are pH-independent, such as ABTS and $K_4[Mo(CN)_8]$, the variation in rate constant observed with pH should decrease with an increase in OH^- concentration. The plot in Fig. 7 shows that this is not the case. Whilst the redox potential of the active site does not change with pH, the structure surrounding the T1 copper atom is affected by it.

These changes, protonation and deprotonation with pH variations, produce different electrostatic interactions between the mediator and the active site. ABTS for instance is neutral at pH lower than 3.5 and anionic at pH above that. Since histidines and methionines at the substrate-binding site of laccase are positively charged at acidic pH, ABTS would be more attracted to this site at pH above 3.5. The maximal rate for $K_4[Mo(CN)_8]$ interaction with laccase is attained, in contrast, at pH 3. It seems appropriate, thus, to state that the optimal pH of laccase-mediator reactions should be determined for each mediator. Furthermore, since the laccase-mediator system for pulp delignification comprises another element, the lignin in the pulp, the overall system optimal pH must take the mediator–lignin reaction into account.

2.2.1.2. Mediator–lignin reaction. We have adopted a method similar to that presented in the last section to evaluate the oxidation rate of lignin in unbleached kraft pulp by mediators. Initially, the method was developed for rapid determination of kappa number and pulp bleachability.[63] While most automated kappa number measurement techniques are based on optical reading, our proposed method correlates a measure of catalytic currents determined using cyclic voltammetry with kappa number. One the main advantages of using an electrochemical method over an optical one is its independence on pulp sample consistency, which varies through the different bleaching stages.

To evaluate lignin oxidation rates, a 10 mg pulp sample is impregnated with a 0.2 mM mediator solution. The pulp sample is then compressed at the surface of an electrode and held in place. The electrode is then immersed in the mediator solution for electrochemical measurements. As for the experiments described in the previous section, cyclic voltammograms are recorded at several scan rates. As shown in Fig. 8, a catalytic response is observed when the mediator is able to oxidise the lignin in pulp. Also presented in Fig. 8 is the CV obtained with a fully bleached pulp sample (negligible residual lignin). As expected, no catalytic current is noted and the CV shape exhibits the characteristic semi-infinite diffusion-controlled response of that obtained for solutions containing the mediator alone. In order to evaluate comparable rates of reaction between mediators and lignin in pulp, the mediator diffusion co-efficient in the pulp, rather than in solution, should be used. This is evaluated from CVs recorded with the mediator and a fully bleached pulp sample, using the Randles–Sevcik equation for reversible semi-infinite diffusion.[64] Since the exact molar concentration of lignin cannot be determined due to its complex and irregular structure, the second order rate constant for the reaction between the mediator and lignin, k_{med} is again unavailable. The pseudo-first order rate constants, k_f, can however be used with confidence to compare the oxidation rates amongst the different mediators, using the same bulk pulp sample.

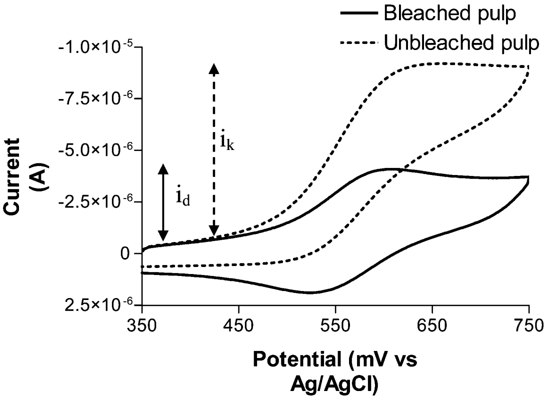


Fig. 8 Cyclic voltammograms of 0.2 mM $K_4[Mo(CN)_8]$ recorded at 250 mV s^{-1} with fully bleached (kappa number = 0) and unbleached (kappa number = 19.9) kraft pulp. The buffer solution is 100 mM phosphate at pH 8.

The plot in Fig. 9 shows the different k_f values obtained for the mediator–lignin reaction as a function of the mediator redox potential. As expected, from a thermodynamic point of view, mediators with high $E^{0\prime}$ tend to have faster oxidation rates. As for the laccase-mediator reaction, ABTS does not follow the general trend for the same reasons as outlined previously. Regarding the optimal mediator, a mediator with high $E^{0\prime}$ that produces a free radical upon oxidation would be best to perform pulp delignification. However, since this mediator must be oxidised by laccase prior to pulp delignification, its oxidation potential should be near or under that of the T1-type copper of laccase. The best mediator for the LMS is therefore that with highest k_f but lowest $E^{0\prime}$. Among the mediators investigated by us, this criteria ranks ABTS, $K_4[Mo(CN)_8]$, and Fe(II)(4,4′-dimethyl-2,2′-bipyridine)$_3$ as the three best mediators for LMS delignification. Indeed, ABTS is the most efficient of these when tested for pulp delignification. However, its efficiency is very close to that of $K_4[Mo(CN)_8]$, which reacts more slowly with both laccase and lignin.[34,35] The high delignification efficiency of $K_4[Mo(CN)_8]$ is a result of its excellent stability; even if this mediator reacts less rapidly than ABTS it can perform oxidation for a longer period of time without degradation of its oxidised form. Analysis of the solution after pulp treatment reveals that the $K_4[Mo(CN)_8]$ concentration remains unchanged from the initial concentration.

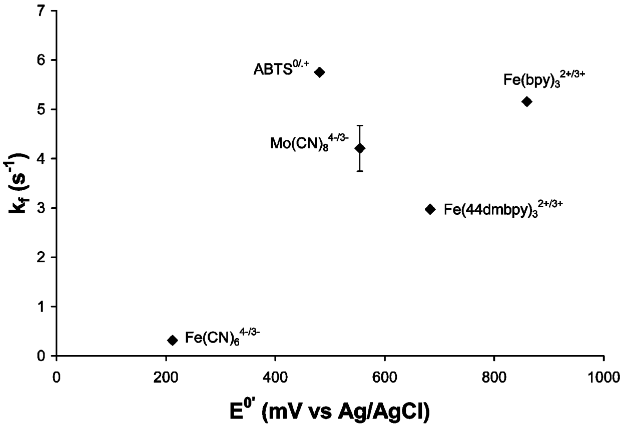


Fig. 9 Pseudo-first-order rate constants for the mediator–lignin oxidation for several mediators (phosphate buffer, pH 8). The abbreviation used for mediators are: ABTS = 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid), Fe(44dmbpy)$_3$ = iron(II) *tris*-(4,4′-dimethyl-2,2′-bipyridine).

The rate constant for the mediator–lignin reaction was also evaluated for $K_4[Mo(CN)_8]$ at varying solution pH values (Fig. 10). The optimal pH range for mediated pulp delignification is located between 8 and 10. Once again, the bell-shaped curve is a result of two factors: lignin reactivity and mediator behaviour. Oxidisable lignin groups such as phenolic moieties are ionised at high pH, making the lignin more solvated and thus more accessible. At high pH however, the $K_4[Mo(CN)_8]$ mediator loses its stability, making the lignin oxidation less efficient. The results (not shown) of stability experiments on $K_4[Mo(CN)_8]$ in alkaline solution showed a decrease of 25% of this mediator concentration within a day.

The conclusion from these oxidation rate experiments is that, unfortunately, the conditions for an efficient enzymatic mediator oxidation (low $E^{0\prime}$ mediator, acidic solution) are unfavourable for the mediator–lignin reaction. A compromise must be achieved at lower than optimal efficiencies of both reactions.

In order to circumvent such a compromise, it has been proposed that the use of bulk electrolysis to replace the enzyme–O_2 biocatalyst as the oxidising agent in the laccase mediator system can result in a system that is much less condition-sensitive than the

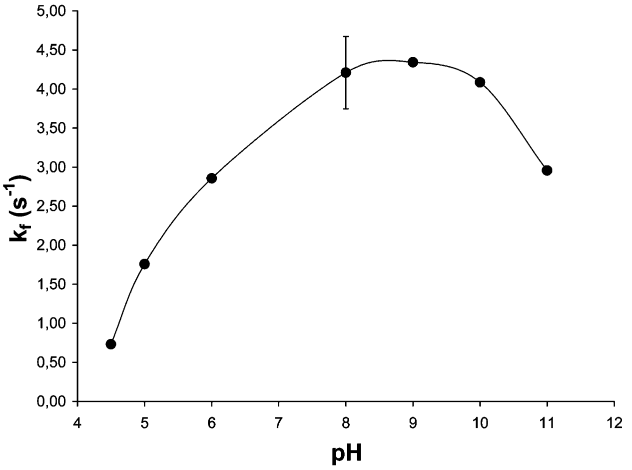


Fig. 10 Variation of pseudo-first-order rate constant of unbleached kraft pulp lignin (K = 19.9) oxidation by $K_4[Mo(CN)_8]$ mediator with different pH values.

LMS and allow efficient mediator oxidation under conditions that favour lignin oxidation.[37,65,66]

2.2.2 Electrolysis. Electrolysis experiments consist of the use of a large surface area electrode such as reticulated vitreous carbon (RVC) that replaces the enzyme–O_2 biocatalyst as the oxidising agent in the laccase mediator system. Lignin model compounds in solution with the mediator are therefore oxidised by the latter and their oxidation products can then be analysed using different techniques (mainly chromatography), just as is the case when using laccase. This method, which is not widely used, can offer very interesting insights into LMC oxidation mechanisms. The effect of dissolved oxygen on such reactions is perhaps the most representative example of the utility of electrolysis. Indeed, the enzymatic oxidation of LMC by a mediator cannot be conducted under anaerobic conditions because without oxygen as a co-substrate, the laccase is incapable of reacting with the mediator in the first place. If the mediator is oxidised at an electrode instead of by the laccase, O_2 can be removed and the oxidation products analysed to evaluate the mediator–LMC reaction under anaerobic conditions. Such experiments, using HBT and $K_4[Mo(CN)_8]$ to oxidise a β-O-4 and a β-1 model compound, respectively, have been conducted in our laboratory, and results recently published.[50] These results showed no significant difference in oxidation efficiency (*i.e.* the amount of model compound oxidised) when O_2 was removed, compared to aerobic experiments. Differences have been attributed to degradation reactions between the oxidised model compound and O_2.[67] We therefore conclude that the mediator does not act as an oxygen activator to delignify, as O_2 is not involved in the reaction between oxidised mediator and lignin model compound.

Other information on the role of the mediator can also be derived from electrolysis experiments. For instance, the role of transition metal based mediators as electron carriers has been clearly demonstrated using electrolysis.[50] In such experiments, a solution of potassium hexacyanoruthenate(II), $K_4[Ru(CN)_6]$, mediator was prepared and oxidised to completion in the electrolysis cell. Veratryl alcohol (VA, see Fig. 3) was then added to the solution and left to react, giving a 27% VA oxidation with a 50 to 1 mediator : model compound ratio. No VA oxidation occurred if the mediator was not first oxidised, nor when the experiment was repeated with equal concentrations of $K_4[Ru(CN)_6]$ and of VA. This suggests that the oxidised mediator is the oxidising agent of the model compound and that there must be a large excess of mediator to drive the oxidation of the LMC. In enzymatic oxidations, when low levels of mediator are used, the turnover of the cycle presented in Scheme 1 is necessary to drive the reaction. These results clearly indicate that the system must provide a continuous source of oxidised mediator in order to efficiently oxidise the lignin model compounds. Stemming from these results, we became interested in exploring the use of an electrochemical means to supply a continuous source of oxidised mediator for pulp delignification.

3.0 Electrochemical aspects of pulp delignification

Several electrochemical techniques have been used for numerous years in the pulp and paper industry. These techniques, mainly focussed on electrosynthesis of bleaching chemicals, such as chlorine, chlorine dioxide, and hypochlorite, were reviewed and presented by Oloman.[68] The application of electrochemistry in the pulping industry is however not limited to the production of these bleaching agents and, quoting Oloman, "The possibilities for new applications are limited only by the imagination".[68] The goal of the last section of this paper is to present a possible role of electrochemistry in mediated kraft pulp delignification.

Of the rich literature content for electrochemistry in pulp and paper production, only few publications directly address delignification.[37,65,66,69–71] This is surprising, as delignification is a result of oxidation (an electrochemical reaction) of functional groups in lignin. Direct oxidation of dissolved lignin at Ni, PbO_2, and dimensionally stable anodes (DSA)[71] has been attempted, but the efficiency of this concept is limited when using pulp, since the lignin may not be accessible to the electrode. Another type of electrochemical delignification found in the literature concerns the *in situ* formation of a delignification[70,72] or a bleaching[73] agent. The latter consists of applying a voltage to an electrolysis cell containing the pulp in an alkaline chloride solution to produce hypochlorite, which bleaches the pulp. Such techniques result in a bleaching efficiency comparable to normal multi-stage bleaching methods but with less AOX produced and a shorter bleaching time. *In situ* electrochemical formation of activated forms of oxygen for use as delignification agents has also been reported.[70,72] For example, when bleaching liquor containing ferrocyanide and dissolved oxygen is passed over an electrode to which a potential is applied, the ferricyanide produced at the electrode appears to ionise some phenolic moieties in lignin, allowing them to react with oxygen to achieve bleaching.[72] Dissolved oxygen could also react with the ferricyanide to form bleaching-active species.

In mediated electrochemical delignification, the laccase and oxygen is substituted by an electrode. The mediator acts as an electron carrier and is the sole agent responsible for the lignin oxidation. Such systems have been proposed using ferrocyanide,[69] violuric acid,[65,66] and $K_4[Mo(CN)_8]$.[37] We focus on transition metal based mediators as we believe that these mediators are well suited for this system because of their stability and of the wide redox potential range offered by this class of mediators. Indeed, mediators such as the iron(II) tris-dipyridyl complexes have high redox potentials, allowing them to oxidise some functional groups in lignin that could not be attacked by other mediators.[37]

Three major advantages arise from the replacement of an enzymatic system with an electrolytic system. Firstly, the problems of enzyme sensitivity to experimental conditions (pH, temperature, presence of inhibitors) are avoided. Secondly, the range of mediators is no longer limited to those which act as substrates of laccase. Finally, mediators of high redox potential can be selected to favour the oxidation of lignin; such mediators are only slowly oxidised by laccase (*vide supra*). The major disadvantage arises from the fact that the use of an electrode creates a heterogeneous system. Since the pulp itself is a heterogeneous suspension, it is more difficult, using electrolysis, to obtain uniform distribution of the oxidised mediator. In an electrochemical system, one oxidation cycle could be viewed as the following sequence: (I) the mediator is oxidised at the electrode, (II) it diffuses in the solution and into the fibre cell walls where the residual lignin is located then (III) oxidises lignin, being itself reduced. The mediator must then (IV) diffuse back to the electrode to begin a new cycle. The solubility of laccase confers a huge advantage since the oxidation agent is uniformly distributed, resulting in a low mediator diffusion time. In an attempt to improve mediator access to lignin in the pulp our electrochemical system comprises an isolated electrolysis cell, in which the mediator is continuously oxidised and then pumped (continuously) through the pulp, which is compressed in a dense pad in a separated cell (see Fig. 11).

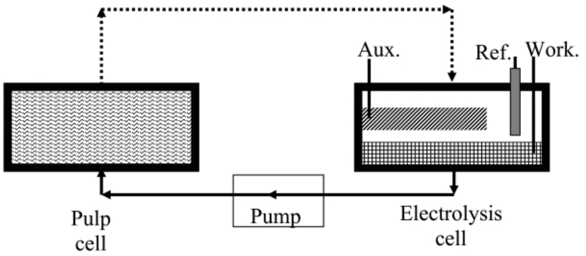


Fig. 11 Electrodelignification experimental setup scheme, showing the flow of mediator solution through the electrolysis cell (right) and the pulp sample (left).

Significant delignification can be achieved using this system: ~30% for a two hour treatment using 1% potassium octacyanomolybdate(IV) as the mediator at pH 5.[37] This result is statistically equivalent to the delignification efficiency obtained with laccase and the same mediator under the same conditions. When conducting the experiment at a pH of 8, delignification (30%) is obtained with the electrochemical system, whilst laccase is completely inactive at this pH and no delignification occurs with the LMS. It is worth noting that no delignification is observed when the electrochemical system is used without mediator or without applying any potential at the electrode. Finally, a 60% delignification can be attained after an extensive 45 hour electrolysis treatment. The importance of this long term experiment is that the electrolysis treatment showed no damage to the cellulose fibre. The viscosity loss of the electrochemical delignification with a transition metal based mediator is minimal, demonstrating that pulp physical properties are preserved during such a treatment.

4.0 Future of mediator bleaching systems

The laccase-mediator system appears to represent a very promising method to bleach kraft pulp. Of course, when dealing with a potential application in the industry, other parameters must be considered. Chlorine dioxide is a cheap, efficient bleaching agent that could not be totally substituted by a laccase-mediator stage without affecting the final bleaching of pulp. Benefits can be accrued, however, by substitution of a fraction of ClO_2 through the addition of a LMS stage in the bleaching sequence of an ECF pulp mill. So far, the cost of mediator has been the limiting step to this substitution. The same cost-related problem is observed for an application in a TCF mill. On the other hand, the laccase-mediator system has the great advantage of being capable of implementation in a mill without any major change in the infrastructure of the bleaching sequence. A solution containing laccase and mediator would just have to be pumped in *via* a currently existing oxygen tower for example. Since the water used in a bleaching sequence is not reused but sent to the activated sludge waste system, one also must ensure that the mediator is not harmful to this biosystem. Since mediators that may be used to bleach pulp may be very stable, particularly the transition metal based complexes, sending them to the water treatment represents a waste of a chemical (and of money) that could be reused. The application of the laccase-mediator system could therefore greatly benefit from the development of a means to separate and recycle the mediator from bleaching waters. To our knowledge, no such attempts have been made to recycle the mediator.

The mediated electrochemical delignification process that we describe holds great promise for application to bleaching. Further research on additional mediators, particularly those of high redox potential, high stability and that are inexpensive and non-toxic, for efficient bleaching of pulps using this approach is warranted. The major drawback to industrial acceptance of this delignification technology, however, is the requirement for capital infrastructure investment by the industry for installation of electrolysis cells, and the alteration of present bleaching processes.

Acknowledgments

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PAPER
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An undergraduate teaching exercise that explores contemporary issues in the manufacture of titanium dioxide on the industrial scale

Steven Grant,[a] Andrew A. Freer,[a] John M. Winfield,[a] Craig Gray,[b] Tina L. Overton[c] and David Lennon*[a]

[a] *Department of Chemistry, Joseph Black Building, The University of Glasgow, Glasgow, UK G12 8QQ*

[b] *Teaching and Learning Service, Florentine House, 53 Hillhead Street, University of Glasgow, Glasgow, UK G12 8QQ*

[c] *Department of Chemistry, University of Hull, Cottingham Road, Kingston upon Hull, UK HU16 7RX*

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A teaching exercise is described that aims to expose undergraduate chemistry students to the type and range of complex and interacting issues that a chemist active in an industrial organisation might typically encounter. The business area selected is the titanium dioxide pigment manufacturing sector, that is meant to be representative of large-scale chemical manufacturing. Although the students are exposed to a range of chemical topics, they are also expected to understand some of the associated economic, environmental and legislative drivers that, inevitably, impinge on the business operations. Indirectly, the exercise aims to make the students aware of the concepts of *sustainable development*, as applied to the chemicals industry.

The students are asked to engage in a mature discussion as to whether a new titanium dioxide manufacturing facility should be constructed within their area. The background information supplied to the students is based around a real situation that existed in 2001. Evaluation of the exercise by the students indicates a definite positive response and suggests that such teaching packages can play a positive role in demonstrating the real issues related to enhanced environmental awareness within the chemicals industry.

1 Introduction

The Department of Chemistry at the University of Glasgow has recently applied the concepts of problem based learning[1–3] to produce new teaching materials for its 2nd year (≡ 1st year in England, Wales and Northern Ireland) undergraduate programme. Two new packages have been produced, that are designed to increase student awareness of the modern chemicals industry. These packages have been termed interactive teaching units (ITUs)[4] and address issues relevant to the industrial scale manufacture of (i) refrigerants (ITU 1 'The Age of Refrigeration') and (ii) chlorine (ITU 2 'Mercury, Membrane or Diaphragm'). The background, approach adopted and an evaluation of these units are described elsewhere.[4] In October 2001 it was decided to produce a new ITU in order to broaden the range of chemistry covered within the ITU format and the purpose of this communication is to describe the background, methodology, content and effectiveness of the new material. It is hoped that, through a wider appreciation of modern industrial chemistry, our students will have a better understanding of the range of topics they are likely to encounter as chemists operating in the industrial sector.

The topic selected for the new unit (ITU 3) was the titanium dioxide industry. The main reason for this selection was because there already existed a problem based learning exercise on this sector that we felt could be extended and adapted to fit our current ITU format. In 1998 researchers at the University of Hull produced a comprehensive package that required undergraduate students, firstly, to understand the background of the modern titanium dioxide industry, and then to consider issues relevant to the successful and continued operation of an existing titanium dioxide manufacturing facility. That work, 'The Titanium Dioxide Project' was produced as a result of the Project Improve initiative and was circulated widely amongst the UK chemistry higher education sector.[5] Unfortunately, the structure of the Hull documentation was not readily transferable to the Glasgow ITU format, which is based on students working through specific tasks in small groups and giving several oral presentations within a designated three hour period. Consequently, we decided to retain the basic theme of 'The Titanium Dioxide Project'[5] but to adapt it and extend it to fit more closely our educational requirements. Specifically, we wished to broaden and increase the number of issues that the students should be aware of when evaluating the large-scale production of commodity chemicals.

A major aim of our new educational package was to expose the students to the general concepts of *sustainable development*[6–9] and to create a scenario where the importance of chemistry, economics, the distribution of the world market, environmental issues, legal requirements and politics could be discussed amongst the student body. These themes commonly come under the banner of Green Chemistry.[10,11] Recent literature had applied the tools of Life Cycle Analysis[12] to the titanium dioxide industry and so we included this important means of evaluating sustainability in the course content. Additionally, it was deemed important to ensure that the new unit had a direct connection to material presented within the traditional lecture-based courses of the 2nd year chemistry programme. This ensures that the students do not see ITU 3 as being something separate from their core studies but rather as a supplement to material they encounter in lectures. Structure/property relationships of metal oxides feature prominently in the solid state chemistry course undertaken by our 2nd year undergraduates and so an exploration of the different structural phases of TiO_2 were included within the exercise.

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2 Aims

The following specific aims were identified for ITU 3:

(1) To develop a broad understanding of the range of complex issues arising in large-scale chemical manufacturing, using the TiO_2 industry as a model.

(2) To develop an understanding of relevant sections of the undergraduate chemistry curriculum, using an applications-led approach.

(3) To promote the need for *sustainable development*[6–9] and, in addition, demonstrate the negative environmental, social and economic consequences of non-compliance with this ideal.

3 Methodology and material selection

Having established the existence of a wealth of diverse information pertaining to the TiO_2 industry, the next task was to select material conducive to the aims outlined above. As a consequence, the unit was developed with three main areas of focus in mind.

Firstly, ITU 3 considers technical issues relating to the current TiO_2 manufacturing alternatives. It was felt that the level of chemical complexity embodied within these processes offered a significant challenge in understanding for the students. Furthermore, the manufacturing options produce different crystal forms of TiO_2 pigment with distinct physical-chemical properties. Accordingly, the new unit seeks to emphasise the 'structure/properties/applications' relationship fundamental to the comprehension of solid state chemistry.

Secondly, the volatile economics of TiO_2 production over the last two decades mirrors the situation, past and present, affecting many other sectors of the bulk chemicals industry. The norm is that most students progressing to a career in industry will have had little or no exposure to such issues. In attempting to redress this imbalance, the unit focuses on two crucial elements disturbing the equilibrium of TiO_2 economics: (1) capacity/demand ratios and, (2) growth levels in TiO_2 markets across the major world regions.

Thirdly, consideration is given to environmental issues associated with TiO_2 manufacture. With the push towards sustainable development continuing to shape the future of the modern chemicals industry, students need to understand this concept. Increasingly restrictive and, crucially, costly EU legislation[13] covering effluent emissions from the TiO_2 industry has made the move towards practising sustainable chemistry a top priority for most TiO_2 manufacturers. ITU 3, therefore, looks at aspects of a contemporary industry's attempts to embrace sustainable development. However, past failures to do so are also highlighted in the unit, demonstrating the negative environmental, social and economic ramifications of non-compliance.

In the essential component of ITU 3, students are asked to consider the process by which a major global TiO_2 producer decides where to locate its new manufacturing facility. The perspective of a major manufacturer, crucial to the debate, was gained from information available on the website of a global TiO_2 company with operations in the UK. *Titox Plc* is a fictitious company, but some of the business scenarios used are related to those of Huntsman Tioxide.[14] Also important to the discussion is a perspective on local economics, which was supplied by a major regional development agency, Scottish Development International.[15]

4 Course content

ITU 3 is composed of six separate sections, each of which is outlined in Fig. 1. The class size for each ITU session typically comprises 45 students, which during Sections B–E are sub-divided into 5 tutorial groups of 9 students, with each tutorial group operating independently in separate locations. An academic member of staff is assigned to each tutorial group, who are further

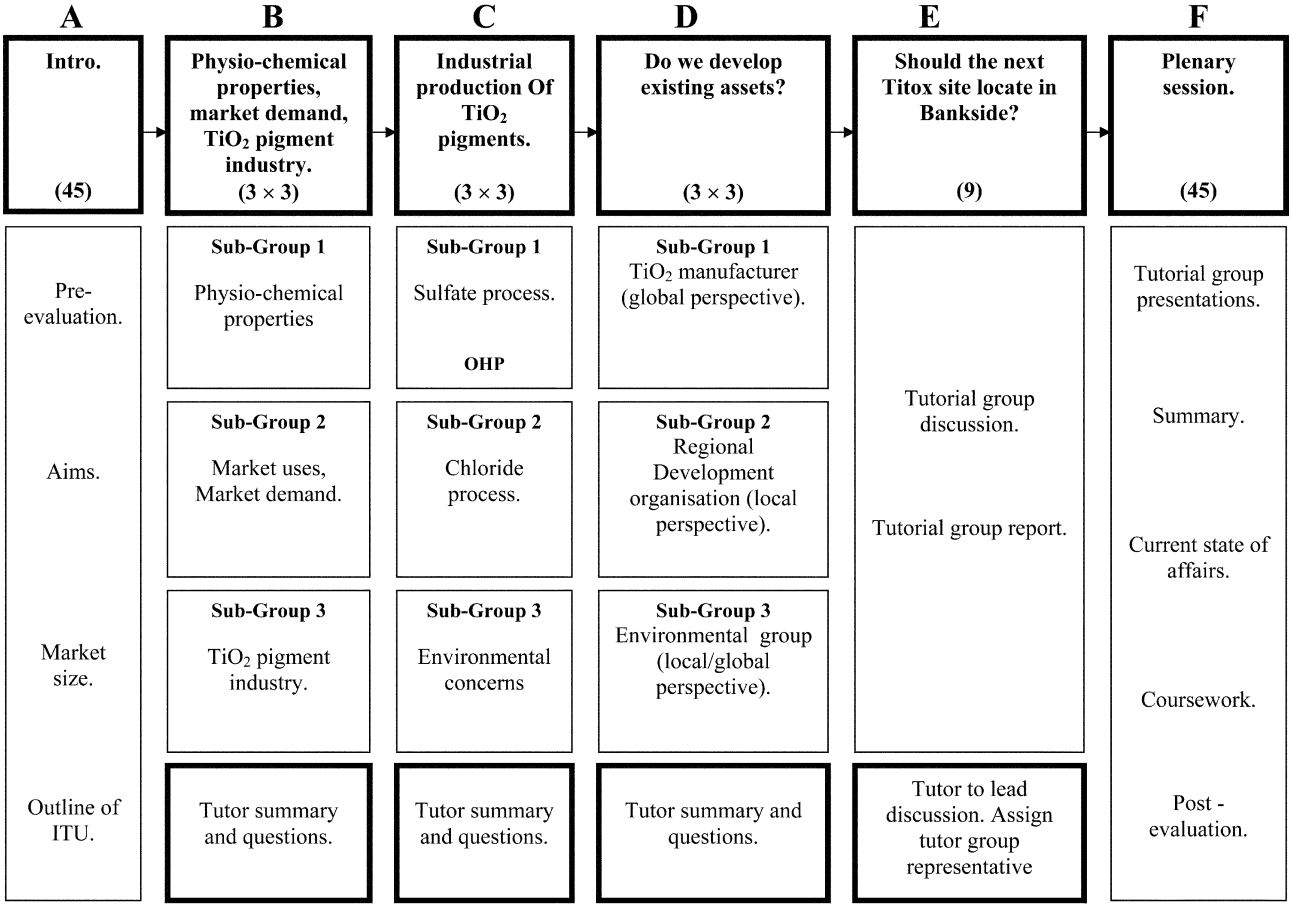


Fig. 1 Structure plan for ITU 3. The bold letters indicate the six sections described in the text. The numbers in parentheses represent the number of students participating in each section.

required to form small sub-groups (sub-groups 1–3) to work together through a series of exercises. Sections B, C and D require each member of the sub-group to make a short oral presentation to the tutorial group and the tutor, who manages the whole exercise. Section E requires the group of 9 students to work together to consider the issues on whether or not a new TiO_2 manufacturing facility should be located in Scotland. Section F reviews the conclusions arrived at by the 5 tutorial groups and finally the lead tutor summarises the current situation in the U.K. and abroad.

Thus, with reference to Fig. 1, the unit operates as an exercise in parallel learning, with each sub-group of 3 students educating their tutorial group of 9 students with distinctly different aspects of TiO_2 production. This parallel format contrasts with that adopted in our first two ITUs,[4] which essentially took a linear approach to raising and solving problems. Having 3 groups of students working on 3 different, but related, problems at the same time means that more material can be covered in a fixed time period and, ultimately, the topic can be explored to a greater degree than that achievable by an essentially linear approach.

A description of the individual Sections of the ITU now follows:

Section A. Introduction to ITU

The unit introduction begins by describing briefly essential properties of titanium metal. The ITU class learns of the metal's excellent strength to weight ratio and high resistance to corrosion, giving it applications in industries such as aerospace, sport and medicine, *etc*.[16] The students are then made aware that the majority of titanium is not used in its elemental form but rather as the oxide, titanium dioxide (TiO_2), which currently accounts for 96% of titanium consumption worldwide.[17] Fig. 2 presents the extent of TiO_2 production since its humble beginnings in 1918.[5] The significance of the scale of the TiO_2 market is conveyed by informing the students that TiO_2 is one of the leading inorganic compounds in production today.[18]

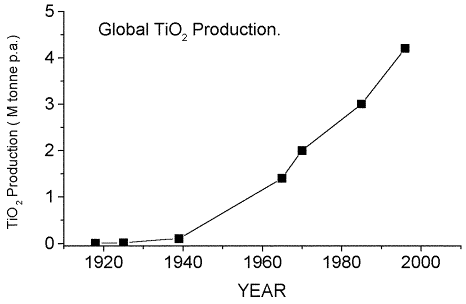


Fig. 2 Global TiO_2 production from the beginning of large-scale manufacture in 1918, through to the present day (1996).[5]

Section B. Physical-chemical properties and market demand

Logistics for Section B see the ITU class divided into tutorial groups containing a maximum of 9 students. Tutorial groups are then further divided into three sub-groups to perform exercises on (i) TiO_2 physical-chemical properties, (ii) product demand and (iii) market share respectively. The sub-groups are required to digest a range of technical information relating to these topics then to give short oral presentations based around an overhead projector to the 9 students plus tutor.

The first sub-group learns that lack of colour, chemical inertness and, most importantly, a high refractive index (conferring high opacity) are the three main desirable properties allotting TiO_2 an increasingly dominant share of the white pigment market.[18] They next examine the unit cells of rutile and anatase, the two commercially viable forms of TiO_2, illustrated in Figs. 3 and 4 respectively.[5,19] It is clear from comparison of the two unit cells that the rutile form is a more closely packed structure than that of anatase. An important consequence of the structural modifications is the extent to which UV light is absorbed. From the UV-visible absorption spectra presented in Fig. 5, the students can conclude that rutile TiO_2 absorbs UV radiation over a greater wavelength range than the anatase form.[20,21] This, coupled with a lower photocatalytic activity,[21] makes rutile TiO_2 the pigment of choice for applications susceptible to UV damage, for example automotive top-coatings. Brief mention is also made of other comparatively distinct properties arising between the rutile and anatase structures including density, refractive index, stability and abrasion.[5]

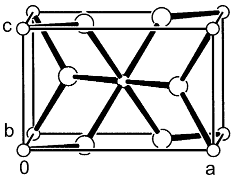


Fig. 3 The contents of the rutile unit cell with $a = b = 4.59$, $c = 2.96$ Å viewed approximately along the *b*-axis. The smaller and larger spheres respectively represent Ti and O atoms.

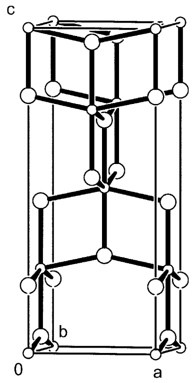


Fig. 4 The contents of the anatase unit cell with $a = b = 3.78$, $c = 9.52$ Å viewed approximately along the *b*-axis. The smaller and larger spheres respectively represent Ti and O atoms.

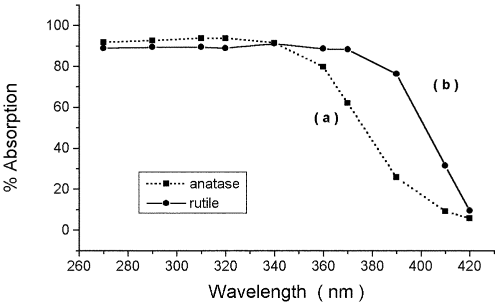


Fig. 5 Absorption of UV-visible irradiation by (a) anatase and (b) rutile forms of titanium dioxide. The figure is re-drawn, with permission from the author and the Vincentz Network, from reference 21.

The second sub-group examines the demand for TiO_2 pigments. The information points to TiO_2 accounting for almost two-thirds of the overall inorganic pigment market (1995) and, more specifically, a three-quarters share of the white pigment market (1996).[18] Next, the major industrial consumers of TiO_2 pigments in 1996 are shown to be paints and coatings, plastics and paper, accounting for 57%, 20% and 10% of world demand, respectively.[22] The remaining demand is attributed to a number of other minor consumers. Sub-group 2 finally moves on to examine indicators for global TiO_2 demand. They are made aware that the vast majority of products pigmented with TiO_2 are quality of life items, examples being car paints, PVC windows/doors, glossy magazines, *etc.* As such, world gross domestic product (GDP), a broad measure of global living standards, correlates closely with world TiO_2 demand, as illustrated by Fig. 6 for the period between 1980–1996.[5] The sudden slump

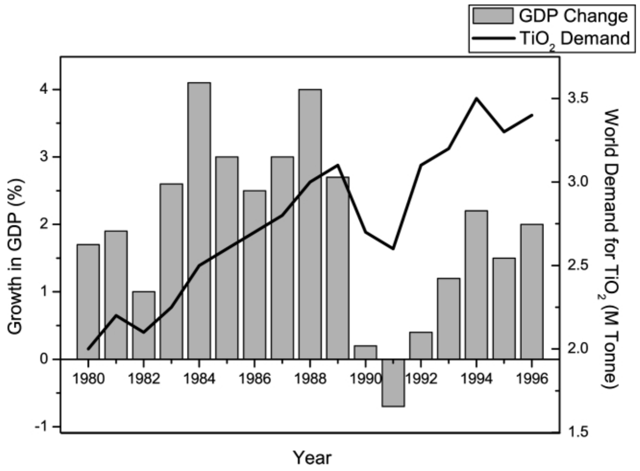


Fig. 6 World TiO_2 demand and global gross domestic product between 1980 and 1996. The figure is adapted from reference 5 with permission from the University of Hull.

seen in global GDP between 1989–1991 serves to highlight the volatile nature of the TiO_2 industry. The students learn of the excessively high capacity to demand ratio around this time, which subsequently left manufacturers with a product reduced in value. A further indicator of TiO_2 demand alluded to, is the industrial operating rate,[23] *i.e.* the percentage of production capacity in use at any given time. Although affected by GDP, other factors such as customer de-stocking and competition between manufacturers, also contribute.

The third sub-group focuses on the distribution of market share within the TiO_2 industry. Initially, they are informed of the world production capacities and geographical capacity distributions for the top four global TiO_2 manufacturers (mid-1996). Next, growth rates in world regional markets are considered. The major finding is that the Asia/Pacific region has increased its world market share, a fact borne out by Fig. 7, which shows a near 9% rise for the period between 1981–1995.[23] By contrast, the data also illustrate the decrease in world share for the remaining regions during the same period. The sub-group finds out that North America and Western Europe have suffered from maturing markets, whilst the decline in the rest of the world is tentatively attributed to political instability and civil unrest.

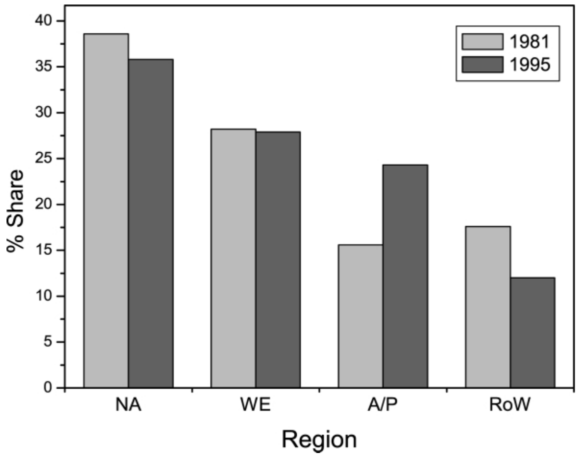


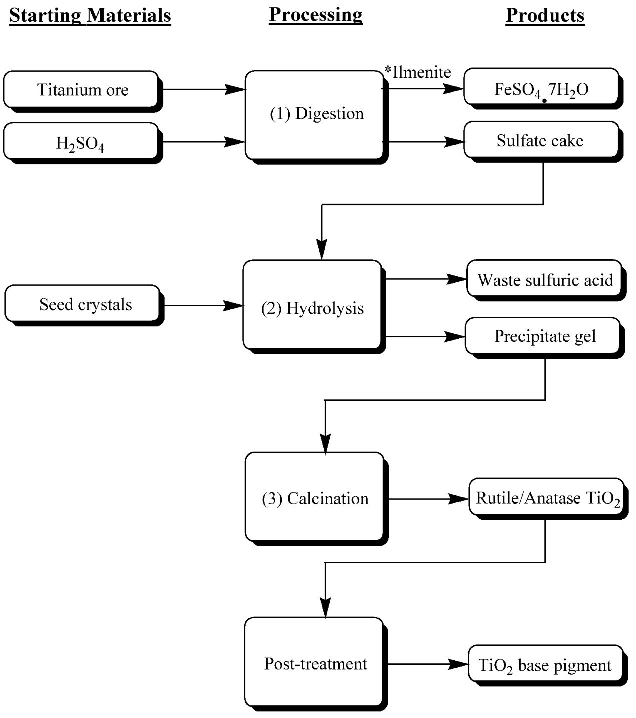
Fig. 7 The geographical world share of the TiO_2 market for 1981 and 1995 between the following major world regions: North America (NA), Western Europe (WE), Asia/Pacific (AP) and Rest of world (RoW). The figure is adapted from reference 23 with permission from the Oil and Colour Chemists Association.

On completion of their set tasks, each sub-group elects a spokesperson to give an oral summary of the material they have covered. The aim is to provide the whole tutorial group with a collective knowledge of the topics discussed.

Section C. Industrial production

Remaining in their sub-groups, students move on to consider the industrial production of TiO_2 pigments. Two sub-groups focus on the two TiO_2 manufacturing alternatives, the Sulfate Process or the Chloride Process. The remaining sub-group is concerned with environmental issues associated with TiO_2 manufacture.

Before examining the various stages of their respective processes, the first two sub-groups discuss the titanium-containing raw starting materials used in each.[18,23] The sulfate process utilises ilmenite ($FeTiO_3$) or its derivative Ti slag, with maximum TiO_2 contents of around 60% and 85% respectively. Naturally occurring rutile or synthetic rutile, the latter again derived from ilmenite, is used in the chloride processing option. Although both these satisfy a desirable TiO_2 content, many manufacturers are reluctantly using Ti slag, as deposits of natural rutile become increasingly scarce. For both manufacturing processes, students are made aware of the inverse relationship existing between TiO_2 content and the contribution to the waste stream. The main steps of each process are then described in some detail.[5,18,24,25] Using this information, both sub-groups are required to complete an industrial flow diagram summarising their particular process. Completed flow diagrams, outlining the various stages pertinent to the sulfate and chloride manufacturing options, are shown in Figs. 8 and 9 respectively.



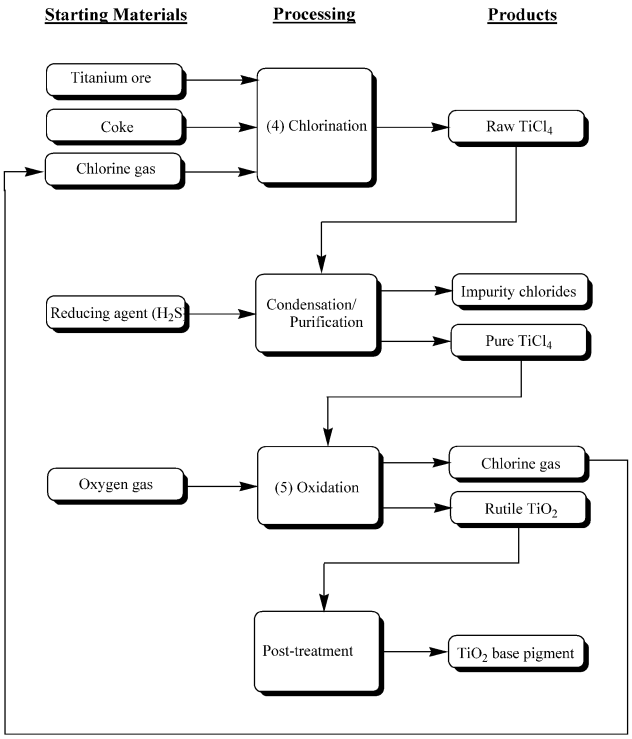
$$FeTiO_3 + 2H_2SO_4 \longrightarrow TiOSO_4 + FeSO_4 + 2H_2O \quad (1)$$

$$TiOSO_4 + (n+1)H_2O \longrightarrow TiO_2 \bullet nH_2O + H_2SO_4 \quad (2)$$

$$TiO_2 \bullet nH_2O \longrightarrow TiO_2 + nH_2O \quad (3)$$

Fig. 8 Industrial flow diagram representing the various stages of the *Sulfate Process* used for the manufacture of rutile and anatase TiO_2 base pigments. Reaction equations, where relevant, are shown for the processing steps. * The use of ilmenite as feedstock produces a significant quantity of iron sulfate heptahydrate by-product. The figure is adapted from reference 18 with permission from Wiley-VCH.

Linkage between the chemical equations and specific stages of the chemical flow sheet are emphasised by the tutor when questioning the groups' oral presentations. Finally, both sub-groups look at a number of comparative advantages and disadvantages existing between the TiO_2 manufacturing alternatives.[5,23,26] For example, the newer chloride process is limited to the production of rutile



$$TiO_2 + 2Cl_2 + C \longrightarrow TiCl_4 + CO_2 \quad (4)$$

$$TiCl_4 + O_2 \longrightarrow TiO_2 + 2Cl_2 \quad (5)$$

Fig. 9 Industrial flow diagram representing the various stages of the *Chloride Process* used for the manufacture of rutile TiO_2 base pigments. Reaction equations, where relevant, are shown for the processing steps. The figure is adapted from reference 18 with permission from Wiley-VCH.

TiO_2 pigment. The older sulfate process can, however, produce both the anatase and rutile TiO_2 forms, depending on the nature of seed crystals introduced during hydrolysis (see Fig. 8). Consequently, the latter process has exclusivity in supplying markets demanding anatase TiO_2, such as fine quality paper and ceramics. On the other hand, rutile TiO_2 produced by the chloride process is free from anatase contamination and is used in a wide range of applications including normal quality paper, paper laminates, plastics, paints, *etc.*, in fact anything other than fibres, food, cosmetics and most inks. Also brought to the attention of the students are the favourable production economics of the *continuous* chloride technology as opposed to the *batch* methodology necessary in the sulfate process.

The remaining sub-group is first made aware of the 1978 EU environmental legislation (and later amendments) imposed on the TiO_2 industry.[13] This was in response to the high volume of wastes, (solid, liquid and gaseous) arising from production, especially through the sulfate processing option. Sulfate technology is becoming increasingly unsustainable, owing to the spiralling cost of compliance with the EU directives in place.[26] The sulfate route is shown to generate up to 8 tonnes of dilute sulfuric acid and 0.6–2.7 tonnes of iron sulfate, whilst the chloride process gives rise to 0.4–0.9 tonnes of mainly impurity metal chlorides, for every tonne of TiO_2 produced.[23] The nature and quantity of these wastes obviously depends on the titanium feedstock utilised in each process. Some of the commonly encountered by-product recycling/disposal options are also discussed.[18,23] Waste acid can be reconcentrated for reuse in the process or neutralised with limestone to form gypsum, which is land-filled or marketed for use in products such as plasterboard and cement. The iron sulfate heptahydrate can be converted to iron(III) sulfate, where it is used in the water treatment industry.[18] Metal impurity chlorides from the chloride process are mostly land-filled[12] or, alternatively, after processing, can be used for water treatment.[18] Lastly, the sub-group considers Life Cycle Assessment (LCA),[12] a component of many contemporary TiO_2 manufacturers' environmental strategy. In general LCA is a "cradle to grave" (extraction of raw materials, manufacture, use and eventual disposal) analysis of the environmental burdens associated with a particular product, in this case TiO_2. Students then examine actual TiO_2 industry LCA results for a sample of five distinct processing options described in Table 1.[12]

Table 1 A range of TiO_2 processing options using differing combinations of feedstock, process type and waste treatment. The table is adapted from reference 12

Option	Feedstock	Process	Waste Treatment
A	Ilmenite	Sulfate	None
B	Ilmenite	Sulfate	Neutralisation to EU standard
C	Slag	Sulfate	Acid reconcentration
D	Slag	Chloride	Neutralisation
E	Synthetic Rutile	Chloride	Neutralisation

The results are based on energy consumption and waste. Fig. 10, for example, compares the liquid (acid and trace metals) discharges to water for the five alternatives. In particular, comparison between options A and B, both sulfate processes utilising ilmenite (see Table 1), demonstrates the dramatic positive effect of EU legislation in reducing effluent emanating from the industry. Caution, however, is advised against viewing LCA as an exact science, given that location specific factors such as sulfuric acid and chlorine availability, type of titanium feedstock, community environmental awareness and by-product outlets are all determinants.[12] LCA is, therefore, only useful as part of a comprehensive environmental strategy. As for the other two sub-groups, oral presentations are used as the medium through which relevant information is distributed among the tutorial group as a whole.

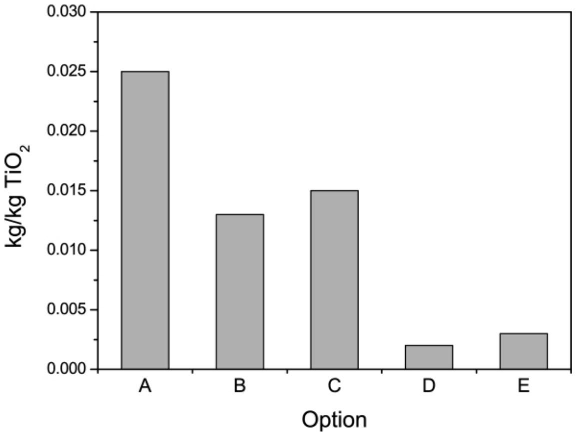


Fig. 10 Liquid (waste acid and trace metals) discharges to water for five distinct TiO_2 pigment processing options as outlined in Table 1. The figure is adapted from reference 12 with permission from the Oil and Colour Chemists Association.

Section C therefore aims to expose the tutorial group to the complexity of the industrial scale TiO_2 manufacturing routes and the fact that different processes exhibit different attributes. Selection of any specific process is rarely a trivial matter. The environmental issues of operating such processes is considered by sub-group 3, who initially concentrate on the waste products and then examine the concept of LCA applied to both processes operating under specified conditions.

Section D. New production facilities?

Furnished with a broad insight into contemporary TiO_2 manufacturing, the tutorial group is next confronted with a problem-based scenario. The tutorial group learns that the fictional manufacturing company, *Titox Plc*, intends to increase its global capacity by bringing on line a new 50,000 tonne per annum chloride processing plant, the location of the new site being either in Scotland or China. This is an example close to a real industrial case[27] but with Scotland selected as the UK option to increase the significance to our students. Based on a range of important criteria (availability of chlorine, ease of imports/exports, energy costs, *etc.*) the UK site was initially favoured. The company, though, has since admitted that further penetration into the rapidly expanding Asia/Pacific market, particularly in China, remains very attractive. Students then find out that the proposed UK site is adjacent to Bankside, a fictitious town that is in serious economic decline, due to the recent demise of surrounding industry, particularly shipyards. Regrettably, this scenario has been common within regions of the west of Scotland and appears credible to the majority of our students. The provision of high value jobs associated with TiO_2 manufacturing, *via* the *Titox Plc* investment, would undoubtedly improve the economic situation in the area. As such, *Scottish Development International* (*SDI*), a regional development agency, are very keen to attract the investment. *SDI* is associated with Scottish Enterprise, our local Regional Development Agency, which operates under the auspices of the Scottish Executive.[15] There is, however, strong opposition to the site in the form of a fictional major UK environmental group, *Greenwatch*. To discuss the issues pertinent to the siting of the new facilities, the three previously established sub-groups adopt the respective positions of *Titox Plc*, *SDI* and *Greenwatch*.

This arrangement, where sub-groups engage in a degree of role play, leads to an informed discussion within the tutorial group ultimately to approach a significant, technically-based decision. It is an important part of the ITU construction. Experience with the previous 2 ITU exercises[4] has shown that the discussions will be active and informed only if the students have a reasonable technical exposure to 'their' topics, and that their interest levels/connectivity has been built up through prior exercises.

In their capacity as board members of *Titox Plc*, the first sub-group finds out that the initial leaning towards the UK site has been heavily criticised. Superior market growth, cheaper labour costs and potentially relaxed environmental legislation are all cited as reasons by major investors as to why the company should locate in China. It is suggested, however, that the UK boasts an, historically, more stable and robust economy than that for the Asia/Pacific region. Moreover, the company has a well-established technical base in the UK, making installation, manufacture and maintenance at the UK site altogether easier tasks. Also concerning investors, is the negative publicity surrounding the proposed new investment thanks to the involvement of *Greenwatch*. In the Company's defence, the sub-group discuss and present results that outline recent positive strides taken in significantly reducing virtually all the environmental burdens arising from *Titox Plc's* operations.[28] The tutor draws the students' attention to the fact that the constraints on global warming performance are limited by Equations (4) and (5) in Fig. 9, where every mole of TiO_2 results in production of 1 mole of CO_2, a potent greenhouse gas.[29]

The second sub-group, representing *Greenwatch*, are first reminded that, whilst the burdens associated with the sulfate route are of global concern, *Titox Plc* intend using the more sustainable chloride technology at their new facility. Concerns are nevertheless raised over two recent incidents of non-compliance, within the space of two years, at the Company's UK Deeside plant. Firstly, hazardous titanium tetrachloride was allowed to mix with a quantity of cooling water, sending a dense hydrochloric acid mist into the atmosphere. Evasive action had to be taken by residents in the area and an adjoining road was closed. The Environment Agency (EA) served the plant with a prohibition notice, which remained enforced for five weeks. Students are subsequently made aware of the second incident, where 8,000 tonnes of effluent, containing 37 tonnes of concentrated hydrochloric acid escaped onto protected marshland nearby. Affects to wildlife on the marsh was a subject of fierce debate, nonetheless, a court action brought against the company by the EA resulted in heavy fines. All the events outlined above are factual and have been reported elsewhere,[30,31] and are associated with the UK operations of a major TiO_2 manufacturer. The organisation actually associated with these incidents was Tioxide Europe Limited, although that fact is not revealed to the students. Tioxide Europe Limited was at that time part of the ICI Group of companies and is now under the ownership of the Huntsman Corporation.[14] *Titox Plc* is a fictitious organisation that is used as a convenient vehicle to represent milestones in the recent history of the UK titanium dioxide industry.

The remaining sub-group, role-playing *SDI*, has the task of conveying the benefits of locating in Scotland.[15] Recognition is given to the significant number of chemical companies already operating successfully in Scotland. Next, the students look at the wide range of financial incentives available for inward investment, which include Property Support and Regional Selective Assistance grants.[15] Scotland, in addition, boasts excellent transport and communication facilities, essential to the functioning of contemporary industry. Emphasis is also placed on the strong links existing between the chemical industry and educational institutions in Scotland, ultimately aiding the recruitment process for specialist positions. The suggestion is that, allied with moderate wage expenditures, inward investors would benefit from a highly trained, cost effective and flexible Scottish workforce.

Section E. Should *Titox Plc* locate in Bankside?

After giving oral presentations to demonstrate their initial viewpoints, the sub-groups amalgamate for a tutor-led discussion and debate on the issue of whether *Titox Plc* should locate in Scotland or, alternatively, China. Students who are against location in Scotland are asked to consider the implications of such a decision for the local and national economy. They must be made aware of the long-term and high value jobs a modern chemical plant, with ancillary research and development facilities, offers to a region. With respect to the environmental concerns, the attitude of many students may be 'not in my back yard'. However, the demand for TiO_2 is such that production will undoubtedly continue, if not in the UK, then elsewhere in the world. Assuming a global perspective, it is likely that environmental burdens would be better managed in areas of the planet (*i.e.* the UK) with the infrastructure in place to deal effectively with such problems. It is also possible that the group discussion can swing strongly in favour of a purely environmental perspective, and reject the premise that new TiO_2 plants should be constructed anywhere. The tutors are instructed to tolerate any perspective from their groups, as long as the students can reasonably defend the stance adopted.

Section F. Plenary session

The three-hour ITU concludes with a plenary session involving the whole class and led by a senior tutor. Each tutorial group elects a spokesperson to deliver its conclusions on the location of the new TiO_2 facility. As regards the actual scenario at the time the ITU was constructed,[27] the class are informed that no decision has yet been reached on whether to locate in the UK or China. However, a senior company executive has been quoted as saying "Its not if but when" in relation to developing in China.[32] Finally, the students are provided with some documentation demonstrating that TiO_2 has uses other than just as a pigment. A brief review of photocatalysis reminds the students of material encountered within their solid state chemistry lectures. They are then given short briefing notes on aspects of water treatment,[33] air purification[34] and solar energy.[35] This brief and broad overview is meant to demonstrate the wide range of applications to which this important and interesting chemical compound can be utilised.

5 Assessment

Experience has shown that a post-ITU assessment requirement, that carries a substantial contribution to the overall class mark, enhances student participation in the whole ITU exercise. The ITU format forces the students to work in small groups, give modest oral presentations and to work through technically-based issues with some recognition of the associated economic, environmental and/or political issues. To further supplement their communication skills, the students are then asked to prepare a short technical report that is connected to the overall ITU. For example, a representative assignment would require the students to provide a brief development plan that identifies the main issues for a chemical manufacturer considering entering the TiO_2 pigment manufacturing business. The students would be expected to cover the following points: (i) scale of TiO_2 demand, (ii) structural aspects of TiO_2 crystals, (iii) the chemical manufacturing process, (iv) customer base and (v) how LCA can be applied to evaluate the environmental burden of the process selected. Full ITU documentation is accessible to the students *via* the Chemistry Branch Library. Written communication skills are an essential prerequisite for a successful chemist and the students, generally, rise to the occasion to produce well-rounded reports.

6 Student evaluation

To gauge the effectiveness of this teaching initiative, a pre/post evaluation exercise was implemented for ITU 3. Representative results from student evaluation of ITU 3 in 2001 are shown in Table 2. Prior to the unit, less than half of the ITU class felt they could attain job satisfaction working in the chemical industry. However, after exposure to the dynamics of the TiO_2 industry, this increased to over two-thirds of the student group. The result suggests that a significant proportion of the class became more aware and also, more receptive to the rewards of working in the industry. Also interesting was the significant polarising effect the unit had on student attitudes towards environmental performance within the TiO_2 industry. A significant percentage of student opinion, unsure of whether or not the industry deserved criticism over its environmental performance, was seen to diverge equally towards agreement and disagreement after completing the unit. It could be argued that the result reflects the particular viewpoints adopted by the different sub-groups. However, it is just as likely that the high level of interaction and debate between the groups provided students with the opportunity to make an informed decision. ITU 3 ultimately aims to present the facts, with no bias intended, in relation to TiO_2 manufacture and the environment. An overwhelming majority of students also registered enjoyment in participating in the unit. This is all the more encouraging in view of the demand on *every* student to give an oral presentation at some stage during the exercise.

6 Concluding remarks

Sustainable Development is at the heart of Green Chemistry. It is important that chemistry graduates realise the vocational nature of their discipline but also that successful operation of large-scale industrial facilities requires an awareness of a broad range of issues, not always chemical in nature. The TiO_2 manufacturing industry is well developed and its operation represents a good example of the dynamics generally active in the chemical manufacturing industry. Although undergraduate teaching packages highlighting aspects of TiO_2 production are already available,[5] the concepts of problem based learning incorporated into the interactive teaching format presented in ITU 3 has been shown to enhance the students' awareness of sustainable development. It is important that undergraduate chemistry courses are occasionally supplemented with such exercises. They illustrate to the students that the chemical industry exists to meet the requirements of a complex consumer society and that chemists play a vital role in ensuring the safe operation of the, often complex, manufacturing units required to meet that consumer demand. Presently, the Chemistry Department of the University of Glasgow operate four ITU exercises. All four teaching packages will shortly be available *via* the Royal Society of Chemistry website (http://www.rsc.org/lap/educatio/rsedhome.htm).

8 Abbreviations and glossary of terms

ITU	Interactive teaching unit.
ITU 1	The Age of Refrigeration, University of Glasgow, 1997.
ITU 2	Mercury, Membrane or Diaphragm, University of Glasgow, 1998.
ITU 3	Industrial Chemistry: Titanium Dioxide, University of Glasgow, 2002.
GDP	Gross domestic product.
EU	European Union.
LCA	Life cycle assessment.
SDI	Scottish Development International.
EA	Environmental Agency.
Full class	45 students + 5 tutors.
Tutorial group	9 students + 1 tutor.
Sub-group	3 students.

Acknowledgements

This paper is dedicated to Dr Craig Gray, who tragically died in March 2003. Craig demonstrated considerable wisdom, patience and foresight that ensured that this ITU made the transition from an initial concept to an active part of our undergraduate teaching programme. He is sorely missed.

The authors acknowledge assistance from two organisations indirectly featured in the ITU 'game' presented to the students. Firstly, Huntsman Tioxide have demonstrated a commitment to chemical education and public awareness of chemical processing by providing some technical guidance. Secondly, Scottish Enterprise are thanked for providing information on the range of options typically offered by competitive Regional Development Organisations. Assistance from these two organisations has permitted a more realistic scenario to be presented to our students. Finally, the authors wish to acknowledge the assistance of the ITU team. Dr John Dymond, Dr Louis Farrugia, Dr Justin Hargreaves, Professor Neil Issacs, Dr Malcolm Kadodwala, Dr Adrain Lapthorn, Dr

Table 2 Examples of student evaluation results for ITU 3 (The Titanium Dioxide Industry). The sample relates to the response received from a total of 88 students spread over 3 sessions completed in 2001

Sample Evaluation Questions	Response							
Do you think working within the chemical industry would provide you with a varied and stimulating career?	Strongly disagree		Disagree		Not sure		Agree	
	Pre 0 (0.0%)	Post 0 (0.0%)	Pre 4 (4.9%)	Post 2 (2.3%)	Pre 38 (46.3%)	Post 25 (28.4%)	Pre 40 (48.8%)	Post 61 (69.3%)
ITU3 investigates issues in the manufacture of TiO_2. Environmental pollution attributed to the industry has resulted in accusations of placing profit before environmental issues. To what extent would you agree, or disagree, with that accusation?	Strongly disagree		Disagree		Not sure		Agree	
	Pre 4 (4.9%)	Post 4 (4.9%)	Pre 16 (19.5%)	Post 38 (44.2%)	Pre 59 (71.9%)	Post 17 (19.8%)	Pre 3 (3.7%)	Post 27 (31.4%)
Did you enjoy participating in ITU 3?	Yes 76 (87.3%)				No 11 (12.7%)			

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Ligandless Stille cross-coupling in ionic liquids†

Cinzia Chiappe,*[a] Giovanni Imperato,[a] Elio Napolitano[b] and Daniela Pieraccini[a]
[a] *Dipartimento di Bioorganica e Biofarmacia, via Bonnanno 33, Pisa, Italy.*
E-mail: cinziac@farm.unipi.it; Fax: +39 050 43321; Tel: +39 050 44074
[b] *Scuola Normale Superiore di Pisa, Piazza dei Cavalieri 7, Pisa, Italy.*
E-mail: eliona@farm.unipi.it

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The Stille cross-coupling reaction has been investigated in ten different ILs to evaluate how the different physico-chemical properties of the medium can affect the transfer of vinyl and alkyl groups, as well as the efficiency of the extraction processes. The possibility of working in the absence of ligand has been also evaluated.

Introduction

Room Temperature Ionic Liquids (RTILs) are promising green alternatives to conventional solvents in transition-metal catalyzed reactions such as the Heck[1] insertion reaction and Suzuki[2] and Stille[3] cross-coupling. The advantages of the elimination of highly toxic co-solvents, the ease of work-up (products can be isolated from the reaction mixture either by decantation or extraction with a variety of solvents, including CO_2 under supercritical conditions), and the possibility of recycling the catalyst have already been demonstrated.[4] Besides providing eco-friendly reaction media, one further step toward the effective and rational use of ILs in cross-coupling reactions would be an understanding of the way ILs can interact with reaction processes. In fact, ionic liquids, although sharing the important physical property of being non volatile, can exhibit quite distinct chemical properties in terms of polarity, nucleophilicity and hydrogen bonding properties,[5] so that their ability to affect reaction pathways can be expected to be dependent on their structure, as is observed with common organic solvents. As a part of a general program aimed at understanding how ILs properties may affect reactivity[6] and providing a rational basis for choosing among different ILs, we investigated the Stille coupling of aryl iodide with vinyl and alkyl stannanes in ten ionic liquids (Fig. 1), which have different physico-chemical properties according to the nature of the anion and cation (namely, N-butyl-N-methylimidazolium bromide [bmim][Br], hexafluorophosphate [bmim][PF_6], bis(trifluoromethylsulfonyl)imide [bmim][Tf_2N], tetrafluoroborate [bmim][BF_4], octylsulfate [bmim][$C_8H_{17}SO_4$], N-ethyl-N-methylimidazolium tosylate [emim][OTs], 1-butyl-2,3-dimethylimidazolium hexafluorophosphate [bm_2im][PF_6], bis(trifluoromethylsulfonyl)imide [bm_2im][Tf_2N], N-butyl-N-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide [bpyrr][Tf_2N] and N-hexylpyridinium bis(trifluoromethylsulfonyl)imide [HPy][Tf_2N]).

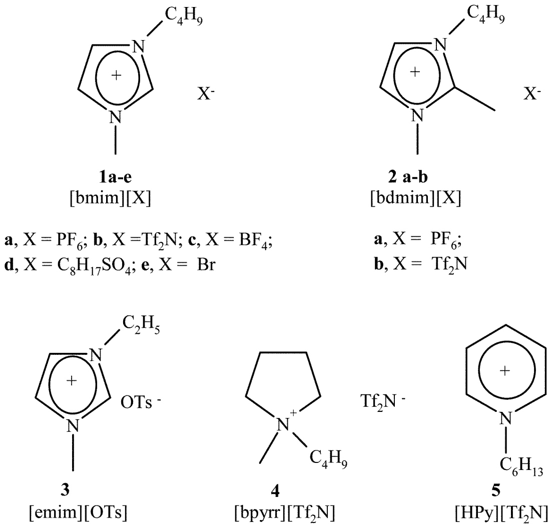

Fig. 1 ILs used.

We considered the reaction of tributylvinylstannane, tetramethylstannane and tetrabutylstannane with iodobenzene in presence or in absence of $AsPh_3$ (“ligandless” coupling). When $AsPh_3$ was present, $Pd_2(dba)_3$ was the source of catalyst; otherwise $Pd(OAc)_2$ was adopted in the ligandless reaction. Although palladium catalysts rapidly dissolve in the ionic media at the reaction temperature, reagents and products are only slightly soluble, so a biphasic system resulted. In these cases cross-coupling products could, in principle, be isolated by decantation. Only in the very lipophilic [bmim][$C_8H_{17}SO_4$] did the reaction occur in a homogeneous phase. In order to obtain comparable data, however, products were isolated in all cases by *n*-pentane extraction.

Results

The coupling with the vinylstannane by the Pd(0)/$AsPh_3$ system was practically quantitative after 4 hours at 80 °C regardless of the nature of the ionic solvent (data not reported). Therefore, in order to evaluate how the solvent affected reactivity we measured the reaction progress after 1 hour (Table 1). The degree of conversion as well as the actual mass balance, which is related to the ease of extraction of reactants and products from the ionic medium, were evaluated by GC after the addition of an internal standard.

The data summarized in Table 1 show that [bmim][$C_8H_{17}SO_4$] is the best solvent for the Stille coupling of vinylstannane and iodobenzene both in terms of yield of reaction and extraction from the reaction medium (entry 4), followed by bis(trifluoromethylsulfonyl)imide salts ([bmim][Tf_2N], [HPy][Tf_2N], [bpyrr][Tf_2N], entries 1, 9, 10, respectively). In contrast, significantly lower yields of styrene were obtained in nucleophilic solvents like [bmim][Br] and [emim][OTs]. Modification of the structure of the cation determines appreciable variations in the coupling rate only for hexafluorophosphate derivatives (compare entries 2 and 7 with 1, 8, 9, 10). The difference seems related to a different hydrogen-bond acidity; the cation which is unable to form a hydrogen bond performs better than the other one.

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† Electronic supplementary information (ESI) available: Stille coupling of iodobenzene with tributylvinylstannane in ionic liquids with complexed palladium catalyst. See http://www.rsc.org/suppdata/gc/b3/b313221h/

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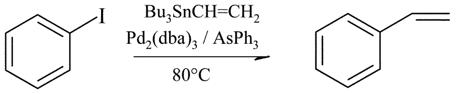
The ligandless Stille coupling was significantly less effective, as compared to the reaction with $AsPh_3$ complexed catalyst, in all ionic liquids: up to 24 hours (as compared to 4 h) were necessary to achieve quantitative coupling. It is worth of note that under these conditions the reduction of Pd(II) to Pd(0) is immediate, therefore the reduced efficiency of the ligandless coupling cannot be attributed to this step. The data, summarized in Table 2, show that $[Tf_2N]$ derivatives give the highest reaction rates. It is worth noting that, in absence of $AsPh_3$, the reaction seems to be more sensitive to the cation, so that ILs unable to give hydrogen bonding ensure the highest percentage of conversion (entries 8–7 *vs.* 1–2).

The reuse of catalyst was briefly investigated for the reaction in $[bmim][C_8H_{17}SO_4]$, $[bmim][Tf_2N]$, $[bpyrr][Tf_2N]$, and $[HPy][Tf_2N]$: the data reveal a modest decrease in activity for Pd(II) in $[bpyrr][Tf_2N]$ (20%) and a complete loss of activity of the catalyst in the remaining ILs; the loss of catalytic activity is probably due to the precipitation of Pd(0) at the end of the extraction process.

The transfer of alkyl groups from simple tetraorganotin to iodobenzene still remains difficult in the ionic medium and, in the case of methyl introduction, it is generally accompanied by the formation of biphenyl (Table 3). When Me_4Sn was used as reactant and $[bmim][C_8H_{17}SO_4]$ as solvent, the introduction of the alkyl group also proceeded with the uncomplexed catalyst, although a slightly higher amount of biphenyl was detected (entries 1, 2). Once again, $[bmim][C_8H_{17}SO_4]$ and $[bmim][Tf_2N]$ are the best choice solvents for this Stille cross-coupling.

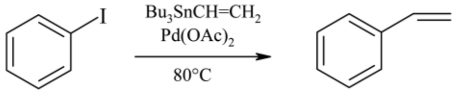
Table 1 Stille coupling of iodobenzene with tributylvinylstannane in ionic liquids with the complexed palladium catalyst



	Solvent	Time/h	Mass balance[a] [%]	Conversion[b] [%]
1	$[bmim]Tf_2N$	1	> 99	73
2	$[bmim]PF_6$	1	92	49
3	$[bmim]BF_4$	1	91	50
4	$[bmim]C_8H_{17}SO_4$	1	95	99
5	$[bmim]Br$	1	20	41
6	$[emim]OTs$	1	72	36
7	$[bm_2im]PF_6$	1	32	75
8	$[bm_2im]Tf_2N$	1	98	69
9	$[HPy]Tf_2N$	1	> 95	85
10	$[bpyrr]Tf_2N$	1	90	74

[a] Determined using benzonitrile as internal standard. [b] Determined by GC analysis.

Table 2 Stille coupling of iodobenzene with tributylvinylstannane in ionic liquids with uncomplexed palladium catalyst



	Solvent	Time/h	Mass balance[a] [%]	Conversion[b] [%]
1	$[bmim]Tf_2N$	4	> 99	75
2	$[bmim]PF_6$	4	92	30
3	$[bmim]BF_4$	4	90	49
4	$[bmim]C_8H_{17}SO_4$	4	85	55
5	$[bmim]Br$	4	38	10
6	$[emim]OTs$	4	68	63
7	$[bm_2im]PF_6$	4	40	79
8	$[bm_2im]Tf_2N$	4	74	94
9	$[HPy]Tf_2N$	4	80	84
10	$[bpyrr]Tf_2N$	4	88	85

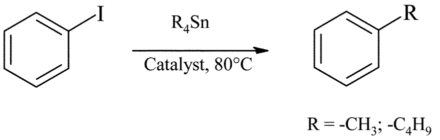
[a] Determined using benzonitrile as internal standard. [b] Determined by GC analysis.

On the other hand, the introduction of *n*-butyl was extremely slow and always stopped before completion. Moreover product extraction with *n*-pentane was particularly ineffective as compared with previous examples. It is however worth noting that, when $[bmim][Tf_2N]$ was used as solvent, 60% of butylbenzene was obtained without the formation of the side product.

Discussion

When nucleophilic ionic liquids ([bmim][Br] and [emim][OTs]) were used as solvents in the coupling of tributylvinylstannane and iodobenzene in presence of $AsPh_3$, only low to moderate yields of product were obtained. Non nucleophilic salts gave uniformly better results, showing that the anion identity has a great influence on the outcome of the reaction. Among all the solvents taken into account in this work, Tf_2N^- based ionic liquids and $[bmim][C_8H_{17}SO_4]$ gave the highest reaction rates. This could be ascribed, in the case of Tf_2N^- derivatives, to a nucleophilic assistance in the transmetallation step: indeed, several reports[7] have recently appeared demonstrating the importance of coordinative expansion at the tin atom produced by nitrogen nucleophiles. It is worthy of note that the ability of the anion to interact with the tin atom is also affected by the nature of the cation. A competition

Table 3 Alkyl transfer from tetraorganotin to iodobenzene in ionic liquids



	Solvent	Catalyst	Ligand	R	Time/h	Mass balance[a] [%]	Ph–R[b] [%]	Biphenyl[b] [%]
1	$[bmim]C_8H_{17}SO_4$	$Pd_2(dba)_3$	$AsPh_3$	$-CH_3$	24	100	31[c]	n.d
2	$[bmim]C_8H_{17}SO_4$	$Pd(OAc)_2$	—	$-CH_3$	24	100	48[c]	6
3	$[bmim]Tf_2N$	$Pd_2(dba)_3$	$AsPh_3$	$-CH_3$	24	90	62[c]	27
5	$[bmim]Tf_2N$	$Pd(OAc)_2$	—	$-CH_3$	24	70	12[c]	30
4	$[bmim]PF_6$	$Pd_2(dba)_3$	$AsPh_3$	$-CH_3$	24	87	54[c]	28
6	$[bmim]C_8H_{17}SO_4$	$Pd_2(dba)_3$	$AsPh_3$	$-C_4H_9$	48	50	15[c]	< 1
7	$[bmim]C_8H_{17}SO_4$	$Pd(OAc)_2$	—	$-C_4H_9$	48	52	21[c]	n.d.
8	$[bmim]Tf_2N$	$Pd_2(dba)_3$	$AsPh_3$	$-C_4H_9$	48	70	60[c]	n.d.
9	$[bmim]OTs$	$Pd_2(dba)_3$	$AsPh_3$	$-C_4H_9$	48	30	20[c]	n.d.
10	$[bmim]Br$	$Pd_2(dba)_3$	$AsPh_3$	$-C_4H_9$	48	30	8[c]	n.d
11	$[HPy]Tf_2N$	$Pd_2(dba)_3$	$AsPh_3$	$-C_4H_9$	48	55	9[c]	n.d

[a] Determined using benzonitrile as internal standard. [b] Determined by GC and GM analysis. [c] The unreacting material was always represented by iodobenzene.

between the cation and the Sn atom for the anion, due to the equilibria reported in Scheme 1, can be hypothesized:

$$[\text{cation}]^{+} \quad + \quad [\text{anion}]^{-} \rightleftharpoons [\text{cation}]\text{---}[\text{anion}]$$

$$[\text{anion}]^{-} \quad + \quad R_4Sn \rightleftharpoons R_4Sn\text{--anion}$$

Scheme 1

The strong cation–anion interaction present in [bmim][Br] could reduce the ability of this anion to nucleophilically assist the transmetallation and could therefore explain the low rate of the Stille cross-coupling reaction performed in this solvent, as compared[1c] to other Pd-mediated reaction performed in tetrabutylammonium bromide. Competing equilibria have been proposed by Welton to explain the effect of hydrogen bonding in Diels–Alder reaction and in recent polarity mesurements.[8,9] Though in Diels–Alder reaction it is the ability of the cation to act as a hydrogen bond donor that determine the *endo* selectivity, in the Stille cross-coupling it is the hydrogen bond acceptance of the anion that can influence the result of the reaction. Therefore, it seems that both in hydrogen bond donation and acceptance, competition between the solute and the proper counterpart of the ionic liquid can be important in determining the result of a given reaction.

On the other hand, the high efficiency of the reaction in [bmim][$C_8H_{17}SO_4$] might be related to more favorable intrinsic properties of this new ionic liquid or to the fact that reaction occurs in a homogeneous phase.

The structure of the cationic counterpart has little effect on the vinyl transfer from tetraorganotin to iodobenzene. The data reported in Table 1 show that, mantaining the anion, ionic liquids derived from different classes of organic compounds, that is imidazolium, pyridinium and pyrrolidinium salts, give almost identical results. The ability of the cation to form hydrogen bonds seems, however, to have some consequences. In particular, the introduction of a methyl group between the two nitrogen atoms in imidazolium derivatives, that should suppress the hydrogen bond acidity of the solvent, has a different effect depending on the nature of the negative counterpart: it enhances the rate of cross-coupling in the hexafluorophosphate series, whereas it has no effect on the bis(trifluoromethylsulfonyl)imide derivatives.

The data seem also to demonstrate that the reaction rates are not dependent on viscosity: comparable results are obtained for the homologous [bmim][Tf_2N] and [bm_2im][Tf_2N], which at least at room temperature have quite different viscosities.[10,11] Therefore, although the reactions occur under heterogeneous conditions, mass transfer is not the rate determining step. However, this physical property is probably more important during the isolation of the product; because of the poor material balance, the three most viscous ILs, namely [bm_2im][PF_6], [emim][OTs], and [bmim][Br], cannot be advantageously used as solvent for the Stille reaction (entries 5, 6, 7 from Table 1).

As shown in Table 2, ILs can effectively replace toxic solvents like HMPA in ligandless Stille cross-coupling.[12] As with Pd($AsPh_3$)$_2$, non nucleophilic ionic liquids having bis(trifluoromethylsulfonyl)imide as the anion are the best choice for the ligandless cross-coupling reactions (entries 1, 8, 9, 10). Apparently, when ligands are not present, the possibility of N–Sn intermolecular interactions enhances the reactivity of the system so that the coupling is complete in reasonably short times (4 hours). Furthermore, under these conditions the rate of the reaction is more sensitive to cationic structure, so that ILs incapable of forming H-bonds are preferred (compare entries 1 and 2 with 7 and 8). As in conventional solvents, the lack of coordinating ligands negatively affects the stability of the catalyst, so that recycling of the system is often difficult.

Much of the discussion of Pd catalyzed reactions in ionic liquids has focused on the possible formation of imidazolidene complexes either by deprotonation of the imidazolium cation[1b,13] or by oxidative addition of the cation to the metal centre.[14] As the Stille cross-coupling under investigation is sensitive to the presence of $AsPh_3$ and the yields of conversion in [bpyrr][Tf_2N] and [HPy][Tf_2N] are very similar to those obtained in [bmim][Tf_2N], we believe that the involvement of a metal carbene complex formed *in situ* is unlikely under our conditions. However, our data do not give information about the nature of the really reactive palladium species, so it is not possible to exclude the presence of Pd nanoparticles.[15]

Finally, although with a lower efficiency, ILs can also be used to transfer alkyl groups using simple commercial tetraalkylstannanes. Besides, the yields for methyl and butyl transfer are similar to or higher than those reported in conventional organic solvents.[16] Anyway, the use of ionic liquids as the reaction media cannot be considered a variant to the use of stannatranes[17] which, although not easy to synthesize, remain the reagents capable of significantly improving the alkyl transfer in Stille coupling.

Conclusion

The efficiency of Stille cross-coupling in ionic liquids is not insensitive to the nature of the ionic media. The best solvents are [bmim][$C_8H_{17}SO_4$], [bmim][Tf_2N], [bpyrr][Tf_2N], and [HPy][Tf_2N] either in terms of conversion or mass balance. The introduction of a vinyl group is also possible in the absence of $AsPh_3$, even if longer reaction times are needed. On the other hand, the cross-coupling of simple tetraalkylstannanes such as Me_4Sn and But_4Sn with iodobenzene still remains difficult in the ionic media.

Experimental

GC-MS spectra were carried out on a 30 m DB5 capillary column using an instrument equipped with an ion trap detector. GC analyses were carried out using an ECONOCAP EC-5 column (30 m). Iodobenzene, tributylvinylstannane, tetrabutylstannane and tetramethylstannane were used without purification. [bmim][PF_6], [bmim][Tf_2N], [bmim][Br], [bm_2im][Tf_2N], [bpyrr][Tf_2N], [HPy][Tf_2N], were prepared following the reported procedures;[10,18] [bm_2im][PF_6], [emim][OTs], [bmim][$C_8H_{17}SO_4$] were supplied from Solvent Innovation. The purity of ILs was checked as previously reported.[6b]

Reactions were carried out in a screw cup with Teflon-faced rubber septum vials under magnetic stirring. To a suspension of $Pd_2(dba)_3$ (0.025 mmol) and Ph_3As (0.05 mmol) or $Pd(OAc)_2$ (0.025 mmol) in 1 ml of ionic liquid were added iodobenzene (0.5 mmol) and the organostannane (0.6 mmol). The mixtures were stirred at 80 °C for the times reported in Tables 1, 2 and 3. The products were extracted with *n*-pentane (10×1 ml), the organic layers were dried over $MgSO_4$ and diluted to an exactly known volume. A portion of this solution, exactly measured, was analyzed by GC-MS and the remaining by GC, after the addition of an appropriate amount of an internal standard (benzonitrile).

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Structure–reactivity correlations in the selective aerobic oxidation of cinnamyl alcohol: *in situ* XAFS

Adam F. Lee* and Karen Wilson
Department of Chemistry, University of York, York, UK YO10 5DD. E-mail: afl2@york.ac.uk;
Fax: +44 1904 432516; Tel: +44 1904 434470

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The structural evolution of a Pd/C catalyst during the liquid phase selective aerobic oxidation of cinnamyl alcohol has been followed by *in situ* XAFS and XPS. The fresh catalyst comprised highly dispersed, heavily oxidised Pd particles. Cinnamyl alcohol oxidation resulted in the rapid reduction of surface palladium oxide and a small degree of concomitant particle growth. These structural changes coincided with a large drop in catalytic activity. Prereduced Pd/C exhibited a significantly lower initial oxidation rate demonstrating the importance of surface metal oxide in effecting catalytic oxidation. Use of a Pd black model system confirmed that the oxide→metal transformation was the cause, and not result, of catalyst deactivation.

Introduction

The selective oxidation of alcohols finds application in the synthesis of many valuable intermediates for the food and pharmaceutical industry. Supported platinum-group metals have long shown promise in the aerobic partial oxidation of carbohydrates and alcohols[1] over wide temperature, pressure and solvent regimes and have been extensively studied over the past decade.[2] Bimetallic variants incorporating a second inert component have also been shown to enhance the selectivity of such catalysts though the origin of such promotional effects remains contentious. Despite their potential as generic selective oxidation catalysts, further development is hindered by the complexity of the three-phase system, and severe deactivation of these materials. Two issues in particular require addressing; the nature of the active site and the deactivation mechanism.

Three main sources of catalyst deactivation have been advanced in the literature for the liquid phase oxidation of alcohols. First, so called chemical poisoning, *i.e.* the irreversible adsorption of strongly bound hydrocarbons, including reaction intermediates and (by) products such as carboxylic acids. This is commonly reported in aqueous media working at low pH[3] or over reduced metal surfaces (low catalyst potential),[4] although secondary alcohols are reported as insensitive to pH.[5] Despite many electrochemical studies of related poisoning phenomena[6–8] there are no direct measurements on the nature or binding strength of such adsorbates over dispersed noble metal catalysts. Surface restructuring and corrosion may also contribute to catalyst deactivation, most notably for promoted catalysts wherein the inactive component (usually Bi, Pb or Sn) is readily leached into aqueous solution.[9] This is most problematic when reactions are performed in the presence of chelating agents or at acidic pH.[3,10–12] Under aqueous conditions leaching is minimised through the use of a Na_2CO_3 or Li_2CO_3 buffer to maintain pH > 8. However the most important deactivation process relates to the oxidation state of the catalyst surface. From electrochemical measurements, it is widely held that alcohol oxidation occurs over metal (Pt^0) sites[2] and that poor rates are observed over heavily oxidised catalysts.[13,14] However inefficient reactant diffusion under these simulated reaction conditions and the inherent invasive nature of electrochemical measurements may result in perturbation of the chemical state of the catalyst surface. Thus despite this common assertion there remain no *direct* structural investigations of the working catalyst during reaction. Consequently, in the absence of oxygen mass-transport limitations, it has been proposed that over-oxidation causes the rapid deactivation of catalysts with intrinsically poor activity.[15] Indeed it has been suggested that bulk platinum oxides[13] or a platinum-oxygen solid solution[14,15] can form under these mild reaction conditions. In contrast Baiker and coworkers suggest that over-oxidation is the result (not cause) of chemical poisoning, noting that a partial oxygen coverage is essential for preserving high activity.[16] Indeed cinnamyl alcohol oxidation is greatly suppressed over reduced Pt,Bi/Al_2O_3 in comparison with its oxidised counterpart.[17] Clearly a subtle interplay exists between competitive adsorption of organic moieties and oxygen.

Identification of the reaction-induced morphological and chemical changes from these early studies are also complicated by the use of aqueous reaction media necessitating surfactants and pH regulation *via* base addition; the latter may induce oscillations in the steady state oxidation rate.[18] Utilisation of aqueous solvents is often justified on the grounds that for safety reasons industrial scale oxidation reactions cannot be performed in hydrocarbon solvents and that water is the ideal 'green' solvent. However there are several problems associated with the use of water, namely that many organic compounds require the use of surfactants to solubilise them, increasing the processing steps and associated solvent waste produced on extraction of the product. Additionally the aqueous waste stream contaminated with any soluble organic components is particularly difficult to treat.[19] Thus the environmental impact of both treating the waste water, and energy input to separate the surfactant from the product *versus* distillation and recycling of a benign organic solvent, must be considered.

In situ XAFS has emerged as a powerful technique for studies of catalyst evolution during activation treatments[20] or steady state measurements of catalyst oxidation.[21] Previously we have shown that allylic alcohol oxidation can be performed effectively in an organic solvent (ethanol, toluene),[22] vastly simplifying catalytic

Green Context

The selective oxidation of organic compounds is probably the most widely used synthetic transformation in chemistry. Catalytic aerobic oxidation is normally regarded as the best green chemistry option but such systems are generally poorly understood. Here the structural evolution of a typical oxidation catalyst, supported palladium, during an aerobic oxidation is studied using *in situ* XAFS. The study proves to be viable and proves the importance of surface oxide sites. The better understanding of such procedures should help us to develop and apply many more green oxidation systems based on heterogeneous catalysts. ***JHC***

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mechanistic studies. Here we address the role of metal oxidation state in cinnamyl alcohol oxidation in a hydrocarbon solvent *via* spectroscopic measurements of a monometallic Pd/C catalyst. By omitting promoters we avoid issues concerning their disruption of the active ensemble through surface decoration or alloying. Complications arising from modified oxygen/substrate activation and associated spillover processes are also eliminated. Likewise use of a hydrocarbon solvent eliminates the necessity for surfactant, and improves diffusion of organic reactant. Specifically we build upon our original report[23] of the application of *in situ* XAFS to follow the *real-time, dynamic* structural evolution of a heterogeneous catalyst during a liquid phase organic reaction. A transformation from oxidic to metallic Pd particles precisely correlates with severe catalyst deactivation demonstrating the importance of surface oxides in selective oxidation.

Experimental

In situ XAFS measurements were made on Station 9.2 of the Daresbury SRS facility, using a Si(311) double-crystal monochromator with a beam current/energy of 150 mA/2 GeV. Pd (24.35 keV) Quick XAFS spectra were acquired in a specially constructed, aluminium recirculating trickle-bed reactor based on an existing design.[21,24] Approximately 0.1 g of 5 wt% Pd/charcoal catalyst powder was diluted with 0.7 g of boron nitride and loaded into the cell, supported on a silica wool bed between 25 μm Kapton windows giving an overall X-ray path length of 13 mm. The reaction mixture, comprising 5 mmol cinnamyl alcohol (Aldrich 99%) in 60 ml toluene, equivalent to a 1 : 112 molar ratio, was fed from an oxygen-saturated external reservoir at ~20 ml min^{-1}. Before reaction, both the reservoir and catalyst were heated to 60 °C before circulating the reaction mixture. XAS spectra were taken every 3 minutes for a 10 h period after which cinnamyl alcohol conversion reached a plateau. Spectra were fitted using the Daresbury ECABS and EXCURV98 packages for background subtraction, and phaseshift determination and fitting procedures respectively. Reference transmission XAFS of PdO (>99% Lancaster) and a 10 μm Pd foil standard were also recorded.

An inert internal standard, mesitylene (Aldrich 99%) was included for calculation of product yields and to ensure closure of the carbon mass balance (>95%). Aliquots (0.1 ml) of the reaction mixture were periodically withdrawn for off-line analysis using a Perkin-Elmer 8500 GC and a 30 m × 0.25 mm HP5 capillary column. Cinnamaldehyde was the principal reaction product, with a small amount of phenylpropanol and trace cinnamic acid also formed. There were no side-products attributable to solvent oxidation. Quoted conversions are ± 1% and selectivities ± 3%. Cinnamyl alcohol oxidation was also followed *in situ* by monitoring the oxygen uptake from the reservoir deadspace (maintained at 1 bar O_2) using a Buchi Pressflow Gas Controller.

X-Ray photoelectron spectra were acquired using a Kratos Axis HSi instrument operating at 225 W with a Mg Kα excitation source (1253.6 eV) and a CHA analyser selecting at 20 eV pass energy. The sample was charge neutralised and Pd 3d, and C and O 1s spectra recorded at normal emission to the surface. Binding energies were referenced to the C 1s of graphite at 285 eV. X-Ray diffractograms were recorded on a Siemens D5000 diffractometer using Cu Kα radiation and a 2θ scan range of 10–105° in 0.02° steps. Surface areas were determined by N_2 physisorption and metal dispersions by CO chemisorption.

Results and discussion

X-Ray photoelectron spectroscopy

Changes in the surface oxidation state during cinnamyl alcohol oxidation were determined from Pd XP spectra of the fresh and spent Pd/charcoal catalysts (Fig. 1). The Pd 3d spectra show that the fresh, untreated catalyst contains two palladium states consistent with metallic and oxidic (2+) environments,[25] the $3d_{5/2}$ components at 335.5 eV and 337.3 eV binding energy (BE) respectively. Approximately 70% of the total surface palladium is initially present as oxide, indicative of small particles (<50 Å)[26,27] in accordance with surface energy constraints.[28] Fig. 1 shows that catalytic oxidation of a 5 mmol cinnamyl alcohol mixture under mild reaction conditions dramatically reduces the amount of surface PdO_x to below 12%. The total Pd surface concentration is unchanged during reaction, consistent with ICP analysis of hot filtered, post-reaction catalysts which reveal negligible metal leaching. The corresponding O 1s XP spectra (not shown) reveal a 55% decrease in surface oxygen confirming the reduction of surface Pd during cinnamyl alcohol oxidation. Fig. 1 also shows that *in situ* chemical reduction yields a similar spectrum to that obtained from Pd/C directly reduced *via* H_2 at 190 °C. The stoichiometry of the initial surface oxide can be calculated from the relative $Pd^{\delta+}$ 3d : O 1s peak intensities and taking into account the appropriate correction factors yields a 1 : 1 ratio consistent with the presence of PdO.

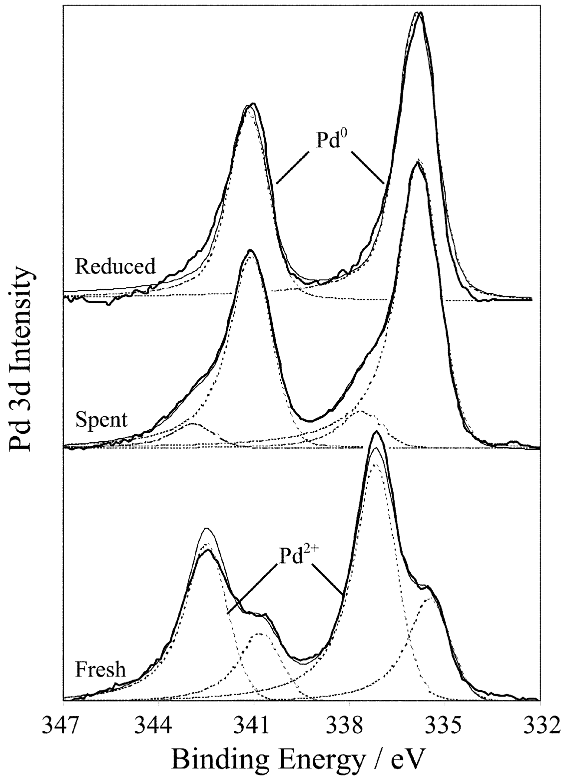

Fig. 1 Pd 3d XP spectra of fresh and spent Pd/C catalyst after 10 h cinnamyl alcohol oxidation. A spectrum of the H_2 reduced catalyst is shown for comparison.

In situ EXAFS

In order to follow the dynamics of this reduction process Pd K-edge EXAFS were acquired *in situ* during cinnamyl alcohol oxidation, Fig. 2. Measurements of the fresh catalyst within the reaction cell confirm the presence of both Pd oxide and metal environments. Fig. 3a and b show the respective raw χ data and radial-distribution function prior to reaction: Pd–O and Pd–Pd coordination shells (r) are present at ~2.03 and 2.75 Å respectively. The low coordination numbers (CN) shown in Table 1 are consistent with small (<20 Å) Pd particles capped by a truncated, surface oxide phase. The alternative possibility, that the catalyst comprises a mixture of discrete oxide and metal crystallites is unsupported by XRD.

The Pd K-edge spectra remain unchanged for ~40 min following introduction of the reaction medium to the catalyst, Fig. 4, a period during which cinnamyl alcohol oxidation proceeds with a constant (maximum) rate. Subsequently the white line intensity (edge-jump), a direct measure of the Pd oxidation state,[29] shows a

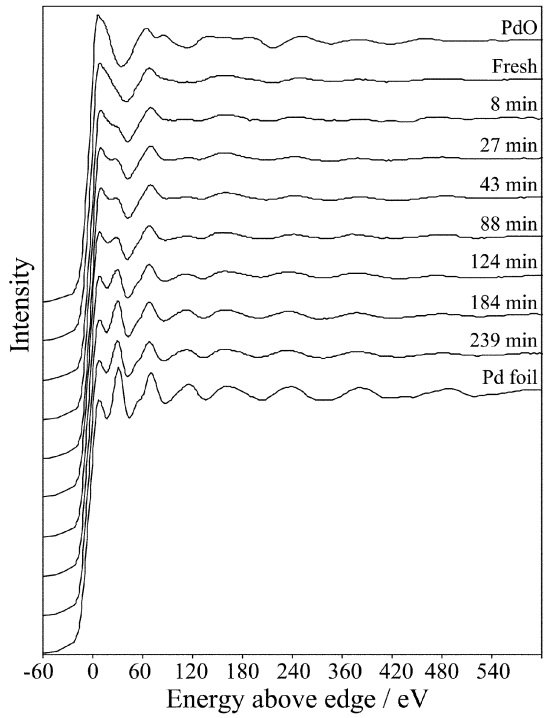

Fig. 2 Time-resolved Pd K-edge quick XAFS of a Pd/C catalyst during cinnamyl alcohol oxidation. Reference spectra of PdO and a Pd foil are shown for comparison.

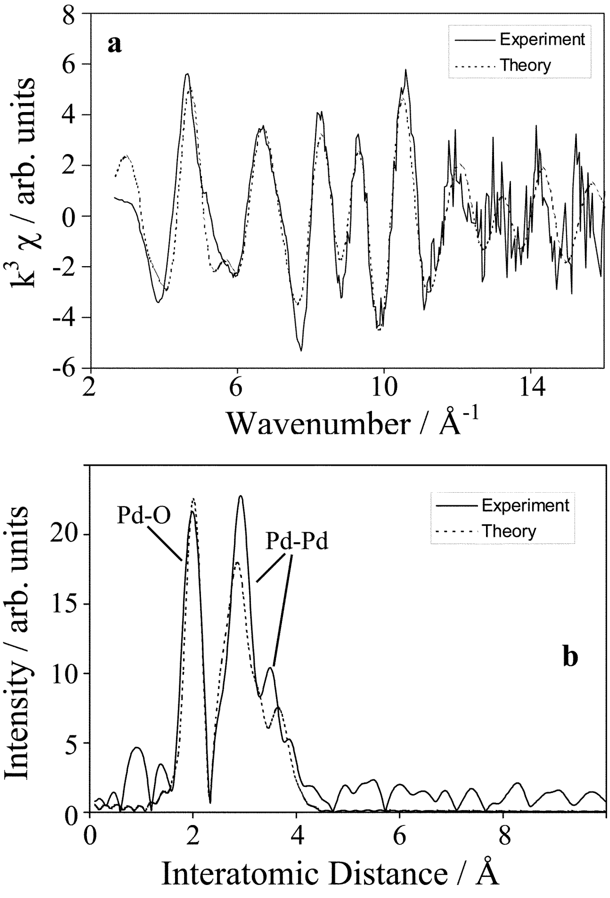

Fig. 3 Pd K-edge (a) k^3-weighted raw EXAFS and (b) pseudo-radial distribution function of a fresh Pd/C catalyst.

Table 1 Structural parameters derived from fitted EXAFS of fresh and spent Pd/C catalysts

Parameter	PdO	Fresh	Spent	Pd Foil
CN^1_{Pd-O}	4	2.5	—	—
CN^1_{Pd-Pd}	8	1.7	4.45	12
CN^2_{Pd-Pd}	2	2.8	—	6
r^1_{Pd-O} / Å	2.03	2.04	—	—
r^1_{Pd-Pd} / Å	3.07	2.76	2.76	2.74
r^2_{Pd-Pd} / Å	3.45	3.43		3.87
σ^1_{Pd-O}	0.007	0.007	—	—
σ^1_{Pd-Pd}	0.017	0.012	0.011	0.014
σ^2_{Pd-Pd}	0.005	0.018	—	0.02

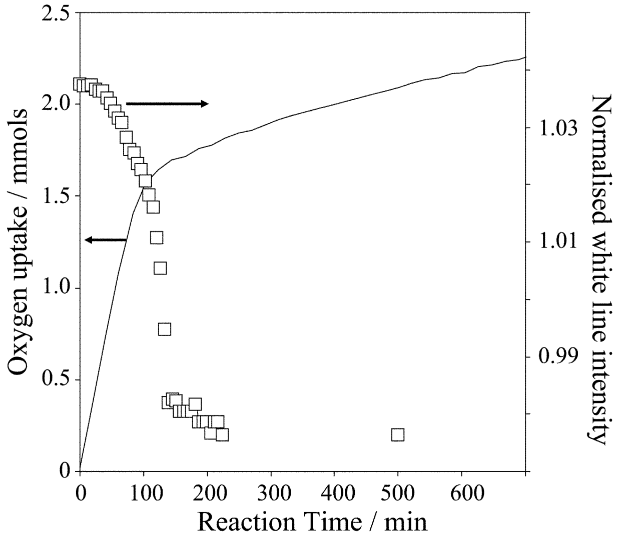

Fig. 4 Correlation between oxygen uptake and normalised Pd K-edge white line intensity as a function of reaction time.

sharp drop which is complete after 120 min reaction, associated with a transformation from oxidic to metallic palladium.

The fitted χ data and radial-distribution function (Fig. 5a and b) confirm the loss of the Pd–O coordination shell and concomitant increased Pd–Pd scattering consistent with pure Pd particles. This structural evolution coincides with a rapid decrease in catalyst activity; the oxidation rate falls from ~ 0.18 to 0.02 mmol min^{-1} (g cat)$^{-1}$. Loss of activity due to particle sintering upon PdO reduction can be discounted as XAFS provides both oxidation state and particle size information, and reveals that the latter remains unchanged over this time period. Following this chemical reduction the average Pd coordination number begins to rise giving a limiting particle size of ~ 80 Å (confirmed by XRD and TEM measurements). In all cases the Debye–Waller factors (σ), a measure of vibrational disorder, were low and in good agreement with the respective Pd oxide or metal standards. Of course it is important to establish whether these values represent true catalytic rates [eqn. (1)] or simply reflect the stoichiometric consumption of PdO [eqn. (2)].

$$Ph\text{–}CH\text{=}CH\text{–}CH_2OH + \tfrac{1}{2}\,O_2 \rightarrow Ph\text{–}CH\text{=}CH\text{–}CHO + H_2O \quad (1)$$

$$Ph\text{–}CH\text{=}CH\text{–}CH_2OH + PdO \rightarrow Ph\text{–}CH\text{=}CH\text{–}CHO + Pd + H_2O \quad (2)$$

From XPS the fresh catalyst contains ~ 2.86 × 10^{-5} moles of PdO. Assuming a 1 : 1 stoichiometry for the reaction between O_a, liberated by PdO decomposition, and cinnamyl alcohol to form cinnamaldehyde, and that catalyst reduction is complete after 120 minutes, a maximum rate of ~ 0.0024 mmol min^{-1} (g cat)$^{-1}$ is obtained. This value is much less than the measured rates and we can thus neglect direct contributions from the catalyst reduction.

Bulk catalyst properties

Gross morphological changes accompanying oxidation were examined *ex situ* by TEM and X-ray diffraction of the fresh and post-reaction Pd/C catalysts. Both techniques gave an average initial Pd particle size of ~ 20 Å, consistent with the EXAFS estimate[30,31]

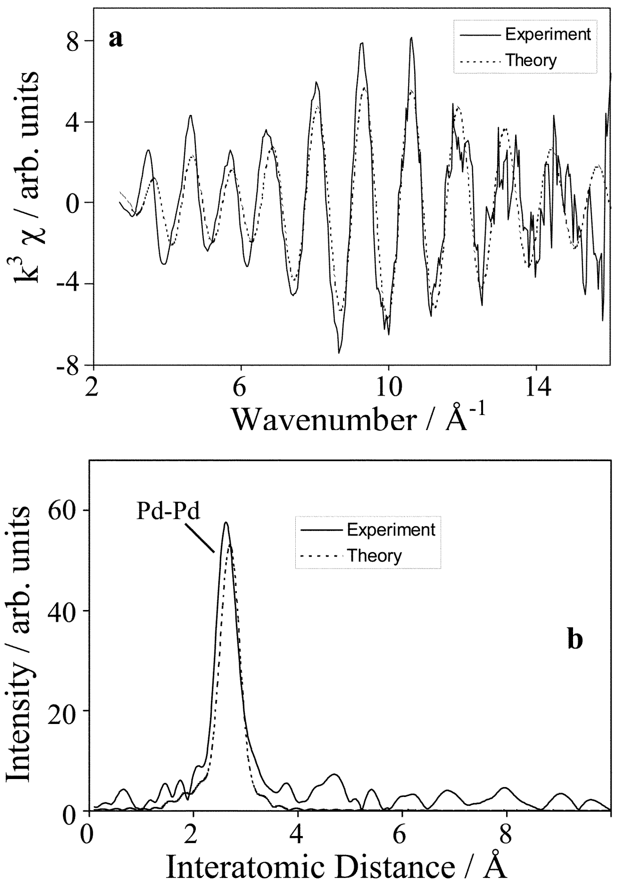

Fig. 5 Pd K-edge (a) k^3-weighted raw EXAFS and (b) pseudo radial distribution functions of a spent Pd/C catalyst.

and the high dispersion (d_{Pd} = 1.02) indicated from CO titration. Following reaction the particle size increased to ∼100 Å in accordance with the stronger XAFS oscillations. A similar increase was observed following H_2 pretreatment at 190 °C.

Reactor studies

The preceding structural measurements showed the loss of surface Pd oxide during the initial stages of cinnamyl alcohol oxidation, with the limiting performance of a fresh Pd/C catalyst of ∼98% conversion and ∼90% selectivity towards the aldehyde after ∼10 h. In order to explore whether catalyst reduction was a cause of the rapid deactivation or simply a side-effect, a fresh catalyst was prereduced under H_2 (190 °C) prior to reaction. The resulting catalyst was transferred under nitrogen to the trickle-bed reactor and monitored *via* on-line oxygen consumption and GC sampling. Fig. 6 compares the activity of the fresh and prereduced catalysts over the course of reaction. It is immediately apparent that the initial oxidation rate is much slower over prereduced Pd/C at only ∼0.11 mmol min^{-1} (g cat)$^{-1}$. The reduced catalyst undergoes somewhat slower deactivation than fresh Pd/C but attains a similar low steady state reaction rate consistent with a common (metallic) surface environment. This limiting rate is likely controlled by the accumulation of irreversibly bound (by) products which strongly chemisorb to metal sites.

Model catalyst studies

The hypothesis that metal oxide sites play an essential role in cinnamyl alcohol oxidation over Pd/C was tested using Pd black as a model catalyst to eliminate metal-support interactions and spillover effects. The fresh Pd black sample comprised large particles with a volume-averaged particle diameter of 180 Å from XRD (Fig. 7). The total surface area of fresh Pd black was only ∼30 m^2 g^{-1} corresponding to a metal dispersion of only 0.08. Palladium 3d XP spectra in Fig. 8 show that the fresh catalyst contains ∼33% oxide, the greater proportion of metallic palladium reflecting the much lower dispersion compared to the Pd/C catalyst.

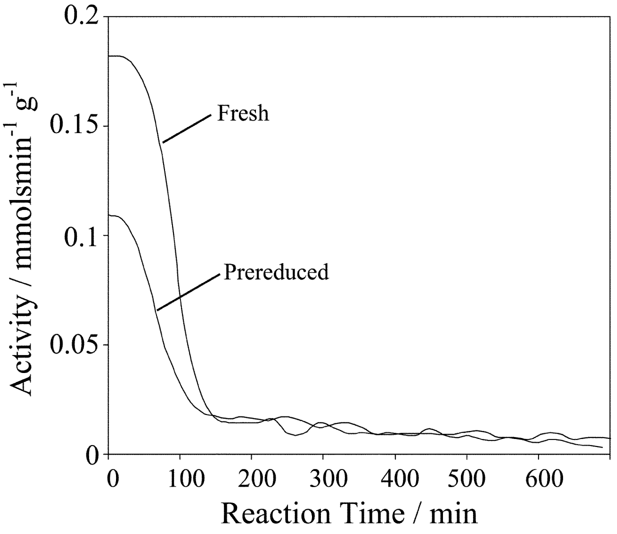

Fig. 6 Comparison of cinnamyl alcohol oxidation rates over fresh and prereduced catalysts.

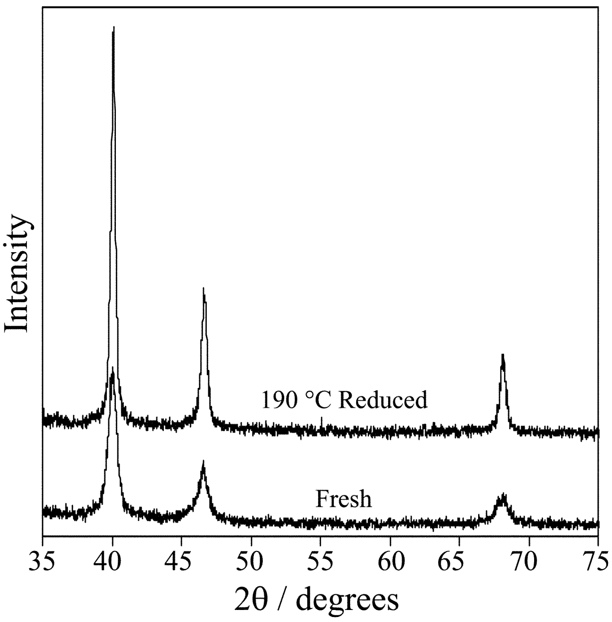

Fig. 7 X-Ray diffractograms of fresh and 190 °C H_2 reduced Pd black.

Direct low temperature (<200 °C) reduction under H_2 was subsequently attempted. As expected reduced Pd black samples transferred under nitrogen showed a significant increase in average particle size determined by XRD, reaching ∼600 Å after 190 °C reduction. The associated Pd 3d XP spectra reveal a dramatic change in surface composition with only metallic Pd sites remaining following reduction. Fig. 9 compares the catalytic performance of fresh and reduced Pd black samples towards cinnamyl alcohol oxidation. Conversion over fresh Pd black was significantly lower (∼19%) than that observed over Pd/C under identical reaction conditions reflecting the great difference in overall metal dispersion. Reduction temperatures as low as 130 °C proved sufficient to dramatically decrease catalytic activity, which was completely suppressed above 190 °C.

This transformation correlates directly with the loss of active surface palladium oxide (and not particle size effects). Since reduced samples were cooled under nitrogen any contribution from a palladium hydride phase may also be discounted. Confirmation

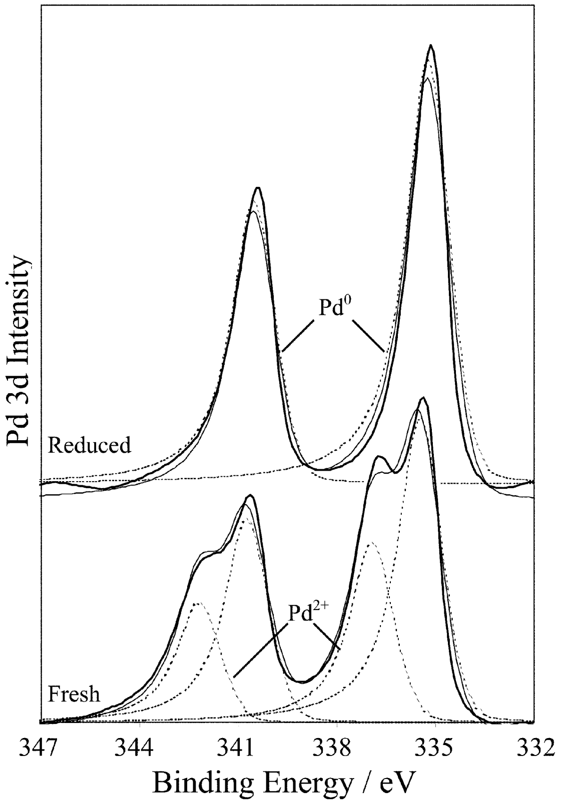

Fig. 8 Pd 3d XP spectra of fresh and prereduced Pd black.

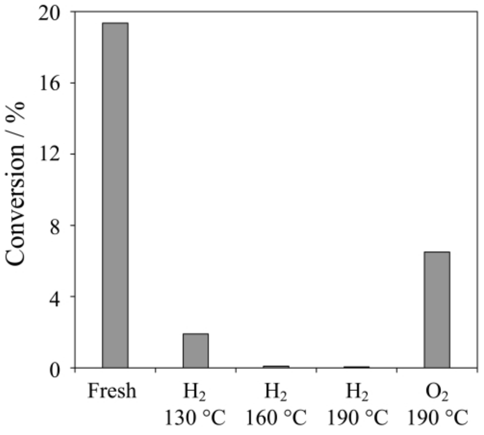

Fig. 9 Effect of catalyst pretreatment on cinnamyl alcohol conversion over fresh, reduced and reoxidised Pd black after 10 h reaction.

for the crucial role of surface oxide in cinnamyl alcohol reaction was obtained from the reoxidation of fully reduced Pd black; calcination under oxygen (10 ml min^{-1} at 190 °C for 2 h) resulted in partial regeneration of the original oxidation performance. A similar effect was observed following ambient addition of 40 w/v% H_2O_2 solution to reduced Pd black followed by filtration and drying. These results also demonstrate that poisoning due to surface reduction *alone* is reversible. In contrast pure PdO particles showed no activity towards cinnamyl alcohol presumably reflecting the high thermodynamic stability of bulk *versus* surface oxides.

In situ XAFS has enabled us to identify the reduction of catalytically active PdO_x surface sites during Pd/C catalysed allylic alcohol oxidation. That this proposed deactivation mechanism differs from reactions performed in aqueous media may be ascribed to the relative solubilities of the reactants. Operation in aqueous solvents, wherein allylic alcohol solubilities and diffusion rates are so poor as to necessitate surfactant addition, result in high O_2 : substrate ratios which thereby favour catalyst overoxidation. However in organic media, cinnamyl alcohol diffusion to the catalyst surface is facile, preventing overoxidation. The predominant catalyst deactivation route now occurs *via* reduction of surface PdO→Pd and associated build-up of irreversibly adsorbed by-products on the resultant metal surface. Recent ATR measurements support that under these conditions catalyst deactivation occurs *via* site blocking by adsorbed CO[32] formed during decarbonylation reactions.

Conclusions

In situ XAS has been shown to be a viable tool for following structural changes within working supported heterogeneous catalysts during liquid phase reactions. The rate of cinnamyl alcohol oxidation to cinnamaldehyde directly correlates with the oxidation state of highly dispersed Pd particles. A surface palladium oxide layer is essential for maintaining high selective oxidation activity. Adsorbate-induced catalyst reduction and restructuring (prevalent under oxygen mass-transfer limited conditions), dramatically lowers catalyst activity possibly associated with the rapid deactivation of Pd metal *versus* oxide surface sites.

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PAPER

www.rsc.org/greenchem

The development of an environmentally benign synthesis of sildenafil citrate (Viagra™) and its assessment by Green Chemistry metrics†

Peter J. Dunn,[*a] **Stephen Galvin**[b] **and Kevin Hettenbach**[c]

[a] *Department of Chemical Research and Development, Pfizer Global Research and Development, Sandwich, Kent, UK CT13 9NJ*

[b] *Pfizer Ireland Pharmaceuticals, Ringaskiddy API Plant, P.O. Box 140, Ringaskiddy, County Cork, Ireland*

[c] *Department of Chemical Research and Development, Pfizer Global Research and Development, Groton, CT-06340, United States*

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The process development and scale-up of the sildenafil citrate process is reviewed. Key environmental metrics are reported at several time points during the development process. Significant achievements during the development of sildenafil citrate were (i) discovering a convergent, efficient synthetic route (ii) designing 7 process steps so that there was no extractive work-up in any step (iii) implementing efficient solvent recovery early in the product's commercial lifetime. The result of this work is that the E-factor for the process is very low with just 6 Kg of waste per kilogram of product compared with an industry average of 25–100 Kg. Pfizer received the 2003 UK Award for Green Chemical Technology (Best Process category) for the sildenafil citrate process.

Introduction

Sildenafil citrate is a selective inhibitor of phosphodiesterase 5 (PDE5) and was the first agent with this mode of action for the treatment of male erectile dysfunction (a disease that was more commonly known as male impotence). This new drug was approved for prescription use within the United States, the European Union and Japan during 1998 and immediately became a major seller, achieving sales of more than $1 billion during its first year on the market. With such a rapid sales take off it was critical that the environmental performance of the synthesis was good from the outset.

A crude assessment of the environmental performance of a synthesis is provided by the E-factor[1] and Sheldon[1] has given broad levels of environmental performance for different categories of the Chemical Industry as shown in Table 1.

Table 1 The E-factor per industry segment

Industry segment	Annual product tonnage	Kg waste/ Kg product
Oil refining	10^6–10^8	*ca.* 0.1
Bulk chemicals	10^4–10^6	< 1–5
Fine chemicals	10^2–10^4	5– > 50
Pharmaceuticals	10–10^3	25– > 100

There are many reasons why waste levels are generally higher for pharmaceutical compounds. For example, typical syntheses involve complex molecules with demanding quality standards, often requiring batch processing; there are greater regulatory constraints and in general high value, low volume products are being made. Some earlier publications by GlaxoSmithKline have looked at assessing general reaction types by Green Chemistry metrics.[2,3] This paper assesses a specific process, the sildenafil citrate process, using various Green Chemistry metrics, including the E-factor proposed by Sheldon, and examines how the process compares with industry norms. Data at various points in the chemical development process are also reported.

Medicinal chemistry route and "quick fixes" for early scale-up

The medicinal chemistry route is shown in Scheme 1.[4]

The first task of the process chemist was to prepare a few kilograms of material for early toxicology studies. The following four changes were made for early batches to improve the environmental performance of the synthesis.

- The removal of the tin chloride reduction. Tin is a heavy metal and a major environmental polluter.
- The use of stoichiometric quantities of thionyl chloride in a solvent, rather than thionyl chloride as solvent in the preparation of compound **(2)**. This is much safer and has a reduced environmental impact.
- The elimination of hydrogen peroxide from the synthesis. Hydrogen peroxide causes burns on contact with skin and is a fire and transportation hazard especially in contact with organic materials.
- The use of thionyl chloride rather than oxalyl chloride for the preparation of 2-ethoxybenzoyl chloride. This change gave an improvement in worker safety by avoiding carbon monoxide emissions.

Medicinal chemists employed a tin chloride reduction because standard reduction by hydrogenation was not effective. Investigation showed that the failure of the hydrogenation was due to trace levels of sulfur impurities, from the previous thionyl chloride reaction, poisoning the hydrogenation reaction. Careful control of these sulfur impurities (for example, switching to stoichiometric thionyl chloride use) allowed tin to be removed from the process and replaced with a simple catalytic hydrogenation reaction. Catalytic hydrogenations are among the cleanest environmental chemical steps. For a reduction of a nitro group to an amine, the only by-product is water and there are recovery options for solvent and catalyst.

The medicinal chemistry method to cyclise compound **(4)** to the pyrazolopyrimidinone **(5)** used an aqueous alcoholic solution of sodium hydroxide and hydrogen peroxide in 72% yield. A literature

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† This chemistry was presented at the Green Chemistry Symposium at the American Chemical Society in Florida, April, 2002 and at the IUCT 4th Green Chemistry conference in Barcelona 11th/12th November, 2002.

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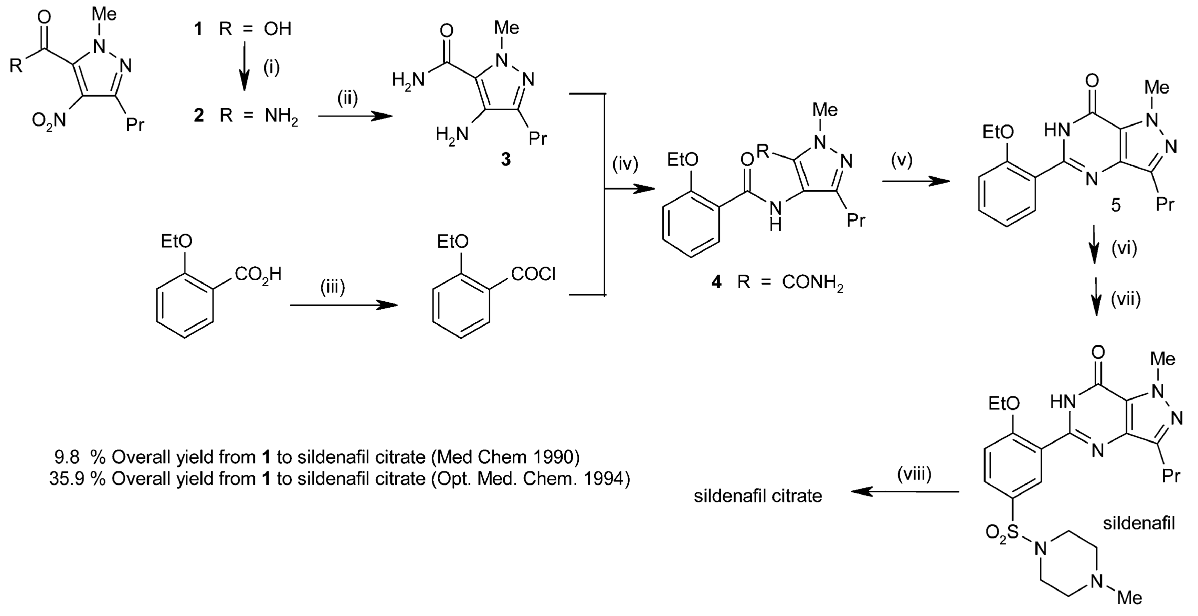


9.8 % Overall yield from **1** to sildenafil citrate (Med Chem 1990)
35.9 % Overall yield from **1** to sildenafil citrate (Opt. Med. Chem. 1994)

Med Chem Process (1990)

(i) Step 1, Δ $SOCl_2$, acetone / NH_3 (aq) (78 %), (ii) Step 2a $SnCl_2$, ΔEtOH (94 %) (iii) Step 2b $(COCl)_2$, CH_2Cl_2, distillation (89 %), (iv) Step 2b, **3**, 2-ethoxybenzoyl chloride, Et_3N DMAP (cat), CH_2Cl_2, 25°C, chromatography (40%) (v) Step 3, NaOH, EtOH, H_2O_2; CH_2Cl_2 : MeOH extraction, chromatography (72 %) (vi) Step 4, $ClSO_3H$, H_2O quench, CH_2Cl_2 : MeOH extraction (vii) Step 4, *N*-methylpiperazine, EtOH
(viii) Step 5, salt formation details as below.

Optimised Med Chem Process (1994)

(i) Step 1, $SOCl_2$, toluene 50-60°C (92%), (ii) Step 2a H_2, Pd / C, EtOAc (100%), (iii) Step 2b, $SOCl_2$, DMF (cat), EtOAc (100 %) (iv) Step 2b, **3**, 2-ethoxybenzoyl chloride, pyridine, EtOAc (84 %) (v) Step 3, KOBu^t, Δ *t*-BuOH (100%) (vi) and (vii) Step 4, $ClSO_3H$, H_2O quench, CH_2Cl_2 extraction, replacement with toluene, *N*-methylpiperazine, (71 %), 2-butanone recrystallisation (80%) (viii) Step 5, citric acid, acetone (91%), aqueous acetone recrystallisation (90 %).

Scheme 1 The medicinal chemistry route to sildenafil.

review of alternative cyclisation methods revealed that such reactions had only previously been performed in moderate yield (30–70%).[5] It was found that by employing KOBu^t in ^{t}BuOH in the cyclisation reaction, a 100% isolated yield was obtained with no impurities detected. Finding this very clean and high yielding reaction impacted on the way the commercial route was designed.

Selection and development of the commercial route

A summary of the two routes is outlined in Scheme 2. The flow diagrams in Scheme 2 clearly show that the strategic advantages of the commercial route were as follows:

- Greater convergency
- The clean cyclisation reaction is now at the end of the synthesis in the final bond-forming step. The potentially toxic materials now occur near the start of the synthesis.
- The environmental and scale-up issues associated with the chlorosulfonation step (*i.e.* large volumes of aqueous acidic waste that require neutralisation and increased levels of hydrolysis during increased quench time on a larger scale) are reduced by placing the chlorosulfonation reaction earlier in the synthesis. A simple, low molecular weight starting material (2-ethoxybenzoic acid) is used, hence less chlorosulfonic acid is needed and the problem is much reduced.

Once selected, the commercial route was subjected to further, detailed development and the optimised synthesis is outlined in Scheme 3.[6]

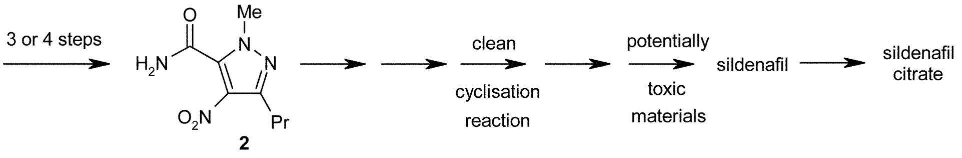
2-Ethoxybenzoic acid is chlorosulfonated using chlorosulfonic acid along with 1 mol of thionyl chloride, to ensure that the intermediate sulfonic acid is converted to the sulfonyl chloride. 2-Ethoxybenzoic acid is a low melting solid (mp 19–20 °C) and hence could be used as a melt, allowing the use of relatively low volumes of chlorosulfonic acid and thionyl chloride as there were no solubilisation issues. Following aqueous quench, the product is isolated as a water wet sulfonyl chloride. For simplicity and efficiency, the sulfonyl chloride is then resuspended in water and reacted with *N*-methylpiperazine. At the end of the reaction, the pH is adjusted and the sulfonamide **(6)** is collected by filtration. Hence, no organic solvent is used for the preparation of the sulfonamide.

As mentioned earlier, the original procedure to convert pyrazole **(1)** into the amide **(2)** used a neat reaction in thionyl chloride. The introduction of toluene as a heat sink/solvent both increased the safety of the process and allowed reduction of the levels of thionyl chloride to 1.2–1.6 equivalents. The toluene in this reaction is recovered and reused.

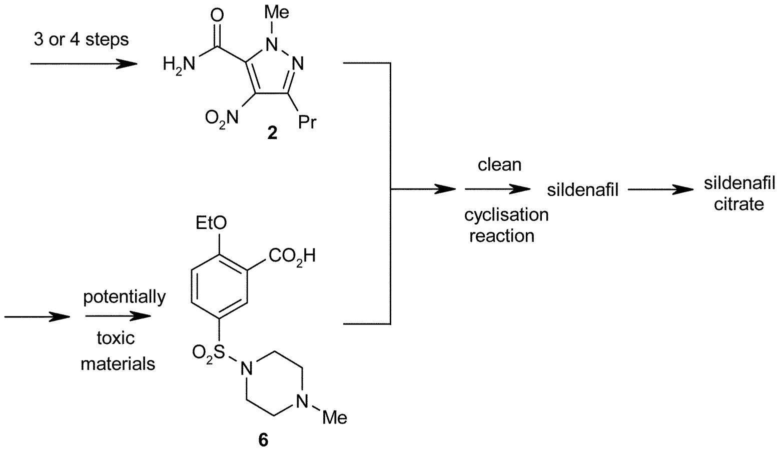
Heterogeneous hydrogenation in ethyl acetate was used to convert the nitropyrazole **(2)** to the amine **(3)**. Activation of the acid **(6)** was examined with a number of reagents including thionyl chloride, oxalyl chloride and *N*,*N*′-carbonyldiimidazole (CDI). CDI was selected, despite its higher cost because this reagent:

- Provided clean, robust chemistry and high quality product.
- Allowed all three reactions (hydrogenation, activation and acylation) to be combined.
- Enabled a single solvent to be employed (ethyl acetate), allowing simple solvent recovery with low energy use.
- Avoided VOC emissions (EtCl) from the interaction of either thionyl chloride or oxalyl chloride with ethyl acetate.
- Provided a simple process – mix streams, concentrate and filter. This simplicity led to low energy use.
- High chemical yield, (90%) over three chemical steps (subsequently optimised to 96%).

The resulting coupled product **(7)** is then cyclised with *t*-BuOH and *t*-BuOK. The process is run at high concentration (2.5–3.75 L Kg^{-1}) in order to minimise environmental waste. At the end of the

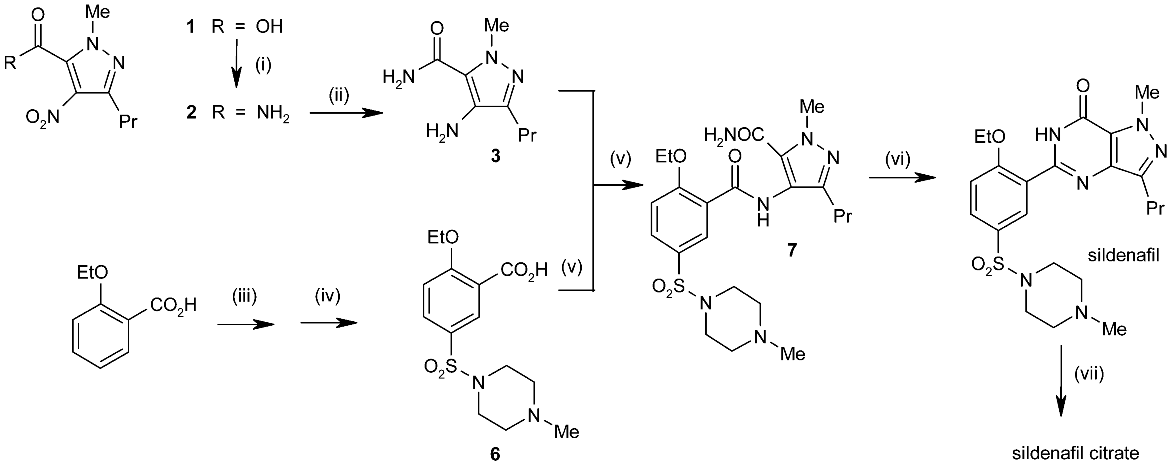


Optimised Medicinal Chemistry Route : Completely linear, the clean reaction is in the middle of the synthesis and the potentially toxic materials are in the final bond forming step



Commercial Route : The synthesis was redesigned to introduce convergency. The clean cyclisation reaction forms the final step resulting in very clean product.

Scheme 2 Strategic commercial route selection.



75 % Overall yield from **1** to sildenafil citrate (1997 process)

(i) Step 1, SOCl$_2$, DMF (cat.), Δ toluene; NH$_3$ (aq) (92%) (ii) Step 3a, H$_2$ Pd/C EtOAc (100%) (iii) Step 2, ClSO$_3$H, SOCl$_2$ 25°C (iv) Step 2, *N*-methylpiperazine, water, 25°C then neutralisation (v) Step 3b, **6** + CDI, EtOAc, add **3** (90 %) (vi) Step 4, KOBu^t, Δ *t*-BuOH, (92 %) (vii) Step 5, citric acid, 2-butanone (99 %).

Scheme 3 The commercial route to sildenafil citrate.

reaction, water is added and the pH adjusted to the isoelectric point to precipitate pure sildenafil, which is collected by filtration. For Viagra™, the citrate salt is required. The process to covert sildenafil to sildenafil citrate has been carefully designed to give both a high yield and high quality. A 98–100% yield is routinely obtained for this step. By 1997 the overall yield from the pyrazole **(1)** to sildenafil citrate had risen to 75%, and the high yields late in the synthesis minimised the environmental impact of the earlier steps.

Once the steps were developed, diligent solvent recovery was required to fully optimise the environmental performance. Recovery of toluene and ethyl acetate was introduced in 1998, the year Viagra™ was launched, and production scale trials for the recovery of 2-butanone are now complete. A summary of the solvent usage at various stages of development is given in Fig. 1. Of particular note is the complete elimination of chlorinated solvents and the elimination of highly volatile solvents such as diethyl ether, methylene chloride, methanol and acetone. The elimination of these highly volatile solvents reduces the atmospheric emissions as will be seen later.

A further improvement in the synthesis (described in Scheme 3) was the replacement of *t*-butanol. This solvent is completely water

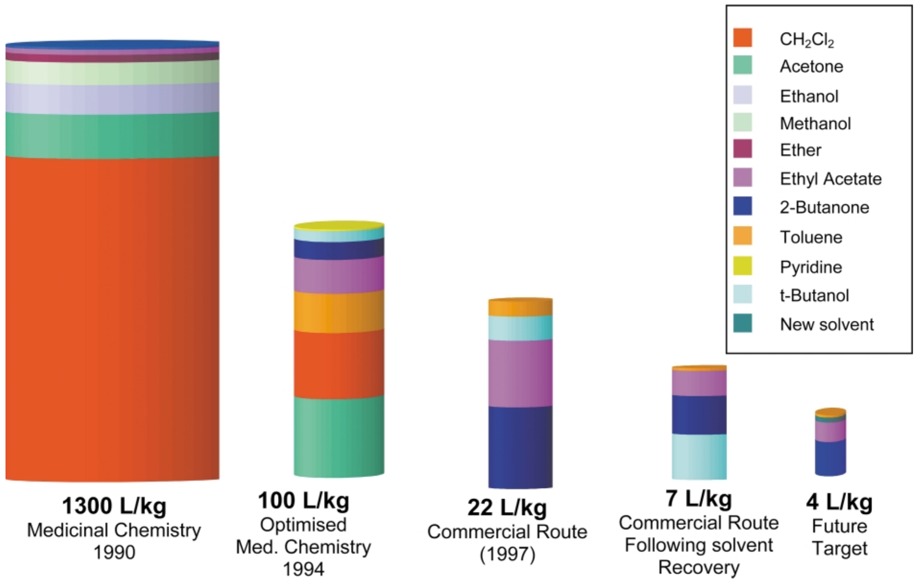


Fig. 1 The amount of organic waste produced by the sildenafil citrate processes at various time points.

soluble in all proportions and is difficult to recover for reuse. There is a continued drive for improved environmental performance and *t*-butanol will be switched to another reaction solvent that can be recovered. This new process was developed and optimised in Ringaskiddy and has been demonstrated in the production plant in Ireland. When fully implemented this will give the final optimised solvent usage of 4 L Kg^{-1}.

A more detailed environmental analysis of the optimised medicinal chemistry synthesis (1994), the 1997 commercial route and the future target follows, using such measures as atom economy, reaction mass efficiency, chemical yield, organic waste, aqueous waste, atmospheric emissions, energy usage and the E-factor. The original medicinal chemistry process (1990) is not analysed here, since it was only ever intended for laboratory scale synthesis.

Atom economy, reaction mass efficiency and chemical yield

The concept of atom economy was first introduced by Barry Trost[7] as a prompt to synthetic chemists to pursue "greener chemistry". The method of calculating atom economy was kept deliberately simple and is a percentage of how much of the reactants remain in the final product. Hence, atom economy ignores reaction yield and reagent excess. It also does not account for solvent usage. Further information on how to calculate atom economy can be found in *Green Chemistry*.[3]

Reaction Mass Efficiency (RME)[2,3] is a more sophisticated measure of "greenness" which allows for the effect of yield and the excesses of reagent used. RME does not account for solvent usage.

For a generic reaction A + B = C

$$\text{Reaction mass efficiency} = \frac{\text{Mass of product C} \times 100}{\text{Mass of A} + \text{Mass of B}}$$

The atom economy, reaction mass efficiency and chemical yields for the sildenafil citrate processes in 1994 (optimised medicinal chemistry route), 1997 (commercial route) and the future target (commercial route) are shown in Tables 2 to 4.

Table 3 Commercial process (1997)

Reaction type	Step number	RME	Atom econ.	Yield
Amide formation	1	40%	61%	92%
Chlorosulfonation/sulfonamide formation	2	30%	74%	68%
Reduction (nitro to amine)	3a	83%	83%	100%
Activation/acylation	3b	61%	73%	90% from **(2)**
Cyclisation	4	65%	83%	92%
Salt formation	5	98%	100%	99%
Overall process		26%[8]	54%	75% from **(1)**

As can be seen from the data, the atom economy of the process has remained essentially constant over time. Improvements have been made in yield and through a greater degree of convergency in the synthesis, but these are not measured by atom economy. In contrast, there was a substantial improvement in both RME and chemical yield between 1994 and 1997 when the new route was introduced. There has been a further significant incremental improvement since 1997. A summary of the data in Tables 2–4 is given in Fig. 2.

Table 2 Optimised medicinal chemistry process 1994

Reaction type	Step No	RME	Atom econ.	Yield
Amide formation	1	25%	61%	92%
Reduction (nitro to amine)	2a	83%	83%	100%
Activation/acylation	2b	48%	71%	84% from **(2)**
Cyclisation	3	61%	65%	100%
Chlorosulfonation/sulfonamide formation	4 Reaction	73%	90%	71%
	4 Purification	80%	100%	80%
Salt formation	5 Reaction	91%	100%	91%
	5 Purification	90%	100%	90%
Overall process		10%[8]	56%	36% from **(1)**

Table 4 Commercial process (future target)

Reaction type	Step number	RME	Atom econ.	Yield
Amide formation	1	40%	61%	92%
Chlorosulfonation/sulfonamide formation	2	30%	74%	68%
Reduction (nitro to amine)	3a	83%	83%	100%
Activation/acylation	3b	67%	73%	96% from **(2)**
Cyclisation	4	73%	83%	95%
Salt formation	5	99%	100%	99%
Overall process		29%[8]	54%	82% from **(1)**

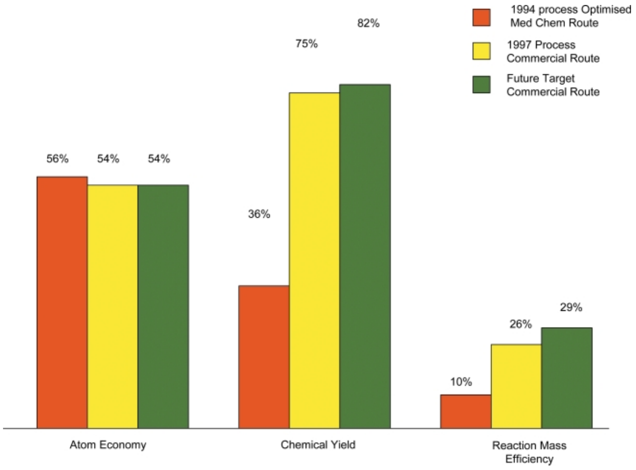


Fig. 2 Atom economy, chemical yield and RME at various time points in the sildenafil citrate process.

Organic waste, aqueous waste, atmospheric emissions and energy usage

The levels of organic waste, aqueous waste and atmospheric emissions for the sildenafil citrate process at three time points are shown in Fig. 3. The three time points are 1994, when the optimised medicinal chemistry was being used, 1997, following the switch to the commercial process and the future target, which includes solvent recovery, and switching from *t*-butanol to a solvent that can be recovered. Each time point is given as a percentage of the 1994 process.

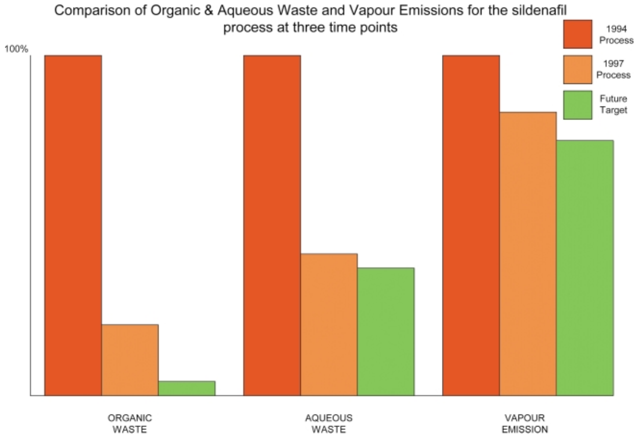


Fig. 3 Comparison of organic and aqueous waste and vapour emissions for the sildenafil citrate process at three time points.

The organic and aqueous wastes are actually measured; the atmospheric emissions are estimated from a modelling process using Batch Plus.[9] It can be seen that for aqueous waste, there was a large reduction between 1994 and 1997 when the new route was introduced while subsequent improvements will be incremental. This shows the importance of route selection in controlling and eliminating waste. For the organic waste there was again a large reduction between 1994 and 1997 upon introduction of the commercial route. However, there was a further large reduction post 1997 due to the impact of introducing solvent recovery operations and reuse in the process. Interestingly, vapour emissions have also been reduced over time but by a much smaller amount. Energy use was also estimated by the "Batch Plus" software[9] and it was found that there was a 35% reduction between 1994 and 1997. There were two possible reasons why reductions in vapour emissions and energy usage were smaller:

1. There is a significant level of solvent stripping performed in the commercial process to maximise the yield.

2. Parameters such as yield, aqueous waste and organic waste were actively managed and followed by the chemistry team as the process was developed, whereas volatile emissions were calculated retrospectively. It is interesting to speculate whether volatile emissions and energy use would have been lower if the chemistry team had used Batch Plus in real time to monitor volatile emissions and energy use as the process was being developed.

The E-factor

The future target process generates 4 L Kg^{-1} of organic waste along with 2 Kg Kg^{-1} of salts (mainly from neutralising chlorosulfonation waste). Hence the total kilos of waste per kilo active of sildenafil citrate is around 6 Kg Kg^{-1}. The performance of the sildenafil citrate process against industry norms is shown in Table 5. The sildenafil citrate process is more similar to a bulk chemical or an efficient fine chemical synthesis in terms of its waste generation. However the annual volumes produced are in the lower end of the range for a Pharmaceutical given in Table 5.

Table 5 Comparison of the E-factor of sildenafil citrate with industry norms

Industry segment	Annual product tonnage	E-factor
Oil refining	10^6–10^8	*ca.* 0.1
Bulk chemicals	10^4–10^6	< 1–5
Sildenafil citrate	**30–40**	**6**
Fine chemicals	10^2–10^4	5– > 50
Pharmaceuticals	10–10^3	25– > 100

As total annual waste is the multiple of the E-factor and the annual product volume it can be seen that the sildenafil citrate process produces exceptionally low levels of waste per annum.

Conclusions

Green Chemistry metrics have been presented at different time points in the development of the sildenafil citrate process. With the exception of atom economy, there was an improvement in the environmental performance as the process was developed, and for the most important measures there was a major improvement. The future target for the E-factor is 6 (for 7 process steps) which is significantly less than the industry standard (25–100). When both E-factor and the relatively low volume (of this high value, relatively complicated chemical product) are taken into account, the amount of waste produced per year is extremely low. Pfizer received the UK Award for Green Chemical Technology for the sildenafil citrate process in 2003.[10]

Experimental

Details of the commercial route to sildenafil citrate can be found in reference 6. Details of the 1990 medicinal chemistry synthesis can be found in reference 4. Aqueous waste, organic waste, atom economy and reaction mass efficiency were determined by the Batch Plus program then reality checked by human calculation.

Energy usage and atmospheric emissions were estimated using the Batch Plus software.[9] Batch Plus is a recipe based modelling program designed for simulating pharmaceutical/chemical batch operations. Batch Plus has the capability of performing process mass balance calculations based on a specified amount of product, and estimating the corresponding aqueous and organic waste stream amounts and atmospheric emissions. Batch Plus was shown to be a quick and efficient tool for assigning green chemistry metrics as the process was developed from laboratory to production scale.

Acknowledgements

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10 The UK Awards for Green Chemical Technology were sponsored by the Crystal Faraday Partnership and administered by the Green Chemistry Network.

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Ene reaction of allylbenzene and *N*-methylmaleimide in subcritical water and ethanol

Antero Laitinen,*[ab] Yoshihiro Takebayashi,[b] Irene Kylänlahti,[c] Jari Yli-Kauhaluoma,[c] Tsutomu Sugeta[b] and Katsuto Otake[b]

[a] *Industrial Chemistry Research Group, VTT Processes, Biologinkuja 7, P.O. Box 1602, FIN-02044 VTT, Espoo, Finland. E-mail: antero.laitinen@vtt.fi*

[b] *Research Institute for Green Technology, National Institute of Advanced Industrial Science and Technology (AIST), Higashi 1-1, Tsukuba, Ibaraki 305-8565, Japan*

[c] *Department of Pharmacy, Viikki Drug Discovery Technology Center, P.O. Box 56, FIN-00014 University of Helsinki, Finland*

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Ene reaction of allylbenzene and *N*-methylmaleimide was studied in water and ethanol solvents at subcritical temperatures (220–310 °C). Subcritical water was inappropriate for this reaction, because it rapidly hydrolyzed *N*-methylmaleimide. Subcritical ethanol was found to be a very promising solvent. The highest ene product yield in ethanol reached 40% in 480 min, and the highest *trans*-selectivity was 92%. The yields in pure ethanol were comparable to those in 1,2,4-trichlorobenzene with 10% hydroquinone added as a polymerization inhibitor. Addition of hydroquinone had a negligible effect on the yield in ethanol, suggesting that the solvent ethanol itself acts as an inhibitor of the side reactions. It is also expected that the polar environment and the high vapor pressure of ethanol favored pericyclic association between the apolar starting compounds.

1 Introduction

Ene reaction is a general category of pericyclic organic reactions, and is of great potential use in chemical industries associated with polymer cross-linking and paper chemical synthesis.[1–3] However, the application of ene reactions in practical synthesis has been hindered by their necessity for high temperatures. High temperature brings about dirty side reactions, *e.g.* polymerization and decomposition of starting materials. To avoid this problem, the conventional method requires the use of polymerization inhibitors, dangerous and expensive catalysts, as well as harmful chlorinated solvents with high boiling temperatures. In the present work, we investigate the applicability of water and ethanol as efficient and environmentally benign solvents for the ene reaction shown in Fig. 1.

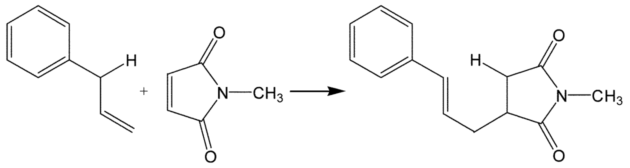

Fig. 1 Ene reaction between allylbenzene and *N*-methylmaleimide.

Pericyclic reactions, including ene reactions and Diels–Alder ones,[4] are the most powerful tools in carbon–carbon bond-forming synthesis. In the case of ene reaction, an alkene containing an ene double bond reacts with a compound containing an enophilic double or triple bond (*e.g.* C=C, C=O, and C≡C) to form a new σ-bond with a migration of the double bond and a concomitant [1,5]-hydrogen shift *via* a cyclic transition state.[1–3] Unfortunately, ene reactions typically need higher reaction temperatures (140–300 °C) than those of the related Diels–Alder reactions, limiting the synthetic utility of ene reactions. A major limiting factor is the polymerization of the reactants at the high temperatures. Thus additives such as hydroquinone are commonly used to slow down the rate of polymerization. It is also well-known that the rate of ene reaction can be enhanced by using Lewis acid catalysts, *e.g.* $AlCl_3$, $SnCl_4$ and $TiCl_4$.[5,6] However, the catalysts are often expensive and hazardous to use.

Here we study utilization of water and ethanol as solvents for ene reactions, instead of conventionally used solvents such as 1,2,4-trichlorobenzene. The beneficial effect of water solvent for pericyclic reaction was first suggested in 1939.[7] An obvious example was reported by Breslow and Rideout that a cycloaddition between cyclopentadiene and methyl vinyl ketone is accelerated by a factor of 700 by using water as a solvent instead of isooctane.[8] The acceleration was explained by the hydrophobic association of the apolar reactants. It was also pointed out by Albisetti *et al.* that in their ene experiments between alkenes and acrylonitriles at 200–300 °C the use of water as a solvent prevents the formation of tars of the polymerizable nitriles.[9] In recent years, water above the critical temperature (374 °C) has received much attention as a novel medium for Diels–Alder reactions due to the high solubility of organic reactants in it.[10] The observations above show that water can be an efficient solvent in both the acceleration of ene reactions and the inhibition of side reactions. In addition to water, ethanol is also tested here as a promising solvent for ene reaction due to its high polarity.

Ene reaction of allylbenzene and *N*-methylmaleimide (Fig. 1) was chosen here as a model system. This system is of great interest due to its potential use for the cross-linking of polymers, in particular between a cyanate ester resin and a bismaleimide one.[11] The system is also closely related to the synthesis of paper sizing chemicals.[12] We investigate the reaction in water and ethanol solvents at several temperatures below the critical point (< 374 °C

Green Context

The replacement of volatile organic solvents in organic reaction processes is an important green chemistry goal. The use of water and ethanol being biodegradable and readily available is attractive. Here ethanol is shown to be effective in the synthetically useful ene reactions of allylbenzene and *N*-methylmaleimide. ***JHC***

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for water, and < 241 °C for ethanol). The effects of temperature, reaction time, presence of hydroquinone, and amounts of starting compounds on the reaction are discussed in comparison with those in 1,2,4-trichlorobenzene solvent.

2 Experimental

Reagents

Allylbenzene (98%, FW 118.18), *N*-methylmaleimide (97%, FW 111.10), and *trans*-anethole (99%) were purchased from Aldrich Chemical Company, and hydroquinone (99%) from Nacalai Tesque. *Trans*-anethole was used as an internal standard in the product analysis. Ethanol (99.5%) and 1,2,4-trichlorobenzene (> 95%, bp 214 °C) were purchased from Wako Pure Chemicals. Water was purified by Milli-Q Gradient (Millipore Co. Ltd.). The solvents were deoxygenated before use. Other reagents were used as received.

Reaction and analysis

Experiments were carried out with a batch-type high-pressure reactor. The reactor tube (10.6 mL) was made of SUS-316 stainless steel. In typical experiments, allylbenzene (1.7–8.5 mmol), *N*-methylmaleimide (4.5–18 mmol), and hydroquinone (0.45 mmol, if added) were weighed into the reactor with solvent water (5 g, 0.28 mol), ethanol (4 g, 87 mmol), or 1,2,4-trichlorobenzene (4 g, 28 mmol). The free volume in the reactor was purged with argon to remove the air entrapped before the reactor was sealed. The reactor was immersed into a salt bath equipped with a mechanical shaking system (Perker Netsushori Kogyo Co. Ltd.). The shaker moved the ends of the reactor tube up and down, thereby stirring the reaction mixture, in the molten salt heated at the reaction temperature (220–310 °C). The mixture in the vessel was self-compressed up to the vapor pressure of the solvent at the reaction temperature: in the case of water, 2.4 MPa at 221 °C, 4.0 MPa at 251 °C, and 9.9 MPa at 310 °C,[13] while in the case of ethanol, 4.2 MPa at 220 °C.[14] After the required reaction time (30–780 min), the reactor was quickly cooled down by immersing it in water. In the case of water solvent, the crude reaction mixture was evaporated *in vacuo*, and subsequently extracted with ethyl acetate. In the case of ethanol and 1,2,4-trichlorobenzene solvents, the samples were directly injected into a gas chromatograph without evaporation of the solvent. This reaction proceeds at high temperature and pressure conditions and precautionary measures are necessary.

The yields and conversions were determined by GC-MS: HP-6890 gas chromatograph (GC) equipped with HP-5973 mass selective detector (MS). The capillary column used was HP-1 (25 m × 0.2 mm, 0.33 μm). The carrier gas was He. The oven temperature program was 80 °C–10 °C min^{-1}–290 °C. Injection and detection temperatures were 250 and 290 °C, respectively. The amounts of ene product and remaining starting compounds were calculated using *trans*-anethole as an internal standard. The yield of ene product is reported as a percentage of the theoretical maximum. The reaction produces tars as side products. It was very difficult to collect and analyse this polymerised material. For this reason we were not able to calculate the mass balances. The reproducibility of the method was tested by performing multiple runs using water and ethanol solvents. The RSD values were within 7%.

Synthesis of reference compounds

The *trans* and *cis* isomers of the ene product, 1-methyl-3-(3-phenylallyl)pyrrolidine-2,5-dione, were prepared by the ene reaction of allylbenzene and *N*-methylmaleimide with minor modifications of the general procedure reported by the Cunningham group.[11] A stirred mixture of allylbenzene (6.64 mL, 50.0 mmol), *N*-methylmaleimide (5.56 g, 50.0 mmol), and hydroquinone (0.551 g, 5.00 mmol) in 1,2,4-trichlorobenzene (6.25 mL) was flushed with argon and heated under argon at 200 °C for 24 h. The cooled reaction mixture was distilled under a reduced pressure to give a distillation residue containing a mixture of the crude product and polymeric residue. The residue was dissolved in acetonitrile (*ca.* 1 g residue in 4–5 mL of acetonitrile). The oligomers and polymers were precipitated by a slow addition of diethyl ether to the magnetically stirred acetonitrile solution which was previously cooled down to the ice-water bath temperature. After filtration, the precipitated polymers were washed with small quantities of diethyl ether. The combined diethyl ether filtrates were evaporated *in vacuo* to give the crude ene product (1.53 g). The crude product was chromatographed on silica gel (100% *n*-hexanes gradient to *n*-hexanes : CHCl$_3$ 3 : 1 followed by the gradient to 100% CHCl$_3$) to give the *cis* isomer (42 mg, 0.37%), the *trans* isomer (460 mg, 4.0%), and a mixture of these isomers (253 mg, 2.2%).

Trans isomer

R_f (*n*-hexane : acetone : CHCl$_3$ 4 : 1 : 5) 0.60; LRGC-MS [HP-5MS, 12 m × 0.25 mm, 0.25 μm, 100 °C–20 °C min^{-1}–310 °C, flow rate 1.1 mL min^{-1}] t_{ret} 6.44 min *m/z* 229 (43%) [M]$^+$, 157 (3%), 143 (6%), 129 (20%), 117 (100%), 104 (6%), 91 (25%), 77 (4%); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.38 (m, 1 H), 2.43–2.57 (m, 1 H), 2.59–2.63 (m, 1 H), 2.74–2.83 (m, 2 H), 2.97 (s, 3 H), 6.03–6.13 (td, *J* 15.7, 7.2 Hz, 1 H), 6.63 (td, *J* 15.6, 1.3 Hz, 1 H), 7.17–7.37 (m, 5 H).

Cis isomer

R_f (*n*-hexane : EtOAc : CHCl$_3$ 4 : 1 : 5) 0.67; LRGC-MS [HP-5MS, 12 m × 0.25 mm, 0.25 μm, 100 °C–20 °C min^{-1}–310 °C, flow rate 1.1 mL min^{-1}] t_{ret} 6.20 min, *m/z* 229 (43%) [M]$^+$, 222 (25%), 143 (20%), 129 (20%), 117 (100%), 104 (4%), 91 (21%); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.37 (m, 1 H), 2.57–2.66 (m, 1 H), 2.78–2.82 (m, 1 H), 2.88–2.97 (m, 2 H), 2.98 (s, 3 H), 5.50–5.59 (td, *J* 11.7, 7.1 Hz, 1 H), 6.63 (d, *J* 11.1 Hz, 1 H), 7.16–7.39 (m, 5 H); ^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 24.5, 29.6, 33.7, 39.9, 126.7, 127.2, 128.4, 128.7, 132.7, 136.4.

3 Results and discussion

Water solvent

Water as a solvent was first studied at the subcritical temperatures of 221, 251, and 310 °C. The subcritical water proved to be inappropriate for our purpose due to the occurrence of hydrolytic side reaction. In all of the experimental runs shown in Fig. 2, *N*-methylmaleimide was totally hydrolyzed within a short reaction time (30 min) except for a small amount ene reacted, limiting the synthetic applicability of water as a solvent in this reaction. The major hydrolytic product was *N*-methylmaleic acid monoamide. The rapid hydrolysis can be explained by the catalytic effects of H$^+$ and OH$^-$ produced from water; the value of the ionization constant of water reaches its maximum value (*ca.* 10^{-11}) around 250 °C.[15] The yield of ene product was only 2–6%, when equal amounts (0.5 g each, 4.2 mmol allylbenzene, 4.5 mmol *N*-methylmaleimide) of the starting compounds were used. The yield increased slightly with temperature from 2–3% at 220 °C to 5–6% at 310 °C. The temperature effect is partly due to the increase in the solubility of allylbenzene into water as well as the increase in the thermal energy.

By using a larger excess (2–8 times, mole based) amount of *N*-methylmaleimide at 221 and 251 °C, the ene yield increased up to 12%. However, the increase in the product yield cannot compensate the larger loss of *N*-methylmaleimide on an economical basis. Curiously, the yield decreased with increasing temperature from 251 to 310 °C. No higher yield than 6% was obtained at 310 °C, regardless of the excess ratio of *N*-methylmaleimide. At 221 and 251 °C, allylbenzene still remained after the reaction, whereas at 310 °C no starting compounds were found in the reaction mixture.

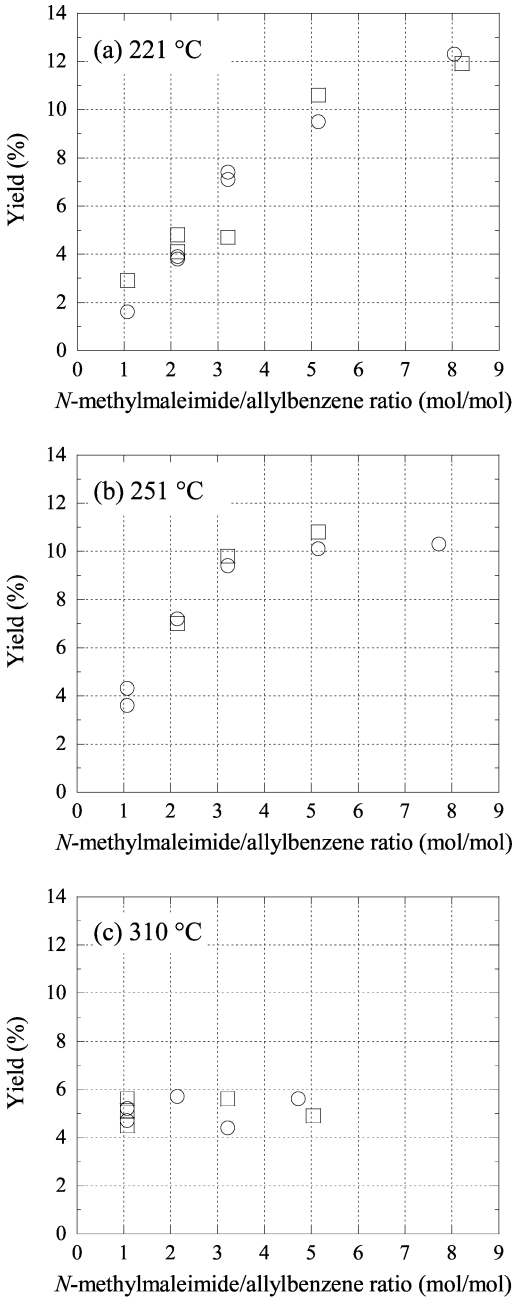

Fig. 2 Yield of ene reaction between allylbenzene and *N*-methylmaleimide in water at (a) 221 °C, (b) 251 °C, and (c) 310 °C as a function of the excess mass ratio of *N*-methylmaleimide. ☐ without hydroquinone; ○ with hydroquinone. Reaction time is 30 min.

It is thus suggested that the yield at 310 °C was limited by the rapid polymerization or other side reaction of allylbenzene accelerated with temperature. We should note, however, that the polymerization in water solvent was much less evident than that in apolar solvent, and that the addition of hydroquinone had a negligible effect on the ene yield. The selectivities for the *trans* isomer in water were 90–94%, which are slightly higher than those in 1,2,4-trichlorobenzene (87–91%). The *trans*-selectivity decreased slightly with temperature.

Ethanol solvent

Ethanol at 220 °C was found to be a very promising solvent for the ene reaction, mainly because the side reaction in ethanol is slow enough. The results in ethanol are summarized in Table 1, in comparison with those in 1,2,4-trichlorobenzene. In ethanol solvent, the yield of ene product increased with reaction time. The highest yield obtained was 31%, when equal amounts (0.5 g each, 4.2 mmol allylbenzene, 4.5 mmol *N*-methylmaleimide) of the starting compounds were applied. When the amount of allylbenzene was doubled, the yield reached 40% at 480 min. No evident increase in the yield was observed at longer reaction times, where practically all the loaded *N*-methylmaleimide was already consumed due to side reactions, such as polymerization and ethanolysis. The selectivities for the *trans* isomer in ethanol (88–92%) were comparable to those in 1,2,4-trichlorobenzene (87–91%).

In ethanol solvent, no hydroquinone was required as an additive into the reaction mixture. As shown in Table 1, the ene yield in ethanol was sufficiently high without hydroquinone, and the addition of hydroquinone had a small effect on the yield. This result is in good contrast to that in 1,2,4-trichlorobenzene. In the conventional solvent, the highest yields in the absence of hydroquinone (13–20%) were much lower than those in ethanol (27–38%). Additive hydroquinone was indispensable in 1,2,4-trichlorobenzene to obtain higher yields (31–38%) comparable to those in ethanol. This is mainly because the starting compounds, *N*-methylmaleimide in particular, were easily consumed in 1,2,4-trichlorobenzene by the polymeric side reactions. The polymerization was less evident in ethanol, suggesting that the solvent ethanol itself acts as an inhibitor of the side reactions. A possible explanation is that the ethanol molecule serves as a radical scavenger: the radicals thermally formed are immediately trapped by the surrounding ethanol molecules. Another possible reason is the high polarity of ethanol solvent: the polar environment is less favorable for the radical reactions than apolar conditions.

The high yields in ethanol can be explained partly by the following two factors, the high polarity and high vapor pressure of the ethanol solvent. The high solvent polarity is generally known to enhance the solvophobic association of the apolar reactants, and the high pressure to accelerate the pericyclic reactions with negative activation volume.[16] The vapor pressure of ethanol amounts to 4.2 MPa at 220 °C, thus is in favor of the pressure effect, although the pressure obtained here is much lower than those commonly employed in high-pressure organic synthesis (*ca.* 50–1000 MPa).

Finally, we should note that methanol is unsuitable as a solvent for this reaction due to the occurrence of methanolytic side reactions. Methanol has a much higher reactivity than that of ethanol, and the too high reactivity destroyed *N*-methylmaleimide within 30 min, as in water solvent. This is the reason why ethanol was chosen here as a solvent instead of methanol or water.

4 Conclusion

The ene reaction of allylbenzene and *N*-methylmaleimide was studied in water and ethanol solvents at subcritical conditions. Subcritical water was unsuitable for this reaction, because the reactant *N*-methylmaleimide was easily hydrolyzed due to the high reactivity of water. Subcritical ethanol proved to be a very promising solvent. The yields of ene product in pure ethanol were comparable to those in 1,2,4-trichlorobenzene with hydroquinone. In ethanol solvent, the highest yield amounts to 40% in 480 min, and the yield was weakly influenced by the presence of hydroquinone, possibly because the solvent ethanol itself acts as a polymerization inhibitor. In addition, the high polarity and high vapor pressure of ethanol is considered to accelerate the pericyclic association of the apolar reactants. As a result, subcritical ethanol serves as an efficient and relatively environmentally benign solvent compared with the conventional solvents such as 1,2,4-trichlorobenzene, without any additives. In the subsequent work, we will explore other feasible reaction systems in order to elucidate the novel potential of the subcritical polar solvent in organic synthesis.

Table 1 Conversions and reaction yield of ene reaction between allylbenzene and *N*-methylmaleimide at 220 °C as functions of the solvent, the presence of hydroquinone, the mole ratio of starting compounds, and the reaction time

No.	Mole ratio of allylbenzene : *N*-methylmaleimide/mmol	Reaction time/min	Allylbenzene conversion (%)	*N*-methylmaleimide conversion (%)	Ene product yield (%)
Solvent: ethanol (87 mmol)					
1	4.2 : 4.5	90	43.8	46.0	13.4
2	4.2 : 4.5	240	41.5	71.1	26.1
3	4.2 : 4.5	480	41.0	87.1	27.2
4[a]	4.2 : 4.5	90	41.2	33.7	16.3
5[a]	4.2 : 4.5	240	47.9	60.7	27.0
6[a]	4.2 : 4.5	480	40.7	80.0	31.5
7	8.4 : 4.5	90	47.4	61.2	16.5
8	8.4 : 4.5	240	37.5	84.6	32.3
9	8.4 : 4.5	480	33.0	> 99.0	33.9
10	8.4 : 4.5	720	36.3	> 99.0	35.1
11	8.4 : 4.5	720	38.7	> 99.0	38.3
12[a]	8.4 : 4.5	90	45.7	45.3	23.3
13[a]	8.4 : 4.5	240	42.6	85.3	33.4
14[a]	8.4 : 4.5	480	52.6	93.1	40.0
Solvent: 1,2,4-trichlorobenzene (28 mmol)					
15	4.2 : 4.5	90	47.4	82.7	7.6
16	4.2 : 4.5	240	55.7	97.0	10.7
17	4.2 : 4.5	240	55.0	93.6	13.3
18[a]	4.2 : 4.5	90	27.6	50.6	17.3
19[a]	4.2 : 4.5	240	51.5	84.7	31.2
20	8.4 : 4.5	90	34.1	89.9	9.4
21	8.4 : 4.5	240	41.8	97.5	20.4
22[a]	8.4 : 4.5	90	34.5	70.2	23.0
23[a]	8.4 : 4.5	240	44.4	99.0	38.3
24[a]	8.4 : 4.5	780	52.7	> 99.0	34.2

[a] With hydroquinone (0.45 mmol).

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PAPER

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Chitosan-based heterogeneous catalysts for Suzuki and Heck reactions

Jeff J. E. Hardy,[a] Sandrine Hubert,[a] Duncan J Macquarrie*[a] and Ashley J Wilson[b]

[a] *Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: djm13@york.ac.uk; Fax: 0044 1904 434550; Tel: 0044 1904 434533*

[b] *Department of Biology, University of York, Heslington, York, UK YO10 5DD*

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Novel supported palladium catalysts have been developed based on chitosan as a support. These catalysts display excellent activity in the Suzuki and Heck reactions.

Introduction

The development of heterogeneous catalysts for fine chemicals synthesis has become a major area of research recently, as the potential advantages of these materials (simplified recovery and reusability, the potential for incorporation in continuous reactors and microreactors) over homogeneous systems can make a major impact on the environmental performance of a synthesis.[1,2] The majority of these novel catalysts are based on silicas, primarily since silica displays many advantageous properties – excellent stability (chemical and thermal), high surface area, good accessibility, and organic groups can be robustly anchored to the surface, to provide catalytic centres. However, it does have drawbacks – it has limited stability in aqueous – especially basic – conditions, and it cannot easily be formed into membranes or into other forms which could be attached to novel reactors for use in intensive processing applications.

Chitosan is produced by the deacetylation of chitin, a major naturally occurring biopolymer, which is one of the key constituents of the shells of crustaceans, and is a by-product of the fishing industry. Its structure is shown in Fig. 1. It has many applications as an adsorbent of metals, and also in medicine, where it is used in several applications, including wound dressings/artificial skin, in drug delivery and contact lenses, amongst others and is readily formed into films or fibres for many of these applications.[3] The flexibility of the material, insoluble in the vast majority of solvents, but capable of being cast into films and fibres from dilute acid, along with its inherent chirality, makes chitosan an excellent candidate as a support for catalysis. In this respect, several groups have demonstrated the catalytic activity of salts physisorbed onto chitosan and reduced to the metal for the reduction of (a) chromate (using Pd),[4] (b) phenol (Pd),[5–7] and (c) nitro-aromatics (Ni, Cu, Cr, Zn).[8] Asymmetric hydrogenation has been described by Yuan *et al.*[9] Quignard *et al.* have utilised the hydrophilic nature of chitosan to prepare supported aqueous phase (SAP) catalysts for the Pd-catalysed allylic substitution reaction.[10,11] Functionalisation of the chitosan to provide co-ordination sites has also been carried out and has provided catalysts for cyclopropanation of olefins (Cu-Schiff's base),[12] oxidation of alkylbenzenes (Mn or Ni-Schiff's base),[13] and the oxidation of DOPA (3,4-dihydroxyphenylalanine)–(Co-salen).[14] The latter example involved the dissolution of chitosan in acetic acid, functionalisation and re-precipitation, whereas the others involved the direct functionalisation of the solid chitosan.

We now present our work on the catalytic activity of Pd-iminopyridyl complexes supported on chitosan for the Suzuki and Heck reactions.

Experimental

All chemicals were purchased from Aldrich or Lancaster, and used without further purification. Chitosan was provided by Prof. A. J. Wilson of the Department of Biology, University of York in a powdered form.

Elemental analysis was provided by the University of Newcastle (combustion analysis for CHN and ICP analysis for Pd). Samples for Pd analysis were stirred with 10% HCl twice (24 h each) and the liquids combined to provide the ICP samples.

Modification of chitosan

Chitosan (1.0 g, equivalent to 6 mmol NH_2) and 2-pyridinecarboxaldehyde (0.643 g, 6 mmol) were added to ethanol (50 mL) and refluxed for 18 h. The resultant mixture was cooled and the solid filtered, washed with ethanol and dried under vacuum for 6 h to give **1**.

1 (1.0 g) was then treated with a solution of palladium acetate (0.112 g, 0.5 mmol) in acetone (50 mL). After adsorption of the palladium, the solid was preconditioned by washing thoroughly to remove any loose Pd species. The washing consisted of three 3 h refluxes in each of ethanol, toluene, and acetonitrile. Finally the catalyst was dried at 90 °C for 18 h to give the catalyst **2**.

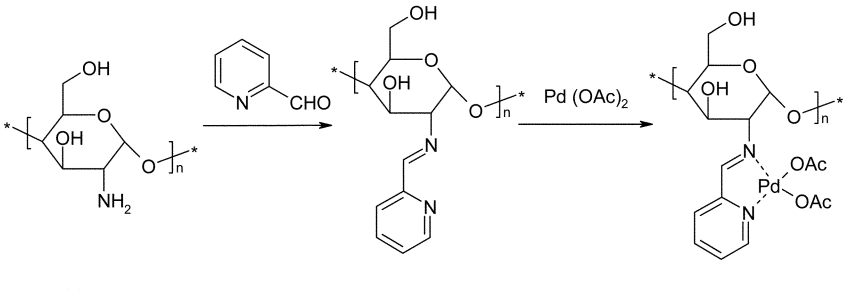

Fig. 1 The synthesis of chitosan-pyridyl imine complex and its conversion to the related Pd complex.

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Typical Suzuki reaction

A quantity of **2** (see Fig. 1, Results and discussion) was suspended in *o*-xylene (20 mL) and benzene boronic acid (0.914 g, 7.5 mmol), bromobenzene (0.805 g, 5.1 mmol), potassium carbonate (1.382 g, 10 mmol) and *n*-dodecane (0.749 g, 4.4 mmol) were added. The reaction was then heated at the appropriate temperature and followed by GC using *n*-dodecane as internal standard.

Typical Heck reaction

2 (25 mg) was suspended in anhydrous dioxane (30 mL). To this were added iodobenzene (1.03 g, 5.3 mmol), *n*-butyl acrylate (0.68 g, 5.3 mmol) and triethylamine (0.98 g, 10 mmol). The mixture was refluxed and followed by GC, using *n*-dodecane as internal standard. In a second reaction, styrene and bromobenzene were coupled.

Results and discussion

Preparation and analysis of catalyst

CHN analysis of the chitosan indicated, as expected, the presence of *N*-acetyl groups due to incomplete hydrolysis of the chitin precursor. From the analysis, approximately 35% of the nitrogen sites are acetylated, leaving a total of 3.7 mmol g^{-1} present as free NH_2 units. Of these, 38% appear to have been functionalised with pyridylimine groups during the formation of **1**. Analysis after addition of palladium acetate and thorough preconditioning by multiple washing indicates that some of these groups are lost during the preconditioning step, and the final loading of the pyridylimine group drops to 25%, corresponding to a loading of 0.92 mmol g^{-1} of ligand sites. The Pd content of the final catalyst was measured before and after preconditioning. Before this step, the content was 0.22 mmol g^{-1}, while after the washing steps, this had dropped to 0.16 mmol g^{-1}. Thus, the final catalyst has approximately 18% of the ligands occupied by metal.

This low loading may reflect that many of the sites in chitosan are inaccessible to the ligand or to the Pd source during preparation. Given that chitosan is a very weakly swelling polymer, this is likely to be a reasonable explanation, although no attempts have been made to increase this figure by *e.g.* extended reaction times. Our previous experience with Pd catalysts has indicated that low metal loadings do not necessarily detract from activity.[15] Others have reached similar conclusions.

The preconditioning steps have been previously developed to avoid leaching on silica-based analogous catalysts, by removing loosely bound Pd;[15] we and others have noted that leaching does occur with these silica materials during reaction when this step is not carried out.[15,16]

Infra-red analyses of the chitosan catalysts were carried out using Diffuse Reflectance IR. The spectrum of chitosan has a strong and broad OH absorption centred around 3500 cm^{-1} which masks the N–H str. A diagnostic peak appears on condensation of the pyridine-aldehyde with the amine group at 1638 cm^{-1} corresponding to the formation of the pyridylimine unit. No H-bonded or free aldehyde were evident in the range 1675–1710 cm^{-1}. Complexation of the palladium led to minor changes in the IR spectrum, as expected from previous work using this ligand system supported on silica, and from the relatively low degree of adsorption of Pd which leaves most of the imine sites unaltered.

Initial runs in the Suzuki reaction were carried out using 100 mg of catalyst (to 5.1 mmol substrate) at 130 °C. With catalyst **2** this led to a 48% yield of biphenyl after 1 h and 55% after 6 hours. Thus the reaction proceeds successfully with **2** and is almost complete after 1 h. Variation of the amount of catalyst was investigated, with the results being displayed in Fig. 2. It was found that the optimum amount of catalyst corresponded to a substrate : Pd molar ratio of 1200, with no significant benefit in larger amounts of catalyst, and a significant tail-off at lower quantities. Runs without benzene boronic acid or without bromobenzene failed to produce any biphenyl, indicating the absence of any homo-coupling in the reaction.

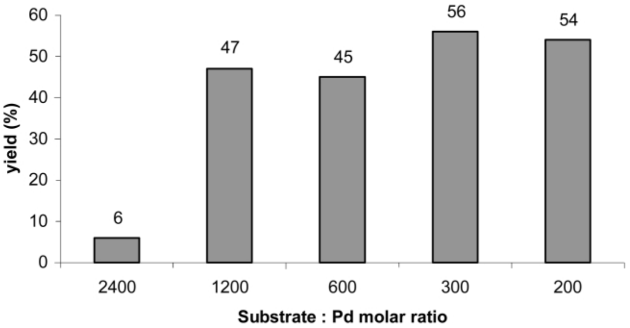


Fig. 2 Effect of substrate : Pd ratio on yield of biphenyl at 130 °C.

An analogous catalyst based on salicylaldehyde (instead of the pyridyl aldehyde) was prepared, but gave poor results. Salicylaldehyde-based ligands on silicas also gave poor results.[15,17]

Increasing the reaction temperature to reflux (143 °C) improved the yield significantly (Table 1), with lower temperatures leading to lower conversions. All further reactions were therefore carried out at this higher temperature.

Table 1 Dependence of conversion on temperature of PhBr + $PhB(OH)_2$

Temperature/°C	% Biphenyl[a]	% PhBr remaining[a]
75	11 (13)	84 (85)
100	25 (29)	72 (70)
130	48 (55)	49 (46)
143	80 (87)	17 (13)
143[b]	53 (57)	50 (45)
143[c]	78 (86)	20 (13)
143[d]	74 (81)	22 (15)

[a] After 1 h (figures in brackets denote conversions after 6 h). [b] Catalyst reused directly. [c] Catalyst from run (a) reused after washing with methanol. [d] Catalyst after 5 uses.

Catalyst reuse

After the first run at 143 °C, the solids were filtered and directly added to a second run at the same temperature. In this case the conversion was 57%. Isolation of the catalyst after this run, followed by washing with aqueous methanol, methanol and drying at 90 °C reactivated the catalyst, and a subsequent run yielded 86% of product (Table 1). This regeneration process could be repeated five times, without appreciable loss of activity. Thus, catalyst reuse is possible after isolation and washing of the catalyst. This washing step presumably is effective in removing the waste inorganics from the catalyst which begin to block access to the active sites.

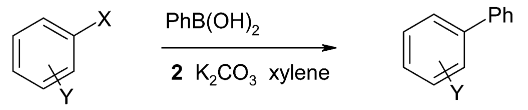
Extension to other substrates

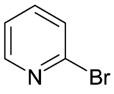
The optimal reaction conditions were applied to a series of substituted halobenzenes and the results are tabulated in Table 2.

As can be seen, good to excellent yields are obtained for a range of aromatic substrates, with slightly better results being obtained for substrates with electron donating substituents, although nitro-containing substrates caused problems and appeared to decompose the catalyst leaving a black solid behind. In all other cases high yields were achieved, with excellent selectivity, generally in short reaction times. Bromo and iodo compounds both are active but, as expected, chlorobenzene was virtually inert.

Comparative reactions have been carried out with a homogeneous equivalent of the supported catalyst (prepared from butylamine, pyridine-2-aldehyde and $Pd(OAc)_2$).[17] While the initial rate of reaction was slightly more rapid than the supported version, the catalyst deactivated quickly (TON = 75 for PhBr + $PhB(OH)_2$), and the separation of product and catalyst was difficult. While a

Table 2 Suzuki coupling of selected reaction partners





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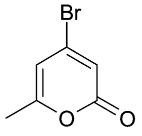

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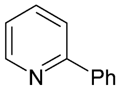

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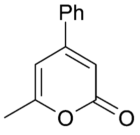

13

compound	X	Y	Conditions	Yield
3	Br	4-Me	143 °C, 1 h	89%
4	Br	4-MeO	143 °C, 1 h	92%
5	Br	4-CN	143 °C, 1 h (3 h)	68% (78%)
6	Br	2-NO_2	143 °C, 1 h (6 h)	35% (36%)
7	Br	4-NO_2	143 °C, 1 h (6 h)	3% (3%)
8	I	H	143 °C, 1 h	85%
9	Cl	H	143 °C, 1 h (18 h)	2% (3%)
10	—	—	143 °C, 6 h	74%
11	—	—	143 °C, 4 h	81%

detailed comparison of the homogeneous and heterogeneous catalysts has not been attempted, the similar rates of reaction indicate that diffusion is not a major problem for **2** under the conditions used here, and the extended lifetime may be a feature of the Pd being tethered to the support at a low density, stopping deactivation through clustering. Thus the supported versions of the catalysts do indeed allow for a more efficient reaction and for simpler and cleaner separation of product and recovery/reuse of catalyst.

2-Bromopyridine **10** was also investigated as a representative of a class of substrates which have found much use in the synthesis of multidentate ligands[18–20] and in pharmaceutical applications.[21,22] Our system gave a 74% yield of 2-phenylpyridine **12** from the Suzuki coupling after 6 hours, indicating that it is a good catalyst for such systems. Literature yields[18–22] for this type of substrate vary considerably from poor to very good.

Bromopyrones are currently of interest in the synthesis of 4-substituted pyrones, which are showing promise as anti-cancer and anti-microbial agents.[23] Suzuki and Sonagashira coupling methodologies have previously been applied successfully to these syntheses using homogeneous Pd catalysts. Using our chitosan-supported catalyst, the bromopyrone **11** was converted to the 4-phenyl derivative **13** in high yield after chromatographic separation. Around 10% of the unchanged 4-bromopyrone was recovered after chromatography.

Reactions at lower temperature

Since the analogous pyridylimine-Pd silica-based catalysts demonstrate good activity even at 90 °C, it was decided to investigate the reasons for the lower conversions achieved with **2** at temperatures below 143 °C. It was clear that as the temperature was reduced, the conversions dropped too, and that no further conversion occurred after *ca.* 1 h. A mass balance on bromobenzene indicated that no side reactions were occurring with this reaction partner, but it was found, by ^{11}B CP MAS NMR of the entire reaction mixture after solvent removal, that the only boron-containing species present was borate. This was true for all temperatures, and indicated that extensive destructive decomposition of benzene boronic acid was occurring. Addition of extra boronic acid portionwise over several hours led to further product formation, consistent with the NMR results. Further addition of other reaction components (base, catalyst, bromobenzene), on the other hand, had no effect.

Whilst the majority of papers on the Suzuki reaction do not mention this side reaction at all, a few do discuss such reactions, although in little detail. Protodeborylation of aryl boronic acids is known to occur, typically under acidic conditions (either aqueous acids or carboxylic acids under non-aqueous conditions.[24–27]) However, deborylation of arylboronic acids has occasionally been reported under basic conditions, for example during Suzuki coupling in the synthesis of a natural product.[28] In this case, aqueous K_2CO_3 was used, indicating that protodeborylation can occur (in this case to *ca.* 40%) under basic conditions. These conditions often lead to excellent yields, although, as in almost all examples of Suzuki reactions, the boronic acid is used in excess. Other comments in the literature indicate that, while protodeborylation is often suppressed by using anhydrous conditions,[29,30] in some cases it can occur to similar extents with or without water.[31] Given that the more expensive and less readily synthesised boronic acid is the reagent used in (10–50%) excess, one can surmise that the majority of Suzuki reactions proceed with some protodeborylation. This side reaction therefore appears to be a significant difficulty in the development of truly green Suzuki methodology.

A particularly curious feature of our system is that protodeborylation is prevalent at low temperatures, but decreases significantly in importance as the temperature increases (no unreacted boronic acid can be found in any of the reactions after 6 h). Nothing in the literature could be found to indicate such a dramatic swing in selectivity with temperature. Work is in progress aimed at casting more light on this curious effect.

The Heck reaction

The Heck reaction was also investigated at substrate to Pd molar ratios of 1325 and 650. Under the first of these conditions, iodobenzene and butyl acrylate gave an 82% yield of butyl cinnamate in 42 h at 100 °C. With the higher catalyst quantity, an 87% yield was obtained after 20 h. Similar activity was also found with the same catalyst system immobilised on silica.[32] Coupling of styrene and bromobenzene was also successfully accomplished at a substrate : Pd ratio of 1420, giving an 88% yield of stilbene after 42 h, with a TON of 1250. Doubling the amount of catalyst led to a similar yield (85%) in 20 h.

Conclusions

Chitosan-based Pd catalysts have been successfully prepared in a stable form. These catalysts prove to be active and reusable catalysts for both the Suzuki and Heck reactions. High yields of aryl-coupled products can be obtained in short times – these include model reactions on bromopyrones which are relevant to anti-cancer therapies. An unusual twist in the selectivity profile means that protodeborylation appears to be the dominant pathway at lower temperatures, but is almost absent at higher temperatures. Efficient recovery and reuse has been demonstrated.

This work, along with other published work, indicates that chitosan is a particularly interesting support for catalysis – its stability, lower acidity (compared to supports such as silica), its film-forming properties, which can be exploited in intensive processing reactors, and its inherent chirality will form the basis for further applications of this fascinating material.

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PAPER

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Rare-earth metal triflates as versatile catalysts for the chloromethylation of aromatic hydrocarbons

Toru Kishida,[a] Takayoshi Yamauchi,[a] Yoshihiro Kubota[b] and Yoshihiro Sugi*[b]

[a] *K. K. Nissei Kagaku Kogyosho, 2-18-110 Juhachijyo, Yodogawa-ku, Osaka 532-0001, Japan*
[b] *Department of Materials Science and Technology, Faculty of Engineering, Gifu University, Gifu 501-1193, Japan. E-mail: sugi@apchem.gifu-u.ac.jp*

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Rare-earth metal triflates, such as Sc(OTf)$_3$, Yb(OTf)$_3$, and Sm(OTf)$_3$ work as highly effective catalysts for the chloromethylation of aromatic hydrocarbons with hydrochloric acid and trioxane. They are active enough in aqueous solution at a concentration of less than 1–5% of the substrate under heterogeneous conditions of organic and aqueous phases. The triflate stays in the aqueous phase after the catalysis, and the organic products are easily separated from the catalyst. Sc(OTf)$_3$ was stable under the reaction conditions. The catalyst in the aqueous solution could be recycled and used for further reactions without significant loss of activity. The chloromethylation of *m*-xylene catalyzed by Sc(OTf)$_3$ gave 2,5-bis(chloromethyl)-*m*-xylene with 1,2,4,5-substitution, which is expected to be a key intermediate for pyromellitic dianhydride. The catalysis occurred *via* the formation of a chloromethylated triflate complex, and electrophilic addition to an aromatic hydrocarbon.

1 Introduction

Chloromethyl substituted aromatic hydrocarbons are promising key intermediates because of easy transformation to many chemicals such as fine-chemicals, pharmaceuticals, and polymers. The chloromethylation of aromatic hydrocarbons has been well documented in previous papers.[1–6] The reaction of aromatic hydrocarbons with hydrochloric acid and trioxane or paraformaldehyde as a formaldehyde precursor sometimes gave the chloromethylated products without a catalyst,[5,6] however, the rate is slow and insufficient for practical chemical processes. Lewis acids such as zinc chloride, stannic chloride, and boron trifluoride are well known catalysts for the reaction; among these acids, zinc chloride is an effective catalyst in hydrochloric acid solution,[1,2] however, a stoichiometric amount of catalyst to substrate is required, making the work up procedure tedious. These catalysts, in general, suffer from the inherent problems of corrosiveness, high susceptibility to water, difficulty in catalyst recovery, environmental hazards, waste control after the reaction, *etc*. It is important to replace these highly corrosive, hazardous and polluting acid catalysts with environmentally conscious catalysts which are active under mild conditions, and can be easily recovered after the reactions and reused for new reactions.[7] Recently, it has been shown that rare-earth metal triflates act as Lewis acids in aqueous medium; they are stable in water, and are active catalysts for organic synthesis.[8–12] In this paper, we report that some rare-earth metal triflates are highly active for the chloromethylation of many aromatic hydrocarbons.

2 Experimental

2.1 Reagents

Scandium, ytterbium, samarium, hafnium, and indium triflates were purchased from Tokyo Kasei Chem. Ind., Co. Ltd., Tokyo, Japan. Zinc chloride and trioxane were obtained from Kishida Chemicals Co. Ltd., Osaka, Japan.

2.2 Reaction procedures

Typical procedures for the chloromethylation are shown in the case of *m*-xylene as follows: a mixture of *m*-xylene (**I**; 1.0 g, 9.4 mmol), trioxane (1.3 g, 14.1 mmol), 35% aqueous hydrochloric acid (4.9 g, 47 mmol), and scandium triflate (50 mg, 0.094 mmol) was stirred in a 30 ml round flask for 5 h at 70 °C. After cooling, the organic products were extracted with cyclohexane, and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated *in vacuo*, and the organic residue was resolved in cyclohexane again, and analyzed by hlpc using Finepack SIL C-18-5 φ 4.6 × 250 mm (JASCO, Tokyo, Japan). The yields of chloromethyl-2,4-dimethylbenzene (**II**) and 1,5-bis(chloromethyl)-2,4-dimethylbenzene (**III**) were 73 and 20%, respectively. Each product was separated by silica gel column chromatography, and identified by ^{1}H and ^{13}C NMR, IR, and elemental analysis. Residual aqueous catalytic solution was evaporated *in vacuo* to a white solid, which was dissolved in a small amount of water, and treated with activated carbon. The filtrate was evaporated to dryness *in vacuo* to give scandium triflate in 94% yield. Scandium triflate was identified by IR in comparison with an authentic sample.

The products from *o*-xylene and pseudocumene were identified by the comparison of NMR spectra of original and hydrogenated products. Properties of 1,2,4,5-substituted products from *o*-, *m*-, and *p*-xylene isomers are as follows:

1,5-bis(chloromethyl)-2,4-dimethylbenzene. m.p., 100.7–101.8 °C, IR(KBr): 656(C–Cl) cm^{-1}. NMR: ^{1}H-NMR(CDCl$_3$); 2.386 (s, 6H, CH$_3$), 4.574 (s, 4H, CH$_2$), 7.045 (s, 1H, ArH), 7.254 (s, 1H, ArH) (ppm). ^{13}C-NMR(CDCl$_3$); 18.38, 44.34, 131.21, 133.25, 133.51, 137.95 (ppm). Elemental analysis:

Green Context

The chloromethylation of aromatic molecules is a very useful reaction since the products can be used as intermediates on route to many valuable products. The reaction of the aromatic substrate with a formaldehyde source such as trioxane and hydrochloric acid is a popular and atom economic route but catalysts are required to achieve reasonable reaction rates and traditionally these have been required in large, often stoichiometric quantities and cannot easily be recovered. Here it is shown that metal triflates are effective catalysts for aromatic chloromethylations under atom-efficient conditions. The catalysts are active at very low concentrations and are easily recoverable. ***JHC***

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C, 59.14, H, 5.96% calculated from $C_{10}H_{12}Cl_2$. Observed: C, 59.01, H, 5.97%

1,4-bis(chloromethyl)-2,5-dimethylbenzene. m.p., 129.3–133.7°C, IR(KBr): 688(C–Cl) cm^{-1}. NMR: ^{1}H-NMR($CDCl_3$): 2.382 (s, 6H, CH_3), 4.561 (s, 4H, CH_2) 7.150 (s, 2H, ArH) (ppm). ^{13}C-NMR($CDCl_3$): 18.135, 44.281, 132.146, 135.026, 136.030 (ppm). Elemental analysis: C, 59.14, H, 5.96% calculated from $C_{10}H_{12}Cl_2$. Observed: C, 59.33, H, 5.99%.

1,2-bis(chloromethyl)-4,5-dimethylbenzene. m.p., 106.3–106.9°C, IR(KBr): 687(C–Cl) cm^{-1}. NMR: ^{1}H-NMR($CDCl_3$): 2.254 (s, 6H, CH_3), 4.702 (s, 4H, CH_2), 7.149 (s, 2H, ArH) (ppm). ^{13}C-NMR($CDCl_3$): 19.360, 43.292, 132.065,133.496,138.017 (ppm). Elemental analysis: C, 59.14, H, 5.96% calculated from $C_{10}H_{12}Cl_2$. observed: C, 59.10, H, 5.83%

The amount and efficiency of HCl and CH_2O in the organic product were calculated on the basis of the comparison with introduced amounts.

2.3 Recycling of catalyst

The reaction catalyzed by $Sc(OTf)_3$ was carried out in the same manner as in the previous section. After the separation of the organic layer, the aqueous catalytic solution was saturated with HCl by bubbling with dry HCl gas, and subjected to further reaction. The reaction was carried out by the addition of *m*-xylene (1.0 g) and trioxane (1.3 g) for 5 h at 70 °C. The analysis of products was carried out as described previously.

3 Results and discussion

The chloromethylation of *m*-xylene with hydrochloric acid and trioxane as a formaldehyde precursor was examined, using a rare-earth metal triflate as a catalyst. Typical results are shown in Fig. 1.

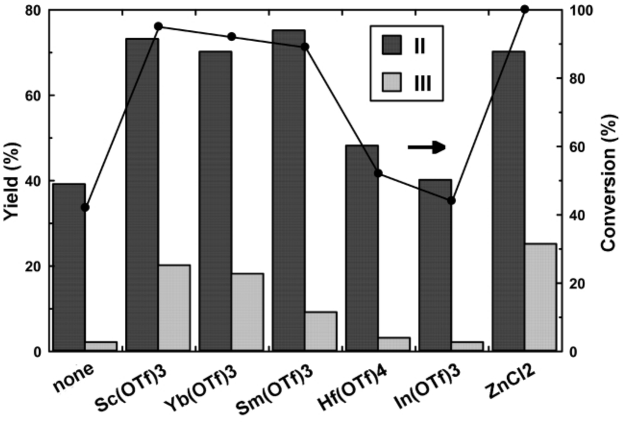


Fig. 1 Chloromethylation of *m*-xylene catalyzed by rare-earth metal triflates. Reaction conditions: rare-earth metal triflate, 0.94 mmol; *m*-xylene, 1.0 g (9.42 mmol); conc. HCl, 4.9 g (47 mmol); trioxane 0.4 g (4.7 mmol); temperature, 70 °C; period, 5 h.

m-Xylene gave chloromethyl-2,4-dimethylbenzene (**II**) and 1,5-bis(chloromethyl)-2,4-dimethylbenzene (**III**) without a catalyst, however, the combined yield of **II** and **III** was as low as 20%. On the other hand, rare-earth triflates such as scandium, ytterbium, samarium, indium, and hafnium triflates are excellent catalysts for the chloromethylation of *m*-xylene with hydrochloric acid and trioxane. Triflates are sufficiently active for the chloromethylation of *m*-xylene in catalytic amounts. The conversion of *m*-xylene is in the order: $Sc(OTf)_3 \approx Yb(OTf)_3 \approx Sm(OTf)_3 \gg Hf(OTf)_3 > In(OTf)_4 >$ none; however, the yield of **III** decreased in the order: $Sc(OTf)_3 > Yb(OTf)_3 > Sm(OTf)_3 \gg Hf(OTf)_3 > In(OTf)_4 >$ none. From these results, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Sm(OTf)_3$ have higher activity among the triflates for the chloromethylation. The catalysis occurred under heterogeneous conditions of organic and aqueous phases: the catalysts were easily separated from the reaction mixtures after the reaction, and recycled for new reaction without significant loss of activity. The chloromethylation using $ZnCl_2$ as catalyst gave the products at the same level; however, it was necessary to use an approximately stoichiometric amount for corresponding yields. Hereafter, we chose $Sc(OTf)_3$ as the catalyst in experiments to elucidate the factors controlling the catalysis, because it possessed the highest activity among the triflates.

The effects of reaction temperature on the chloromethylation are shown in Fig. 2 (trioxane/*m*-xylene = 0.5). The catalytic activity increased with temperature. The reaction was enhanced significantly around 50–60 °C. The yield of **II** increased with temperature, reached a maximum at 70 °C, and then decreased above 80–90 °C. However, the yield of **III** increased with temperature. The formation of tris(chloromethyl)-2,4-dimethylbenzene increased as the yield of **II** decreased at higher temperatures.

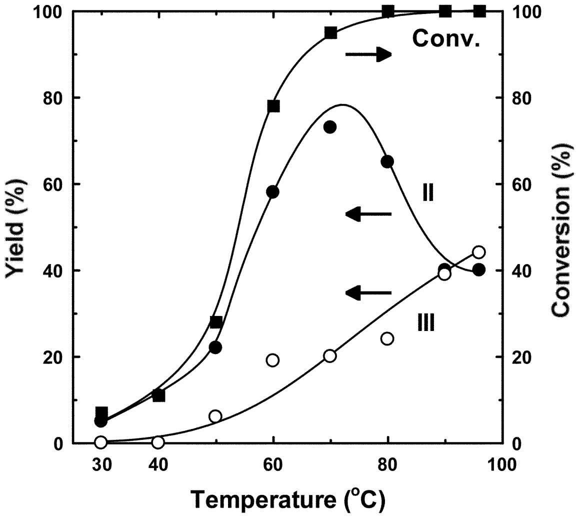


Fig. 2 Effects of reaction temperature on the chloromethylation of *m*-xylene catalyzed by $Sc(OTf)_3$. Reaction conditions: $Sc(OTf)_3$, 0.05 g (0.94 mmol); *m*-xylene, 1.0 g (9.4 mmol); conc. HCl, 4.9 g (47 mmol); trioxane 0.4 g (4.7 mmol); period, 5 h.

The effect of the concentration of hydrochloric acid at 70 °C is shown in Fig. 3a. No reaction occurs in the absence of hydrochloric acid. The activity was a function of the concentration of hydrochloric acid: an increase of the concentration increased the formation of **II** and **III**. The rate was saturated at an HCl concentration of around 20% (HCl/*m*-xylene = ~ 3). However, the yield of **III** increased slightly with the decrease of that of **II** at higher HCl concentration. These results show that the concentration of hydrochloric acid solution is not the principal factor controlling the catalysis. Fig. 3b shows the amount of HCl and formaldehyde in the products, and their efficiencies during the reaction. An increase of the amount of HCl enhanced the amount of CH_2O and HCl in the products. However, the efficiency of CH_2O increased with the concentration of hydrochloric acid although the efficiency of HCl for the reaction decreased. These results show that the activation of formaldehyde or its hydrate is not involved in the acid catalysis of triflate, and that HCl plays an important role in the reaction: the formation of chloromethanol ($ClCH_2OH$) and subsequent formation of chloromethyl complex are key steps for the chloromethylation.

Fig. 4a shows the effects of the ratio of trioxane and *m*-xylene. The conversion of *m*-xylene was high enough for the formation of **II** even with the ratio of trioxane/*m*-xylene = 0.5 (formaldehyde/*m*-xylene = 1.5), and the yield of **II** was around 70%. The addition of trioxane in excess amount enhanced the formation of **III**, and reached the maximum yield of *ca*. 70% at a trioxane/*m*-xylene ratio of 4. Further addition of trioxane decreased the formation of **III** to yield polychloromethylated products as a by-product. Fig. 4b shows that the amount of formaldehyde and hydrochloric acid in the products was maximized at a ratio of trioxane/*m*-xylene = 1.5 (formaldehyde/*m*-xylene = 4.5), and decreased with further addition of trioxane. However, the efficiency of CH_2O was decreased with the increase of its concentration, whereas the efficiency of HCl remained almost constant with the increasing amount of CH_2O. It is considered that trioxane forms formaldehyde before the reaction with *m*-xylene. These results indicate that the activation of formaldehyde is a key step for enhancement of the chloromethylation.

Fig. 5 shows that the amount of the catalyst is not a crucial issue for the enhancement of the catalysis, although the rate was rapidly increased up to 1 mol% of the catalyst.

The catalysis under our conditions occurs in a heterogeneous mixture composed of *m*-xylene, trioxane, and triflate in aqueous hydrochloric acid. The organic compounds were added to accelerate the reaction by improvement of the contact of the reactant with the triflate in the aqueous phase. Fig. 6 shows the effect of some organic additives. Formic and acetic acids enhanced the formation of **III**. However, the addition of nitrobenzene and methylcyclohexane decreased the activity, and the yield of **III** was decreased. The addition of dioxane also promoted the formation of **III**. The amount of acetic acid was examined to elucidate the effect of acid addition. Fig. 7 shows the effects of acetic acid on the chloromethylation. A small amount of acetic acid enhanced the yield of **III**; however, further addition decreased the yield of **III**. These results show that acetic acid promotes the catalysis effectively by addition in a small amount; however, it retards the catalysis by the further addition.

It is important to evaluate the recyclability of catalysts. We examined the recovery and recyclability of $Sc(OTf)_3$ catalyst using two methods. First, the catalyst was recycled and reused as aqueous solution for further reaction. After the reaction was finished, the aqueous catalytic solution was recovered by separation of the organic layer. The aqueous solution was saturated with HCl by bubbling with HCl gas, and the reaction was carried out using recovered catalytic solution by the addition of *m*-xylene and trioxane. The change in catalyst performance is summarized in Table 1. The catalytic activity decreased gradually by recycling to result in a decrease of the yield of **II** and **III**. The decrease should be due to incomplete recovery of the catalyst, and also to the different reaction conditions from the original process. Optimization of conditions will improve the yield of recycled reactions.

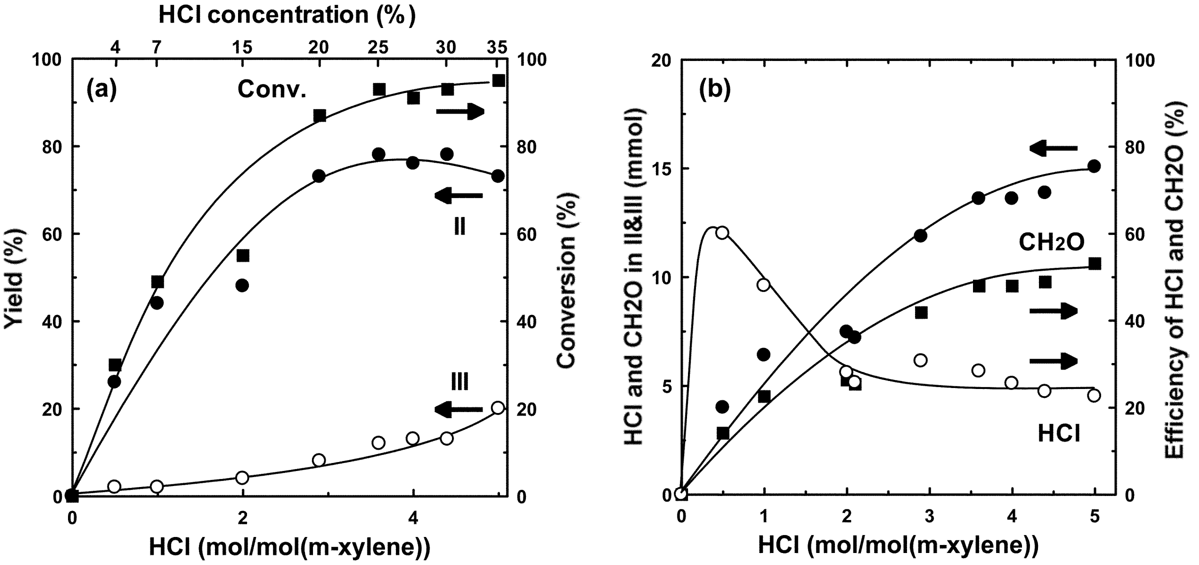


Fig. 3 Effects of the concentration of hydrochloric acid on the chloromethylation of *m*-xylene catalyzed by $Sc(OTf)_3$. (a) catalytic feature. (b) balance of CH_2O and HCl. Reaction conditions: $Sc(OTf)_3$, 0.05 g (0.094 mmol); *m*-xylene, 1.0 g (9.4 mmol); conc. HCl, 4.9 g (47 mmol); trioxane 0.4 g (4.7 mmol); temperature, 70 °C; period, 5 h.

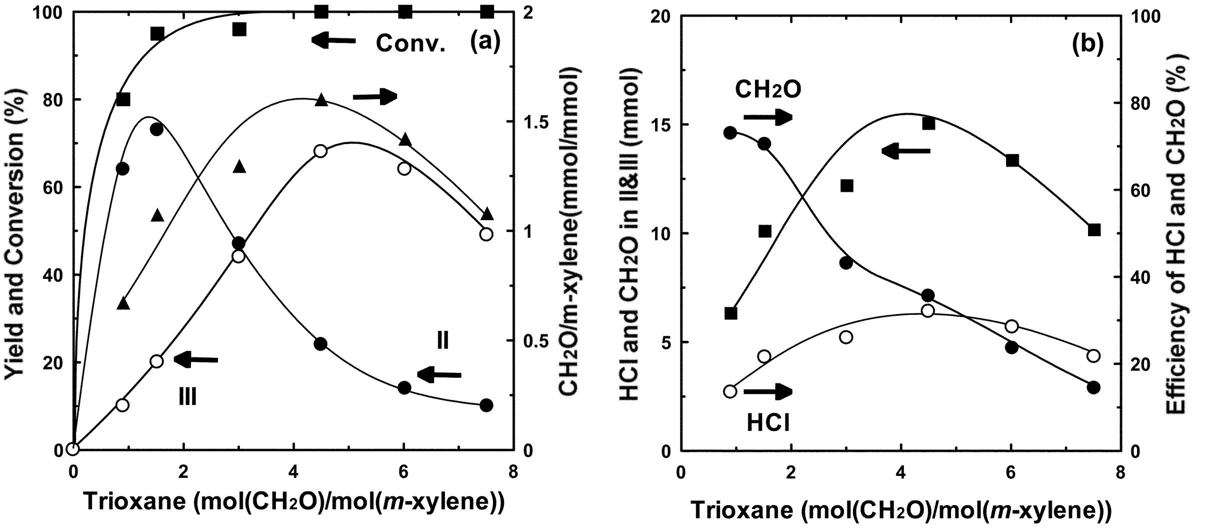


Fig. 4 Effects of the ratio of trioxane to *m*-xylene on the chloromethylation of *m*-xylene catalyzed by $Sc(OTf)_3$. (a) catalytic feature. (b) balance of CH_2O and HCl. Reaction conditions: $Sc(OTf)_3$; 0.05 g (0.094 mmol); *m*-xylene, 1.0 g (9.4 mmol); conc. HCl, 4.9 g (47 mmol); temperature, 70 °C ; period, 5 h.

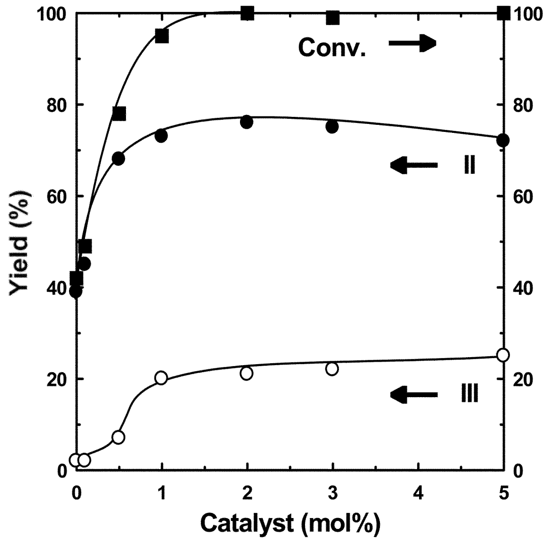


Fig. 5 Effects of catalyst amount on the chloromethylation of *m*-xylene catalyzed by Sc(OTf)$_3$. Reaction conditions: Sc(OTf)$_3$, 0.0–0.25 g (0.094–0.47 mmol); *m*-xylene, 1.0 g (9.4 mmol); conc. HCl, 4.9 g (47 mmol); trioxane 0.4 g (4.7 mmol); temperature, 70 °C; period, 5 h.

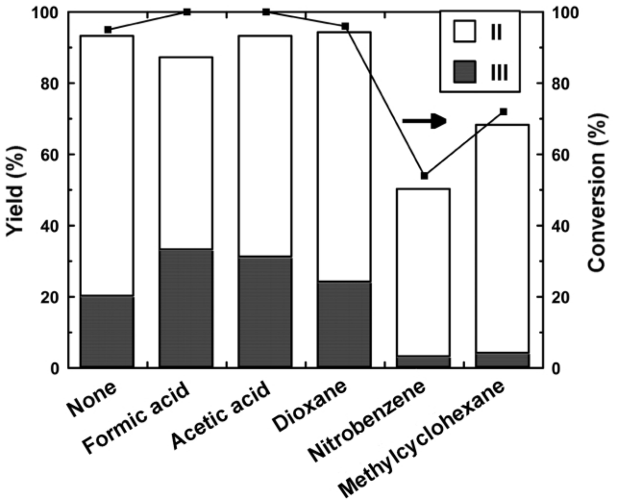


Fig. 6 Effects of organic additives on the chloromethylation of *m*-xylene catalyzed by Sc(OTf)$_3$. Reaction conditions: Sc(OTf)$_3$, 0.05 g (0.094 mmol); *m*-xylene, 1.0 g (9.4 mmol); conc. HCl, 4.9 g (47 mmol); trioxane 0.4 g (4.7 mmol); additive, 1.0 ml; temperature, 70 °C; period, 5 h.

Secondly, recovery of Sc(OTf)$_3$ was examined by evaporation of the catalytic solution. The residual solid was treated with activated charcoal to give Sc(OTf)$_3$ in high yield. Recovered triflate can be used as fresh catalyst for the chloromethylation. These results show that the triflate is not hydrolyzed in the presence of an excess of hydrochloric acid. These two methods of catalyst recovery indicate that triflate is stable under the reaction conditions and easily recycled after the reactions.

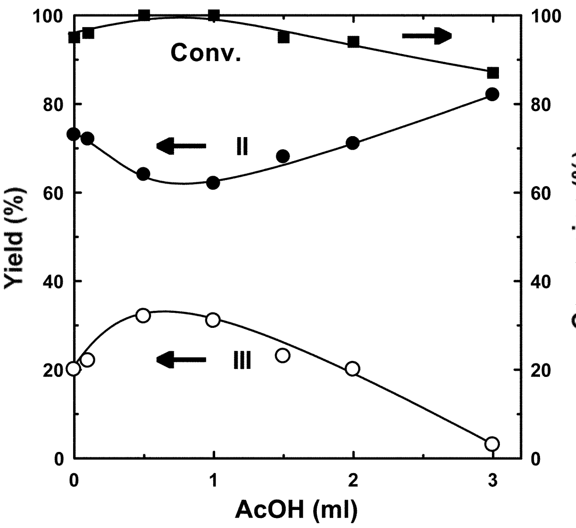


Fig. 7 Effects of acetic acid on the chloromethylation of *m*-xylene catalyzed by Sc(OTf)$_3$. Reaction conditions: Sc(OTf)$_3$, 0.05 g (0.094 mmol); *m*-xylene, 1.0 g (9.4 mmol); conc. HCl, 4.9 g (47 mmol); trioxane 0.4 g (4.7 mmol); temperature, 70 °C; period, 5 h.

Table 1 Recycling of catalytic solution in the chloromethylation of *m*-xylene over Sc(OTf)$_3$

Catalytic cycle	Conversion (%)	Yield (%)	
		II	**III**
1st	95	73	20
2nd	79	65	11
3rd	70	62	7

Reaction conditions: *m*-xylene, 1.0 g (9.4 mmol); trioxane 0.43 g (4.7 mmol); Sc(OTf)$_3$, 0.046 g (0.094 mmol); temperature, 70 °C; period, 5 h.

Table 2 summarizes the application of Sc(OTf)$_3$ to the chloromethylation of aromatic hydrocarbons. Although the reaction was carried out under relatively mild conditions such as 70 °C, and at a molar ratio of trioxane/alkylbenzene of 0.5 (formaldehyde/alkylbenzene = 1.5), benzene, toluene, xylenes, mesitylene, pseudocumene, and durene gave the chloromethylated product in good to excellent yields. The hydrocarbons gave monochloromethylated hydrocarbons in high yield, and also gave disubsutituted products in low yield. The product distributions are similar to the conventional zinc chloride method: the substitution occurred in the *o*- and *p*-direction. The less bulky isomer was predominant, especially for the monochloromethylation. The difference in the products for the xylene isomers is interesting. *m*-Xylene gave **III** selectively, whereas *p*-xylene also gave 1,4-bis-(chloromethyl)-2,5-dimethylbenzene. The introduction of two chloromethyl groups to the *m*- and *p*-xylenes occurred selectively at the neighbor of the methyl groups to yield the dichloromethylated products with 1,2,4,5-substitution. On the other hand, the dichloromethylated products from *o*-xylene are 1,2-bis(chloromethyl)-4,5-dimethylbenzene and 1,4-bis(chloromethyl)-2,3-dimethylbenzene. The chloromethylation of pseudocumene also gave two isomers, 1-chloromethyl-2,4,5-trimethylbenzene and 1-methyl-2,3,6-trimethylbenzene, and the formation of the product with 1,2,4,5-substituted products was not selective. Cumene and *t*-butylbenzene showed low activity for the reaction. Bromobenzene and benzonitrile were also inactive for the chloromethylation.

Scheme 1 shows a plausible mechanism for the catalysis. First, trioxane yields formaldehyde by acid catalysis of hydrochloric acid. Then, formaldehyde and HCl react with triflate to yield chloromethylated triflate complex (**X**). The formation of the complex should occur either way:

(A) Formaldehyde and HCl give the chloromethanol and react with triflate to yield **X**.

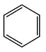
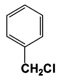
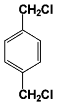
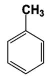
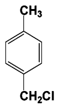
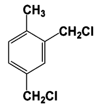
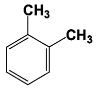
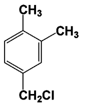
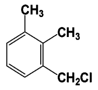
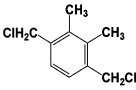
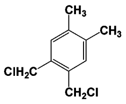
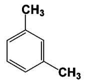
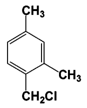
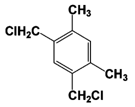
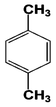
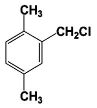
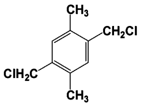
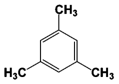
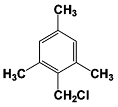
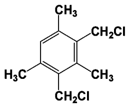
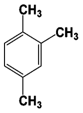
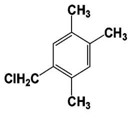
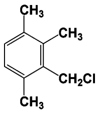
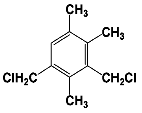
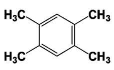
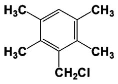
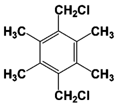
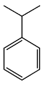
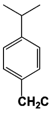
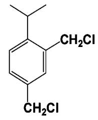
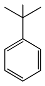
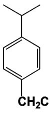
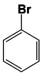
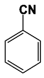
(B) The hydroxymethyl triflate complex is formed from formaldehyde, and then OH is substituted with Cl to form **X**.

Mechanism (A) is more plausible than (B) because no reaction occurs in the absence of hydrochloric acid. Complex **X** reacts with aromatic hydrocarbon to yield the chloromethylated product and triflate by electrophilic substitution. This mechanism is close to the classical zinc chloride catalysis.[1]

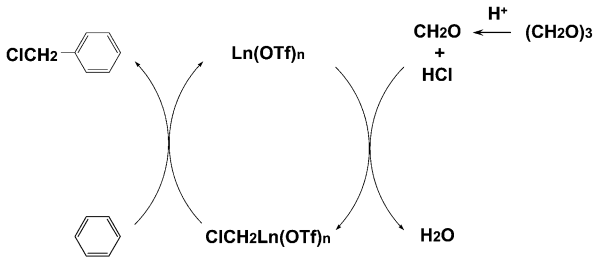
4 Conclusions

Rare-earth metal triflates are highly active for the chloromethylation of various aromatic hydrocarbons. The most important

Table 2 Chloromethylation of alkylbenzenes

Entry	Substrate	Conv. (%)	Products and yield (%)							
1		73		67		3	—	—	—	—
2		100		37		32	—	—	—	—
3		100		35		11		28		22
4		95		73		20	—	—	—	—
5		92		69		19	—	—	—	—
6		100		70		30	—	—	—	—
7		100		48		10		33	—	—
8		91		74		16	—	—	—	—
9		26		17		4	—	—	—	—
10		9		6	—	—	—	—	—	—
11		0	—	—	—	—	—	—	—	—
12		0	—	—	—	—	—	—	—	—

Reaction conditions: substrate, 1 g; $(HCHO)_3$, 0.5 equiv.; conc. HCl, 5 equiv.; $Sc(OTf)_3$, 1 mol%; temperature, 70 °C; period, 5 h.



Scheme 1 Plausible mechanism.

characteristic is that a catalytic amount of triflate was effective for the chloromethylation. Two or three times the amount of hydrogen chloride compared to chloromethyl groups in the products is sufficient for reasonable conversion of hydrocarbons. The catalysis by triflates easily occurs in a heterogeneous mixture of hydrocarbon, trioxane, and triflate in aqueous hydrochloric acid. Since the triflate stays in the aqueous phase during the reaction, the catalyst was easily separated from the products, and recycled for further reaction. The catalyst was stable under the reaction conditions.

From an environmental point of view, rare-earth metal triflates are active enough for the green chloromethylation of aromatic hydrocarbons. Further aspects of the catalysis and the application to organic syntheses and practical chemical processes are under investigation.

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Marked enantioselectivity enhancements for Diels–Alder reactions in ionic liquids catalysed by platinum diphosphine complexes

Simon Doherty,*[a] Peter Goodrich,[b] Christopher Hardacre,*[ab] He-Kuan Luo,[a] David W. Rooney,[bc] Kenneth R. Seddon[ab] and Peter Styring[d]

[a] *School of Chemistry, Queen's University Belfast, Belfast, Northern Ireland, UK BT9 5AG. E-mail: c.hardacre@qub.ac.uk, s.doherty@qub.ac.uk*
[b] *QUILL, Queen's University Belfast, Belfast, Northern Ireland, UK BT9 5AG*
[c] *School of Chemical Engineering, Queen's University Belfast, Belfast, Northern Ireland, UK BT9 5AG*
[d] *Department of Chemical and Process Engineering, University of Sheffield, Sheffield, UK S1 3AD*

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Asymmetric Diels–Alder reactions using platinum complexes of BINAP, or of conformationally flexible NUPHOS-type diphosphines, have been compared in dichloromethane and selected ionic liquids. Significant enhancements in the enantioselectivity (Δ*ee* ≈ 20%), as well as reaction rate, were achieved in ionic liquids compared with the organic media.

Introduction

In general, the design of asymmetric catalysts has been based upon conformationally-restricted, enantiopure ligands which impart their chirality on a transformation to achieve high enantioselectivities. Recently, this concept has been challenged by the discovery of asymmetric activation, a process that involves activation of an enantiopure catalyst with a chiral activator, selective activation of one enantiomer of a racemic catalyst, and more recently the formation of highly effective catalysts based on a conformationally-flexible ligand coupled with a chiral activator.[1] For example, Mikami and Matsukawa have used BINOLate-titanium based catalysts activated with enantiopure 1,1′-bi-2-naphthol (BINOL) to achieve an *ee* of 90% in the asymmetric carbonyl-ene reaction,[2] and 84% in the asymmetric Diels–Alder reaction of the Danishefsky diene with glyoxylate.[3] Becker *et al.* have also shown that coordination of 1,1′-bis(diphenylphosphino)biphenyl (BIPHEP) to platinum significantly slows atropinversion such that the enantiopure Lewis acid fragment λ/δ-{Pt(BIPHEP)}$^{2+}$, generated from either λ/δ-[(BIPHEP)Pt{(*S*)-BINOL}] or λ/δ-[(BIPHEP)PtCl$_2$], is highly selective for the Diels–Alder reaction between acryloyl-*N*-oxazolidinone and cyclopentadiene, giving *ee* values as high as 94%.[4]

Recently, Doherty and co-workers reported the synthesis of a new class of conformationally flexible diphosphine, R$_4$-NUPHOS (Fig. 1), based on two diphenylphosphino- groups linked by a four-carbon conjugated tether.[5] Preliminary studies have shown that the platinum group metal complexes of R$_4$-NUPHOS diphosphines are highly active for Kumada cross-coupling reactions and the transfer hydrogenations of ketones.[6] Recently, efficient Diels–Alder reactions between acryloyl-*N*-oxazolidinones and cyclopentadiene (Cp–H) catalysed by platinum and palladium complexes of NUPHOS-type diphosphines have been observed.[7] Following the procedure reported by Becker *et al.*,[4] enantiopure Lewis acids of the type δ-[(R$_4$-NUPHOS)Pt(OTf)$_2$] gave good conversions and high enantioselectivities for the low temperature Diels–Alder reaction between **1a** or **1b** and Cp–H, although notably the same catalysts gave low conversions and only moderate *ee*'s at 20 °C (Fig. 2).

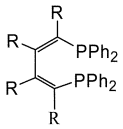

Fig. 1 Schematic of R$_4$-NUPHOS.

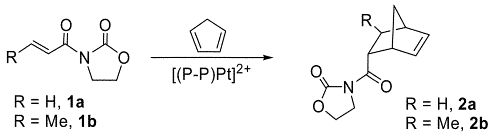

Fig. 2 Asymmetric Diels–Alder reaction between acryloyl-*N*-oxazolidinone and cyclopentadiene.

These low conversions appear to be due to rapid and quantitative formation of the catalytically inactive cation [(R$_4$-NUPHOS)Pt(η^5-Cp)]$^+$ (*vide infra*). Becker *et al*. have noted that a similar η^5-Cp complex also forms at low temperature;[4] however, the Diels–Alder reaction between **1a** and cyclopentadiene is fast compared with the formation of this cation, and therefore the reaction can proceed. In contrast, at room temperature, formation of the inactive complex dominates.

Solvent effects are known to have a strong influence on Diels–Alder reactions and, recently, ionic liquids have been reported to show large increases in reaction rates.[8] Thus, we reasoned that ionic liquids could be used to overcome the problems found in

Green Context

There has been an extraordinary growth in the research work on ionic liquids in recent years. These fascinating substances offer the potential for carrying out many chemical processes without the need for environmentally threatening volatile organic solvents. Here their use as a VOC substitute is made more useful through an improvement in reaction selectivity. Diels–Alder reactions in ionic liquids have previously been demonstrated but here useful improvements in enantioselectivity are also achieved. ***JHC***

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dichloromethane by stabilising the catalyst with respect to deactivation and/or reducing the reactions times which would limit the extent of atropinversion.

Ionic liquids are one of a number of possible 'green' alternatives to conventional solvents due to their low vapour pressure. A wide range of reactions have been performed in ionic liquids to date including alkylations,[9] C–C bond coupling reactions,[10–12] polymerisations,[13–15] hydrogenations,[16–18] hydroformylation,[16] and alkoxycarbonylation.[19] These reactions have been extensively reviewed recently.[20] Ionic liquids have also been used for asymmetric transformations; however, these have often been performed in the presence of a co-solvent, and in many cases without any beneficial effect on the enantioselectivity compared to conventional media. For example, Song and Roh demonstrated that Jacobsen's chiral [(salen)Mn(III)] ([*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] manganese(III) chloride) epoxidation catalyst performed similarly in CH_2Cl_2 and a CH_2Cl_2-[bmim][PF_6] mixture.[21] Similar results have been reported for asymmetric ring opening of epoxides,[22] asymmetric hydrogenations,[23] asymmetric dihydroxylation of olefins[24] and kinetic resolution of epoxides[25] The ionic liquid does, however, allow the catalyst to recycle a number of times without reduction in the enantioselectivity. Jessop *et al.* have shown that ionic liquids can enhance the enantioselectivity in the asymmetric reduction of tiglic acid using ruthenium BINAP (2,2′-bis(diphenylphosphino)-1′1-binaphthyl) based catalysts.[26] Using a range of ionic liquids, the *ee*'s reported were found to increase from 88% in MeOH to 95% in [emim][$N(O_2SCF_3)_2$] ([emim][NTf_2]). Baudequin *et al* have recently reviewed the effect of ionic liquids on enantioselective reactions.[27]

To date, only one asymmetric Diels–Alder reaction performed in ionic liquids has been reported. Meracz and Oh observed an *ee* of 96% for the Diels–Alder reaction of oxazolidinone **1b** and Cp–H at room temperature using a rigid copper bisoxazoline-based chiral Lewis acid with a yield of 65% in 1,3-dibutylimidazolium tetrafluoroborate. This was compared with dichloromethane which showed only 76% *ee* with a yield of only 4%.[28]

In this paper we also report that ionic liquids provide an ideal medium in which to perform the room temperature Diels–Alder reaction between oxazolidinone **1a/b** and Cp–H (Fig. 2) catalysed by platinum complexes of conformationally rigid (BINAP) and flexible (NUPHOS, BIPHEP) diphosphines. Mechanistic information is also presented which is used to understand the promoting effect of the ionic liquid.

Experimental

General procedures

1-Ethyl-3-methyimidazolium bis{(trifluoromethyl)sulfonyl}amide ([emim][NTf_2]), 1-butyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}amide ([bmim][NTf_2]) and 1-methyl-3-octylimidazolium bis{(trifluoromethyl)sulfonyl}amide ([omim][NTf_2]) were prepared following the method of Bonhôte *et al.*[29] 1-Butyl-3-methyl imidazolium hexafluorophosphate ([bmim][PF_6]) was prepared following the method of Seddon and co-workers.[30] *N*-butyl-*N*-methylpyrollidinium bis{(trifluoromethyl)sulfonyl}amide ([C_4mpyl][NTf_2]) was prepared following the method of MacFarlane *et al.*[31] The NUPHOS, BINAP and BIPHEP catalyst precursors (**3**, **5**, **7** and **9**) were prepared following methods reported by Doherty and co-workers,[6a] Gugger *et al.*[32] and Tudor *et al.*,[33] respectively. Oxazolidinones **1a** and **1b** were prepared using methods reported by Evans *et al.*[34] Cyclopentadiene was distilled by cracking dicyclopentadiene and used immediately. ^1H and $^{31}P\{^1H\}$ NMR spectra were recorded on Bruker AC 200, AMX 300 and DRX 500 spectrometers.

All manipulations involving air-sensitive materials were carried out in an inert atmosphere glove box, or using standard Schlenk line techniques, under an atmosphere of dinitrogen or argon in oven-dried glassware. Diethyl ether and hexane were distilled from potassium/sodium alloy, tetrahydrofuran from potassium, dichloromethane from calcium hydride, and methanol from magnesium. Deuteriochloroform was pre-dried with calcium hydride, vacuum transferred, and stored over 4A molecular sieves. Unless otherwise stated, commercially purchased materials were used without further purification. Purification of reaction products was carried out by column chromatography on reagent silica gel (60–200 mesh). Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 1100 series HPLC instrument, using HPLC grade hexane : ethyl acetate : isopropanol (94 : 4 : 2) as the eluent at 1 cm^3 min^{-1} flow rate. Enantioselectivities were determined using a Diacel Chiralcel OD–H reverse phase column. The retention times of the *endo* enantiomers were 15.79 min ($endo_{2S}$) and 17.21 min ($endo_{2R}$). The absolute configuration of the *endo* cycloadduct was assigned by comparison with the retention times of samples prepared from (*R*)- and [{(*S*)-BINAP}$PtCl_2$].[35]

Catalyst activation

Two methods of catalyst activation were used. In method (i), a solution of the platinum complex **3** or **5** (0.032 mmol, 20 mol%) and Ag[SbF_6] (2.0 equiv.) in dichloromethane (2.0 cm^3) was stirred under a dinitrogen atmosphere for 1 h at 20 °C, after which time the resulting solution was filtered using a filter cannula. In method (ii), a rapidly stirred solution of complex **7** or **9** (0.016 mmol, 10 mol%) in dichloromethane (*ca.* 2 cm^3) was treated with HOTf (2.2 μL, 1.4 equiv.), resulting in an immediate colour change from deep yellow–orange to near colourless. The resulting mixture was stirred for 5 min at 20 °C.

General procedure for enantioselective Diels–Alder reactions between cyclopentadiene and oxazolidinone in dichloromethane

A dichloromethane solution (2.0 cm^3) of catalyst activated according to method (i) or (ii) was cooled to −78 °C and oxazolidinone **1a** or **1b** (0.16 mmol) and cyclopentadiene (1.2 mmol) added. The reaction mixture was allowed to warm to the desired temperature and left to stir. At the end of the reaction, the solution was quenched with (*S*,*S*)-1,2-diphenylethylenediamine (*S*,*S*-dpeda) and the dichloromethane removed under vacuum. The crude mixture was purified by column chromatography over silica gel (60–200 mesh, 30% ethyl acetate–hexane) and the products analysed by ^1H NMR spectroscopy and HPLC. Conversions were calculated using samples taken directly from the reaction solution. All conversions reported are ±10%.

General procedure for enantioselective Diels–Alder reactions between cyclopentadiene and oxazolidinone in ionic liquids

Ionic liquid (2.0 cm^3) and oxazolidinone **1a** or **1b** (0.16 mmol) were added to a dichloromethane solution (2.0 cm^3) of the catalyst prepared according to methods (i) or (ii). After stirring for a short while the dichloromethane was removed under vacuum and cyclopentadiene (1.2 mmol) added. The resulting mixture was stirred at room temperature for 1 h, after which time the ionic liquid was extracted with diethyl ether (5 × 3 cm^3) in air. The organic phase was analysed by ^1H NMR spectroscopy and HPLC, and the crude product remaining purified by column chromatography over silica gel (60–200 mesh, 30% ethyl acetate–hexane).

Ionic liquid recycle experiments

Following extraction with diethyl ether, the ionic liquid solution was flushed with inert gas and charged with further portions of oxazolidinone **1b** (0.16 mmol) and cyclopentadiene (1.2 mmol) at room temperature, and left stirring for a further 1 h.

Diels–Alder reactions in the presence of diethyl ether

To a dichloromethane solution (2.0 cm^3) of the activated catalyst **7** was added [emim][NTf_2] (0.2 cm^3) and oxazolidinone **1a** or **1b** (0.16 mmol). After stirring, the dichloromethane was removed under vacuum and diethyl ether (6.0 cm^3) added, followed by cyclopentadiene (1.2 mmol). The resulting biphasic reaction mixture was stirred rapidly under an inert atmosphere for 1 h, after which time the diethyl ether was decanted and analysed by ^{1}H NMR spectroscopy and HPLC.

Kinetics

Aliquots of a freshly prepared dichloromethane or [emim][NTf$_2$] solution of the activated catalyst, δ-**7a**, were taken at regular time intervals at room temperature and quenched with excess (*S*,*S*)-1,2-diphenylethylenediamine to afford a diastereotopic mixture. From ^{31}P NMR spectroscopic data, the diastereoisomer ratio was analysed using first order reversible kinetic analysis to yield the rate constant.

Results and discussion

Table 1 Enantioselective Diels–Alder reaction at 20 °C using 20 mol% catalyst for the Diels–Alder reaction between **1b** and Cp–H

Solvent (temp.)	Catalyst	% conv^{ad} (time)	% *endo*^{bd}	*endo ee*^{cd} (config)
[emim][NTf$_2$]	δ-**4a**	100 (1 h)	87	90 (2*R*)
[bmim][PF$_6$]	δ-**4a**	100 (1 h)	89	93 (2*R*)
[omim][NTf$_2$]	δ-**4a**	100 (1 h)	77	90 (2R)
[C$_4$mpyl][NTf$_2$]	δ-**4a**	88 (1 h)	77	90 (2*R*)
[emim][NTf$_2$]	λ-**4b**	90 (1 h)	89	91 (2*S*)
CH$_2$Cl$_2$	δ-**4a**	45 (20 h)	80	67 (2*R*)
CH$_2$Cl$_2$ (−20 °C)	δ-**4a**	60 (20 h)	84	88 (2*R*)
CH$_2$Cl$_2$	λ-**4b**	22 (20 h)	88	71 (2*S*)
[emim][NTf$_2$]	*S*-**6**	100 (1 h)	80	92 (2*R*)
[emim][NTf$_2$]	*R*-**6**	78 (1 h)	84	94 (2*S*)
CH$_2$Cl$_2$	*S*-**6**	37 (20 h)	85	84 (2*R*)
[bmim][PF$_6$]	δ-**8a**^{e}	69 (1 h)	89	78 (2*R*)
[bmim][NTf$_2$]	δ-**8a**^{e}	71 (1 h)	82	90 (2*R*)
[emim][NTf$_2$]	δ-**8a**^{e}	93 (1 h)	88	90 (2*R*)
[omim][NTf$_2$]	δ-**8a**^{e}	63 (1 h)	73	90 (2*R*)
[C$_4$mpyl][NTf$_2$]	δ-**8a**^{e}	86 (1 h)	76	95 (2*R*)
CH$_2$Cl$_2$	δ-**8a**^{e}		*no reaction*	
CH$_2$Cl$_2$ (−20 °C)	δ-**8a**^{e}	7 (24 h)	88	93 (2*R*)
[emim][NTf$_2$]	λ-**8b**^{e}	74 (1 h)	81	91 (2*S*)
[emim][NTf$_2$]	λ-**10**^{e}	35 (1 h)	70	85 (2*S*)
CH$_2$Cl$_2$	λ-**10**^{e}		*no reaction*	

^{a} Determined by HPLC/^{1}H NMR spectroscopy. ^{b} *Endo*/*exo* ratio determined by ^{1}H NMR spectroscopy. ^{c} Enantiomeric excess was determined by HPLC (Daicel Chiralcel OD–H). ^{d} Average of three runs. ^{e} 10 mol%.

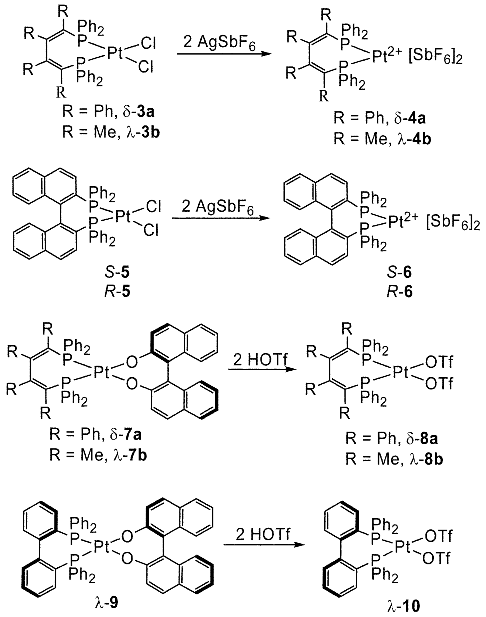

Fig. 3 Formation of Lewis acid catalysts [(P–P)PtX$_2$].

Table 1 summarises the results of a comparative study of the Diels–Alder reaction between oxazolidinone **1b** and Cp–H in ionic liquids and dichloromethane using catalyst **4a**, formed by activation of δ-[(Ph$_4$-NUPHOS)PtCl$_2$] (**3a**) with Ag[SbF$_6$] (Fig. 3). For each of the ionic liquids studied, significantly higher enantioselectivities were obtained compared with dichloromethane. For example, reaction in [emim][NTf$_2$] gave an *ee* of 90%, whereas the corresponding reaction in dichloromethane only gave an *ee* of 67%. While [emim][NTf$_2$] has been chosen for the majority of our studies, catalysts generated in a range of other ionic liquids including [bmim][PF$_6$], [omim][NTf$_2$], and [C$_4$mpyl][NTf$_2$] also performed equally well. It should also be noted that all the ionic liquid reactions were significantly faster than those performed in dichloromethane. Typically, high conversions were achieved in only 1 h at 20 °C, whereas reaction times in excess of 20 h were required to achieve similar levels of conversion in dichloromethane. Although it was possible to achieve high enantioselectivities in dichloromethane with this catalyst, low temperatures and long reaction times were required. Even at −20 °C, the *ee* of 88% is still slightly lower than that of 93% obtained in ionic liquid at room temperature, which highlights the beneficial influence of ionic liquids over dichloromethane. An enhancement in enantioselectivity was also obtained with catalysts based on the atropisomeric diphosphine BINAP in [emim][NTf$_2$] compared with dichloromethane. For example, under identical conditions, catalyst generated from [{(*S*)-BINAP}PtCl$_2$] (*S*-**5**) and Ag[SbF$_6$] gave an *ee* of 92% in [emim][NTf$_2$] and only 84% in dichloromethane. As expected catalysts generated from *R*- and *S*-[(BINAP)PtCl$_2$] gave the cycloadduct **2b** with opposite absolute configurations and comparable enantioselectivities.

We are confident that the enhancement in the *ee* observed with catalysts based on Ph$_4$-NUPHOS in the ionic liquids does not simply reflect the increased rate of Diels–Alder reaction in the two solvents since the rate of racemisation is also decreased significantly in ionic liquids. ^{31}P NMR data acquired after quenching the catalyst with *S*,*S*-dpeda gave a first order racemisation rate constant of 9×10^{-6} s^{-1} in dichloromethane whereas no racemisation occurred in [emim][NTf$_2$] within the NMR detection limit. However, there also appears to be an enhancement in enantioselectivity with the atropisomeric catalyst, δ-**6**, albeit smaller than that found for catalysts based on conformationally flexible ligands, indicating that the ionic liquid has an intrinsic effect on the *ee*.

As noted above, the Lewis acid fragments δ/λ-(R$_4$-NUPHOS)-Pt(OTf)$_2$ (**8a/b**), generated by protonation of δ/λ-(R$_4$-NUPHOS)Pt{(*S*)-BINOL} (**7a/b**) with triflic acid, (Fig. 3) are highly effective catalysts for the Diels–Alder reaction between oxazolidinone **1b** and Cp–H at −20 °C. However, it has not been possible to perform the Diels–Alder reaction with oxazolidinone **1b** at 20 °C in dichloromethane due to the instability of the catalyst with respect to cyclopentadiene. Even addition of diene to a dichloromethane solution of catalyst δ-**8a** at −78 °C and subsequent warming to 20 °C resulted in the rapid appearance of a characteristic deep blue–green coloration and after 1 h conversions were less than 5%. ^{31}P NMR analysis of this reaction mixture revealed a singlet at δ −5.7 flanked by platinum satellites ($^1J_{\text{Pt–P}}$ = 4542 Hz) which corresponds to the catalytically inactive cation [(Ph$_4$-NUPHOS)Pt(η^5-Cp)]$^+$, based on the similarity of its spectroscopic data with that of [(BIPHEP)Pt(η^5-Cp)]$^+$, reported earlier by Becker *et al.*[4] This species does not form in ionic liquids and the reaction proceeds with high enantioselectivity at room temperature giving an *ee* of 90% and high conversions. Moreover, a comparison of the data in Table 1 clearly shows that the performance of catalysts generated from δ-(Ph$_4$-NUPHOS)Pt{(*S*)-BINOL}(δ-**7a**) are comparable to those generated by halide abstraction from the corresponding dichloride complex δ-(Ph$_4$-NUPHOS)PtCl$_2$ (δ-**3a**). It should be noted that the Diels–Alder reaction does proceed in dichloromethane at or below −20 °C using the catalyst generated from δ-(Ph$_4$-NUPHOS)Pt{(*S*)-BINOL}(δ-**7a**). However, the *ee* of

93% obtained at −20 °C is only comparable with that obtained in ionic liquid at room temperature. At this stage we believe that the difference between the dichloromethane and the ionic liquids is due to the stability of catalyst generated from the BINOLate precursors δ/λ-**7a/b** and not to a difference in stability of the [(Ph$_4$-NUPHOS)Pt(η^5-Cp)]$^+$ cation, which has been independently prepared and shown to be stable but inactive in [emim][NTf$_2$]; a catalytic reaction giving less than 2% conversion at 20 °C. Similarly, catalyst mixtures generated from λ-(Me$_4$-NUPHOS)Pt{(*S*)-BINOL} (λ-**7b**) in [emim][NTf$_2$] show high enantioselectivity for the Diels–Alder reaction at room temperature, giving an *ee* of 91%, but no reaction in dichloromethane. Not surprisingly, catalyst generated from λ-(BIPHEP)Pt{(*S*)-BINOL} (λ-**9**) also showed comparable behaviour in ionic liquids at 20 °C but again little conversion in dichloromethane due to rapid formation of [(BIPHEP)Pt(η^5-Cp)]$^+$.

Whilst it is not straightforward to recycle the catalyst in dichloromethane, simple extraction with diethyl ether allowed the ionic liquid systems to recycle efficiently. Table 2 summarises a series of recycle experiments using δ-[(Ph$_4$-NUPHOS)Pt(SbF$_6$)$_2$] (δ-**4a**) and [{(*S*)-BINAP}Pt(SbF$_6$)$_2$] (*S*-**6**) and δ-[(Ph$_4$-NUPHOS)Pt(OTf)$_2$] (δ-**8a**) in [emim][NTf$_2$], and δ-[(Ph$_4$-NUPHOS)Pt(SbF$_6$)$_2$] (δ-**4a**) in [bmim][PF$_6$]. The extractions were performed in air and no significant change in the *ee* was found for successive reactions. In general, the catalyst–ionic liquid systems tested showed only a small decrease in activity on each recycle. ICP analysis of the ether extract showed that the platinum leaching was below the detection limit and therefore it is possible that this reduction is due to the gradual build up of inactive platinum complexes, possibly based on the cyclopentadiene.

Table 2 Recycle Diels–Alder reactions in ionic liquids for the Diels–Alder reaction between **1b** and Cp–H

Ionic liquid	Catalyst (mol%)	Run: % conv^{ad}	% *endo*^{bd}	*endo ee*^{cd} (config)
[bmim][PF$_6$]	δ-**4a** (20)	1: 100	89	93 (2*R*)
		2: 96	87	90 (2*R*)
		3: 90	84	90 (2*R*)
[emim][NTf$_2$]	δ-**4a** (20)	1: 100	87	90 (2*R*)
		2: 100	85	91 (2*R*)
		3: 96	85	89 (2*R*)
[emim][NTf$_2$]	*S*-**6** (20)	1: 100	80	92 (2*R*)
		2: 100	69	94 (2*R*)
		3: 96	82	91 (2*R*)
[emim][NTf$_2$]	δ-**8a** (10)	1: 71	82	90 (2*R*)
		2: 64	79	88 (2*R*)
		3: 65	79	89 (2*R*)

[a] Determined by HPLC/^{1}H NMR. All reactions run for 1h [b] Determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess was determined by HPLC (Daicel Chiralcel OD–H). [d] Obtained from single run only.

Preliminary data have also shown that there is potential for the ionic liquid process to be scaled up using a continuous extraction and only a nominal volume of ionic liquid. Reactions performed using 10 mol% of the catalyst system generated from δ/λ-[(R$_4$-NUPHOS)Pt{(*S*)-BINOL}] (R = Ph, **7a**; R = Me, **7b**) in 0.2 cm^3 of [emim][NTf$_2$] (compared with 2.0 cm^3 for the reactions described above) with 6.0 cm^3 diethyl ether as an immiscible co-solvent for extraction showed slower reaction kinetics but with an increased *ee*, 96% *vs*. 90% (Fig. 4). As found for reactions in the absence of diethyl ether, good recyclability is found in the biphasic solvent system.

In order to obtain high *ee*'s for the Diels–Alder reaction between oxazolidinone **1a** and Cp–H using the catalyst system generated from δ-[(Ph$_4$-NUPHOS)Pt{(*S*)-BINOL}] (δ-**7a**), the reactions had to be performed at −20 °C or below. Unfortunately, ionic liquids have relatively high viscosity below 0 °C and this in turn can result in significantly reduced reaction rates. This was overcome by performing these reactions in ionic liquid–diethyl ether mixtures, which increased the stirring efficiency compared with the pure ionic liquid and resulted in good conversions. As with the reactions described above between **1b** and Cp–H, the ionic liquid increased both the reaction rate and *ee* compared with CH$_2$Cl$_2$. Fig. 5 shows the variation in conversion and *ee* at −20 °C and −40 °C in [emim][NTf$_2$]–diethyl ether and CH$_2$Cl$_2$, respectively. Clearly the rate is much higher in the mixed solvent system compared with CH$_2$Cl$_2$. Although this could be due to the difference in reaction temperature, it should be noted that at −20 °C, only 45% conversion (48% *ee*) was obtained in CH$_2$Cl$_2$ over 24 hours due to the slow formation of the inactive [(Ph$_4$-NUPHOS)Pt(η^5-Cp)]$^+$ cation compared with 99% conversion (93% *ee*) after 2 h in [emim][NTf$_2$]–diethyl ether. In contrast, the *ee* normally increases with decreasing temperature; however, it is evident that, despite the higher temperature, the ionic liquid–diethyl ether system results in a significantly higher *ee* than found in CH$_2$Cl$_2$ at all conversions. Unlike in the ionic liquid–diethyl ether system, the *ee* is also found to decrease as the reaction proceeds in CH$_2$Cl$_2$. As found for reactions in the absence of diethyl ether, good recyclability is found in the biphasic solvent system.

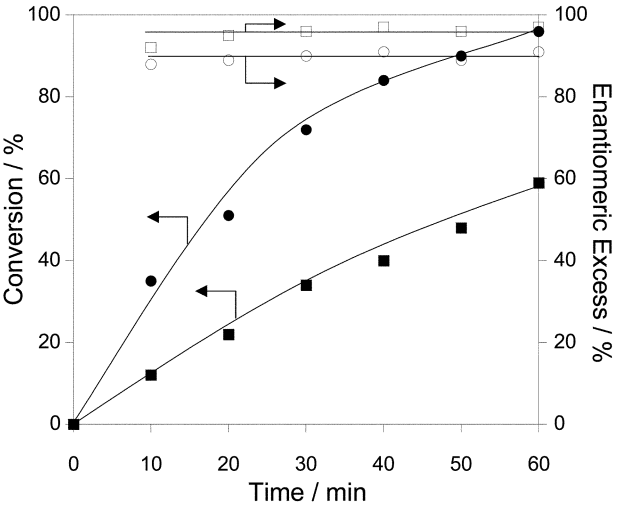

Fig. 4 Variation in %conversion (closed symbols) and %*ee* (open symbols) for the Diels–Alder reaction between **1b** and Cp–H catalyzed by δ-**8a** (10 mol%) in [emim][NTf$_2$] (circles) and [emim][NTf$_2$]–diethyl ether (squares) with respect to time at 20 °C.

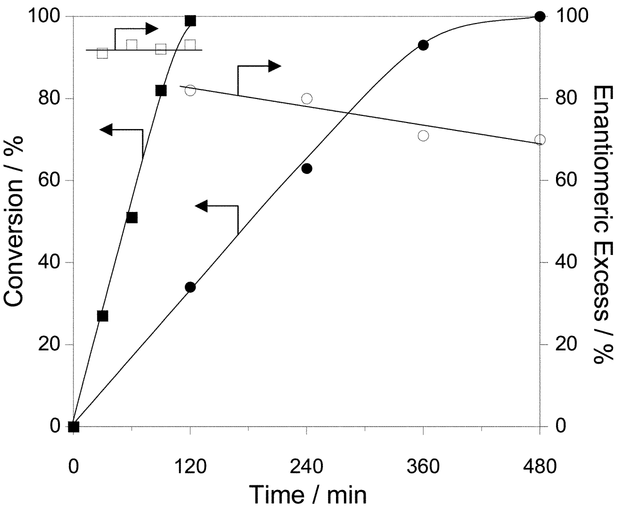

Fig. 5 Variation in %conversion (closed symbols) and %*ee* (open symbols) for the Diels–Alder reaction between **1a** and Cp–H catalyzed by δ-**8a** (20 mol%) in [emim][NTf$_2$]–diethyl ether at −20 °C (squares) and in dichloromethane at −40 °C (circles) with respect to time.

In conclusion, we have demonstrated that ionic liquid can not only significantly increase the rate of Diels–Alder reactions and the recyclability of the catalyst but also allow high enantioselectivities to be achieved without the need to recourse to low temperatures. This coupled with the use of conformationally flexible inexpensive ligands and the ability to perform semi-continuous reactions allows the possibility of scale-up. Ionic liquids also have the potential to replace chlorinated hydrocarbons often used for this type of Diels–Alder reaction.

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